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# Vulval intraepithelial neoplasia: current perspectives

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The heterogeneous clinical features of vulval intraepithelial neoplasia (VIN), its uncertain and variable natural history, difficulties in the management of certain cases and the frequency of recurrences provide a continuing challenge for gynaecologists. Patients with VIN present to a diverse range of physicians, all of whom provide differing perspectives on the multifarious issues relating to the condition. The importance of VIN relates principally to the symptoms it causes and its potential to progress to invasive vulval cancer.

Both the International Society for the Study of Vulvovaginal Diseases and the International Society of Gynaecological Pathologists have stressed the importance of eliminating eponymous terminology and recommend only the term vulval intraepithelial neoplasia (VIN). This terminology includes both squamous and non-squamous varieties (Table 1). The latter includes both Paget's disease of the vulva and melanoma in situ. Non-squamous VIN will not be considered in this paper.

Until 30 years ago VIN was an uncommon condition, seen principally in middle and later life. The incidence particularly in younger women has increased significantly since then [1-3]. Since that time the mean age in our unit has fallen from 52.7 years to 35.8 years (Figure 1) [2]. The increasing incidence of the condition parallels similar trends in cervical intraepithelial neoplasia (CIN) and relates at least in part to changing sexual morés, human papilloma virus (HPV) infection, and cigarette smoking.

## Clinical Features

Most women with VIN present with symptoms - in particular pruritus, soreness, dyspareunia or lumps. The symptoms are frequently mistaken for candidiasis and if a lump(s) is present, the lesion may be mistaken for condyloma(s). Approximately 20% of women are asymptomatic, the lesion being detected during clinical examination of the vulva. Significant delays in presentation are common [2].

VIN 3 lesions demonstrate a striking diversity of clinical features. Such lesions are invariably visible to the naked eye. Magnification (vulvoscopy) either with a colposcope or a loupe significantly enhances the examination, particularly the recognition of small multifocal lesions, vascular patterns and other subtle changes which may suggest early invasion. It also assists in the siting of representative biopsies. Application of 5% acetic acid for 5 minutes enhances certain lesions (especially red), but can confuse the clinical appearances because clinically unimportant subclinical HPV infection becomes apparent. Stefanon and De Palo have reported that vulvoscopy is unreliable for the differentiation of high grade VIN from some types of subclinical (macular) and clinical (papillomatous) HPV infection [4]. However, they point out that vulvoscopy is useful in identifying and defining the extent of the vulval lesion(s). Toluidine blue staining is a sensitive method for the detection of VIN 3, though false positive results may be associated with squamous hyperplasia [5]. Lesions may occur anywhere on the vulva, perianal skin and periurethral skin. The lesion may extend into the anal canal, the gluteal cleft, the vagina, the adjacent thigh and buttock. The lesions can be pigmented, red, white or mixed colouration, and may be flat, papular or papillary. Atypical vascular patterns may be visible in red lesions during vulvoscopy, though keratin frequently limits such assessment. Multifocal lesions are seen more commonly in younger women and unifocal lesions in older women.

Table 1.

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| A. Squamous intraepithelial neoplasia |
| VIN 1 mild dysplasia |
| VIN 2 moderate dysplasia |
| VIN 3 severe dysplasia or carcinoma in situ |
| B. Non-squamous vulval intraepithelial neoplasia |
| Paget's disease of the vulva |
| Melanoma in situ |

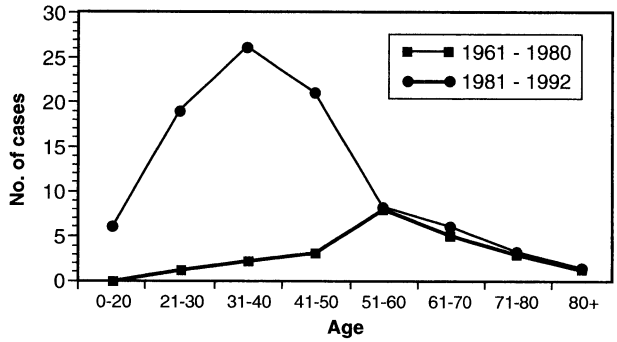


Figure 1. — Age at diagnosis of VIN 3. Permission - *Obstetrics and Gynecology* 1994, *84*, 741.

Up to 50% of women with VIN will have antecedent or concomitant neoplasia, usually cervical intraepithelial neoplasia (CIN) elsewhere in the lower genital tract [2, 6]. Thorough colposcopic evaluation (with cervical cytology), of the entire lower genital tract is therefore mandatory.

Biopsies should be performed of the most significant lesions under local anaesthetic with a 4 mm disposable punch biopsy. Multiple "mapping" biopsies are required for extensive lesions. Photography or accurate diagrams are of assistance when reviewing extensive, recurrent or difficult cases. Occult invasive vulval carcinoma has been reported in 18-22% of excised specimens in women in whom a pretreatment biopsy reported VIN alone [7-9].

Congenital, acquired or iatrogenic immunosuppression is associated with a significantly increased risk of lower genital tract intraepithelial or invasive neoplasia. A number of studies have reported high rates of vulval cancer in immunosuppressed organ transplant recipients and women with systemic lupus erythematosis [10,11,12]. The increased risk of human immunodeficiency virus (HIV) noted in some series of VIN has to date not been associated with a reported increase in incidence of invasive vulval cancer, but follow-up is limited [13]. There appears to be an association between cigarette smoking and VIN 3 [14]. It has been proposed that smoking leads to immunosuppression which could activate latent HPV [15].

## Pathology

The histological classification system for VIN is similar to CIN. While the classical histological description denotes atypia limited to the basal one-third as VIN 1, more obvious abnormalities involving the basal two-thirds as VIN 2 and full thickness abnormalities as VIN 3, the severity of the lesion is important in establishing the grade of the lesion. A biological continuum between VIN 1 and VIN 3 has not been demonstrated and the VIN grading system should be regarded as a convenient histological description of a spectrum of intraepithelial abnormalities. Skin appendages are involved in up to half of the cases, though VIN does not usually reach the deepest parts of the appendages. There are variations in the reported depth of VIN in skin appendages [16-18]. From the practical perspective of laser vaporisation, VIN rarely extends deeper than 2 mm in hairy and 1 mm in non-hairy skin [17]. A recent study reported good agreement between expert histopathologists in the diagnosis of VIN 2 and 3, but the diagnostic category VIN 1 was not reproducible [19]. A histological diagnosis of VIN 1 should be established with caution; most represent HPV infection, inflammatory or reactive change. VIN 1 should not be regarded as a cancer precursor. The use of the immunohistochemical antibody MIB 1 appears to assist in the grading of VIN [20]. VIN 2 is a relatively uncommon histological finding and at present should probably be regarded as a biological high grade abnormality similar to VIN 3.

VIN 3 can be histologically subclassified into warty (Bowenoid), basaloid (undifferentiated) and differentiated. Warty and basaloid VIN frequently coexist and the majority are HPV positive. Differentiated VIN (carcinoma simplex type) is rarely diagnosed in isolation, is usually HPV negative and is seen most frequently in older women with squamous hyperplasia and/or lichen sclerosus and has a strong association with squamous cell carcinoma [21]. Differentiated VIN has characteristic features limited to the basal epithelium and the VIN 1 to VIN 3 grading system is not applicable. Some have debated whether differentiated VIN merits inclusion within the current VIN classification [22].

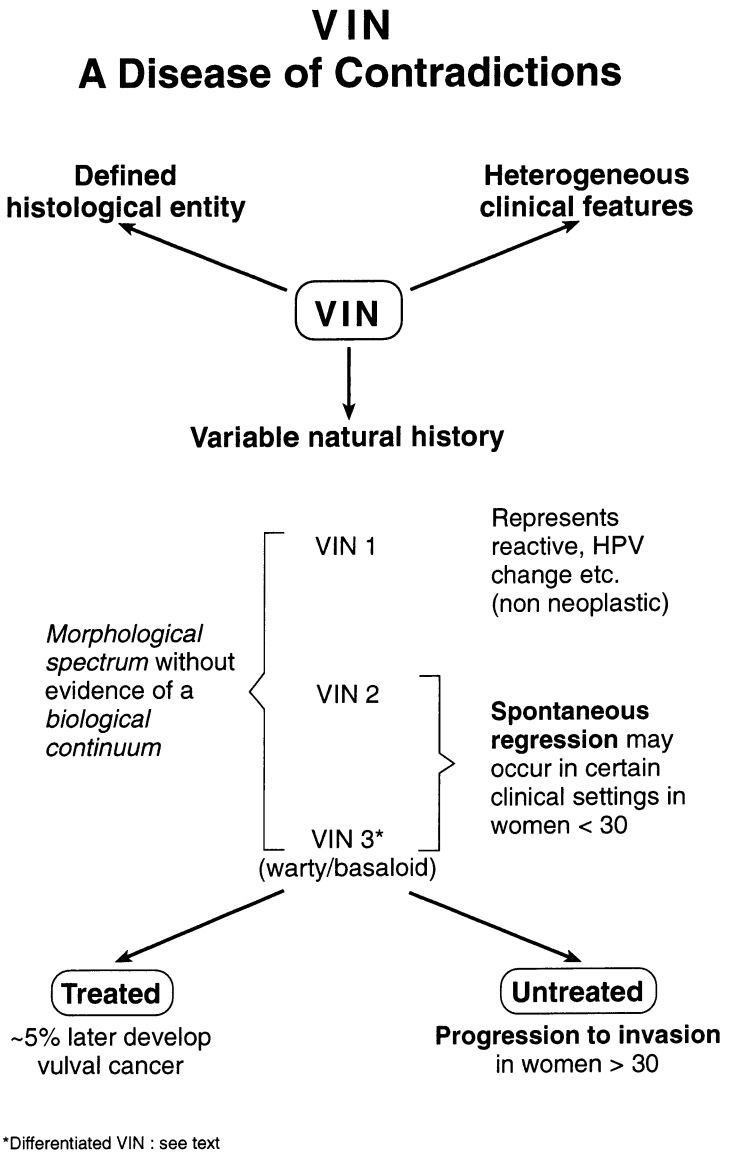


Figure 2. — VIN: a disease of "contradictions".

HPV has been demonstrated in 60-90% of warty/basaloid VIN 3 lesions, of whom more than 80% contain HPV 16 [23-25].

Monoclonality has been considered to be synonymous with squamous neoplasia and has been demonstrated in CIN and VIN [26,27]. However, the multicentric nature of VIN suggests the existence of multiple cells of origin and it is possible that polyclonal lesions also exist.

A key step in tumour development is the switch to an angiogenic phenotype. Compared with VIN 1 and 2 lesions, VIN 3 lesions demonstrate a dense network of microvessels under the dysplastic epithelium and an intense expression of an angiogenic peptide (vascular endothelial growth factor) [28].

The histological classification of VIN and CIN are similar, but there are marked differences in the frequency and significance of reporting the various grades of abnormality. Low grade (CIN 1/HPV) lesions predominate in cervical biopsies, while VIN 3 is the predominant grade of VIN biopsy. While there is evidence to support a biological continuum in some CIN lesions, this has not been established with VIN. CIN

3 is seen adjacent to 90% of squamous cell cervical cancers, but VIN 3 is found adjacent to only 30% of squamous cell vulval cancers. Finally, the annual progression rate of untreated VIN 3 to invasion is at least 10% [2], while that for CIN 3 is approximately 2% [29].

## Natural History

The natural history of VIN remains one of the contentious issues in gynaecological oncology [30, 31]. Management strategies require an understanding of the neoplastic potential of the condition. By 1960, the body of clinical observations had firmly established VIN 3 as a precursor of invasive vulval cancer [32-34]. Coinciding with the increasing frequency of the condition from the 1970s, there was a significant shift in opinion with respect to the "preinvasive" nature of the condition. A number of factors were responsible for this change. Most importantly, a number of series reported "low progression rates" (of about 2-4%) to invasive vulval cancer [35-40]. Surprisingly, only recently has it been appreciated that the quoted "low progression rates" do not reflect "progression" but the outcome following treatment which had aimed to eliminate the lesion. In addition, a number of reports of spontaneous regression of histologically confirmed high grade lesions also served to question the true nature of VIN [41, 42]. Finally, it was considered that the 35-year-interval between the mean ages at presentation of VIN and squamous cell carcinoma of the vulva tended to exclude a causal relationship. It is now established that vulval cancer usually occurs within ten years of the diagnosis and/or treatment of VIN 3 [2, 6]. It should be acknowledged that certain authors in the 1970s did question what the outcome might be if the untreated lesion was observed over many years [43, 44].

### *(a) Morphological evidence suggesting the neoplastic potential of VIN*

VIN can be demonstrated in the epithelium immediately adjacent to approximately 30% of invasive vulval cancers, suggesting a possible causal relationship [45]. In addition, the majority of early (Stage 1A) vulval carcinomas are noted to arise in a field of VIN 3 [46]. A number of studies have addressed the question of occult invasion in surgical specimens where pretreatment biopsies have reported VIN 3 alone. The striking concordance of occult invasion reported in these studies (18% to 22%) should be of concern to those who use laser vaporisation or medical therapies [7-9].

As has been noted, the VIN 1-3 descriptive histological grading system carries the implicit inference of a biological continuum that may end in vulval cancer. Such a continuum has not been demonstrated and only rarely has there been documented evidence of progression from VIN 1 to VIN 3 [47].

### *(b) Clinical evidence*

There are very few reported cases of untreated VIN 3, and these have either progressed to invasive vulval cancer or resolved spontaneously. There have been no reports of the persistence of VIN 3 for decades (as has been recorded in CIN 3). Youth and specific clinical features are associated with lesions which resolve spontaneously. Progression to invasion in healthy non-immunosuppressed women in the third and fourth decades of life is documented [2].

*(i) Progression of VIN to invasive carcinoma.*

The first modern series of untreated cases of VIN 3 in women over 30 years of age reported five middle-aged women with untreated VIN 3, all of whom progressed to invasion within eight years [48]. All of these women had associated lower genital tract malignancy and four had received pelvic radiotherapy. An updated study in 1994 [2] reported two additional untreated cases involving otherwise healthy women in their thirties without other modifying influences. In addition, there are a small number of case reports of untreated VIN 3 where progression to invasion has been noted [49, 50].

A recent review of 22 published studies of VIN 3 since 1970 (minimum 25 cases) has reported 2-5% (range 0-10%) of treated cases developed squamous cell carcinoma of the vulva during follow-up [51].

This outcome following treatment is approximately ten times the rate of cervical cancer following adequate treatment of CIN [29].

The impression that the 35-year-interval between the mean ages at presentation of VIN and squamous cell cancer of the vulva excluded a causal relationship has been disproved in a recent review which reported that

in women who present with VIN 3, invasive vulval cancers develop within ten years of the treatment of VIN in 93% of cases [51]. The transit time to invasion appears to be similar in both treated and untreated cases of VIN, suggesting that some vulval cancers which follow treatment for VIN, may represent inadequate primary treatment. On the other hand, recurrences of VIN and invasive vulval cancer are seen in women who have had clear surgical margins, implying that new disease or cancer developed in a "field at risk" [3]. It is noteworthy, that with increasing time high grade VIN progressively extends over increasingly large areas of skin, correspondingly increasing the risk of invasion [52].

Evidence with respect to differences in the invasive potential of unifocal and multifocal lesions is conflicting [53]. To date, there is no evidence pointing to lesion colour as an indicator of invasive potential.

Recent studies report a striking increase in the number of women under 50 years presenting with vulval cancer, linking this with the increasing incidence of VIN 3. A New Zealand study reported invasive squamous cell vulval cancer in 1.8% in a cohort of women under 50 years of age in the years 1965 to 1974 and 21% in a cohort of women under 50 years of age in the years 1990 to 1994. The incidence of invasive vulval cancer in women over 50 years was identical in the two cohorts. Seventy-eight percent of women under 50 years had a warty/basaloid VIN associated with the invasive vulval cancer, compared with only 13% in women over 50 years [54]. This strongly suggests that the increasing incidence of VIN seen in younger women in recent decades is now being reflected in VIN-associated squamous cell carcinoma of the vulva in younger women. An Austrian study has reported similar findings [55].

*(ii) Regression*

Case reports of the spontaneous regression of lesions with the histological features of VIN 3 appeared in the 1970s, influencing the perception that VIN was a generally banal condition [41, 42]. Spontaneous regression occurs in a well-defined clinical setting. A recent study reported regression in a group of non-white women under 30 years (median 19.5 years), sometimes in association with pregnancy and with a median transit time to disappearance of 9.5 months. Many cases were asymptomatic, the lesion being an incidental finding in a group of women with a history of previously treated vulval condyloma. The VIN 2-3 lesions, which were frequently asymptomatic, were noted to be multifocal, pigmented and usually papular [56]. The term bowenoid papulosis has been applied to the clinical variant of VIN 2-3 with the features described above. While the literature predominantly portrays bowenoid papulosis as a benign condition, caution is necessary because there are reports of such cases progressing to invasion, including in very young women [57].

## Management

The management of VIN 3 continues to be the subject of considerable controversy, with opinions ranging from the observation of asymptomatic lesions to the removal of all affected skin [2, 30]. These differences reflect differing views on the nature of VIN and the desire to avoid unnecessary and potentially mutilating surgery. Nonetheless our increasing understanding of the pathology, clinical features and natural history does provide some guidance with respect to management. Except for the small group of women who present with clinical features which might point to potential spontaneous regression (see above), few would advocate "watchful neglect" of women with high grade VIN. With rare exceptions, simple vulvectomy has been abandoned and the focus today relates to how conservative treatment can be. Management strategies need to be carefully balanced between the adverse sequelae (vulval mutilation, psychosexual trauma, etc.) associated with a radical approach to treatment and the potential risks of vulval cancer associated with an excessively conservative approach.

Treatment needs to be individualised and should be as conservative as possible with the object of the relief of symptoms, the prevention of cancer, the avoidance of vulval mutilation and the maintenance and enhancement of sexual activity. The potential for psychosexual dysfunction must be taken into account when planning treatment [58].

The patient's age, sexual history, the site and extent of the lesion, the knowledge and skill of the clinician and the facilities available (e.g. laser) all need to be taken into account. Extensive lesions in young women

should always be managed by an experienced clinician. Before treatment commences, the woman should be warned of the possibility of recurrences, the small future risk of invasive cancer and the importance of follow-up. The use of a magnifying instrument such as a colposcope improves assessment of the lesion and facilitates treatment.

(1) Excisional techniques

Local excision is the most universally applicable method of treatment and should be the only option where the possibility of invasion exists. Most high grade VIN lesions have a sharp transition (both clinically and histologically) with normal skin and there is no advantage in performing "wide" excisional techniques. Excision is the method of choice for small unifocal lesions. The excision should be superficial, allowing preservation of the subcutaneous tissue. Primary closure with cosmetically satisfying results can usually be achieved even when large areas are excised. Occasionally, flaps and grafting are required. Fine 40 absorbable polyglyconic suture materials provide excellent results. Skinning and split skin grafts can also achieve satisfactory results. The laser can be used for excisional purposes, but requires additional skill.

Simple vulvectomy was the standard management technique until 30 years ago. It should now be regarded as an unnecessary and mutilating procedure. Rarely, it may be an option in the elderly woman with an extensive lesion(s).

(2) $CO_2$ laser

The role of laser vaporisation techniques continues to stimulate debate. If the studies referred to above, demonstrating occult invasion in approximately 20% of cases of VIN 3, are indeed representative, there can be no case for ablative therapy [7-9]. However, in the absence of controlled studies and in the knowledge of the heterogeneity of VIN, an empirical approach to the use of ablative laser techniques will continue. Reid has described the principles and techniques in detail and has stressed that "it is a safe and efficient procedure in the hands of expert physicians, but should not be attempted by those who are less experienced" [59, 60]. This point cannot be stressed enough. Exclusion of invasion must be the priority of the laser ablative surgeon. This involves thorough preoperative vulvoscopy and mapping biopsies by an experienced clinician. Laser vaporisation is best suited to young women with extensive multifocal disease, and where preservation of vulval appearance is a priority. A detailed knowledge of the anatomy of vulval skin and its appendages is imperative.

Laser vaporisation is best employed in non-hairy skin where VIN usually does not usually extend deeper than 1mm. VIN in hairy skin is best excised because the skin appendages can extend 3mm into the dermis. Sometimes VIN involves both hairy and non-hairy skin and in this situation combined excisional and laser ablative techniques may produce the best results [61]. Sideri et al noted that while laser vaporisation produced good cosmetic results, laser excision revealed unrecognised early invasion in 12% of cases [62].

Electrocoagulation, cryosurgery, loop excision and ultrasonic aspiration techniques have all been described but none appear to have worthwhile advantages [63].

(3) Medical therapy

A variety of medical therapies have been employed to treat VIN. The majority are novel and have not become standard therapy. These include topical dinitrochlorobenzine, topical immunotherapy, topical and intradermal bleomycin, photodynamic therapy, interferon and peptide vaccine [64-68]. The major concern with any form of medical treatment is of unrecognised invasive cancer. Spiritos noted that 9% of patients initially entered into their interferon study were found to have invasive cancer [66]. Five of 12 women treated with bleomycin progressed to invasive disease. Attempts to treat VIN with topical 5FU have largely been abandoned. Sillman [69] reviewed the literature on 5FU and recorded remissions in 34% and failure in 59%. Imiquimod (Aldara 3M), an immune response modifying agent which is effective against external genital warts, has recently been shown to be effective in certain VIN lesions [70]. The agent has a number of theoretical and potential advantages but its place has yet to be established by properly designed clinical studies.

## Special sites

The clitoris, external urethral meatus and perianal skin present particular difficulties in management. The apparent excess of invasive cancers noted in some studies at these sites in women who have previously been treated for VIN may reflect persistent disease [2]. However, it is possible that "transitional" type epithelium at these meatal sites may be more vulnerable to carcinogenic influences. Thorough preoperative assessment of these sites is essential if effective treatment is to be performed.

Laser treatment to the clitoris is theoretically appealing but the irregular surface topography of the small organ creates difficulty with optimum laser application. Residual islands of VIN create the potential for later invasive disease. Complete skinning of the glans clitoris with a scalpel (sometimes with grafting) without removal of the clitoris avoids this possibility.

Perineal involvement with VIN should always raise the possibility of perianal or anal canal involvement. The laser has no place in the treatment of perianal or anal canal disease and complete excision is the preferred management. Similarly, involvement of the epithelium at the external urethral meatus demands an excisional procedure, with care being taken to ensure that there are negative margins.

## Recurrences

Recurrences are to be expected in up to 30% of cases [71]. Surgical principles would suggest that the status of surgical margins should provide some indication of potential future recurrences. Surprisingly, the evidence is conflicting. While Rettermann *et al.* [72] found no relationship between surgical margins and recurrences, Modescitt et al [8] established the recurrence rate was three times higher when surgical margins were positive. Other studies have demonstrated a relationship between positive margin status and recurrences [73]. A recent large Norwegian study failed to demonstrate a relationship between positive surgical margins of VIN and future invasive vulval cancer. Eight of 16 women who later developed invasive vulval cancer had negative resection margins at the time of primary surgery for VIN [3]. The finding of van Buerden et al of a higher incidence of recurrences in women who had "extensive" surgery compared with those who underwent "restricted" surgery defies established surgical principles and can probably be explained by the biological differences between the two study groups [30].

The risk of recurrent VIN is significantly higher in women with multifocal VIN compared with unifocal VIN [71, 73]. Kupper's study failed to establish a relationship between smoking and recurrences. One must conclude that while many recurrences reflect persistent disease, some recurrences do represent new disease. New disease may arise in grafted skin and following simple vulvectomy [48, 74].

## Follow-up

Life-long surveillance of all women who have had a previous diagnosis of VIN 2-3 is essential. Whilst most recurrences occur in the early years following initial treatment, recurrences of VIN and the development of invasive vulval cancer can rarely occur decades later. The follow-up examination must include annual cervical cytology, together with colposcopic assessment of the entire lower genital tract. The initial follow-up intervals of between three and six months may be relaxed to annual examinations when the risk of recurrence is considered to be low; the immunosuppressed patient requires at least six-monthly follow-up for life. The onset of vulval symptomatology warrants urgent reassessment in all patients with a history of VIN.

The concept of screening for VIN and other vulval dermatoses with the potential for neoplastic transformation has yet to be explored. Women with a history of multiple lower genital tract neoplasia and those with immune deficiency are "at risk" groups in whom regular detailed inspection by an experienced clinician is necessary. Finally, all women should be encouraged to inspect the vulva regularly with the assistance of a mirror.

## Conclusion

VIN is in many respects a disease of contradictions and these are summarised in Figure 2. A more active approach to the diagnosis and management of VIN 3 may often prevent the development of vulval cancer [75]. The increasing incidence of VIN and VIN-associated vulval cancer in younger women provides a continuing challenge for clinicians.

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