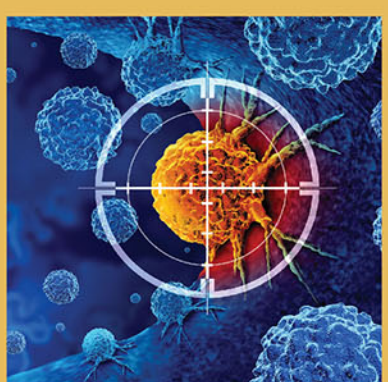
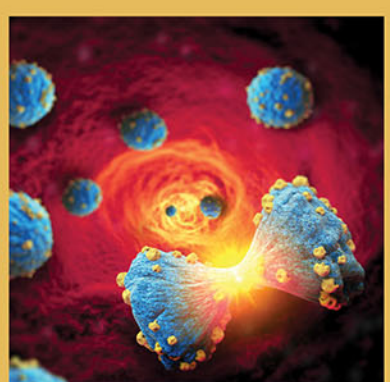
ebrothers.com, for detailed information on obstetrics and gynecology books, visit our website www.jaypeebrothers.com, for detailed information on obstetrics and gynecology books

Screening & Management of Gynecological Cancers





Editors
Renu Tanwar
Poonam Kashyap
YM Mala

Foreword
Reva Tripathi

JAYPEE

Content

SECTION 1: CERVICAL CANCER

1. **Poonam Sachdeva, Peuly Das, Divya Singh, Ishita Aggarwal 3**
   Management of Abnormal PAP Smear
2. **Management of Cervical Intraepithelial Neoplasia 14**
   Deepti Goswami, Aishwarya Chaudhari
3. **Management of Early Cervical Cancer 30**
   Poonam Kashyap, Vedika Bali
4. **Management of Advanced and Recurrent Cervical Cancer 41**
   YM Mala, Saloni Chadha
5. **Human Papillomavirus Vaccination 48**
   Krishna Agarwal, Saloni Chadha, Neha Khatri

SECTION 2: ENDOMETRIAL CANCER

6. **Management of Endometrial Hyperplasia 59**
   Sangeeta Gupta, Parminder Kaur, BS Sadhavi
7. **Management of Endometrial Cancer 68**
   Madhavi M Gupta, Nitisha Verma
8. **Fertility-Sparing Management of Endometrial Carcinoma 78**
   YM Mala, Mona Mishra, Arushika Yedla
9. **Management of Uterine Sarcoma 83**
   Bidhisha Singha, Mrinalini Dhakate
10. **Management of Gestational Trophoblastic Neoplasia 88**
    Anjali Tempe, Priyanka Khandey

SECTION 3: OVARIAN CANCER

11. **Screening and Risk Assessment for Ovarian Cancer 97**
    Chetna A Sethi, Reetu Yadav
12. **Management of Low Malignant Potential Tumors in Ovarian Cancer 108**
    Renu Tanwar, Baseerat
13. **Management of Nonepithelial Ovarian Cancer 114**
    Latika Sahu, Kalyani Nair
14. **Management of Epithelial Ovarian Cancer 123**
    Niharika Dhiman, Anoosha Ravi

SECTION 4: VULVAL AND VAGINAL CANCER

15. Management of Preinvasive Vulval Lesions 139
Poonam Kashyap, Kalyani Nair

16. Management of Vulval Cancer 148
Shikha Sharma, Parminder Kaur, Bharathi Priya AM

17. Management of Vaginal Cancer and Vaginal Intraepithelial Neoplasia 159
Nidhi Garg, Poonam Kashyap

SECTION 5: MANAGEMENT OF FAMILIAL GYNAECOLOGICAL CANCERS

18. Screening and Management of Familial Gynecological Cancers 167
Reena Rani, Subhashree Sethi, Anmol Dewan

SECTION 6: CHEMOTHERAPY AND RADIOTHERAPY GYNECOLOGICAL CANCERS

19. Principles of Chemotherapy in Gynecological Cancers 179
Kumar Prabhat, Kishore Singh, Sadhana Singh

20. Principles of Radiotherapy in Gynecological Cancers 190
Arun Kumar Rathi, Wineeta Melgandi, Faiz Akram Ansari, Kavita Sehrawat, Savita Arora, Ankaj Krishnatre

SECTION 7: NEWER MODALITY: TARGETED THERAPY IN GYNAECOLOGICAL CANCER

21. Targeted Therapy in Gynecological Cancers 201
Gauri Gandhi, Divya Singh

SECTION 8: MISCELLANEOUS

22. Screening for Breast Cancer 209
Bharathi Priya AM, Sangeeta Bhasin

23. Management of Hydatidiform Mole 216
Rachna Sharma, Reetu Yadav, Ojaswini Sharma

24. Emergencies in Gynecological Cancers 222
Nalini Bala Pandey, Divya Prasad, Sarah Fatima Siddiqui, Sunita Naik

25. Hormone Replacement Therapy after Gynecological Cancer 230
Shakun Tyagi, Sakshi Aggarwal

26. Perioperative Care in Gynecological Cancer 240
Shalini Shakarwal, Preeti Singh

27. Palliative Care in Gynecological Cancer 250
Pushpa Mishra, Bhupali Das

SECTION 9: ANNEXURES

Annexure 1: Staging of Cervical Cancer 265

Annexure 2: Staging for Carcinoma of the Ovary 267

Annexure 3: Staging of Cancer of the Endometrium 268

Annexure 4: Staging for Carcinoma of the Vulva 269

Annexure 5: Staging for Carcinoma of the Vagina 270

Index 271

CHAPTER

15

Management of Preinvasive Vulval Lesions

Poonam Kashyap, Kalyani Nair

INTRODUCTION

Preinvasive lesions of the vulva include various vulvar disorders, which form precursors for the development of invasive cancer of the vulva. A thorough and detailed knowledge of these lesions is of utmost importance, as early diagnosis and adequate treatment of these lesions are the only form of secondary prevention, currently available. These lesions have a great variability in their presentation, high risk of occult invasive disease at the time of diagnosis, multiple therapeutic options, and high percentage of relapse after treatment, establishing the complexity of this pathology.[1]

CLASSIFICATION AND TERMINOLOGY

The etiopathogenesis of vulvar squamous cell carcinoma (SCC) encompasses two different entities, which are human papillomavirus (HPV)-dependent and HPV-independent pathways (from precursor lesions secondary to chronic skin diseases).[1,2] This is based on the new terminology published by the International Society for the Study of Vulvovaginal Disease (ISSVD) in 2015. In 2015, the ISSVD took into consideration the World Health Organization (WHO) classification and published the new terminology for vulval squamous intraepithelial lesion (SIL) **(Table 1)**. This classification is being recognized and is more reproducible by pathologists than the previous ones.[3,4]

EPIDEMIOLOGY

Vulvar intraepithelial neoplasia (VIN) is an under-diagnosed and under-reported entity; hence, it is difficult to determine the actual incidence.[1] The incidence in Nordic countries is between 2.5 and 3.1 per 100,000 women/year, with cases increasing after 40 years of age.[5]

TABLE 1: 2015 ISSVD terminology of vulvar SIL.[3]

LSIL of the vulva	Vulvar LSIL, flat condyloma, or HPV effect
HSIL of the vulva	Vulvar HSIL, VIN usual-type
dVIN	VIN differentiated type

(dVIN: differentiated vulvar intraepithelial neoplasia; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; ISSVD: International Society for the Study of Vulvovaginal Disease; LSIL: low-grade squamous intraepithelial lesion; SIL: squamous intraepithelial lesion; VIN: vulvar intraepithelial neoplasia)

RISK FACTORS

- *Human papillomavirus:* HPV positivity is found in almost 90% of VIN lesions. HPV infection can occur with sexual contact, including genital, anal, or oral contact to the vulva. Its transmission can occur without vaginal intercourse.
- Low-risk HPV subtypes (6 and 11) are often found to be associated with low-grade SIL (LSIL), while high-risk types (16, 18, 31) are found in high-grade SIL (HSIL).[6]
- HPV associated squamous neoplasia found at other genital tract sites is also associated with vulvar SIL/intraepithelial neoplasm. Approximately 60% of patients with vaginal intraepithelial neoplasia (VaIN) 3 or VIN have coexisting cervical intraepithelial neoplasia (CIN).[7]
- HPV-associated vulvar HSIL are found more commonly in premenopausal patients, while postmenopausal patients are more likely to have non-HPV-associated vulvar SIL.
- *Cigarette smoking:* Cigarette smoking has been strongly associated with development of vulvar SIL and its disease recurrence.[8]
- *Immunodeficiency:* It has been found that vulvar SILs are more common in patients infected with HIV.[9,10]

JAYPEE BROTHERS

- *Differentiated VIN (dVIN):* It is more commonly associated with vulvar dermatosis, such as lichen sclerosus. The risk of vulvar squamous carcinoma in patients with dVIN with lichen sclerosus is approximately 5%.[11] The evidence suggests that timely management and early detection of lichen sclerosus can reduce the risk of development of SCC.

PATHOGENESIS

The lower anogenital epithelium is derived from the embryonic cloaca, and it includes the lower 3 cm of the rectal mucosa up to the dentate line, anus, cervix, vagina, and vulva. This area is susceptible to similar exogenous agents (e.g., HPV infection), therefore SILs in this area are often both multicentric (i.e., foci of disease involving more than one organ) and multifocal (i.e., multiple foci of disease within the same organ). Thus, patients with vulvar SIL needs to be evaluated for any metachronous or synchronous squamous neoplasia of other lower genital tract sites.

Compared to LSIL and HSIL, the pathogenesis of dVIN is not well understood. The diagnosis of solitary dVIN is at times very challenging. It is usually unifocal and unicentric and most commonly associated with lichen sclerosus and not with HPV infection. dVIN is less common than HSIL and accounting for 2–29% of premalignant vulvar lesion. dVIN is found to have more rapid progression to SCC and is often present adjacent to the majority of vulvar SCC.[6] Those patients with lichen sclerosus and showing dyskeratosis and parakeratosis, hyperplasia, and/or basal cellular atypia have the highest propensity to progress to SCC. No biomarkers are available to reliably identify the patients at highest risk.[11]

NATURAL HISTORY—PROGRESSION, REGRESSION, AND ASSOCIATION WITH CONCURRENT AND FUTURE INVASIVE CANCER

- If vulvar SIL is left untreated, it may persist, progress, or resolve.
- Vulvar SILs are skin manifestations of HPV infection and are benign, except in rare cases. They usually resolve within 1–2 years.
- Vulvar HSILs are intraepithelial neoplasms and are found to be associated with 20% of SCC of vulva. In one systematic review of 61 patients with VIN 3, 27 patients had macroscopic VIN even after treatment. Approximately 9% progressed to invasive vulvar carcinoma over 1–8 years. Out of these patients, four had received previous radiation therapy to the lower genital tract, and one was found immunosuppressed. In other 13 studies, reported complete spontaneous regression was observed in 1.2% of patients. In all such cases, they were below the age of 35 years (mean 20 years). In 17 cases with regression, pregnancy was related.[12]
- dVIN has the highest risk of progression to SCC in approximately 33%. In approximately 80% of the cases of SCC, dVIN is found as the putative precursor lesion.[6,13] In the European database, the 10-year cumulative risk of developing vulvar SCC with dVIN was 50% [95% confidence interval (CI) 22–78%].

Symptoms and Appearance

- *Vulvar pruritus:* Patients with VIN are asymptomatic in 50% of the cases. Others present predominantly with pruritis. They can also present with complaints of a lump, burning sensation, irritation, or pain in the vulva.[5,8] A systematic review of 19 studies done on 3,300 patients with VIN 3 observed that pruritus was chief complaint in 64% patients. Careful inspection of the vulva, perineum, and perianal area during routine pelvic examination under good light has to be done to identify the lesions.[8]
- *Vulvar lesion:* These lesions may be picked up during a routine gynecological examination or at colposcopy done for abnormal cervical cytology. These lesions could be in various forms.
  - Pale areas that vary in density (milder forms of VIN)
  - Papules or macules (more severe forms) that are coalescent or discrete, single or multiple
  - Lichenified or hyperkeratotic plaques or white epithelium on cutaneous surface of vulva **(Fig. 1)**. Hyperpigmented lesions are seen in 10–15% of the patients, which are mahogany to dark brown in color **(Fig. 2)**. Pigmented lesions need to be differentiated from benign conditions like lentigo. In case of VIN, lesions are raised and hyperkeratotic. Lesions may be present in areas like the gluteal cleft or hemorrhoidal tags when multifocal.[5]
- *Persistent abnormal cervical cytology:* As SILs in this region are often multicentric, so they can present with abnormal cervical cytology and with no abnormality identified on cervical biopsy. The nearby

JAYPEE BROTHERS



Fig. 1: Raised white plaques [high-grade squamous intraepithelial lesion (HSIL)]. *(For color version, see Plate 3).*

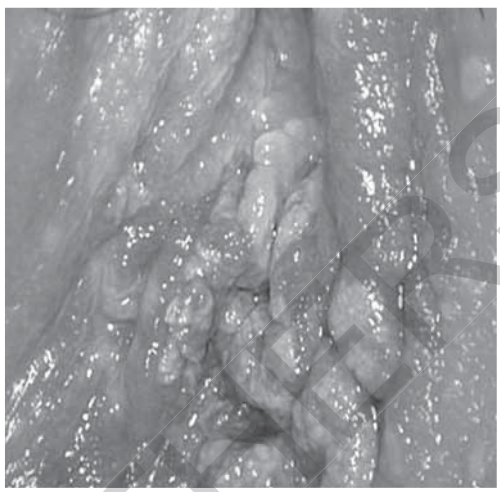


Fig. 3: Vulvar condyloma. *(For color version, see Plate 3).*

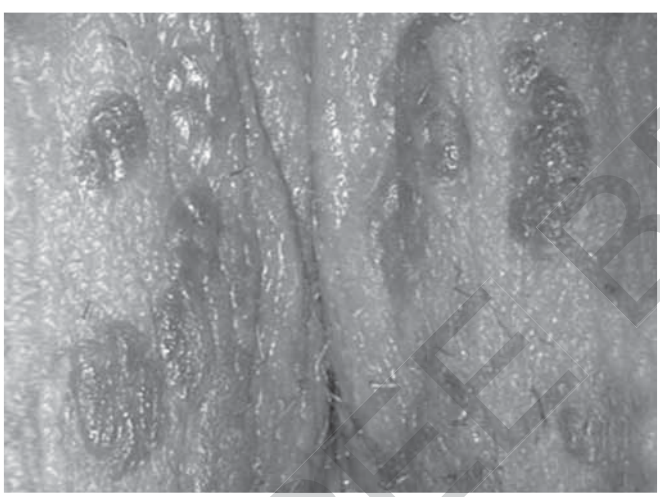


Fig. 2: Vulvar intraepithelial neoplasia (VIN): Multifocal hyperpigmented raised plaques. *(For color version, see Plate 3).*

areas such as the vulva, vagina, and anus need to be evaluated for SILs.

DIFFERENTIAL DIAGNOSIS

Vulvar SILs are usually multifocal, and they have variable appearance. Therefore, it needs to be differentiated from other vulvar lesions, which can mimic vulvar SIL, including condyloma acuminatum **(Fig. 3)**, lichen sclerosus, vulvar cancer, lichen planus, or condyloma latum. The best way to diagnose and differentiate from other lesions is vulvar biopsy.

Other vulvar lesions associated with vulvar pruritus and pain include dermatitis, candidiasis, molluscum contagiosum, lichen simplex chronicus, psoriasis, and herpes simplex virus.

ROLE AND METHOD OF VULVOSCOPY AND COLPOSCOPY

Vulvoscopy is a diagnostic method for examining vulva, vestibule of the vagina, the labia minora and majora, and the clitoris by using a special optical technique. As part of screening of vulval diseases and cancer, vulvoscopy must always precede colposcopy. Contraindications to extended vulvoscopy are allergic reactions to solutions that are used to visualize vulvar injuries and acute inflammations and pathogenic foci.[14]

Vulvoscopy is performed in suspicion of VIN, chronic inflammatory conditions, neoplasm of vulva, vulvodynia, and when dubious result on cytology. It is done 1–3 days before menstruation or 1–3 days after it ends not to have secretion in the area of interest. Women should exclude sexual contact and use of intimate hygiene products, douching, ointments 3–4 days prior to examination. Hair should be cut short with scissors. First, the examination of area of the external genitals is done without optical equipment and then examination is done with a minimum magnification (7.5 times) to be able to assess the overall condition of this area. The vulvar area is to be inspected for changes of color, presence of swelling on surface, and loss of substance. The vulva should be examined in a systematic fashion to include the mons pubis and labia majora, labia minora, clitoral prepuce, clitoris, perineum, and anal areas. The most frequent location of pathological

JAYPEE BROTHERS

areas is the inner surface of the lower third of the labia minora. Approximately 50% of cases are multifocal lesions throughout the vulva and 35% are multicentric lesions together with involvement of the cervix and vagina. The clitoris is affected only in 9% of cases. Up to 75% of lesions are located outside the hairline.[15]

Colposcopy

After a lesion has been clinically diagnosed, colposcopy is done after applying 3–5% acetic acid. The keratinized epithelium of the vulva requires application of acetic acid for at least 5 minutes for the lesions to become apparent, which can be achieved using cotton soaked balls or sponges.[5] Pathological tissues become whitish due to a specific vascular reaction. Examination may be done further after application of 1% aqueous solution of toluidine blue that fixes the nuclei. Suspicious areas with increased nuclear activity become deeply stained (royal blue), whereas the normal skin takes up little or no dye. But hyperkeratotic lesions are lightly stained and benign excoriations are stained brilliantly, giving rise to false negative and false positive results, respectively. Toluidine blue is infrequently used as it has low specificity in diagnosing HSIL.[15]

Vulvar Biopsy

- Vulvar biopsy is indicated for confirmation of diagnosis of any suspicious lesions, visible lesions not responding to usual therapy and for lesions for which definitive diagnosis cannot be made on clinical grounds. Vulvar lesions that can be diagnosed by vulvar biopsy are lichen sclerosus, molluscum contagiosum, VIN, condyloma, and vulvar carcinoma.[16]
- It can be done under local anesthesia (lignocaine or bupivacaine) with the help of a Keyes dermatologic punch (4–6 mm) or a shave biopsy may be performed using a scalpel or scissors. Generally, a punch biopsy is used for flat or slightly raised lesions, and scalpel or scissors for raised or pedunculated lesions. Keyes punch biopsy is particularly useful when depth of lesion is important. The Keyes punch is a pen-sized instrument with sharp, cutting edge used to cut tissue in a twisting motion **(Fig. 4)**. If an ordinary knife "shave" biopsy is used, one must be careful enough as to include a full thickness skin specimen up to adipose tissue for adequate sampling of deeper layers. Multiple biopsies may be required as there is risk of missing invasive disease. Once an adequate sample has been obtained, the specimen should be carefully placed in a fixative solution, such as 10% formalin and sent for histopathological examination.
- Hemostasis is achieved using silver nitrate, Monsel's, a stitch, or a piece of absorbable gelatin powder, which is placed with a small dressing for at least 24 hours. It should be ensured that the patient's cervical cytology is up to date as cases with CIN are associated with VIN (due to HPV). In case of any perianal lesions, appropriate referral for anoscopy is recommended.[17]
- There are no absolute contraindications to vulvar biopsy, but relative contraindications include infection at the site, coagulopathy, and allergy to local anesthetic.

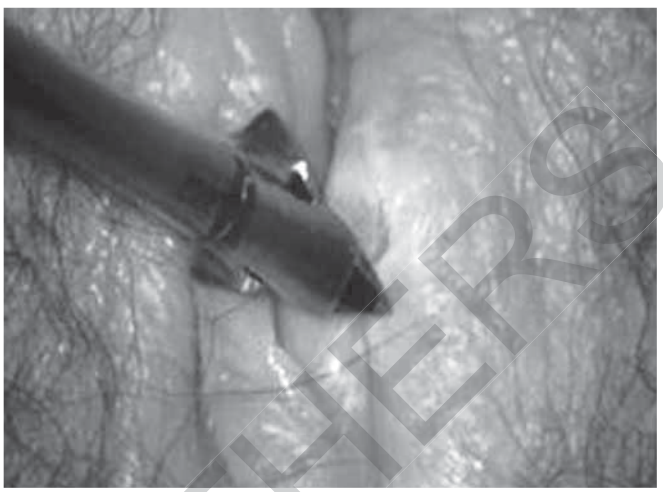


Fig. 4: Vulvar biopsy with Keyes punch.
(For color version, see Plate 3).

TREATMENT (FLOWCHART 1)

Low-grade Squamous Intraepithelial Lesions

Vulvar low-grade SILs are not considered as neoplastic lesions and are equivalent to condyloma acuminata (anogenital warts); these do not require treatment unless symptomatic.

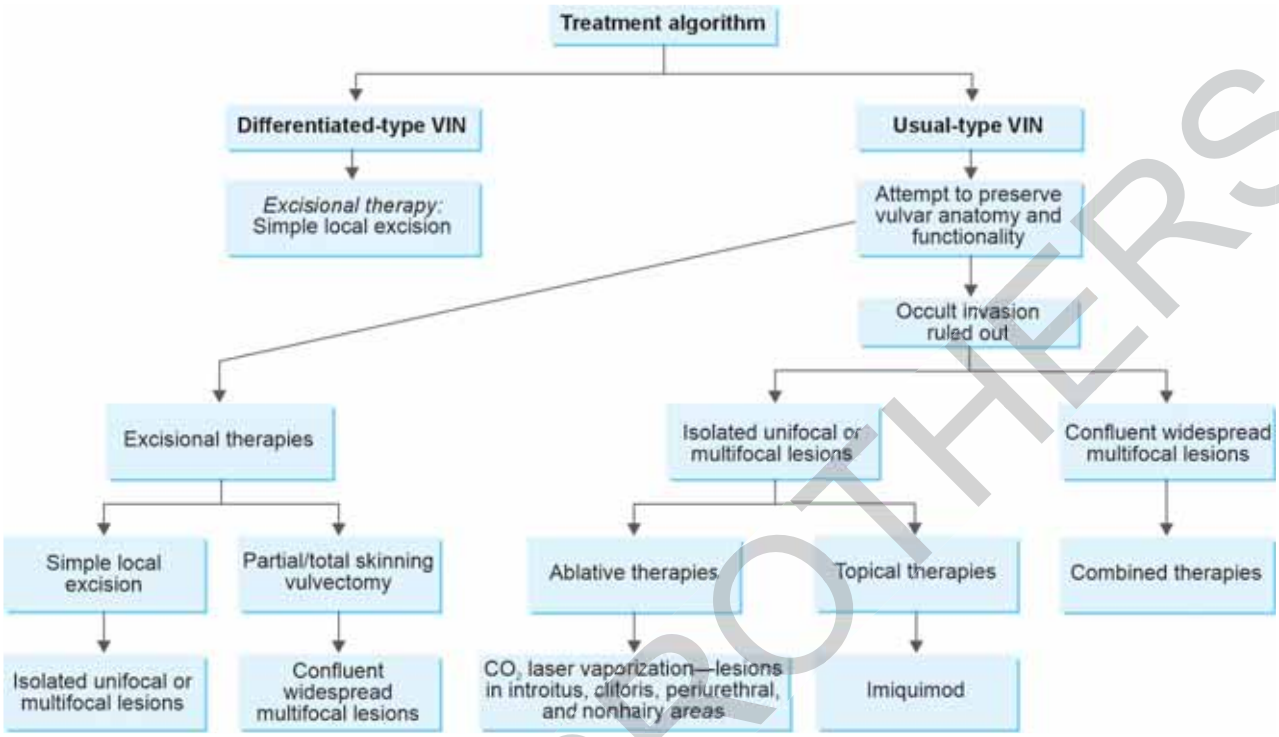
High-grade Squamous Intraepithelial Lesions

The aim of treatment is to improve symptoms and prevent the development of vulvar carcinoma, while preserving the normal anatomy and function of vulva.

High-grade SILs could be managed by *excision, ablative therapy, and topical treatment* depending on the level of concern for invasive disease, the location and focality of the lesion(s), and prior treatment history. Guiding principles are described here.

JAYPEE BROTHERS

Flowchart 1: Treatment of vulvar intraepithelial neoplasia (VIN).



Surgical

- *Surgical excision is indicated for patients with vulvar HSIL who have the following:*
  - A lesion with possibility of invasive disease (e.g., ulcerative, raised, or with irregular borders), irrespective of results from colposcopy/biopsy
  - If significant risk factors for invasive disease are present, such as:
    - Previous history of vulvar HSIL
    - Immunosuppression
    - Lichen sclerosus
    - dVIN
    - Vulvar carcinoma

Wide local excision is most commonly performed in lesions where macroscopic disease can be removed with negative margins. It is the mainstay of treatment. The goal is to obtain 5 mm to 1 cm disease-free margin. In the studies, it was found that recurrences were three times higher in cases with positive margins.[5,9] The margins of normal skin can be close if the lesion is benign, but in case of a lesion that is suspicious for cancer (severe VIN or by appearance), it is preferred to excise circumferentially with the aim of achieving a 1 cm margin and the depth of excision extending till the underlying adipose tissue or to the deep fascia. Wide local excision can be done in small lateralized vulvar carcinomas with resection taken down to the deep fascia. The advantage with excisional procedure when compared to ablative procedure is that complete histological assessment (confirmation of diagnosis, existence of invasions, and margin status) is possible with the ability to detect early invasion. There is no definitive evidence to show that vulvectomy is better than wide local excision, but the morbidity associated with vulvectomy is higher. After wide local excision, end-to-end approximation of the defect is done. As the vulvar skin and mucous membrane is very elastic, it provides satisfactory cosmetic results.[18]

For preinvasive lesion and close to clitoris or urethra, the margins of the lesion can be <1 cm to avoid disruption of functional and structural anatomy of vulva and the laser ablation of the surrounding skin can be done if fear complete excision. The shape of the excision should be in the form of elliptical with longest axis running parallel to neighboring structures.

Complications: The data regarding the complications following vulvar wide local excision is sparse, but they are rare.

JAYPEE BROTHERS

The complications which can occur include infection, excessive bleeding, hematoma, and scarring.

- *Skinning vulvectomy* is rarely indicated and is performed in case of large, confluent multicentric lesions. It is also used in few patients in whom prior treatments such as topical, laser ablation, or excision have failed. Here, the involved skin is excised along avascular plane and substituted with a split skin graft taken from the buttocks or the inner aspect of the thigh **(Fig. 5)**. The advantage with this procedure is the preservation of the subcutaneous tissue of the vulva, hence giving a better cosmetic and functional result.[1,5,19]

Complications: Although skinning vulvectomy is a safe procedure, but following complications can occur following skinning vulvectomy: Graft sloughing, partial or complete, fever, and dyspareunia related to introital narrowing.

- *Simple vulvectomy* is performed for benign or malignant lesions of vulva, which are extensive or multifocal and cannot be treated with local excision alone. Here the vulvar skin, labia majora, minora, and clitoris are removed. The procedure distorts the vulvar contour and anatomy; therefore, it is reserved for older patients where sexual function is not required. As the skinning vulvectomy and skin grafting require prolonged bed rest for 6–7 days, the potential for morbidity is increased, and therefore, it is not preferred in old patients. The procedure of simple vulvectomy is considered excessive for an intraepithelial lesion causing major deformity of the external genitalia. Regardless of the patient's age it is important to take into consideration the patients' desire for better cosmetic results and sexual function.[20,21]



Fig. 5: Incision of skinning vulvectomy.

Ablation

Ablative therapy can be used in patients of HSIL in which there is no risk of invasion and also if disease is multifocal and involving urethra, clitoris, anus or vulvar introitus to preserve the vulvar anatomy. CO_2, argon laser, and ultrasonic surgical aspirator can be used. Careful selection of patients is required before opting this modality as histological assessment is not possible. Small areas can be ablated on an OPD basis, but large areas require general anesthesia.[1,5,10]

This procedure requires greater expertise. A depth of 1 mm destruction is adequate for nonhair-bearing epithelium, and if the skin appendages are involved then a depth of 2.5–3 mm is required. Surgical planes were defined in the vulva by Reid to guide laser therapy. Plane one (involving surface epithelium only along with basement membrane) or plane two (involving the dermal papillae) is destroyed in case of nonhair-bearing skin. Plane three (involving upper and midreticular area) is destroyed in hair-bearing tissue.

There may be cosmetic advantage with superficial ablative therapy over excisional procedures. Another advantage with such a procedure is its usefulness where lesions are close to external sphincters. In such cases, excisional procedures can cause sphincter weakening. Laser procedures are also less invasive and give excellent cosmetic results.[10]

The main complication with ablative procedure is pain, which can be severe. In case of deep wound, it can lead to formation of a necrotic ulcer causing delayed healing. Bleeding and infection are other complications.[22]

Other procedures like photodynamic therapy have been tried in case of HSIL with response rates of around 48–55%. There is little scientific evidence for the clinical application of this treatment modality.[1]

Cavitational Ultrasonic Surgical Aspirator

This is another procedure which uses ultrasound to produce tissue destruction. Patients treated with cavitational ultrasonic surgical aspirator (CUSA) had lesser postoperative pain and scarring with similar recurrence rates. It also allows histological diagnosis of the specimen obtained. Data from prospective randomized trial shows a recurrence rate of 25%.[10]

JAYPEE BROTHERS

Topical Therapy

The benefit of medical therapy is the avoidance of disfiguring surgery. These are not indicated in case of differentiated type VIN. Its indications are:

- Imiquimod cream is often the preferred initial treatment for recurrent vulvar HSIL.
- It can also be used in patients with clitoral lesions who prefer to avoid excision and ablation, but patients need to take treatment for long period (typically 16 weeks).

Imiquimod: This is an immune response modulator, which activates the macrophages and dendritic cells to release interferon α and other cytokines, to provoke an antigen-specific immune response. It has antiviral and antitumor properties. It is used as 5% cream before bedtime for 2–3 weeks for a maximum of 12–20 weeks with follow up every 4–6 weeks. Side effects in the form of itching, redness, and severe inflammatory response can be seen. It was used in patients with HPV-associated genital warts and has great promise in the treatment of VIN. A complete response was observed by De Witte and colleagues in 5–88% of patients in 13 of 14 studies featuring 780 women.[10]

5-Flourouracil (5-FU)

This drug produces chemical peeling when 5% cream is used 1–2 times a day for 6–10 weeks. Monitoring is recommended every 4–6 weeks. Side effects such as erythema, edema, skin desquamation, and significant pain may develop in which case frequency of application can be reduced. Complete tissue healing occurs in 4–6 weeks. It has shown to be effective in 75% of cases, but due to its side effects, use is very limited.[1,11]

Combined modality therapy: There is limited data on combined modality therapy for both primary and recurrent disease and as such, this option is reserved for particular group of patients whose disease requires multimodality therapy to avoid significant disruption of normal anatomy. A retrospective analysis of 303 patients suggested that the patient treated with individual treatment modalities such as excision, laser, and imiquimod produced the same effects. It was observed that the combination of excision and laser vaporization produced worst recurrence-free survival. Therefore, the combined modality treatment is reserved for particular group of patients.[10]

Cidofovir: This is cyclic nucleoside analog with antiviral properties. A topical 1% or 3% cream is used 1–2 times a day for a maximum of 10 weeks. In a phase 2 trial in UK, complete response rates of 87% and 78% were observed for cidofovir and imiquimod, respectively after 12 months follow-up.[13]

Differentiated Vulvar Intraepithelial Neoplasia

As dVIN is associated with high risk of developing invasive carcinoma, therefore such patients are treated with surgical excision rather than ablation or pharmacologic therapy.

POST-TREATMENT FOLLOW-UP

The American College of Obstetricians and Gynecologists (ACOG) recommends follow-up at 6 months, 12 months, and annually thereafter. Increasing size of the lesion, positive margins, smoking, and multifocal disease have been associated with higher recurrence.[10,14] If the patient exhibits symptoms and/or examination findings suggestive of additional disease, then evaluation to be done with colposcopy and biopsies.[22]

Disease Recurrence

There can also be late recurrence in VIN, therefore need a prolonged follow-up. Approximately one-third of patients develop recurrent vulvar SIL irrespective of the treatment modality employed.[23,24]

Recurrence is more in those with following risk factors:

- Large lesion size, e.g., 3 cm (range 1–7 cm).
- Presence of multifocal or multicentric disease (VaIN or CIN).
- Immunosuppression
- Age >50 years
- *Positive margins on the excisional specimen:* Patients with positive margins have threefold high risk of recurrence compared with negative margins on the excisional specimen.
- Cigarette smoking.[25]
- Higher rates of recurrence associated with laser ablation than with excision (42% vs. 26%).
- *Vulvar HSIL:* The risk of subsequent development of locally invasive squamous carcinoma in patients with VIN 3 being treated with initial therapy has been reported to be 2–15. A meta-analysis of randomized trials on 975 patients with vulvar HSIL reported that 15% developed vulvar cancer at median follow-up of 72 months.[24]
- *Differentiated VIN:* The data on the risk of invasive carcinoma in dVIN is not well established as this is

JAYPEE BROTHERS

an uncommon histologic type; however, the risk of invasive carcinoma appears to be very high. Available data reported that in one study of 67 patients with a diagnosis of solitary dVIN, 33% developed vulvar carcinoma.[24,25]

SPECIAL SITUATIONS

Risk of Occult Carcinoma

At initial diagnosis: It has been reported in a retrospective case series that the occult carcinoma is present in 10–22% of patients with a preoperative diagnosis of VIN who were primarily treated with surgical excision.[24]

MANAGEMENT OF VULVAR SQUAMOUS INTRAEPITHELIAL LESION IN PREGNANCY

Any suspicious valvular lesion should be biopsied, and the plan of management should be same as nonpregnant women.[26,27]

Management can be either surgical or expectant.

- *Surgical therapy:* Surgical treatment with either local excision or ablative therapy should follow the same general principles as for the nonpregnant patient. These are the preferred treatment options for HSIL in pregnancy, especially for the patient remote from delivery. Data regarding vulvar HSIL and pregnancy are extremely limited. Approximately 15% of vulvar carcinomas have been reported to occur in patients under the age of 40 years.[28]
- *Expectant management until after delivery:* Once invasive carcinoma has been ruled out histologically, clinicians may consider deferring treatment of HSIL to the postpartum period, especially in patients who are diagnosed in the third trimester. Small series suggest a possibility for spontaneous regression, particularly in asymptomatic patients who are younger than 30 years of age and who present with multifocal pigmented HSIL.[29] While several of these spontaneous regressions were associated with pregnancy, there are no data regarding the incidence of regression in this patient population.

PREVENTION OF VULVAR INTRAEPITHELIAL NEOPLASIA

In age-appropriate individuals, awareness and use of HPV vaccination should be promoted to reduce the incidence of usual-type vulvar intraepithelial neoplasia (uVIN). The 9-valent HPV vaccination can reduce the incidence of uVIN by 80–90%.[30]

KEY POINTS

- Vulvar intraepithelial neoplasia is a highly undiagnosed and under-reported condition. Its incidence is increasing in women in fourth decade.
- It is a premalignant condition, and early diagnosis and treatment is the only form of secondary prevention available at present.
- Detection is done by visual inspection and histopathological examination.
- Treatment is recommended for all women with vulvar HSIL as there is risk of occult invasive disease.
- HPV vaccination should be promoted to decrease the incidence of VIN and invasive vulvar cancer.

REFERENCES

1. AEPCC. (2015). AEPCC Guidelines: Vulvar Intraepithelial Neoplasia (VIN). [online] Available from https://www.aepcc.org/wp-content/uploads/2019/02/AEPCC_guidelines-VIN_en_2102019.pdf [Last accessed August, 2024].
2. Herzog TJ. Invasive cancer of vulva. In: Disaia PJ, Creasman WT, Mannel RS, Mcmeekin DS, Mutch DG (Eds). Clinical Gynecologic Oncology, 9th edition. Philadelphia: Elsevier; 2018. pp. 190-216.
3. Bornstein J, Bogliatto F, Haefner HK, Stockdale CK, Preti M, Bohl TG, et al.; ISSVD Terminology Committee. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions. Obstet Gynecol. 2016;127(2):264-8.
4. Mathews CA, Walker JL. Preinvasive disease of the vagina and vulva and related disorders. In: Disaia PJ, Creasman WT, Mannel RS, Mcmeekin DS, Mutch DG (Eds). Clinical Gynecologic Oncology, 9th edition. Philadelphia: Elsevier; 2018. pp. 20-37.
5. Judson PL, Habermann EB, Baxter NN, Durham SB, Virnig BA. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet Gynecol. 2006;107(5):1018-22.
6. Nygård M, Hansen BT, Dillner J, Munk C, Oddsson K, Tryggvadottir L, et al. Targeting human papillomavirus to reduce the burden of cervical, vulvar and vaginal cancer and pre-invasive neoplasia: establishing the baseline for surveillance. PloS One. 2014;9(2):e88323.
7. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. Obstet Gynecol. 2005;106(6):1319-26.
8. Khan AM, Freeman-Wang T, Pisal N, Singer A. Smoking and multicentric vulval intraepithelial neoplasia. J Obstet Gynaecol. 2009;29(2):123-5.

JAYPEE BROTHERS

9. Edwards SK, Bates CM, Lewis F, Sethi G, Grover D. 2014 UK national guideline on the management of vulval conditions. Int J STD AIDS. 2015;26(9):611-24.
10. Diagnosis and Management of Vulvar Skin Disorders: ACOG Practice Bulletin Summary, Number 224. Obstet Gynecol. 2020;136(1):222-5.
11. Lee A, Bradford J, Fischer G. Long-term management of adult vulvar lichen sclerosus: a prospective cohort study of 507 women. JAMA Dermatol. 2015;151:1061-7.
12. Thuijs NB, van Beurden M, Bruggink AH, Steenbergen RDM, Berkhof J, Bleeker MCG. Vulvar intraepithelial neoplasia: Incidence and long-term risk of vulvar squamous cell carcinoma. Int J Cancer. 2021;148(1):90-8.
13. van den Einden LCG, de Hullu JA, Massuger LF, Grefte JMM, Bult P, Wiersma A, et al. Interobserver variability and the effect of education in the histopathological diagnosis of differentiated vulvar intraepithelial neoplasia. Mod Pathol. 2013;26:874-80.
14. González MG, Ledesma AMM, Monge MN, Fontán JS. Colposcopy of the vulva and perineum. In: Rajkumar R (Ed). Colposcopy and Cervical Pathology. London: IntechOpen; 2017.
15. Kesić V, Vieira-Baptista P, Stockdale CK. Early Diagnostics of Vulvar Intraepithelial Neoplasia. Cancers (Basel). 2022;14(7):1822.
16. von Gruenigen VE, Gibbons HE, Gibbins K, Jenison EL, Hopkins MP. Surgical treatments for vulvar and vaginal dysplasia: a randomized controlled trial. Obstet Gynecol. 2007;109(4):942-7.
17. Holschneider CH, Groff B, Garcia RL, Falk SJ. Vulvar intraepithelial neoplasia. UpToDate; 2015.
18. Preti M, Joura E, Vieira-Baptista P, Van Beurden M, Bevilacqua F, Bleeker MCG, et al. The European Society of Gynaecological Oncology (ESGO), the International Society for the Study of Vulvovaginal Disease (ISSVD), the European College for the Study of Vulval Disease (ECSVD) and the European Federation for Colposcopy (EFC) Consensus Statements on Pre-invasive Vulvar Lesions. J Low Genit Tract Dis. 2022;26(3):229-44.
19. Nelson EL, Bogliatto F, Stockdale CK. Vulvar intraepithelial neoplasia (VIN) and condylomata. Clin Obstet Gynecol. 2015;58(3):512-25.
20. De Witte CJ, Van de Sande AJM, Van Beekhuizen HJ, Koeneman MM, Kruse AJ, Gerestein CG. Imiquimod in cervical, vaginal and vulvar intraepithelial neoplasia: a review. Gynecol Oncol. 2015;139:377-84.
21. Tristram A, Hurt CN, Madden T, Powell N, Man S, Hibbitts S, et al. Activity, safety, and feasibility of cidofovir and imiquimod for treatment of vulval intraepithelial neoplasia (RT3VIN): a multicentre, open-label, randomised, phase 2 trial. The Lancet Oncol. 2014;15:1361-8.
22. Lebreton M, Carton I, Brousse S, Lavoué V, Body G, Levêque J, et al. Vulvar intraepithelial neoplasia: Classification, epidemiology, diagnosis, and management. J Gynecol Obstet Hum Reprod. 2020;49(9):101801.
23. Reyes MC, Cooper K. An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. J Clin Pathol. 2014;67:290-4.
24. Wallbilich JJ, Rhodes HE, Milbourne AM, Munsell MF, Frumovitz M, Brown J, et al. Vulvar intraepithelial neoplasia (VIN2/3): comparing clinical outcomes and evaluating risks factors for recurrence. Gynecol Oncol. 2012; 127:312.
25. Hillemanns P, Wang X, Staehle S, Michels W, Dannecker C. Evaluation of different treatment modalities for vulvar intraepithelial neoplasia (VIN): CO(2) laser vaporization, photodynamic therapy, excision and vulvectomy. Gynecol Oncol. 2006;100(2):271-5.
26. van de Nieuwenhof HP, Massuger LF, van der Avoort IA, Bekkers RL, Casparine M, Abma W, et al. Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age. Eur J Cancer. 2009;45:851-6.
27. Satmary W, Holschneider CH, Brunette LL, Natarajan S. Vulvar intraepithelial neoplasia: risk factors for recurrence. Gynecol Oncol. 2018;148(1):126-31.
28. van Seters M, van Beurden M, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. Gynecol Oncol. 2005;97:645-51.
29. Jones RW, MacLean AB. Letter to van Seters: "Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients". Gynecol Oncol. 2006;101(2): 371-2.
30. Issanov A, Karim ME, Aimagambetova G, Dummer TJB. Does Vaccination Protect against Human Papillomavirus-Related Cancers? Preliminary Findings from the United States National Health and Nutrition Examination Survey (2011-2018). Vaccines (Basel). 2022;10(12):2113.

JAYPEE BROTHERS

for detailed information on obstetrics and gynecology books, visit our website www.jaypeebrothers.com, for detailed information on obstetrics and gynecology books, visit our website

Screening & Management of Gynecological Cancers

This book endeavors to illuminate the multifaceted nature of gynecologic cancers, including their prevention, diagnosis, and treatment. It aims to serve as a comprehensive resource, bridging the gap between current research and clinical practice. The content has been divided into eight sections with elaborate discussion of the particular area. The book contains 27 chapters covering premalignant and malignant lesions, their prevention and management. The content of the book is developed according to the need of postgraduate students and budding gynecologists. Each chapter is designed to provide not only scientific content but also practical approaches to patient care, emphasizing the importance of a multidisciplinary approach in managing these cases. The content is designed to cover preventive oncology also as its importance cannot be highlighted more.

We invite you to explore the pages in the book, whether you are a student or a medical professional interested in the field of gynecologic oncology. Together, we can foster a great understanding of these critical issues, advocate for better care, and ultimately aim for more effective treatment of gynecologic cancers.

Renu Tanwar
Director-Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Hospital
New Delhi, India

Poonam Kashyap
Associate Professor
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Hospital
New Delhi, India

YM Mala
Director-Professor and Head
Department of Obstetrics and Gynecology
Maulana Azad Medical College and
Lok Nayak Hospital
New Delhi, India

Printed in India

Available at all medical bookstores or buy online at www.ejaypee.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers
Follow us on instagram.com/JaypeeMedicalPublishers

Shelving Recommendation
OBSTETRICS & GYNECOLOGY

ISBN 978-93-5696-454-9