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Vaginal Intraepithelial Neoplasia: A Therapeutical Dilemma

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Abstract. *Vaginal intraepithelial neoplasia (VaIN) represents a rare and asymptomatic pre-neoplastic lesion. Its natural history and potential evolution into invasive cancer are uncertain. VaIN can occur alone or as a synchronous or metachronous lesion with cervical and vulvar HPV-related intra epithelial or invasive neoplasia. Its association with cervical intraepithelial neoplasia is found in 65% of cases, with vulvar intraepithelial neoplasia in 10% of cases, while for others, the association with concomitant cervical or vulvar intraepithelial neoplasias is found in 30-80% of cases. VaIN is often asymptomatic and its diagnosis is suspected in cases of abnormal cytology, followed by colposcopy and colposcopically-guided biopsy of suspicious areas. In the past, high-grade VaIN and multifocal VaIN have been treated by radical surgery, such as total or partial upper vaginectomy associated with hysterectomy and radiotherapy. The need to maintain the integrity of reproductive capacity has determined the transition from radical therapies to conservative ones, according to the different patients' characteristics.*

Vaginal intraepithelial neoplasia (VaIN) is a rare pre-malignant lesion characterized by the presence of squamous cell atypia without invasion. The disease is classified according to the depth of epithelial involvement: VaIN 1 and 2 involve the lower one-third and two-thirds of the epithelium, respectively, and VaIN 3 involves more than two-thirds of the epithelium. Carcinoma *in situ*, which involves the full thickness of the epithelium, is included in VaIN 3. The natural history of VaIN is thought to be similar to that of cervical intraepithelial neoplasia (CIN), although there is little information regarding this. The management of this intraepithelial neoplasia should be tailored according to the patient. After early treatment, VaIN frequently regresses, but patients require careful long-term monitoring after initial therapy due to high risk of recurrence and progression. The purpose of this review is to identify the best management of VaIN basing therapy on patients' characteristics.

Epidemiology and Natural History

In the past, VaIN was rarer than vaginal invasive cancer (1) because it was frequently underdiagnosed. Nowadays the incidence of VaIN is expected to rise due to a greater attention to cervical cytological screening and colposcopy (2). The age at diagnosis is related to the degree of VaIN, being about 60 years for VaIN 3 and about 45 years for VaIN 1 and 2 (3). In our experience, the mean age at diagnosis of VaIN was 53 years (range=31-70 years) (4). Other authors have reported an average age of 35±17 years (5) and the diagnosis of VaIN 2-3 was also made in patients under 25 years old (6). In the past twenty years, the diagnosis of VaIN has been made in younger women, due to the spread of the human papillomavirus (HPV) infection. The incidence of VaIN is 0.2-0.3 per 100,000 women (3, 7, 8). The reported frequencies are 0.5% of all neoplastic lower genital tract lesions (9) and 1% of all intraepithelial neoplasias (10). VaIN was associated with CIN in 65% of cases and with vulvar intraepithelial neoplasia (VIN) in 10% of cases (5) in one study, while for others, the association with concomitant CIN or VIN reached 30-80% of cases (1, 5, 8, 10-13).

Among women hysterectomized due to cervical carcinoma, VaIN was found in approximately 5-10% of cases (14-16). However, in another study, VaIN was found in 70% of hysterectomized women for CIN or carcinoma (10). The

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incidence of VaIN in women with a previous hysterectomy for benign uterine pathologies is about 1.3% in 10 years (17). In the etiology of VaIN, HPV plays a role similar to that of CIN and VIN (18, 19). The presence of HPV in low-grade lesions is found in 98-100% of cases, 90-92.5% in VaIN 2-3 and 65-70% for invasive carcinomas (20, 21). VaIN 2-3 are related to high-risk (HR) HPV for up to 65% of cases (21, 22): in particular, HPV 16 and 18 were found in 64% of cases (23-25). The prevalence of HPV 16 and 18 in invasive vaginal cancer is slightly higher, reaching 72% and this confirms that the affinity of HPV for the vaginal epithelium is similar to that for the cervix (26). Among women with any degree of VaIN, 21 types of HPV have been found (27). Other risk factors in addition to HPV include radiotherapy, immunosuppression, prenatal exposure to diethylstilbestrol (DES) and smoking. HPV 16 is more frequent in women subjected to external irradiation for cervical cancer, while those subjected to brachytherapy would be more at risk for infection by other viral types and for developing low-grade lesions (26). In women with iatrogenic immunosuppression (28) or affected by the human immunodeficiency virus (HIV) infection, VaIN rises to 5% (29), perhaps due to a lower immune control of the HPV infection. Twenty years ago, an increased relative risk for CIN 2-3 and VaIN 2-3 was noticed in women exposed to DES *in utero* (30) and this has since been confirmed (31). An association with smoking was found in 41-51% of cases (5, 10): smokers with HR-HPV infection have a significantly higher risk of developing VaIN 2-3, compared to non-smokers (27). The natural history of the disease is not clearly-defined and the true potential of the lesions is not precisely understood. Observational studies have shown that the majority of low-grade VaIN probably regress spontaneously in 90% of cases (7, 32). VaIN 3 lesions have greater malignant potential and there are no data about the spontaneous regression of VaIN 2-3. Concerning its progression, an interval of about 15 years between VaIN 1 and VaIN 2-3 lesions has been reported (2). VaIN 3 biopsies show initial invasion in approximately 10-28% of cases (7, 33-35). The progression to invasive lesions after appropriate treatment ranges from 2% to 5% (5, 8, 36, 37) of cases, ten-fold higher than CIN, when properly treated (0.3-0.5%). The scar of the vaginal vault after hysterectomy may represent a site of progression from high-grade VaIN to invasive cancer (38).

Classification and Topography

VaIN (such as CIN and VIN) is classified into low-grade lesions (mild dysplasia or grade 1) and high-grade lesions [moderate and severe dysplasia, grade 2-3 and carcinoma *in situ* (CIS)]. In 80% of cases, VaIN involves the upper third of the vagina and it is often multifocal (60%) (2, 3, 5-7, 10, 14), mostly in women hysterectomized for CIN 3 or CIS (80%) (2, 10). To explain this preferential location, the embryological origin of the upper vagina and cervix was considered in context of synchronous or metachronous HPV-related cervical lesions. Clinically, it is possible to recognize four situations: *de novo* or found alone; associated with CIN or invasive cervical cancer; associated with VIN or invasive vulvar cancer; associated with CIN or VIN, or their invasive counterparts (39).

Diagnosis

Most patients are asymptomatic or may complain of unusual vaginal discharge, thus the diagnosis is often accidental. In order to perform a correct diagnosis, it is fundamental to know if the patients underwent a previous hysterectomy. In non-hysterectomized patients, an abnormal cytology requires colposcopy as a second-level examination. Colposcopy should carefully examine not only the cervix, but also the entire vagina. After the application of acetic acid (5%), aceto-white areas with a mosaic and punctuation vascular pattern (10, 40, 41) seem to be related to the presence of high-grade lesions (41) which are highlighted after the application of Lugol staining. All the suspicious areas should undergo a biopsy for histological diagnosis. In 2011, the International Federation of Cervical Pathology and Colposcopy (IFCPC) agreed on an international revised colposcopic nomenclature of the vagina (Table I). In patients hysterectomized due to CIN, the diagnosis of VaIN should be suspected after an abnormal Pap test (40) and cytology should be performed regularly once a year (10, 14, 42) for at least 4-10 years (12, 13). Pap test sensitivity after hysterectomy is more than 80% (41, 43, 44). Colposcopy of the vaginal vault after total hysterectomy is more difficult than with an intact cervix as VaIN after hysterectomy commonly occurs at the vaginal suture line and the vaginal angles which are difficult to visualize. In this case, histological diagnosis is also necessary.

Treatment

Treatments need individualization according to the patient's characteristics, disease extension and previous therapeutic procedures. Radical treatment is complex to achieve because the vaginal wall is in close relationship with the urethra, bladder and rectum. This condition also explains the risk of complications related to excisional surgery and the morbidity of radiotherapy.

In the literature, the results of different treatments vary. Remission can occur in 70% of cases after a single treatment and in another 24% of patients after combined therapy (8). The various types of treatments are summarized in Table II.

Surgery. The surgical treatments that can be used are CO_2 laser, loop electrosurgical excision procedure (LEEP) and partial or total vaginectomy. CO_2 laser may be used as both an ablation method and excision one. Therefore, it is

Table I. *2011 International Federation for Cervical Pathology and Colposcopy (IFCPC) clinical colposcopic terminology of the vagina.*

General assessment	Adequate/inadequate for a reason (*i.e.* inflammation, bleeding, scar) Transformation zone
Normal colposcopic findings (squamous epithelium)	• Mature • Atrophic
Abnormal colposcopic findings:	
General principles	Upper-third/lower two-thirds, anterior/posterior/lateral (right or left)
Grade 1 (minor)	Thin aceto-white epithelium Fine punctation Fine mosaic
Grade 2 (major)	Dense aceto-white epithelium Coarse punctation Coarse mosaic
Suspicious for invasion	Atypical vessels Additional signs: fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration (necrotic), tumour/gross neoplasm
Non-specific	Columnar epithelium (adenosis); lesion staining by Lugol's solution: stained/non-stained; leukoplakia
Miscellaneous	Erosion (traumatic), condyloma, polyp, cyst, endometriosis, inflammation, vaginal stenosis, congenital transformation zone

Table II. *Treatment modalities for vaginal intraepithelial neoplasia.*

Agent	Ablation	Excision	Other
Imiquimod	CO_2 laser	CO_2 laser	Chemosurgical treatment (laser+5-FU)
Trichloroacetic acid	Photodynamic therapy	LEEP	Radiotherapy
5-Fluorouracil		Partial upper vaginectomy Total vaginectomy CUSA	

CUSA: Cavitational ultrasonic surgical aspiration; LEEP: loop electrosurgical excision procedure.

considered the treatment of choice by several authors (6, 8, 32, 45). The use of CO_2 laser vaporization has been reported for lesions in locations other than the apex, as well due to the need for continuation of the sexual function in young sexually active women (40). CO_2 laser is useful in the treatment of vaginal areas which are difficult to reach, such as angular recesses of the vaginal vault after hysterectomy (7). Yalcin *et al*. claim that the inaccessible location of some lesions are a likely cause of therapeutic failure (37); for this reason, CO_2 laser surgery should be performed when the operator confirms that the entire lesion is completely visualized (37), when there is no suspicion of invasion, and there is no gross scarring or distortion of the vaginal vault (40). According to these data, it would be recommended to carry out careful vaporization of the vault in hysterectomized women because of the high risk of invasive disease. The minimum depth of this treatment should be 1.5 mm and the thickness of the epithelium affected by VaIN varies from 0.10 to 1.4 mm (46). Laser is effective in 42 to 90% of cases (2, 6, 7, 37, 47). Leneham *et al*. found laser ablation to be less effective than electrocautery or vaginectomy (48). The recurrence rate is reported to be between 0-42% (1, 13, 33, 47, 48, 49-55); moreover, MacLeod *et al*. and Stuart *et al*. demonstrated invasive disease at the time of recurrence in 7.1 and 3.7% of patients, respectively (56, 57). This procedure has many benefits: precision in both localization and depth of destruction (47, 51, 52, 54, 55, 58, 59), repeatability, few side-effects, minimal blood loss, and the possibility of combining laser excision and vaporization. On the other hand, its limitations are the high cost, the long learning curve for excisional techniques, and the missed detection of some of VaIN lesions (37, 40).

LEEP is a surgical excisional treatment which can be used to perform partial upper colpectomy in histologically-confirmed single lesions of VaIN 2-3 (32), combining

treatment with 5-fluorouracil (5-FU) (33). Excision consists of the vaginal mucosa and a portion of the submucosal tissue. The procedure results in minimal lateral tissue damage, similar to the effects of a laser. The recurrence rate reported in a study of 23 patients was 13% at 12 months and 25% at 24 months (60). Complications are rare but significant, such as perforation of the sigmoidal colon (61).

Vaginectomy can be total or partial and has a dual objective: elimination of the neoplastic lesion and ensuring maintenance of the functional anatomic structure, preserving the elasticity, capacity and extention of the vagina. Total vaginectomy is not an advisable procedure because it makes sexual intercourse impossible and thus it must be reserved for exceptional cases, when the spread of recurrent lesions could otherwise not be managed. Partial upper vaginectomy is considered the treatment of choice for apical VaIN 3 or VaIN in the region of the vaginal cuff scar in women hysterectomized for cervical neoplasia (40). It provides a specimen for a complete histopathological diagnosis (34) and permits the identification of underlying cancer as invasive carcinoma is reportedly occult in about 28% of cases (33-35, 62). VaIN is often a multifocal condition and in order to reduce the possibility of persistence or recurrence, it is necessary to obtain wide free margins. In cases of multifocal conditions or lesions that involve the lower one-third of the vagina, upper vaginectomy can be combined with laser vaporization (34). This technique is well-described by Cardosi *et al*. (9), with 10% of major complications, involving the rectum, bladder and ureters; it causes vaginal shortening, leading to difficulty or inability during sexual intercourse, and intra- and postoperative bleeding and sepsis can also occur (34). The success rate of upper vaginectomy ranges from 69-88% (34-36). However, Cheng *et al*. observed recurrence in more than 30% of cases during the follow-up after upper vaginectomy (62). Although upper vaginectomy and total vaginectomy can be considered effective treatments, they do not avoid recurrence (8, 63, 64).

Chemosurgical treatment: microsurgery and 5-FU. For a long time, therapy with 5-FU was associated with microsurgery, particularly using a laser (8, 53, 65) in order to reduce the frequency of recurrence. It was recommended only for completely visible VaIN 2-3 (8). Today, 5-FU treatment is no longer available due to its lack of efficacy and its side-effects.

Cavitational ultrasonic surgical aspiration (CUSA). This treatment is a minimally-invasive procedure that unlike other conservative treatments is performed under general or spinal anesthesia in the operating theatre. The CUSA technique allows for adequate histological examination and the identification of invasive lesions. There is no evidence of residual scars and complications. The recurrence rate is estimated to be between 25% and 34% for VaIN 2-3, like the laser technique, but with less postoperative pain and better healing. It is effective in approximately 50% of cases of recurrence (66, 67).

Photodynamic Therapy

Photodynamic therapy is performed by a laser beam with a wavelength of 635 nm and an output of 80-125 J/cm^2 after the application of a photosensitizer (*e.g*. 10% 5-amino-levulinic acid gel) that selectively targets dysplastic cells. It is used experimentally for VIN and has also been used in studies of VaIN with inconclusive results. Healing time seems to be quicker than that of the CO_2 laser (68).

Topical Treatments

Imiquimod. This is an immune response modifier that induces the secretion of interferon-alpha, interleukin-12 and tumor necrosis factor-alpha (TNF-α), locally stimulates natural killer activity, promotes the maturation and activity of Langerhans cells, and increases the effectiveness of the T-cell-mediated response (69). The treatment is already used in vulvar dysplasia; nowadays, some studies suggest its application in vaginal dysplasia (70, 71). Some have used imiquimod, especially in VaIN 1, where the spontaneous regression rate is high (70). The treatment is complex: invasion must be ruled-out before starting this treatment, it must be carried out at least three times a week for eight weeks under a colposcopic guide, which has a poor compliance by patients and requires a significant commitment by health professionals. Recently it was reported that in patients with VaIN 2-3, an intravaginal application of 5% imiquimod cream may reduce the lesion degree, even if VaIN 2-3 persists in more than 80% of cases (72). Few data are available (73) and the use of imiquimod in VaIN 2-3 remains confined to controlled clinical trials.

Local treatment with trichloroacetic acid (TCA). TCA is a powerful keratolytic agent that can coagulate proteins of the skin, killing all living structures to the level of the reticulary dermis. It has also been shown to have a therapeutic effect on HPV-induced genital warts (74, 75). Considering these results, some authors have experimented with its use in treating intraepithelial neoplasia. Treatment with intravaginal 50% TCA, with a weekly application for 1-4 weeks results in regression of VaIN in 71.4% of cases. Although VaIN 1 probably regresses spontaneously, or after biopsy, VaIN 2-3 may benefit from TCA treatment (68, 76).

Topical therapy with 5-FU. This treatment is thought to be an ideal method for multifocal VaIN and recurrences. Topical administration of 5-FU has the advantage of treating the entire vaginal area, even though only superficially; this

explains the high rate of recurrence. For Dodge *et al*. the recurrence rate is 59% (5), for others is 7-20% (1, 13, 33, 47-55). The local side-effects observed are burning, vaginal discharge and pain that may reduce patient compliance with the treatment (13, 55, 77). The appearance of vaginal adenosis has also been reported (78). The efficacy of topical 5-FU ranges from 30% to 90%, according to different studies (8, 36, 77). This treatment is not effective on the dysplastic epithelium of the vaginal vault scar after hysterectomy because the drug cannot reach it (8, 9).

Radiotherapy

Radiation therapy has a long history of documented efficacy, with control rates ranging between 80% and 100% (79, 80). Few studies have been reported in which both low-dose rate (LDR) and high-dose rate (HDR) intracavitary brachytherapy (ICB) were employed. In some reports, additional external beam radiotherapy was employed, but the risk of pelvic nodal involvement is lower than 1% and, therefore, therapy directed to the pelvic lymph nodes is unwarranted. In the case of the LDR therapy, a wide dose range of 2000 cGy to 16000 cGy has been applied, although the most common dose prescription to vaginal mucosa is 6000 cGy. Using conventional LDR ICB techniques, a mean dose of 60 Gy, in one or two implants, is administered to the mucosal surface. Higher doses may cause significant vaginal fibrosis and stenosis. Pelvic recurrences or distant failures after ICB have not been observed in the absence of the invasive component (81). In recent years, HDR ICB has been used mostly in VAIN 3 cases (82). No studies comparing LDR to HDR were carried out according to the outcomes and acute and late toxicities, but no differences seem to exist between the two techniques (83). There are very few studies regarding the outcome in terms of sexual function after brachytherapy treatment in patients with high-grade VaIN. Woodman *et al*. reported sexual outcomes in 10 patients: 9/10 achieved satisfactory intercourse despite irradiation of the entire vagina (84). In a retrospective series of 22 patients with VaIN 3, treated with medium dose rate brachytherapy, Graham *et al*. reported late vaginal mucosal changes such as atrophy, vaginal dryness and telangiectasia, vaginal stenosis, vaginal ulcers and sexual dysfunction, primarily due to vaginal dryness and dyspareunia rather than any alteration in the vaginal anatomy (85). In cases restricted to the upper vagina, preventing treatment of the entire length of the vagina may help to reduce the late toxicity profile, although this approach would not be ideal for dysplastic changes involving the entire length of the vagina. In recent years, a 3D planned system based on computed tomography (CT) or magnetic resonance imaging (MRI) permits a volumetric distribution of the dose to the target volume with a lower dose to the surrounding organ, leading to a better conformity of the dose to the vaginal mucosa. Brachytherapy based on the 3D technique could be related to better outcome results, with fewer lower-grade late complications.

The majority of studies on vaginal brachytherapy for high-grade VaIN report a recurrence rate in the range of 0%-14%. Overall the local control achieved by brachytherapy is satisfying and homogenously-confirmed across many studies (56, 82, 85-87). Regarding the other therapeutic options, the relapse rate using topical 5-FU, laser therapy and partial colpectomy were 59%, 38% and 0%, respectively (5). The relapse rate after brachytherapy seems lower than, or at least comparable to that after other treatment approaches. Annual colposcopy is advised considering the risk of early or late recurrence. It is important that patients with VAIN 3 are followed-up carefully and for a long period.

The main question is whether brachytherapy in high-grade VaIN is actually successful in patients with occult invasion. The major criticism of radiotherapy as opposed to surgery in the management of high-grade VaIN is that it cannot provide a specimen for detailed pathological diagnosis. Another issue concerns the potential adverse impact of previous brachytherapy treatment for future gynaecological procedures. Surgery after radiotherapy is more complex with a higher rate of perioperative complications.

Another issue concerns the probability of long-term risk of occurrence of a second neoplasm related to the previous course of radiation (88). Moreover, radiation therapy itself can be related to the occurrence of VaIN. In women treated with external beam radiotherapy and/or brachytherapy for gynaecological malignancies, about 20% developed vaginal dysplasia. In patients who had undergone previous radiation treatment, VaIN exhibited more aggressive features: more refractory to treatment, more likely to recur after surgery and ablative therapy, and with a tendency to progress to invasive cancer (89).

In summary, the cure rate achieved by brachytherapy is one of the highest for VaIN, but it is difficult to draw a conclusion regarding the cure rates and toxicity profiles obtained using different brachytherapy regimens. The risk of severe toxicity is low but patients must be counselled appropriately regarding the likelihood of mild/moderate toxicity, including premature menopause and potential sexual dysfunction. Moreover, because patients with high-grade VaIN have a long life expectancy, it is important to minimize the long-term side-effects in order to ensure a good quality of life for them.

Recurrence

After appropriate treatment, the recurrence rate is approximately 33% (5, 8). Risk factors for recurrence are reported in Table III. The recurrence rate related to the different types of treatments is reported in Table IV.

Table III. *Risk factors for recurrence of vaginal intraepithelial neoplasia.*

Study (reference)	Study design	Patients (n)	Follow-up (months)	Multifocality (%)	Site of lesion	CIN (%)	VIN (%)	Hysterectomy (%)	RT (%)	Immunosuppressed (%)
Audet-Lapointe *et al.* (2)	Prospective	76	39.2	-	Upper third of vagina, 92.4%	30.2	5.2	71.2	14.5	2.6
Diakomanolis *et al.* (3)	Retrospective	102	25	62	Upper third of vagina, 92.4%	29	7	36	6	-
Dodge *et al.* (5)	Retrospective	176	7	61	Upper third of vagina, 78%	65	10	23	5	1
Sillman *et al.* (8)	Review	94	63	51	Upper third of vagina, 100%	44.7	1.1	-	24.5	-
Rome *et al.* (7)	Retrospective	132	61	-	Upper third of vagina, 92%	31	4.6	55	16	4.6
Ait Menguellet *et al.* (90)	Retrospective	44	39.8	100	-	44.5	44.5	0	-	34.1
Liao *et al.* (89)	Retrospective	33	37.6	-	-	33	-	97	30.3	-

Recurrences are more frequent in cases of VaIN 2-3, in the presence of other HPV-related intraepithelial neoplasia or invasive lesions of the lower genital tract, and in immunosuppressed patients (8). In the presence of HPV-related dysplasia in several areas of the lower genital tract, recurrences were primarily related to multifocal lesions (3), while smoking, immunological disorders, high-grade lesions and previous non-surgical treatments do not represent significant risk factors for recurrence (90). The location of VaIN, especially of a high-grade, in the vaginal vault after hysterectomy has been associated with a high recurrence rate due to the difficulty of treatment (2), as well as the presence of injury to the vaginal vault (91).

VaIN arising after radiotherapy for gynaecological malignancies is more difficult to treat than those arising in the absence of previous radiation treatment, with a higher frequency of relapses and perhaps a greater tendency to progression (89).

Management of VaIN

There is no unanimous agreement on which is the best way to treat VaIN: each treatment has advantages and disadvantages to be assessed for the individual patient. The treatment choice is usually based on the number of lesions, their grade, location, previous radiation therapy, previous treatments and sexual activity.

The management of VaIN varies according to the grade of the lesion: VaIN 1 should be subjected to follow-up with a Pap test and colposcopy every six months, and after two years of negative cytology, there is a necessity for Pap test examinations every three years. If the lesion persists or becomes worse, treatment should be started (39). VaIN 2-3 should be treated, if possible, with excisional customized techniques (to detect cases of microinvasion already present), depending on location, number of lesions and age of the patients, encouraging their compliance with treatment and follow-up (39). The treatment should be repeated several times in cases of recurrence (7). The efficacy of treatments depends on the operator and their familiarity with the technique used (3, 92).

In the past, partial or total vaginectomy and radiotherapy were considered the best way to treat high-grade VaIN (13, 48, 64, 80, 81). Intracavitary irradiation therapy is reserved for cases where a total vaginectomy is not applicable due to concurrent disease, or the patient's refusal of surgery (48, 56). However, both treatments cause several side-effects that greatly worsen the quality of life. Considering that nowadays more VaIN lesions are diagnosed in younger women than in the past, a conservative approach is preferable. In young women with visible lesions, even if extensive, the treatment of choice is CO_2 laser vaporization with an excisional procedure (6, 36). The CO_2 laser has a success rate of 69% in the case of VaIN 2-3 (7). Multifocal lesions and lesions involving the lower third of the vagina are more commonly treated either with laser vaporization or 5-FU (34). The CO_2 laser therapy can be repeated several times, but in patients who frequently experience relapse at the vaginal vault after hysterectomy, a partial upper vaginectomy may be indicated (92). Despite the young age, the presence of other factors, such as high-grade lesions, occult microinvasive cancer and a history of previous hysterectomy due to a CIN or a cervical carcinoma, does not make a conservative approach advisable. Partial upper vaginectomy is the treatment of choice for apical VaIN 3 or VaIN in the region of the vaginal cuff scar in women hysterectomized due to cervical neoplasia (40);

Table IV. *Recurrence of vaginal intraepithelial neoplasia after different types of treatment.*

Treatment Author, (reference)	Comments	Study type	Patients (n)	Recurrence rate (%)	Latency for recurrence (months)
CO_2 laser					
Frega *et al*., (4)		Prospective	44	18	36
Von Grueningen *et al*., (66)		Randomized controlled trial	110	25	
Yalcin *et al*., (37)		Retrospective	24	25	
Diakomanolis *et al*., (92)		Retrospective	28	32	
Hoffman *et al*., (47)		Retrospective	26	5.5	
LEEP					
Terzakis *et al*., (60)		Retrospective	23	25	24
Fanning *et al*., (33)	Partial upper vaginectomy	Retrospective	15		
Upper vaginectomy					
Indermaur *et al*., (34)		Retrospective	105	6	24
Hoffman *et al*., (35)		Retrospective	32	17	19.5
Diakomanolis *et al*., (92)		Retrospective	24	21	
Wide local excision					
Cheng *et al*., (62)		Retrospective	40	14	
Topical 5-FU					
Gonzalez Sanchez *et al*., (36)	1.5 g once a week for 10 weeks	Retrospective	30	10	
Sillman *et al*., (45)		Retrospective	16	12.5	
Imiquimod, 5% cream					
Haidopoulos *et al*., (72)	Under colposcopic guidance, 3 times a week for 8 weeks	Retrospective	7	28.5	
Buck *et al*., (70)	0.25 g once a week for 3 weeks	Retrospective	42	0	
USA					
Matsuo *et al*., (67)		Retrospective	92	19.6	
CUSA					
Robinson *et al*., (53)	Initial treatment	Retrospective	29	34	14
Irradiation					
Blanchard *et al*., (81)	Low-dose-rate brachytherapy with vaginal mold 60 Gy	Retrospective	28	3.5	
Graham *et al*., (85)	Intracavitary brachytherapy 48 Gy	Retrospective	22	14	
Ogino *et al*., (82)	Intracavitary brachytherapy 23.3 Gy	Retrospective	6	0	
MacLeod *et al*., (56)	High-dose-rate brachytherapy 34-45 Gy	Retrospective	14	7	46
TCA, 50%					
Lin *et al*., (76)	Once weekly for 1-4 weeks	Retrospective	28	28.5	12

LEEP: Loop electrosurgical excisional procedure; USA: ultrasonic surgical aspiration; CUSA: cavitational ultrasonic surgical aspiration; TCA: trichloroacetic acid.

upper vaginectomy also provides a histopathological diagnosis (34) and it has a fairly good success rate (34-36). Radiotherapy is also feasible, but the main issue is the lack of histological specimens and, in addition, the difficulty for subsequent surgery. Moreover, among radiation therapy, surgical extirpation, or local destructive therapy, no single treatment modality offers complete protection against recurrence, persistence or progression to invasive cancer (8, 13, 27, 47, 48, 51, 52, 54-58, 64, 77, 84).

After treatment of VaIN 2-3, follow-up consists of Pap tests and colposcopy every six months for at least two years and then annually for at least five or 10 years. It has been suggested to include the HPV DNA test in the follow-up because it may represent the best method to predict the persistence of VaIN after treatment (4).

The HPV Vaccine: Possible Impact on VaIN

Use of the HPV vaccine could reduce 64% of VaIN 2-3, acting on the lesions caused by HPV 16 and 18 (23). The vaccine may slightly reduce the incidence of VaIN 1 lesions caused by HR-HPV, even though the association of such lesions with HPV 16 is rare (22). Some reports affirmed that the efficacy of the vaccine in preventing VaIN 2-3 caused by HPV 16/18, was 100% in women who have never been infected (91, 93). It is postulated that up to about 60% of vaginal carcinomas could be prevented by the vaccine (20).

In conclusion, VaIN represents a disease of great interest because it is a rare and asymptomatic pre-malignant condition whose discovery is crucial in order to prevent vaginal invasive cancer.

VaIN is often multifocal and multicentric, and can be associated with metachonous and synchronous lesions of the lower genital tract. For this reason, it is important to evaluate patients both in the diagnosis and during the follow-up, carefully, for the prevention of other intraepithelial neoplasias.

In literature, there are contrasting data about, which is the best therapy, with both advantages and disadvantages reported for each treatment. The therapy should be customized to the patient as much as possible, basing it on her needs and characteristics. The treatment must be conservative, especially for young women. However, no single-treatment modality offers complete protection against recurrence, persistence, or progression to invasion. During the follow-up, HPV DNA testing is useful for monitoring patients after treatment in order to optimize costs and benefits. Considering VaIN as an HPV-related disease, it would be recommended to use the HPV vaccine as a preventative measure.

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