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CHAPTER 4

Clinical manifestations of HPV infection

Section A: Benign manifestations of HPV infection

A1. Anogenital condylomas

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KEYWORDS
Condyloma;
Anogenital tract

Abstract The clinical manifestation of infection with HPV is determined by multiple factors which include the type of HPV, the type of skin infected, the status of host immunity and smoking. The incubation period for HPV is 3 weeks to 8 months. While there is no specific anti-HPV therapy, local topical therapy, excision, cautery and laser vaporization have all been used with a range of success rates.

1. Introduction

The clinical manifestation of human papillomavirus (HPV) exposure depends on multiple factors that include HPV type, type of skin infected, host immunity, nutritional factors, and smoking status. Condylomata acuminata, or condylomas, are most often caused by HPV-6 and HPV-11, and the interval between exposure and infection is 3 weeks to 8 months [1]. In an initial, proliferative phase the virus replicates unless it is controlled by medical management or immunologic response. The lesions produce a large number of virions that infect adjacent tissue. During this phase, simple treatments focusing on repetitive topical therapy of visible lesions, are the best.

2. Treatments

2.1. Topical therapy

Biocholoracetic acid (BCA) or trichloracetic acid (TCA) are desiccant acids that are absorbed by the treated tissue. They are especially effective on the moist lesions of mucous membranes, whose water content is high. These acids should be applied directly to the wart, preferably with magnification, to allow precise placement on small lesions and avoid healthy skin. The depth of injury can be limited by close observation of the intensity of whiteness of the treated area. A burning sensation occurs for 5 to 15 minutes, but it may be avoided by spraying a topical anesthetic before treatment. The desiccant acids are not toxic and can be used safely during pregnancy or inside the vagina. For intravaginal or cervical condylomas, the acid is applied with col-

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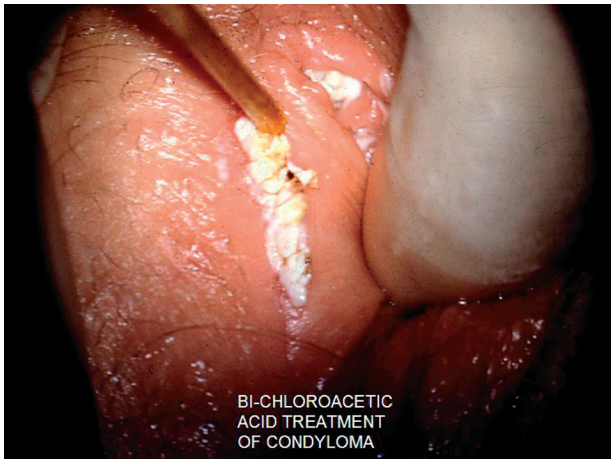

Figure 1 Bichloroacetic acid treatment of condylomas.

poscopic guidance and allowed to dry for 2 minutes before a saline-soaked swab is used to remove the remaining acid. It is not advisable to treat the entire vagina because significant sloughing could occur and lead to stricture. The patient should be treated weekly until all visible lesions are gone.

The other popular topical agent for the treatment of cervical condylomas is podophyllin. Its biologic activity is due to an antimitotic effect, which leads to sloughing of the tissues treated. Unlike with the desiccant acids, its maximum effect takes place several days after application. Podophyllin may have systemic neurologic and bone marrow toxicity when used over a large, moist skin surface, and therefore cannot be used during pregnancy or to treat vaginal condylomas. Since a 25% podophyllin resin contains between 50 and 100 mg/mL of the active agent podophyllotoxin [2], variable efficacy and toxicity occur with this method of treatment. However, a 0.5% podophyllotoxin solution is now available for the treatment of condylomas (Condylax; Oclassen Pharmaceuticals, Inc., San Rafael, California) [3].

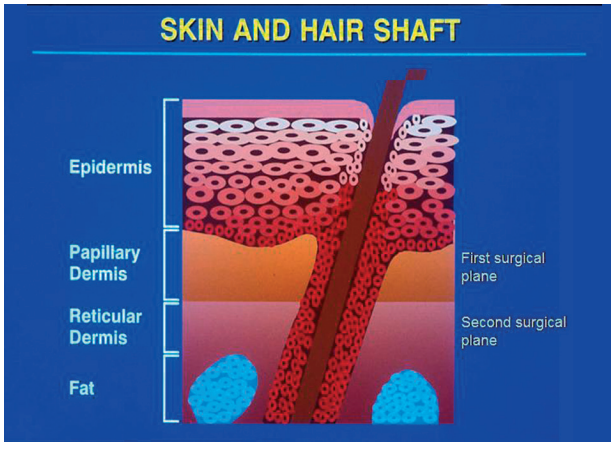

Figure 2 Skin and hair shaft.

The patient applies the solution to warts twice daily for 3 days, followed by 4 days without treatment. Complete clearance occurs in approximately 50% of women after 4 treatment cycles [4].

Topical therapy will initially clear most condylomas, but primary therapy failures and secondary recurrences lead to an overall clearance rate of approximately 50% [4,5]. Subsequent treatment strategies depend on the appearance of the lesions. The thick, chronic, keratinized warts are best treated with tissue-destructive methods and adjuvant interferon therapy. Extensive, diffuse warts that regrow between each treatment visit are best treated with imiquinod. When condylomas are unresponsive to treatment, biopsy is important to exclude an underlying malignancy such as verrucous carcinoma.

2.2. Laser therapy

The laser of choice is the carbon dioxide laser. It is attached to the colposcope, so that the surgeon may identify the dermatologic surgical planes. This tech-

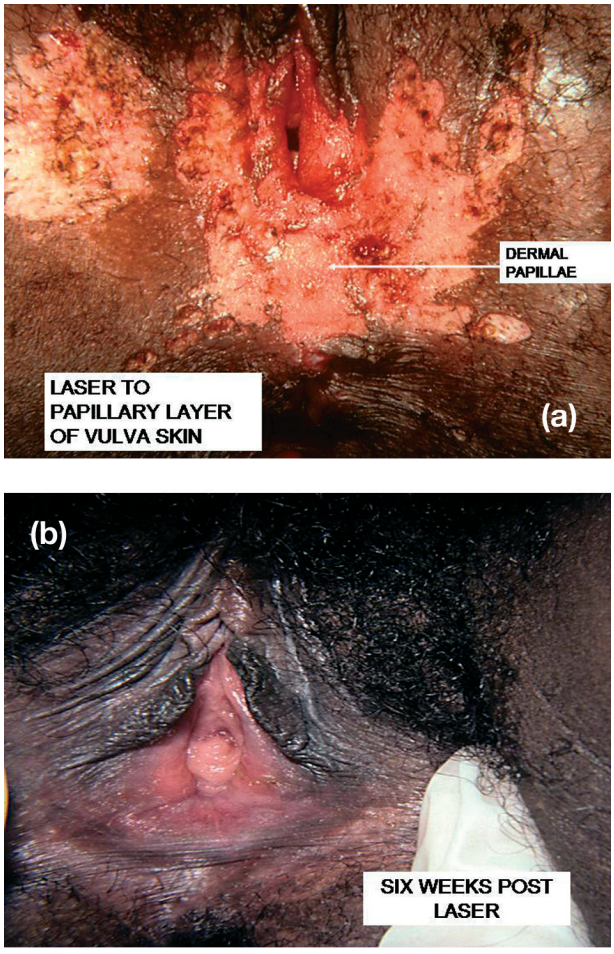

Figure 3 (a) Laser vaporization to papillary layer of vulva skin. (b) Six weeks after laser treatment.

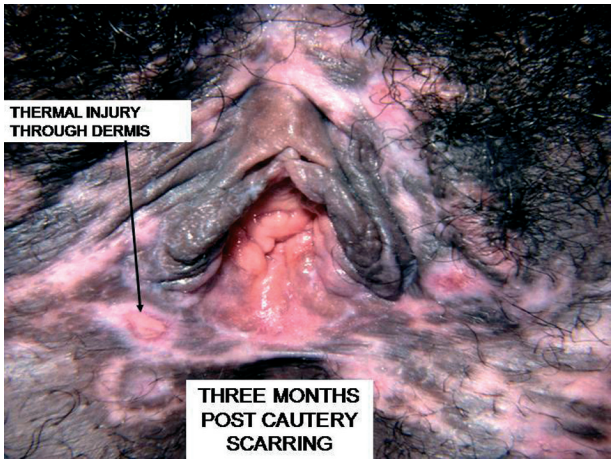

Figure 4 Scarring 3 months after cautery.

nique allows for tissue destruction, which occurs from both immediate vaporization and delayed tissue necrosis, to be confined to the epidermis and superficial papillary dermis [6]. Power density should be set above 750 watts/cm^3 to reduce the delayed tissue necrosis, which results from heat buildup. Whenever possible, outpatient treatment with local anesthesia is preferred. Since the wart is an epidermal growth, only the epidermal layer needs to be removed. During the laser procedure, the vaporized debris is frequently wiped away with wet gauze so that the classic appearance of the papillary dermis can be viewed. The results of laser treatment alone are extremely variable and depend on patient selection, number of treatments used, and volume of skin treated. Initially, cure rates higher than 90% were reported [7], but further follow-up revealed long-term control to be only 67% [8].

For large exophytic lesions, the electrodiathermy loop excision procedure is gaining popularity. Precise control of the depth of destruction is important so that scarring does not result. Electrosurgical excision results in a small amount of thermal damage. Electrocautery or cryocautery, on the other hand, result in thermal injury and lack of control of tissue damage, which lead to a higher risk of scar formation. The efficacy of the electrodiathermy loop excision is not known; however, if used in conjunction with the colposcope to identify and destroy all the lesions, it should achieve results similar to those of laser therapy. Reports from the literature on electrocautery and cryocautery techniques reveal a control rate of 40% to 55% [9,10].

2.3. Imiquimod therapy

Imiquimod is a topical 0.5% cream that that the patient applies weekly for up to 16 weeks. It acts as an immune response modifier with the ability to induce the production of interferon-α, tumor necrosis factor, and various other cytokines. The phase 3 clinical trials of imiquimod have shown a 72% clearance rate, vs. a 20% rate in patients treated with placebo. The adverse effects of imiquimod are local skin reaction, with up to 62% of patients reporting some redness or erythema and 5% reporting ulceration. Only 1% of patients discontinued the medication because of severe local skin reaction. It is not only the local efficacy of imiquimod that is important; it is also the low recurrence rate of approximately 13% in the 3 months of follow-up after treatment. The low recurrence rate is a result of induced immunologic memory to HPV.

2.4. Interferon therapy

Injections of interferon alfa-2 into the wart-bearing skin 3 times weekly for 3 weeks have resulted approximately in a 50% disappearance of the treated warts, vs. 15% in placebo groups [12,13]. The need to inject the interferon and the adverse effects of

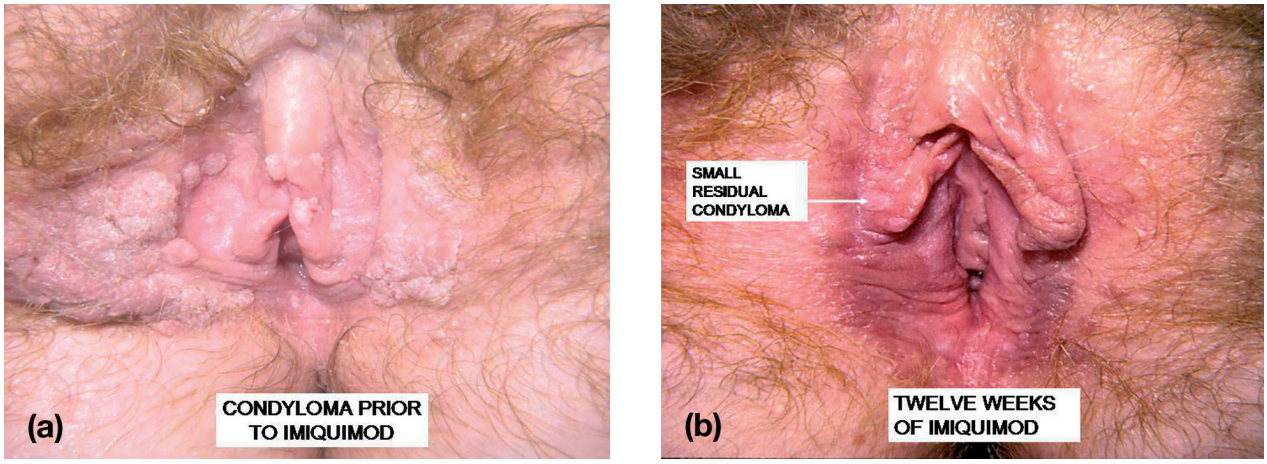

Figure 5 (a) Condylomas prior to imiquimod treatment. (b) Results of 12 weeks of imiquimod treatment.

fever, muscle aches, and flu-like symptoms have limited its use to patients in whom other therapies have failed.

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A2. Vulval intraepithelial neoplasia (VIN)

Kenneth D. Hatch

KEYWORDS
Vulval intraepithelial neoplasia (VIN);
Human papillomavirus

Abstract VIN 3 is most likely a cancer precursor and is induced by infection with high-risk types of HPV. VIN 3 lesions may be asymptomatic or present with itching and/or burning or the appearance of a vulval lesion (often raised and hyperpigmented), which may be unifocal or multifocal. All vulval lesions should be biopsied to confirm the diagnosis. Treatment options include laser vaporization, excision or cautery. Long term follow up is essential.

1. Introduction

In 1986 the International Society for the Study of Vulva Disease (ISSVD) recommended that squamous intraepithelial lesions of the vulva be termed vulval intraepithelial neoplasia (VIN) and be graded similar to cervical intraepithelial neoplasia (CIN). The lesions were graded as VIN 1 (mild dysplasia), VIN 2 (moderate dysplasia), or VIN 3 (severe dysplasia or carcinoma in situ [CIS]) [1]. However, the cytopathic changes diagnosed as VIN 1 were nonspecific, often representing normal skin with superficial trauma or infection, and there had been no evidence that VIN 1 was a cancer precursor [2]. Therefore, in 2004, the ISSVD subcommittee on oncology dropped the term VIN 1 [3]. Women with a histopathologic report of VIN 1 should nevertheless be evaluated and treated for the underlying infection or trauma. VIN 2 and VIN 3 lesions express the p16(INK4a) protein, indicating their potential for malignant transformation, and should be treated [2]. But VIN 2 is rare in most series, with little outcomes data, and the discussion that follows will be primarily focused on VIN 3 lesions (Figure 1).

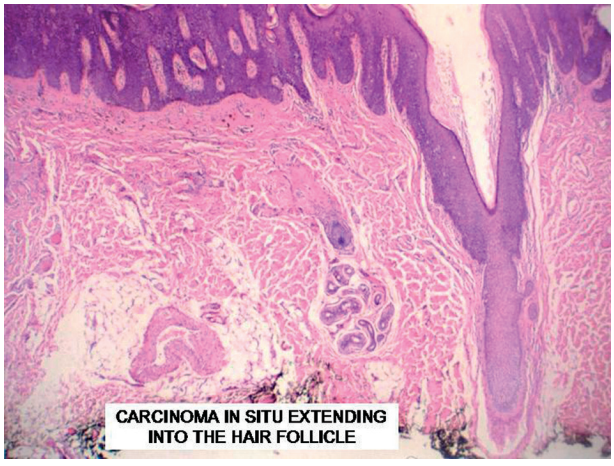

Figure 1 Carcinoma in situ extending into the hair follicle.

2. Signs, screening, and diagnosis

Although the patient may have no symptoms, the most common are itching, irritation, feeling a bump, or bleeding. In the younger patient symptoms are often preceded or accompanied by condylomas.

There is no specific screening test for VIN. All women who complain of a lesion on the vulva should have a complete examination of the vulva, vagina, and perianal area using a magnification technique such as colposcopy. The use of acetic acid is not recommended as it is nonspecific for VIN, and most women will have an acetowhite area around the introitus. Since VIN may coexist with CIN, every woman who had an abnormal Papanicolaou (Pap) smear should have an examination of the vulva.

The diagnosis is made from clinical appearance followed by biopsy findings. VIN can be unifocal or multifocal. Unifocal lesions are most often a raised keratinized lesion located around the introitus (Fig-

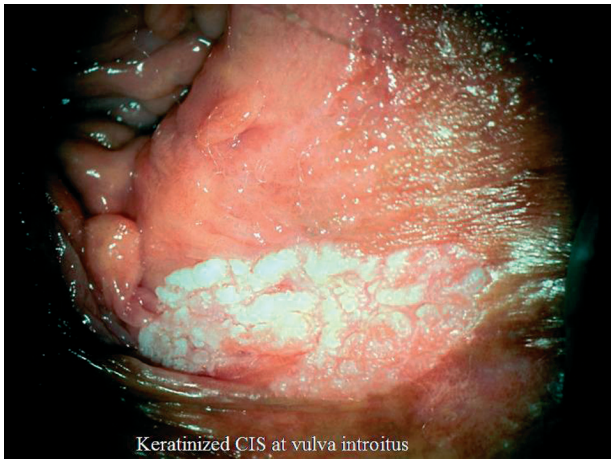

Figure 2 Keratinized carcinoma in situ at the vulva introitus.

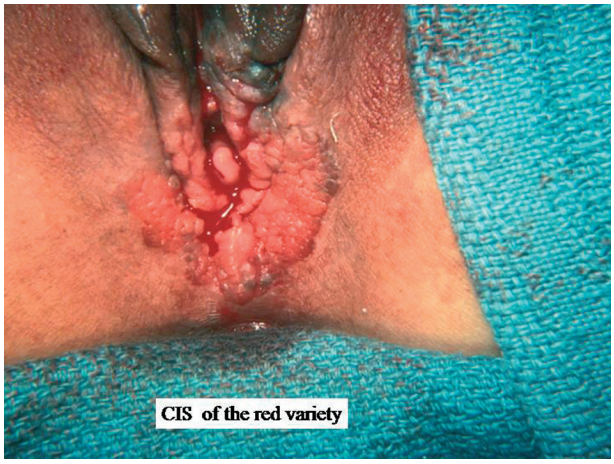

Figure 3 Carcinoma in situ of the red variety.

ure 2). Occasionally the lesions are raised and red (Figure 3). Multifocal VIN 3 typically presents with small hyperpigmented lesions on the labia major or perianal skin (Figure 4). These lesions may be

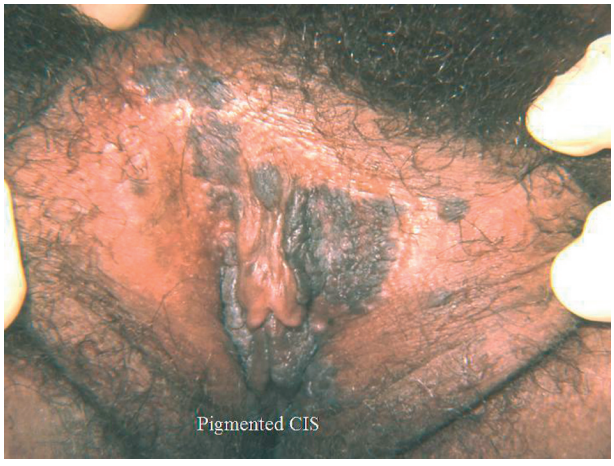

Figure 4 Pigmented carcinoma in situ.

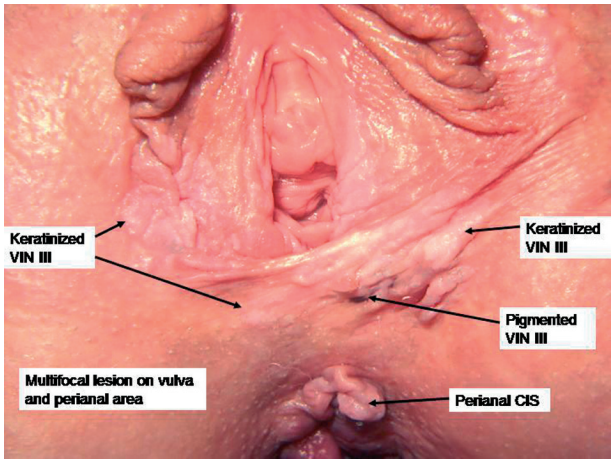

Figure 5 Multifocal lesion on the vulva and perianal area.

clinically misdiagnosed as moles, warts, or skin papillomas. A biopsy should be taken of any raised pigmented lesion on the vulva. Some cases of VIN 3 are more confluent, extending to the posterior fourchette and involving the perineal and perianal tissues. The perianal skin is involved in 10% to 15% of the patients who have VIN 3 (Figure 5).

3. Treatment

The therapeutic alternatives for VIN 3 are simple excision, laser ablation, and superficial vulvectomy with or without split-thickness skin grafting. Skin appendages are involved in approximately 50% of the patients with VIN 3 [4], and hair follicles are the most commonly involved (Figure 1). The VIN may reach 4.6 mm in depth, with an average of 1.2 mm. Therefore, the clinician treating the patient with VIN involving the hair-bearing area of the vulva must consider that recurrence may develop from the hair follicles. Excision of the full epidermal layer to the subcutaneous fat ensures removal of the entire hair follicle and other skin appendages.

Laser vaporization produces its best cosmetic results when it is used to remove the epidermal layer of the skin (Figure 6), leaving the papillary dermis as a foundation over which the new epidermis can migrate. The non-hair bearing skin is the best area for laser treatment. If the laser destruction penetrates through the papillary layer to the deeper levels to remove hair follicles, healing time is lengthened and scarring may result. For hair-bearing lesions greater than 1 cm in diameter excision is recommended over laser vaporization. Less scarring will occur after removal of the larger lesions ($>$1 cm) if excision and primary closure is used.

Areas of VIN 3 may harbor microinvasive vulval le-

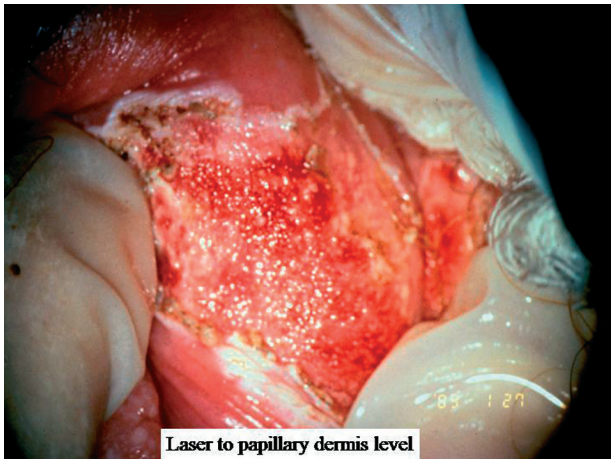

Figure 6 Laser vaporization to papillary dermis level.

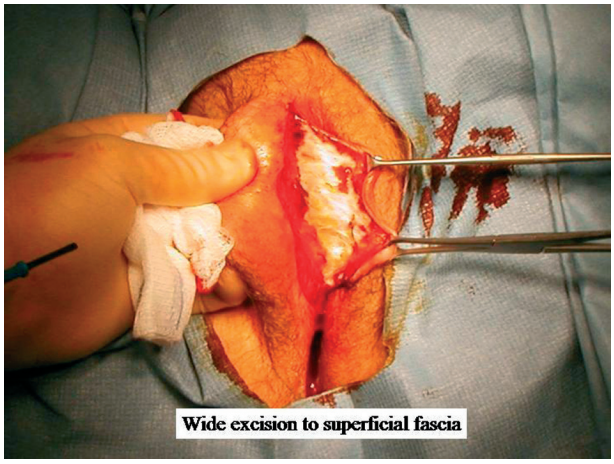

Figure 8 Wide excision to superficial fascia.

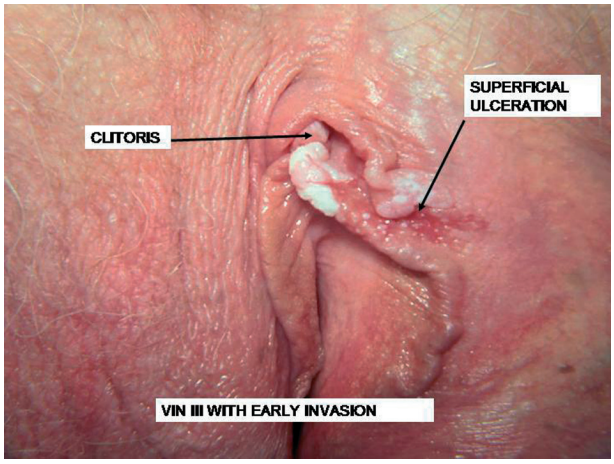

Figure 7 Vulval intraepithelial neoplasia 3 (VIN 3) with early invasion.

sions, particularly in women over the age of 50 years [4]. These women tend to have unifocal lesions and other high-risk physical findings. These include ulceration, increased vascularity on colposcopy, and thicker lesions (Figure 7). Wide excision for full pathologic evaluation is highly recommended for women with high-risk characteristics regardless of the site on the vulva. After excision, evaluation of depth of invasion by the pathologist is of utmost importance. Wilkenson [5] has described a technique of measuring depth of invasion from the nearest normal dermal papillae. When measured in this fashion, patients who have a lesion less than 2 cm in diameter with invasion less than 1 mm in depth can expect to have a virtually zero incidence of node metastasis. This allows the clinician to advise wide local excision only for these patients. When invasion reaches 1 to 2 mm, however, the incidence of positive groin lymph nodes rises to 6.6%; and when invasion reaches 5 mm, the rate of positive groin lymph nodes rises to 25% [6]. Therefore, all patients with a lesion showing 1 mm of invasion or greater must have a groin node dissection.

To fully evaluate the lesion for invasive areas, the entire lesion must be removed with a margin of at least 5 mm (Figure 8). Punch biopsies with the diagnosis of microinvasion are not sufficient to guide final treatment recommendation.

Superficial vulvectomy is appropriate to treat extensive and recurrent VIN 3. The goal of the intervention is to extirpate all of the disease while preserving as much of the normal vulval anatomy as possible. The anterior vulva and the clitoris should be preserved if possible. In some patients, the disease extends to the anus. An effort should be made to close the vulval defect primarily, reserving the use of skin grafts for instances in which the defect cannot be closed because the resection is too extensive. Split-thickness skin grafts can be harvested from the thighs or buttocks, but the latter region is more easily concealed.

4. Results

Jones [8] has published the natural history of 405 cases of VIN 2/3 followed up in New Zealand from 1962 to 2003. In that study the mean age of women with VIN 2/3 was 50 years between 1962 and 1979, and it was 39 years between 1980 and 2003. More than 80% of the women were smokers, which is 3 times the average rate of smoking in New Zealand. Surgical treatment consisted of superficial vulvectomy, local excision, and laser vaporization. Approximately 50% of the women required additional treatment, with a median time to recurrence of 13.7 years. Nearly all of the women with positive margins required additional treatment within 5 years, while those with negative margins had a 15% recurrence rate within 5 years. Invasive vulval, peri-

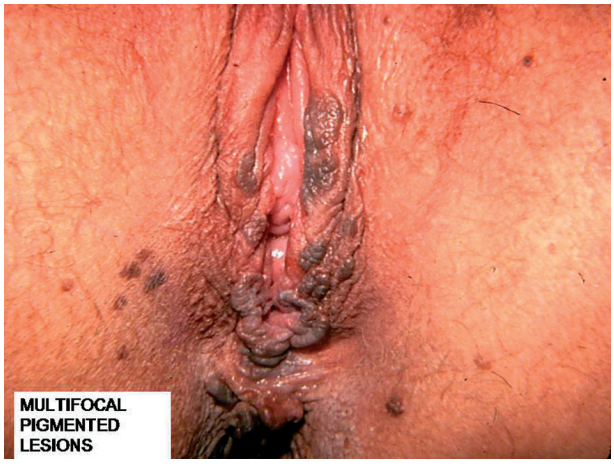

Figure 9 Multifocal pigmented lesions.

anal, or urethral carcinoma occurred in 3.8% of the women originally treated. Twelve (70%) of the 17 cancers arising in previously treated VIN occurred in women younger than 50 years.

Invasive vulval cancer developed in 5 of the 10 untreated women, and the time from diagnosis to invasion was less than 8 years in all untreated women.

The disease regressed after diagnostic biopsy in 47 women, whose ages ranged from 15 to 45 years. All the lesions were multifocal and most were pigmented, warty, and of a basaloid variety. The dermatologic literature describes these lesions as bowenoid papulosis. Although the ISSVD discourages the use of the term, it identifies a subset of women younger than 30 years who may experience spontaneous regression (Figure 9).

This observational study demonstrates the invasive potential of VIN. It is imperative that women with VIN remain under surveillance every 6 months for their lifetime.

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A3. Vaginal intraepithelial neoplasia (VAIN)

Kenneth D. Hatch

KEYWORDS
Human papillomavirus;
Vaginal Intraepithelial neoplasia (VAIN)

Abstract VAIN is much rarer than the equivalent dysplastic changes found in the cervix but may accompany cervical intraepithelial neoplasia. VAIN is also HPV induced and may be an extension of a cervical lesion or a satellite lesion. VAIN lesions are usually asymptomatic and detected by cytologic screening. Lesions can be excised, vaporized or treated locally with medical therapies. The incidence of vaginal cancer is very rare.

1. Introduction

Vaginal intraepithelial neoplasia (VAIN) often accompanies or follows carcinoma in situ (CIN) and is also caused by human papillomavirus (HPV) [1]. These lesions may be CIN extensions into the vagina, or they may be satellite lesions. In that case, they occur mainly in the upper vagina. Because the vagina does not have a transformation zone with immature epithelial cells to be infected by HPV, the mechanism of entry of HPV is by way of skin abrasions from coitus or tampon use.

A history of CIN or invasive cervical cancer is the most important risk factor for VAIN, vaginal intraepithelian neoplasia (VIN), or invasive cancer of the lower genital tract. Vinokurova and coworkers [1] have examined HPV type and integration pattern in women with prior CIN or cervical cancer who developed VAIN, VIN, or invasive cancer of the lower genital tract. By using the site of HPV DNA integration as a marker of clonality, these investigators demonstrated that the lesions were of the same clonal origin.

2. Signs, screening, and diagnosis

VAIN lesions are asymptomatic. Because they often accompany active HPV infection, the patient may complain of vulval warts or an odoriferous vaginal discharge from vaginal warts.

Routine cytologic screening is the usual method of identifying the presence of VAIN. The vagina should be carefully inspected by colposcopic examination at the time of colposcopy for any abnormal finding. Particular attention should be paid to the upper vagina. Women who have positive Papanicolaou (Pap) test results after being treated for CIN should also be examined carefully for VAIN. For women in whom the cervix has been removed because of cervical neoplasia, Pap tests should be performed at 6-month intervals until 3 consecutive negative results have been obtained, and yearly thereafter for a minimum of 5 years before they may resume routine screening [2].

Colposcopic examination and directed biopsy are the mainstays of VAIN diagnosis. Typically, the lesions are located along the vaginal ridges, are ovoid and slightly raised, and often have surface spicules. VAIN 1 lesions usually have indistinct borders and have tiny surface spicules with partial Lugol's iodine uptake (Figure 1). As the lesions progress to VAIN 2, they exhibit a thicker acetowhite epithelium, a

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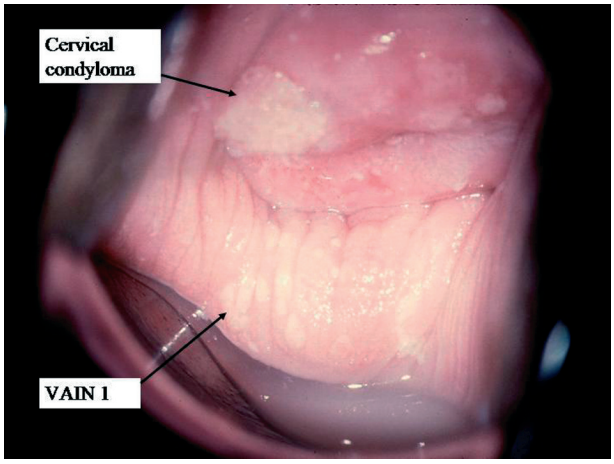

Figure 1 Cervical condyloma.

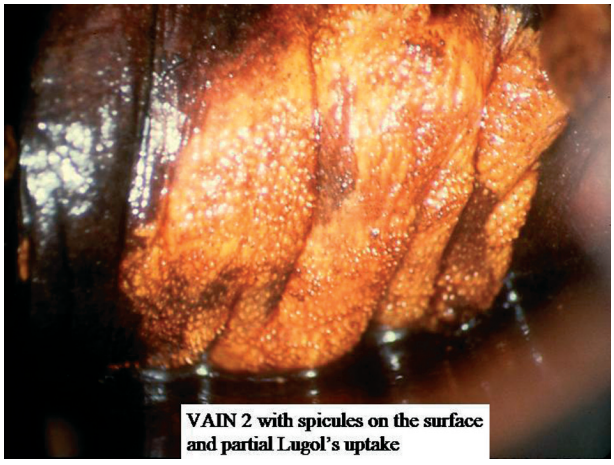

Figure 2 VAIN 2 with spicules on the surface and partial Lugol's iodine uptake.

more raised external border, and less iodine uptake (Figure 2). When VAIN 3 occurs, there is no Lugol's iodine uptake; the surface may be smooth and the edges very distinct on iodine staining (Figure 3); the

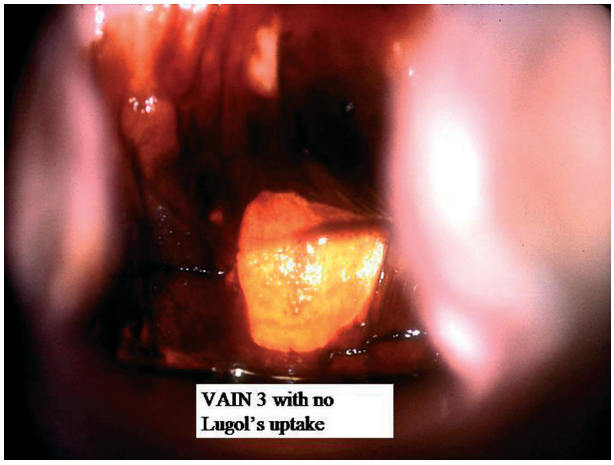

Figure 3 VAIN 3 with no Lugol's iodine uptake.

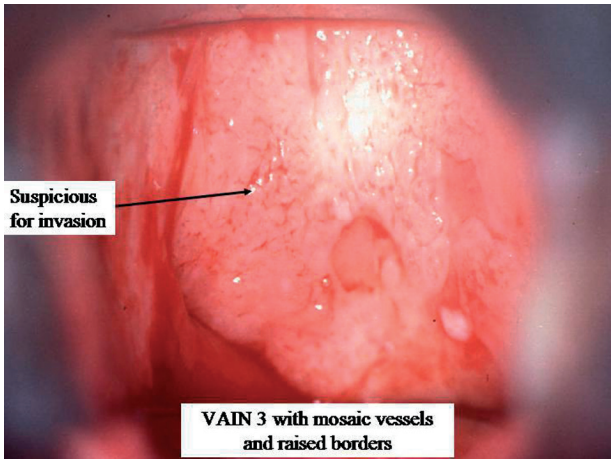

Figure 4 Vain 3 with mosaic vessels and raised borders.

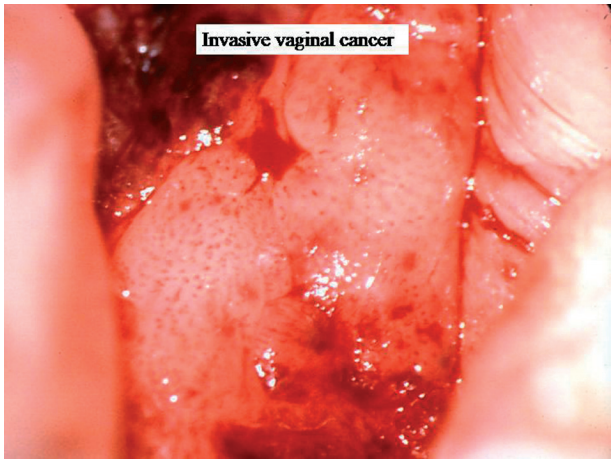

Figure 5 Invasive vaginal cancer.

surface may also become papillary; and vascular patterns of punctuation and mosaic may occur (Figure 4). These lesions may harbor an early invasive focus and should be treated with vaginal excision. More advanced invasion is typified by vascular patterns similar to those seen on the cervix, and is accompanied by ulceration and bleeding (Figure 5).

3. Treatment

Patients with VAIN 1 do not require treatment [3]. These lesions often regress, are multifocal, and are nearly always associated with active HPV infection. If treatment is deemed necessary, cryotherapy or bichloroacetic acid may be used, as for genital warts. When using cryotherapy, the freezing should be superficial and the bladder and rectum should be avoided, as the depth of injury cannot be controlled.

VAIN 2 and VAIN 3 lesions can be treated with equal success using excision or laser vaporization

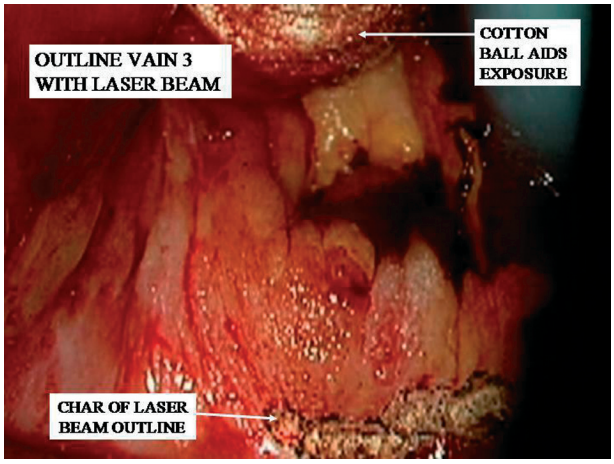

Figure 6 Outline of VAIN 3 with laser beam.

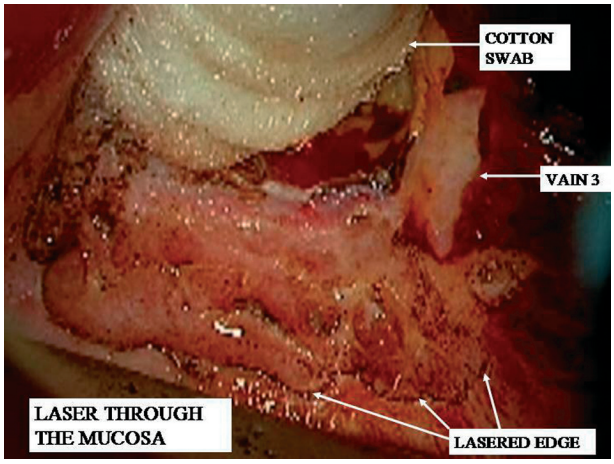

Figure 7 Laser beam through the mucosa.

[3–5], with success in 69% to 79% of cases following either treatment. Selection of treatment depends on a number of factors. VAIN 3 lesions located at the vaginal apex in women who have had hysterectomy for CIN are more likely to become invasive early. In a study of 32 patients with VAIN 3 who underwent upper vaginectomy, 9 (28%) were found to have occult invasive carcinoma [6]. In older patients, it is recommended that VAIN 3 lesions located in the dimples of the vaginal cuff be excised to rule out occult invasive cancer.

Lesions that have been adequately sampled to rule out invasive disease can be treated with laser vaporization therapy. The major advantage of laser vaporization therapy is the ability to control exactly the depth and width of destruction by direct vision through the colposcope (Figures 6 and 7). Another advantage is rapid healing post-treatment. After 3 to 4 weeks, a new epithelium has formed, and in most cases it is a mature, glycogen-containing epithelium.

Electrosurgical techniques have been used to treat VAIN. The fine electrosurgical wire loops used in the loop electrosurgical excision procedure (LEEP) to remove CIN are not recommended, as they may cut deep into the tissue and scar or even damage the bladder or rectum. Electrofulguration using a ball cautery to treat superficial lesions is a safer method, but care must still be taken when treating lesions on the anterior or posterior vaginal wall. And since the only study reporting results reveals a 75% recurrence rate [3], it is not recommended.

Although the overall malignant potential of VAIN appears to be less than that of CIN, reports on 292 patients who had long-term follow-up after treatment with excision or laser vaporization show that vaginal cancer subsequently developed in 13 (4.5%) of these patients [3,5,7].

Intravaginal 5-fluorouracil (5-FU) has been used to treat VAIN for a number of years. Different treatment schedules and dose levels have been tried to maintain efficacy while decreasing adverse effects. Success rates vary from 75% to 90% with 5-FU (Table 1), but its use is now limited to multifocal VAIN too extensive to treat with laser vaporization. The dose should be 1 to 2 mL of 5% cream administered once a week under close observation. When the surface of the lesion peals away, the treatment is stopped (Figures 8 and 9). The major complication with 5-FU is a sloughing of the vaginal epithelium that will not heal (Figure 10). Treatment with 5-FU is contraindicated in pregnancy.

Immunotherapy has not been successful. Imiquimod is contraindicated in the vagina, but inter-

Table 1 Treatment of vaginal intraepidermal neoplasia with 5% 5-fluorouracil cream

Author	No. of cases	Proportion of patients cured	Regimen
Woodruff (1975)	9	89%	5 mL
Petrilli (1980)	15	80%	5 mL twice daily for 5 days
Ballon (1979)	12	75%	Twice daily for 14 days
Caglar (1981)	27	93%	1.5 mL daily for 7 days
Kirwin (1985)	14	93%	2.5 mL once weekly for 10 weeks
Krebs (1989)	16	81%	1.5 mL once daily for 7 days
Krebs (1989)	21	81%	1.5 mL once weekly for 10 weeks

Figure 8 VAIN 2 prior to treatment with 5-fluorouracil cream.

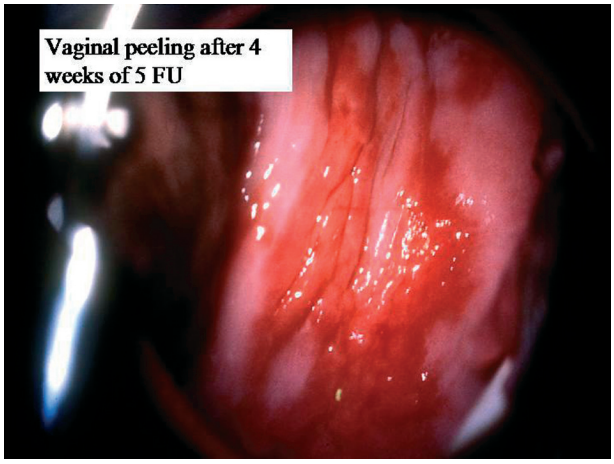

Figure 9 Vaginal peeling after 4 weeks of after treatment with 5-fluorouracil cream.

feron may clear vaginal HPV and VAIN 1 if the external warts are cured.

The incidence of vaginal cancer is 0.6 per 100,000 women/years and the mean patient age is 60 years. The most common site is the upper third of the vagina on the posterior wall. Staging is done on clinical examination only, and 75% of the cancers are stage II, having extended through the vaginal wall but not to the sidewall. Approximately 30% of the cancers occur after treatment for cervical neoplasia. In this case, VAIN represents residual disease in the vaginal cuff after hysterectomy for CIN or an increased susceptibility to neoplasia from HPV infection.

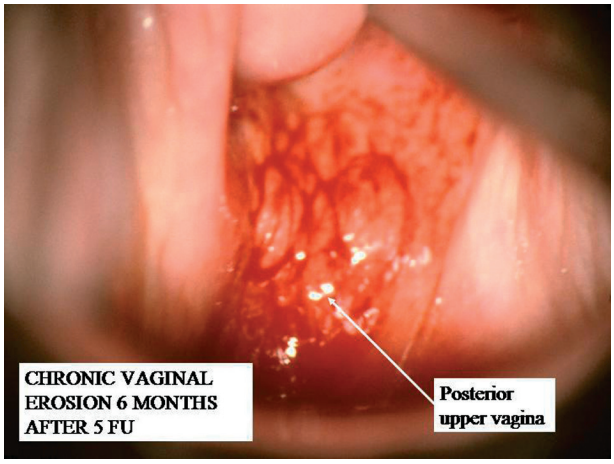

Figure 10 Chronic vaginal erosion 6 months after treatment with 5-fluorouracil cream.

Radiation therapy to the whole pelvis and to the vagina is the most common treatment. However, a radical upper vaginectomy and pelvic lymphadenectomy can be substituted for radiation therapy in patients with stage I disease confined to the upper vagina and not penetrating the vaginal wall.

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A4. Preinvasive lesions of the cervix

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KEYWORDS
Genital warts;
Cervical cancer screening;
Cervical cytology;
Colposcopy

Abstract Low-risk human papillomaviruses (HPVs) can cause genital warts which, although benign, may provoke psychological distress because they are sexually transmitted. High-risk HPVs can cause cervical intraepithelial neoplasia and cancer. Cytology-based screening programs have significantly reduced cervical cancer morbidity and mortality where the programs have been successfully implemented. Women with abnormal cervical smears are referred for colposcopic assessment, which may confirm the presence of a preinvasive lesion; allows the grade and extent of the lesion to be defined; and guides the colposcopist as to the most appropriate site for biopsy and histologic confirmation of the lesion. Excision of the transformation zone of the cervix in an outpatient setting using local anesthetic has greatly simplified the treatment of premalignant lesions, but long-term follow-up is essential to ensure that the lesions neither persist nor recur. Abnormal cytologic findings during adolescence and pregnancy need special management.

1. Introduction

Although human papillomavirus (HPV) infection can be said to be endemic worldwide, the great majority of these infections resolve without epithelial manifestations or serologic evidence of antibody response. Clinical manifestations of persistent HPV infection include exophytic warts and intraepithelial neoplastic lesions. These lesions may manifest at anatomic sites involved in direct epithelial contact, e.g., the head and neck as well as the external and internal lower genital tract.

Exophytic genital warts, or condylomas, do not confer significant risk of invasive cancer, but they are associated with significant psychosocial cost. These lesions are most commonly caused by HPV-6 and HPV-11. In individuals who are sexually active, the lifetime risk of being affected with condylomas is estimated at 10%. Upon diagnosis of external genital warts, women should be evaluated for other HPV lesions in the internal lower genital tract. Treatment strategies include excision of warts, ablation, or topical applications, e.g., with imiquimod. Current treatment modalities can cause physical discomfort and scarring.

The knowledge that these lesions are the direct result of a sexually transmitted infection is both distasteful and frightening for many patients. Because the time from first viral exposure to patent lesions can be months, the patient may not know who may have been the source of the infection. Moreover, the visible manifestation of a viral infection that may or may not be amenable to complete clearance is distressing. Emotions commonly associated with the diagnosis of other sexually transmitted diseases include depression, anger, loss of self-esteem, anxiety, and hostility [1]. Women's reactions to external genital warts are similar to those seen with other HPV-associated diagnoses, including an abnor-

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mal result to a Papanicolou (Pap) test, but external genital warts are also more likely to have a negative impact on sexual relations [1]. Not only are the women afraid of transmitting HPV infection to their partners, they feel less sexually desirable and therefore enjoy sexual contact less than before their diagnosis. This spectrum of reactions to a diagnosis of genital warts can interfere with adherence to treatment and follow-up care.

2. Preinvasive lesions of the cervix

Cervical intraepithelial neoplasia (CIN), or squamous intraepithelial lesions (SILs), are asymptomatic and not visible to naked-eye examination. Cervical smears, however, can detect these lesions which can be visualized and characterized with the aid of colposcopy.

2.1. Cervical cytologic abnormalities

Both HPV infection of the cervix and preinvasive lesions of the cervix lead to abnormal cytologic findings. In the Bethesda Classification of 2001, the affected cell types are designated as squamous or glandular (Table 1) [2].

2.2. Management of abnormal cytologic results [3]

Since cytology is merely a screening tool, further investigation is required to establish the significance of the cytologic abnormality. For cytologic findings of asymptomatic squamous cells of unknown significance (ASC-US), 3 management options can be considered. Colposcopic assessment can be performed either immediately or only if the cytologic abnormality persists for a further 6 to 12 months. Alternatively, testing for high-risk types of HPV can be performed, and only if such a type is detected will the patient be referred for colposcopic examination.

For cytologic findings of low-grade squamous intraepithelial lesions (LSILs), 2 management options can be considered. Colposcopic assessment can be performed immediately or only if a cytologic abnormality is again detected 6 months later.

For cytologic findings of atypical squamous cells — cannot exclude high-grade lesion (ASC-H), high-grade squamous intraepithelial lesions (HSILs), and more serious abnormalities suggestive of invasive disease, colposcopic assessment is recommended. If no abnormality is found on colposcopic examination but a second cytologic evaluation confirms the original cytologic diagnosis, a diagnostic loop electrosurgical excision procedure (LEEP) or a diagnostic cone biopsy should be performed.

In the case of a glandular abnormality, a colposcopic assessment with endocervical sampling evaluation is recommended. Moreover, if atypical endometrial cells are found in the cervical smear, the patient should undergo endometrial sampling, and a colposcopic examination should be performed if the abnormal cytologic finding cannot be explained by the endometrial sampling. If no lesion is found on colposcopic examination and a repeated cytologic evaluation shows persistent atypical glandular cells of unknown significance (AGC-US), a diagnostic LEEP or cone biopsy should be performed. The order of these procedures is shown in Table 2.

Table 1 The Bethesda 2001 System terminology for reporting the results of cervical cytology*

No neoplastic cells
Squamous cell
Atypical squamous cells of undetermined significance (ASC-US)
ASC-H (atypical squamous cells, cannot exclude HSIL)
Low-grade squamous intraepithelial lesion (LSIL)
High-grade squamous intraepithelial lesion (HSIL), HSIL with features suspicious of invasion
Squamous cell carcinoma
Glandular cell
Atypical: endocervical cells, endometrial cells, glandular cells
Atypical, favor neoplastic: endocervical cells, glandular cells
Endocervical adenocarcinoma in situ
Adenocarcinoma: endocervical, endometrial, extrauterine, NOS
Other
Endometrial cells in a woman 40 years or older

* Adapted from reference [2].

3. Colposcopy

Colposcopy is a diagnostic tool that uses magnification and strong illumination to examine the cervix, vagina, and vulva. A 3% to 5% solution of acetic acid, which has a temporary dehydrating effect on squamous cells, is applied to the cervix. The application of acetic acid to the cervix accentuates cells with high nuclear-cytoplasmic ratios, as in high-grade lesions, because the nucleus impedes light transmission [4]. Thus, the higher the grade of the cervical lesion, the more opaque it appears. These lesions are described as “acetowhite”.

Colposcopic evaluation of the cervix begins with using low magnification to gain an overall impression of the cervix and the characteristics of the acetowhitening. Higher magnification is necessary

Table 2 Summary of management of abnormal cytology

ASC-US	AGC-US	ASC-H
	AGC-FN	LSIL*
	AIS	HSIL
	Adenocarcinoma	SCC
Options:		
1. Colposcopy	Colposcopy, ECS, and EA with or without cone biopsy	Colposcopy
2. Repeated cytology in 6 months		
3. High-risk HPV testing		

Abbreviations: AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells – cannot exclude high-grade lesion; ASC-US, asymptomatic squamous cells of unknown significance; AGC-US, asymptomatic glandular cells of unknown significance; AGC-FN, asymptomatic squamous cells, favor neoplasia; EA, endometrial assessment; ECS, endocervical cell sampling; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions; SCC, squamous cell carcinoma.

* With the option of repeating cytologic assessment 6 months later.

to further characterize the lesion, particularly to discern the vascular patterns within the acetowhite area. Visualization of the vessels is made easier using a green-light filter. The most important functions of the colposcopic assessement include the following:

- To confirm the presence of a lesion detected cytologically;
- To define the characteristics of the lesion and to ensure that there is no occult microinvasion;
- To define the extent of the lesion into both the endo- and ectocervix; and
- To guide the colposcopist as to the most appropriate site for biopsy for histologic confirmation of the lesion.

When the entire squamocolumnar junction can be viewed, the colposcopy is judged adequate.

3.1. Normal colposcopic appearance

In the normal cervix, squamous epithelium lines the ectocervix and columnar epithelium lines the endocervix. The healthy squamous epithelium is smooth and pink, does not stain white with acetic acid, and stains brown with Lugol's iodine. The columnar epithelium is a single-layer, mucin-secreting tissue with endocervical glands opening to the surface. On colposcopic examination, the healthy columnar epithelium has a typical grape-like appearance after application of acetic acid and does not stain with Lugol's iodine.

The transformation zone (TZ), which develops as columnar epithelium undergoes metaplasia to form squamous epithelium, is the area between the original squamous-columnar junction (SCJ) and the new SCJ. As the metaplastic epithelium matures, it stains differently with acetic acid and Lugol's iodine. Islands of columnar epithelium, which appear as gland openings, cleft openings, and Nabothian cysts, may be found in the TZ. Although benign conditions may cause squamous epithelium to become acetowhite in places, dysplastic lesions are sharply demarcated from adjacent healthy epithelium and are most often located at the SCJ.

In menopausal women, the transformation zone may recede into the endocervical canal, leading to an unsatisfactory colposcopic assessment.

3.2. Abnormal colposcopic features

After application of a 3% to 5% solution of acetic acid, areas with increased nuclear density appear white. The differential diagnosis of acetowhite changes includes immature metaplastic epithelium, HPV infection, preinvasive cervical neoplasia, and neoplasia. In high-grade cervical dysplasia or intraepithelial neoplasia, the acetowhite reaction appears faster, tends to be more intense, and stays longer. Lesion severity correlates with sharp demarcation, increased vascularity, and densely opaque acetowhitening. As part of the neoplastic process a characteristic proliferation of microvasculature occurs, known as punctation and mosaic.

Punctation describes a pattern of neovasculature seen *en face*, or perpendicular to the surface, and producing a stippled pattern in the acetowhite epithelium. Fine punctation is usually found in low-grade CIN, and as the neoplastic process progresses and vessels enlarge, the pattern becomes coarser. Coarse punctation is likely to denote high-grade CIN.

Mosaic patterns result from vessels that have arborized parallel to the epithelial surface, giving acetowhite areas a partitioned appearance. The more severe the lesion, the more intense the whitening and therefore the more sharply demarcated the margin. A small or fine mosaic pattern is usually associated with low-grade CIN and a coarse or irregular mosaic pattern with high-grade CIN.

Table 3 Colposcopic features of low- and high-grade intraepithelial cervical lesion

Feature	Low-grade lesion	High-grade lesion
Surface and border	Smooth, irregular outer border	Smooth, sharp outer border
Acetowhite test	Mild, slow to appear, quick to disappear	Dense, appears early slow to resolve
Iodine test	Mild, speckled, partial	Negative, yellow
Punctation	Fine	Coarse
Mosaic	Fine and regular	Coarse, irregular

Lugol's iodine, which is often used at the end of colposcopic examinations, stains mature squamous epithelium dark-brown because it contains glycogen. Immature metaplasia, CIN, or the atrophic epithelium found in menopausal women contain far less glycogen than the healthy squamous epithelium of younger women and therefore do not stain well with iodine and are referred to as iodine negative. Usually, Lugol's iodine confers a speckled appearance to immature metaplasia or low-grade CIN, whereas a yellow stain is suggestive of high-grade CIN.

Atypical vessels presenting comma or corkscrew shapes or irregular branching are suggestive of invasion. Other features of an invasive lesion include an irregular, eroded, or ulcerated epithelial surface, intense acetowhiting, and wide, irregular punctation and mosaic (Table 3).

While colposcopy is a useful complementary test to cytology, it may both overcall and undercall lesions, even in experienced hands. Training in colposcopy in essential, and on-going quality control through correlation with histology is important.

4. Treatment

4.1. Low-grade dysplasia

Most LSILs, particularly in women younger than 30 years, will regress spontaneously and do not need treatment. If follow-up is possible, women with LSILs should undergo cytologic and colposcopic evaluations every 6 months until regression or progression is diagnosed. If follow-up is not feasible, it is recommended that LSILs be treated once confirmed histologically. In other words, "look and LLETZ/LEEP" (large loop excision of the transformation zone/loop electrosurgical excision procedure) should not be performed in women with low-grade lesions because of the high likelihood of excessive or unnecessary treatment.

4.2. High-grade dysplasia

The treatment of *HSILs* may be ablative or excisional.

Ablative treatment is only appropriate when the lesion is seen in its entirety on colposcopic evaluation (adequate colposcopic evaluation), and a biopsy of the most abnormal area confirms the presence of a preinvasive lesion. In addition, there should be no evidence of any glandular abnormality or microinvasive disease. Ablative techniques include cryotherapy, cold coagulation, electrocautery, and carbon dioxide laser vaporization.

The most widely used excisional techniques today are LLETZ, also known as LEEP. Both techniques can be performed on an outpatient basis using local anesthetic. Prior to performing LLETZ/LEEP, the criteria for ablative techniques should be fulfilled. Furthermore, wherever expert colposcopy is available, and especially in resource-restricted settings, "look and LLETZ/LEEP" may be appropriate — that is, the procedure is performed on the basis of the colposcopic assessment alone and without histologic confirmation. Because LLETZ yields a high rate of negative results (i.e., no CIN is found on the specimen obtained with LLETZ), this approach is not recommended for low-grade lesions.

In ablative treatment the lesion has to be seen in its entirety and it can be destroyed by heat using diathermy, freezing using cryotherapy, or vaporization using a carbon dioxide laser. Excision of the lesion in the form of a cone can be performed using a knife, laser, or electric (hot) loop. Most of these procedures can be performed in an outpatient setting under local anesthesia or even under no anesthesia. Hysterectomy is rarely indicated in the absence of other indications and is not a superior treatment to local excision or ablation for the prevention of cervical cancer.

Cone biopsy is essentially a diagnostic procedure and is performed when there is significant disparity between the results of different diagnostic tests — e.g., a HSIL cytologic finding when no lesion is seen on colposcopy. Other indications for a cone biopsy include the following: the upper limit of the ace-

Table 4 Different treatment modalities for high-grade cervical intraepithelial neoplasia

Method	Setting	Equipment	Technique	Cure rate
Cryotherapy	Outpatient procedure under no anesthesia	Carbon dioxide or nitrous oxide	The double-freeze technique is used, where the cervix is frozen twice for 3 minutes with a 5-minute interval	86–95%
Loop electrosurgical excision procedure (LEEP)	Outpatient procedure under local anesthesia	High-voltage electrical device	Both the lesion and the transformation zone of the cervix are removed	91–98%
Knife coner	Under regional or general anesthesia	Knife	Both the lesion and the transformation zone of the cervix are removed	90–94%

towhite lesion is not seen; abnormal glandular cells are observed on the cervical smear; there is a suspicion of microinvasion; or there is a high-grade cytologic finding but no access to colposcopy. Cone biopsy may be performed using a knife (cold-knife cone), usually under general anesthesia, or using a large electric loop (hot-knife cone) or laser under local anesthesia (Table 4).

Conization should be performed for lesions that cannot be seen in their entirety because they extend into the endocervical canal. It is important to realize that it is not possible to perform colposcopy of the endocervical canal and if the upper limit of the lesion cannot be visualized it is impossible to rule out occult microinvasive disease.

5. Follow-up

Patients should undergo a colposcopic as well as a cytologic evaluation 6 to 12 months following surgical treatment for preinvasive high-grade intraepithelial lesions. Post-treatment surveillance with annual cervical smears should continue for a minimum of 5 years. If the lesion persists or recurs, repeated treatments should be offered. A return to a normal screening program should only be considered after a minimum of 5 continuous years of normal cytologic findings at intervals of 6 to 12 months.

Recently a number of studies have suggested that testing for high-risk types of HPV may be more sensitive than cytologic studies for the detection of persistent or recurrent disease. If HPV testing is used as an adjunct diagnostic tool during follow-up, follow-up evaluations can be spaced out if no high-risk HPV is detected after treatment [5].

6. Pregnancy

Because progression from CIN 2/3 to invasive cancer over the course of a pregnancy is minimal, and the rate of spontaneous regression is relatively high postpartum [6], CIN 2/3 may be followed up conservatively during pregnancy. Because the complication rate of excisional procedures during pregnancy is high, including significant bleeding and preterm births, the use of excisional procedures during pregnancy should be limited to patients in whom invasive cancer cannot be ruled out, and preferably performed in the first 16 weeks of pregnancy along with cervical cerclage [6,7].

7. Adolescents

HPV-associated lesions are more likely to spontaneously regress in younger women, particularly in adolescents, than in older women, and a biopsy-proven CIN 2 is more likely than a CIN 3 to regress in adolescents [7,8]. Therefore, a biopsy diagnosis of CIN 2, a satisfactory colposcopic examination, and an endocervical sample negative for a glandular abnormality justify conservative management in persons from this age group, provided that they be considered likely to adhere to the follow-up schedule.

Cytologic and colposcopic evaluations at 4- to 6-month intervals are a management option. However, as there is significant interobserver variability regarding the histologic diagnosis of CIN 2, this diagnosis should be used with caution, as well as colposcopic clinical impression.

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Section B:
Malignant manifestations of HPV infection

Carcinoma of the cervix, vulva, vagina, anus, and penis

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KEYWORDS
Cervical cancer;
Vulval cancer;
Vaginal cancer;
Anal cancer;
Penile cancer;
Cancer staging;
Diagnosis;
Treatment

Abstract Cervical cancer remains the commonest cancer among women in developing countries, affecting women at their peak of social and economic responsibility. In poor countries where access to diagnosis and treatment is extremely limited, most of the affected women present with late-stage disease. Many do not even have access to palliative care. Outcome in women treated for cervical cancer is strongly influenced by the stage of diagnosis. The main treatment modalities remain surgical removal for early-stage disease and chemoradiation for late-stage disease.
Cancers of the vulva, vagina, penis, and anus are much less common than cervical cancer although, in most cases, they also are associated with human papillomavirus infection. Diagnosis and chief treatment modalities for cervical and these less common cancers are discussed.

Cancer of the cervix

1. Introduction

Cervical cancer is the second most common cancer in women worldwide and the commonest in women living in Africa (especially in southern and eastern Africa), Latin America, Asia, and South East Asia. In 2000 it was estimated that each year approximately 493,000 women develop cervical cancer and 274,000 die from the disease, with 83% of all cases occurring in low-resource countries [1,2]. Cervical cancer affects women in the fifth and sixth decades of their lives, when they play a critical role in their families, communities, and workplace. In many countries with a high incidence of cervical cancer, access to treatment or early detection is very limited, as is access to palliative care. Consequently, large numbers of women die painful, undignified deaths from a disease that has long been recognized to be largely preventable.

2. Symptoms and signs

It is important to note that macroscopically normal cervices may harbor microinvasive or occult invasive cancers. These cancers are usually detected by screening and their presence confirmed by performing a colposcopy or a cone biopsy.

Symptomatic cancers present with abnormal bleeding such as intermenstrual, postcoital, or postmenopausal bleeding, often in association with an offensive vaginal discharge. A speculum examina-

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tion to view the cervix is therefore mandatory in any woman who complains of abnormal bleeding and/or a vaginal discharge. Most cervical cancers spread locally before metastasizing and may be accompanied by abdominal pain, dyspareunia, vesicovaginal or rectovaginal fistulas, renal failure secondary to ureteric obstruction, urinary retention, and lymphedema. The most frequent sites for metastases are the liver, lungs, and bones; however, metastases may be detected at any site.

3. Diagnosis

The clinical diagnosis, which includes a pelvic and digital rectal examination to assess whether the tumor has spread to the parametria, vagina, and/or uterosacral ligaments, is histologically confirmed from a biopsy sample of the cervical lesion. The physical examination is supplemented by investigations such as a chest radiograph, an intravenous pyelogram or renal ultrasonographic examination to assess ureteric dilatation, renal and liver function tests, and a cystoscopy to rule out occult bladder invasion. It is also recommended that a venereal disease research laboratory (VDRL) test and a HIV test be performed in areas where these infections are endemic. HIV testing is particularly important: because cancer therapy is immunosuppressive, treatment may need to be modified if the patient is infected with HIV.

The differential diagnosis of cervical cancer includes ruling out the following:

- Metastases from other organs, particularly from the upper genital tract
- Other cancers such as lymphoma
- Condylomata accuminata and verrucous carcinoma (a relatively rare variant of condylomata accuminata that behaves in an aggressive fashion locally but does not usually metastasize)
- Infectious conditions such as herpetic infection of the cervix, tuberculosis, schistosomiasis, amebiasis, lymphogranuloma venereum, and granulosa inguinale

The most common histologic type of cervical cancer is squamous cell carcinoma. Adenocarcinoma or adenosquamous carcinoma comprise about 15% of cervical cancers.

4. FIGO staging of cervical cancer

Once the diagnosis is made, it is essential to stage the disease. Staging uses a combination of clinical assessment (the pelvi-rectal digital examination) and the investigations outlined in the previous para-

Table 1 FIGO staging*

Stage 0	Carcinoma in situ, intraepithelial carcinoma
Stage I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
Stage IA	Invasive cancer identified only microscopically. (All gross lesions, even with superficial invasion, are Stage IB cancers.) Measured stromal invasion $\leq$5 mm† in depth and $\leq$7 mm in its greatest width
Stage IA1	Measured stromal invasion $\leq$3 mm in depth and $\leq$7 mm in its greatest width
Stage IA2	Measured stromal invasion between 3 mm and 5 mm† in depth and $\leq$7 mm in width
Stage IB	Clinical lesions confined to the cervix or preclinical lesions greater than those of Stage IA
Stage IB1	Clinical lesion $\leq$4 cm in greatest dimension
Stage IB2	Clinical lesion $>$4 cm in its greatest dimension
Stage II	The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third
Stage IIA	Involvement of up to the upper two thirds of the vagina. No obvious parametrial involvement
Stage IIB	Obvious parametrial involvement but not onto the pelvic sidewall
Stage III	The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or nonfunctioning kidney should be included unless they are known to be due to other causes
Stage IIIA	Involvement of the lower vagina but no extension onto the pelvic sidewall
Stage IIIB	Extension onto the pelvic sidewall, or hydronephrosis/nonfunctioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or is clinically involving the mucosa of the bladder and/or rectum.
Stage IVA	Spread to adjacent pelvic organs
Stage IVB	Spread to distant organs

* Adapted from reference [3].
† The depth of invasion should not be greater than 5 mm from the base of the epithelium, either surface of glandular, from which it originates. Vascular space invasion should not alter the staging.

graph. Staging has a direct impact on management. The current FIGO Staging is shown in Table 1.

5. Additional notes on staging of carcinoma of the cervix

Stage IA carcinoma should include minimal microscopically evident stromal invasion as well as a small cancerous tumor of measurable size. The diagnosis of Stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably of a cone biopsy sample, which must include the entire lesion. The upper limit of Stage IA2 is given by the measurement of the 2 largest dimensions in any given section.

As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the uterine corpus. Extension to the corpus should therefore be disregarded.

A growth fixed to the pelvic wall by a short and indurated but not nodular parametrium should be allotted to Stage IIB. It is impossible, on clinical examination, to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory. Therefore, the patient should be diagnosed with having Stage IIIB disease only if the parametrium is nodular on the pelvic wall or if the growth extends to the pelvic sidewall.

The presence of bullous edema of the bladder mucosa should not permit a diagnosis of Stage IV. Malignant cells in cytological washings from the bladder require further examination and biopsy of the bladder.

If there is doubt regarding the staging, an examination under anesthesia may be appropriate. The clinical stage must under no circumstances be changed on the basis of subsequent findings.

6. Treatment

For early-stage cervical cancer, FIGO Stage IA1 disease, a cone biopsy should be performed if further fertility is desired; if not, a simple hysterectomy is the best choice. For Stage IA2 disease, a spectrum of treatment, from cone biopsy to radical hysterectomy and bilateral pelvic lymphadenectomy, has been practiced.

For Stage IB1 and early Stage II disease, radical hysterectomy and bilateral pelvic lymphadenectomy or chemoradiotherapy is recommended. For women who wish to preserve their fertility, however, radical trachelectomy with bilateral pelvic lymph node dissection is recommended.

For Stage IB2 and later Stage II disease and beyond, chemoradiation or radiotherapy is recommended. Chemoradiation involves radiation treatment with concurrent weekly administration of cisplatinum (50 mg/m^2).

After treatment patients need regular follow-up to detect possible recurrence and proceed to either salvage therapy or palliative care.

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Cancer of the vulva

1. Patients, diagnosis, histology, and treatment

Vulval carcinoma occurs in 2 broad groups of women. One consists of younger women (mean age, 55 years) who have vulval intraepithelial neoplasia (VIN) associated with squamous cell carcinoma of the vulva [1]. A high rate of concomitant vaginal and cervical lesions is found in these women, and HPV is detected in approximately 75% of these lesions — human papillomavirus (HPV)-16 being the most common type identified. The second group consists of older women (mean age, 77 years) who do not have associated VIN and whose lesions only rarely contain HPV. In this group, the type of histologic lesion tends to be well-differentiated squamous carcinoma [1].

The diagnosis of vulval carcinoma is clinical, and in all cases management is best provided by a multidisciplinary team consisting of gynecologic and radiation oncologists [2]. Radical en-bloc surgery is no longer the mainstay of treatment; rather, each case is staged and treatment individualized. In early-stage disease, radical wide local excision with unilateral or bilateral groin node dissection is the treatment of choice. However, where the lesion is centralized and removal would result in sacrificing central structures, e.g., the urethra, anus, and/or clitoris, primary chemoradiation to the vulva and groins is recommended to prevent the necessity of surgical stomas. Following the chemoradia-

Table 1 TNM classification *

T	**Primary tumor**
Tis	Preinvasive carcinoma (carcinoma in situ)
T1	Tumor confined to the vulva and/or perineum, ≤2 cm in greatest dimension
T2	Tumor confined to the vulva and/or perineum, >2 cm in greatest dimension
T3	Tumor of any size with adjacent spread to the urethra and/or vagina and/or the anus
T4	Tumor of any size infiltrating the bladder mucosa and/or the rectal mucosa including the upper part of the urethral mucosa and/or fixed to the bone
N	**Regional lymph nodes**
N0	No nodes palpable
N1	Unilateral inguinal lymph node metastasis
N2	Bilateral inguinal lymph node metastases
M	**Distant metastasis**
M0	No clinical metastasis
M1	Distant metastasis (including pelvic lymph node metastasis)

* Adapted from reference [2].

Table 2 FIGO staging of vulval cancer (clinical and surgical) *

Stage 0	Carcinoma in situ, intraepithelial carcinoma (VIN III)
Stage IA	Lesions ≤2 cm in greatest dimension confined to the vulva or perineum, with stromal invasion ≤1 mm. Nodes are not palpable/no nodal metastases
Stage IB	Lesions ≤2 cm in greatest dimension with stromal invasion >1 mm in depth. No nodal metastases
Stage II	Tumor confined to the vulva and/or perineum >2 cm in its greatest dimension. No nodal metastases
Stage III	Tumor of any size with 1. Adjacent spread to the lower urethra and/or vagina or anus, and/or 2. Unilateral inguinal lymph node metastases
Stage IVA	1. Tumor invades any of the following: upper urethra, bladder mucosa, rectal mucosa, and/or pelvic bone, and/or 2. Bilateral inguinal node metastases
Stage IVB	Any distant metastasis including pelvic lymph nodes

* Adapted from reference [2].

tion treatment, surgical removal of any residual disease is recommended.

2. Tumor node metastasis (TNM) classification

Tumor classifications are based on many systems ranging from the anatomical site and the clinical and pathological extent of the disease to the histologic type and grade of tumor. The TNM system describes the anatomical extent of disease based on the assessment of three primary components:

T, which refers to the extent of the primary tumor
N, which refers to the absence or presence and extent of regional lymph node metastases
M, which refers to the presence or absence of distant metastases.

The TNM system is virtually identical to the FIGO staging system of vulval cancer, which uses a combination of clinical assessment with histologic parameters (see Table 1).

3. FIGO staging of vulval cancer

Vulval cancer has been surgically staged since 1988 and the final diagnosis is dependent on the pathological assessment of the operative specimen (Table 2).

4. Conclusion

The modern management of vulval cancer requires a multidisciplinary team approach and a combination of careful clinical and pathological evaluation to determine the best approach. Because of its rarity (comprising around 4% of all gynecological cancers), data on management is largely confined to retrospective studies rather than randomized trials

– hence the need to individualize the treatment of each patient [3].

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Cancer of the vagina

Vaginal cancer is extremely rare and the incidence is about one fiftieth of the incidence of squamous cell carcinoma of the cervix [1]. Only about 1% of malignant neoplasms of the female genital tract are classified as squamous cell carcinomas of the vagina. The low incidence reflects both the low incidence of cancer of the vagina and the strict criteria for the diagnosis of vaginal cancer, which may lead to an underestimation of its true frequency. To be diagnosed as vaginal cancer, the cancer must be located in the vagina without any histologic evidence of involvement of the cervix or vulva. Thus, a tumor in the upper vagina that has extended to involve the cervix will be diagnosed as a primary cancer of the cervix. Further, a vaginal cancer diagnosed within 5 years of treatment for primary cervical cancer is called a secondary cervical cancer [1].

The mean age at diagnosis of vaginal cancer is 64 years and most patients present with asymptomatic vaginal bleeding and/or discharge, or dysuria with increased urinary frequency. Vaginal carcinoma is staged just like cervical cancer, with clinical assessment of local spread and additional investigations, such as a chest radiograph and radiologic assessment of the ureters and liver, to assess for metastatic spread.

Radiation therapy is the main treatment modality for vaginal cancer, although in relatively rare circumstances a total vaginectomy can be performed.

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Cancer of the anus

1. Incidence

Anal cancer is a rare disease that occurs in middle-aged adults, making up 4% of all cancers of the lower gastrointestinal tract. The annual incidence of anal cancer is around 1 per 100,000 in the heterosexual population, accounting for 500 new cases per year in the United Kingdom and 3500 in the United States. The incidence is much higher in men who practice anal-receptive sexual intercourse (up to 35 per 1,000,000), and it is twice as common among HIV-infected than in HIV-uninfected individuals [1].

2. Causes

Epidemiological and molecular studies have shown that sexually transmitted infection with HPV is the most important etiologic factor [1]. In a process that is very similar to the development of cervical intraepithelial neoplasia, HPV has been shown to cause anal intraepithelial neoplasia that can progress from low-grade, to high-grade, to invasive anal cancer. Some HPV subtypes, particularly HPV-16, are associated with a high risk of malignant transformation. This is important information as it may be that the HPV vaccines will not only protect women from cervical cancer, but men and women from anal cancer as well.

While HPV infection of the anus is the likely causative agent for anal cancer, immunosuppression is probably important for the time of progression to anal cancer [1]. The frequency of anal cancer in the presence of HIV infection is increased, as is its incidence in men and women with therapeutically induced immunosuppression.

Other cofactors include cigarette smoking, anal intercourse, and a high number of lifetime sexual partners.

3. Presentation

Rectal outlet bleeding, i.e., bright-red bleeding on defecation, occurs in about half of patients with anal cancer. Other symptoms include anal pain and incontinence due to anal sphincter involvement. In women, a history of genital warts and cervical or vulval neoplasia should be elicited [2].

On clinical examination the tumor is nearly always palpated. Its exact position should be noted, as well as the extent of its spread to the rectum, perineum, and ischioanal fossa, and whether it is fixed to surrounding structures such as the prostate,

vagina, or bony pelvis. In women a thorough gynecologic examination should be done, if necessary under general anesthesia.

Differential diagnoses include hemorrhoids, lymphogranuloma venereum, warts, anal fissures, leukoplakia, and chronic skin lesions.

4. Gross appearance, diagnosis, and histology

Small tumors may be mobile and verrucous whereas large tumors may be ulcerated and indurated, forming a palpable mass. Rectum and sphincter may be involved. Spread to lymphatic system leads to enlarged inguinal lymph nodes [2].

Gross tumor biopsy is essential to confirm the diagnosis. The most common histologic type is squamous cell carcinoma. Other cell types include adenocarcinoma, transitional cell carcinoma, and basiloid or mucoepidermoid tumors.

5. Treatment

Treatment depends on the stage, location, and depth of invasion of the anal cancer. Small mobile lesions arising below the mucocutaneous junction may be treated by local excision, but larger tumors that invade the sphincter or rectum need radical therapy. Since external radiation with concomitant chemotherapy using 5-fluorouracil (5-FU) and mitomycin C may achieve complete response, and surgery will necessitate a permanent colostomy, radical surgery is reserved for treatment failure or recurrence.

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Cancer of the penis

Penile cancer is also a rare malignancy, with an incidence in the USA of 0.3% to 0.6% of all cancers in men and 2% of all male genital cancers. The incidence is higher in other geographic areas and may reach 10% to 20% of genital tract cancers in men in certain parts of Asia, Africa, and South America [1]. It is most frequently diagnosed in men in their sixth or seventh decade, although in areas with a high incidence of penile cancer the mean age at diagnosis tends to be younger.

Penile cancer is significantly more likely to be diagnosed in uncircumcised males, which is considered an important risk factor for penile in-situ and invasive cancer. However, infection of the penis with HPV is probably an important cause of penile neoplasia [2]. HPV DNA has been detected in penile in-situ and invasive lesions. In addition, a history of anogenital warts is associated with a 5- to 6-fold increase in risk of penile squamous carcinoma. Results from separate studies not using polymerase chain reaction technology (PCR) have estimated the prevalence of HPV in penile cancers to be between 15% and 71%. Other studies using PCR technology, however, have reported detection of HPV types 16, 18, 31, and 33 in up to 82% of invasive and in-situ penile carcinomas [2,3].

Treatment is tailored to stage of disease. For in-situ lesions, surgical excision or local ablative therapies (carbon dioxide laser vaporization, cryotherapy, and topical 5-FU) are used. For invasive lesions, treatment options range from surgical excision to radical radiation.

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