Vulvar intraepithelial neoplasia (VIN) - Diagnostic and therapeutic challenges

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Summary

Purpose: Vulvar intraepithelial neoplasia (VIN) represents a current diagnostic and therapeutic challenge. The present retrospective study is an institutional experience on the diagnosis and management of VIN.

Methods: One hundred and thirteen women with VIN were reviewed and analyzed. Diagnosis was established by colposcopically directed biopsies whereas treatment was performed by either a surgical or a laser CO_2 approach.

Results: The mean age of all VIN patients was 47.4 years. The most common symptom was pruritus (60.1%). The majority of the lesions were multifocal (N=64, 56.6%) and located in the non-hairy part of the vulva (87.6%).

VIN management consisted of laser CO_2 treatment in 51 patients (45.1%), surgical treatment in 37 (32.7%) whereas 25 VIN_I cases were managed by conventional medical treatment.

The risk of disease relapse was not associated with VIN grade ($p = 0.35$) nor with the treatment modality used ($p = 0.42$).

The risk of disease relapse was significantly higher for multifocal lesions ($p < 0.001$).

Long-term follow-up of our patients showed that four patients (3.5%) developed an invasive vulvar carcinoma.

Conclusion: Our study confirms other reports concerning the diagnostic and treatment difficulties of the management of VIN. Although the benefits of treatment are obvious there seems to be no guarantee that invasion will not occur.

Key words: Vulvar intraepithelial neoplasia (VIN); Laser CO_2; Squamous vulvar carcinoma.

Introduction

Intraepithelial neoplasia of the vulva (VIN) is a disease diagnosed with increasing frequency during the last 20 years [1]. However the understanding of the natural history, aetiology and management of this rarely found condition remains unsatisfactory. Beyond that, the progressive potential of VIN to vulvar carcinoma, although unclear, obviously does occur [2, 3].

The striking increase in the frequency of VIN especially in young women under the age of 35, and the management difficulties arising from the anatomical distribution of the disease, represent problems of considerable significance [4, 5]. The various modes of management, the limited number of treated patients and the insufficient follow-up create a lack of consensus regarding the optimal management of the disease. Independently of the method of treatment applied, recurrence of the disease has been reported in 10-25% of patients [6-9]. The neoplastic potential of VIN to vulvar carcinoma is reported to be about 5% [5, 10-12]. Thus, early diagnosis and proper management of the disease is imperative. The objective of the present study was to examine the clinical features and treatment results of 113 VIN cases who were managed at Alexandra Hospital by the Oncology Unit of the 1st Department of Obstetrics and Gynecology of the University of Athens.

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Materials and Methods

The medical records of 113 women diagnosed histologically with VIN between January 1986 to December 1995 were reviewed and retrospectively analyzed. All these women were seen at the Colposcopy Clinic of Alexandra Hospital, mostly being referred from outpatient clinics of other institutions.

The diagnosis was made by vulvoscopy before and after acetic acid application by recording all abnormal findings. Multiple colposcopically directed biopsies were obtained from all suspicious areas for histologic examination. The diagnosis was made according to the histologic criteria of the International Society for the Study of Vulvar Diseases (ISSVD). All cases noted in association with vulvar invasive carcinoma as well as those who developed invasive disease within two years possibly meaning a "missed invasion", were excluded from the study.

Histological diagnosis of "low grade vulvar intraepithelial neoplasia" (VIN_I) is not always straightforward as that of VIN_{II} and VIN_{III}. Thus VIN_I has to be distinguished from reactive cytological changes which may occur in a variety of vulvar inflammatory disorders. For this reason VIN_{II} and VIN_{III} cases were assessed together in our study. Note that the policy of our Department is to treat these lesions and differentiate them from VINI cases for which there is no consensus for management.

Patient demographic details, clinical findings and symptoms at presentation, together with management and follow-up data were recorded. After histologic confirmation, all patients with VIN_{II} and VIN_{III} were treated by either Laser CO_2 or surgical approach. Patients with VIN_I were treated by a similar approach in cases of well circumscribed, unifocal and colposcopically well defined lesions. Multifocal VIN_I lesions of a diffused pattern, usually HPV-related, with concurrent lower genital tract

intraepithelial lesions were not treated but followed-up every three to six months under the protocol of the Unit.

Laser treatment with the Sharplan 1040 CO_2 Laser, was always performed under colposcopic guidance by using a Zeiss OPMI-1 surgical microscope (f.d.: 300 mm). Treatment was performed by a vaporization, excisional or combination mode.

Thus, non-hairy areas of doubtful significance were vaporized, whereas well defined lesions with abnormal colposcopic findings in terms of acetowhite punctated epithelium, erosions, ulcers or areas with leucoplakia, especially in the hairy part of the vulva were excised. Lesions with a diffused pattern and mixed colposcopic findings were treated with the combination mode, by excising the high risk and vaporizing the lower risk areas. In cases of skinning vulvectomy the technique described by Reid was used [13].

We used the continuous mode by setting the laser beam diameter on 0.5-2 mm and applying power up to 30 watts (power density of 500 w/cm^2). The depth of destruction was individualized, based on the anatomical distribution of the disease. Thus, in non-hairy areas a depth of 2 mm and in hairy areas up to 4 mm including the underlying skin appendages was considered adequate. A normal tissue safety rim of up to 0.5-1 cm surrounding the lesion was obtained where available. VIN lesions including the clitoris and the anal sphincter or canal were preferably managed by laser vaporization.

The aim of surgical excision, when applied, was the local control of the disease, but in two cases a radical vulvectomy with inguinofemoral lymphadenectomy (IFLND) was performed due to suspicion of central lesion invasion and palpable lymph nodes. Local excision, simple vulvectomy and knife skinning vulvectomy with skin grafting were the surgical techniques applied. Local excision was the modality used for unifocal disease with a normal remaining vulva whereas vulvectomy was preferred for extensive, multifocal lesions.

All patients were put on a regular follow-up postoperatively, at 3, 6 and 12 months for the first year and every six months thereafter. Follow-up consisted of colposcopy at the outpatient Colposcopy Unit of Alexandra Hospital.

Relapsing disease was considered as any histogically confirmed VIN lesion found during follow-up surveillance. Any relapse diagnosed after the first year of negative follow-up was considered as recurrent disease whereas persistent non-treated lesions or relapses within the first postoperative year were considered as persistent disease. The statistical analysis of our data was performed using the Student's t-test and χ^2 test.

Results

One hundred and thirteen patients with VIN were available for analysis. Of these cases 49 were VIN_I (43.3%) and 64 were VIN_{II} and VIN_{III} (56.7%).

The mean age of all patients was 47.4 years (49.5 years for VIN_I and 45.2 years for VIN_{II-III}) (Table 1). There was a shift of mean age towards younger ages of disease presentation, between patients presenting in the first five years (1986-1990) and those of the latter five years (1991-1995) for both VIN_I and VIN_{II-III} cases (Table 2).

The clinical appearance of the disease was analyzed based on patient records. Thus the most common presenting symptom was pruritus in 68 patients (60.1%). Twenty-four patients (21.2%) presented with soreness or dyspareunia, 20 with a warty lesion (17.6%), 12 with vaginal discharge (10.6%), and 28 with a vulvar discoloration (24.7%) (Table 1). Thirty-eight patients (33.6%) were asymptomatic, the disease being noticed at the time of a routine colposcopic assessment for abnormal smears. The duration of the symptoms ranged from five to 54 months with a mean of 29 months. The majority of the lesions were multifocal (56.6%) with more than one lesion observed. VIN_I disease was predominantly multifocal (63.3% vs 36.7%) whereas in VIN_{II-III} patients unifocal and multifocal lesions were 48.4% and 51.6%, respectively, (p = 0.21) (Table 1).

The majority of the lesions were located in the non-hairy part of the vulva and that was true in both VIN_I and VIN_{II-III} lesions (89.8% and 70.4%, respectively) (Table 1). Disease location and VIN grading were associated (p = 0.042). VIN_I was predominantly located in the non-hairy part of the vulva, whereas VIN_{II}-VIN_{III} was also found in both hairy and non-hairy parts.

The association between VIN and lower genital tract neoplasia is summarized in Table 3. Cervical neoplasia was the most frequent finding, occurring in 21 patients (18.6%) in terms of CIN in 19 and invasive cervical carcinoma in two patients.

Table 1. — *VIN patient characteristics.*

	VIN_I (n = 49)	VIN_{II-III} (n = 64)	Total (VIN_{I-III}) (n = 113)
Age (years)	26-78	18-80	18-80
Mean	49.5	45.2	47.4
Symptoms n (%)			
Pruritus	27 (55.1%)	41 (64.0%)	68 (60.1%)
Soreness-dyspareunia	10 (20.4%)	14 (21.8%)	24 (21.2%)
Warty lesion	7 (14.2%)	13 (20.3%)	20 (17.6%)
Vaginal discharge	5 (10.2%)	7 (10.9%)	12 (10.6%)
Discoloration	9 (18.3%)	19 (29.6%)	28 (24.7%)
Asymptomatic	18 (36.7%)	20 (31.2%)	38 (33.6%)
Disease distribution n (%)			
Unifocal	18 (36.7%)	31 (48.4%)	49 (43.4%)
Multifocal	31 (63.3%)	33 (51.6%)	64 (56.6%)
Disease location n (%)			
Hairy vulva	2 (4.1%)	9 (14.1%)	11 (9.7%)
Non hairy vulva	44 (89.8%)	45 (70.3%)	99 (87.6%)
Both hairy & non-hairy	3 (6.1%)	10 (15.6%)	13 (11.5%)

Table 2. — *Age distribution at year of disease presentation (years).*

	VIN_I			VIN_{II-III}			Total (VIN_{I-III})		
Year at presentation	No. of patients	Age range	Mean	No. of patients	Age range	Mean	No. of patients	Age range	Mean
1986-1990	18	45-78	56.7	25	23-74	54.2	43	23-78	55.2
1991-1995	31	26-77	45.3	39	18-80	41.9	70	18-80	44.5

Table 3. — *Association between VIN and genital neoplasia.*

	Cervical Neoplasia			
	CIN	Ca Cervix	VaIN	AIN
VIN_I (n = 49)	9 (18.3%)	1 (2.0%)	2 (4.1%)	7 (14.2%)
VIN_{II-III} (n = 64)	10 (15.6%)	1 (1.5%)	2 (3.1%)	7 (10.9%)
Total (VIN_{I-III}) (n = 113)	19 (16.8%)	2 (1.7%)	4 (3.5%)	14 (12.3%)

Intraepithelial neoplasia of the anal and perianal area (AIN) occurred in 14 patients (12.4%) and vaginal intraepithelial neoplasia (VAIN) in four patients (3.5%).

Histological changes associated with human papilloma virus (HPV) were seen in 85 patients (75.2%). Patients in the latter part of the study (1991-1995, No: 70) had a higher prevalence of HPV – positivity (82.9%: 58/70) compared with that of patients in the former part (62.8%: 27/43) (p = 0.016). The mean age of the HPV-associated VIN patients was 46.3 years compared to that of 52.8 years for those without.

There were seven patients with some kind of immunosuppression (two following renal transplantation, four HIV-positive and one with autoimmune disease). All these women had multifocal disease whereas extravulvar genital intraepithelial neoplasia was seen in five cases (71.4%).

Excisional surgical procedures and Laser CO_2 were the primary treatment modalities used in 88 patients (77.8%) whereas the remaining 25 (22.2%) were initially managed by observation and conventional symptomatic medical treatment (topical steroids, lignocaine gel, antifungal therapy or systematic use of antidepressants). It is the policy of our Department to treat all VIN_{II} and VIN_{III} lesions. Treatment of VIN_I was based on the histologic and colposcopic appearance of the lesion. Thus VIN_I cases with a lichen sclerosus or squamous cell hyperplastic histologic pattern and cases with well demarcated colposcopic patterns were treated, whereas patients with mild, usually HPV related or atrophic histologic changes or with diffuse multifocal colposcopic pattern were primarily put under conservative medical management and close observation.

The remaining 88 patients were primarily managed by either Laser CO_2 (51/88: 57.9%) or a surgical excisional approach (37/88: 42.1%) (Table 4).

Vaporization, excision and skinning vulvectomy were the Laser CO_2 modalities applied. Local excision, simple vulvectomy, radical vulvectomy with inguinofemoral lymphadenectomy and knife skinning vulvectomy with grafting were the surgical modalities used (Table 4). In seven cases of the total 38 (18.4%) managed by an excisional conservative mode there was disease involvement on the specimen margins.

Eighty-nine cases (78.7%) were followed-up under the protocol of our Unit whereas the remaining 24 (21.3%) were intermittently assessed. The surveillance period ranged from 60 to 178 months (mean 103.5 months).

Follow-up of our patients revealed 18 cases of persistent (15.9%) and 16 cases of recurrent disease (14.1%) resulting in an overall 30% relapsing rate (34/113) (Table 5). The persistence rate for non-treated (VINI) patients was up to 48% (12/25) compared to 20.8% (5/24) the relapse rate of treated VIN_I (p = 0.046) (Table 6).

The risk of disease relapse was not associated with the grade of VIN and that was true between all VIN_I (34.6%) and VIN_{II-III} (26.5%) patients as well as when only treated VINI patients (20.8%) were compared to VIN_{II-III} patients (26.5%) (p = 0.58) (Table 6).

Considering the treatment modality used it was shown that the risk of relapsing disease for VIN_{II-III} lesions was not associated with different treatment modalities (p = 0.42). The highest relapse rate was observed in the group of VIN_{II-III} patients treated by laser CO_2 (30%: 12/40) compared to the relapse rate of patients treated by surgical excision (20.8%: 5/24) (Table 7).

When treating VIN_I the risk of recurrence did not significantly change with different treatment modalities (18.2% for laser treatment vs 23.1% for surgical treatment (p = 0.77).

Table 4. — *Management of VIN.*

Management	VIN_I (n = 49)	VIN_{II-III} (n = 64)	Total (VIN_{I-III}) (n = 113)
No Treatment	25/49 (51.0%)	–	25/113 (22.1%)
Laser CO_2 treatment	11/49 (22.4%)	40/64 (62.5%)	51/113 (45.1%)
– Vaporization	9 (18.3%)	8 (12.5%)	17 (15.0%)
– Excision	2 (4.1%)	12 (18.7%)	14 (12.3%)
– Combination treatment	–	14 (21.8%)	14 (12.3%)
– Skinning Vulvectomy	–	6 (9.3%)	6 (5.3%)
Surgical treatment	13/49 (26.5%)	24/64 (37.5%)	37/113 (32.7%)
– Local excision	10 (20.4%)	14 (21.8%)	24 (21.2%)
– Simple vulvectomy	3 (6.1%)	5 (7.8%)	8 (7.1%)
– Knife skinning vulvectomy + grafting	–	3 (4.7%)	3 (2.6%)
– Radical vulvectomy	–	2 (3.1%)	2 (1.7%)

Table 5. — *Association between VIN treatment and disease relapses.*

	Treated cases (n = 88)	Non-treated cases (n = 25)	Total (n = 113)
Persistent disease	6 (6.8%)	12 (48.0%)	18 (15.9%)
Recurrent disease	16 (18.2%)	–	16 (14.1%)
Total relapsing disease	22 (25.0%)	12 (48.0%)	34 (30.0%)

Table 6. — *Association of grade of VIN and relapse rates.*

	Relapsing disease	
VIN_I (non treated) (n = 25))	12 (48.0%)	17/49 (34.7%)
VIN_I (treated) (n = 24)	5 (20.8%)	
VIN_{II-III} (treated) (n = 64)	17 (26.6%)	
Total (n = 113)	34 (30.0%)	

Table 7. — *Association of grade of VIN and different treatment relapse rates.*

	Disease relapses								
	No treatment			Laser treatment			Surgical treatment		
	Persistent	Recurrent	Total	Persistent	Recurrent	Total	Persistent	Recurrent	Total
VIN_I	12	–	12/25 (48.0%)	1	1	2/11 (18.2%)	-	3	3/13 (23.1%)
VIN_{II-III}	–	–	–	4	8	12/40 (30.0%)	1	4	5/24 (20.8%)

The association of relapse rate and focal distribution of the disease showed that the risk of relapsing VIN patients with multifocal disease (28/64: 43.8%) was significantly higher than that of patients with unifocal disease (6/49: 12.2%, $p < 0.001$).

Disease relapse on the other hand was not significantly higher in cases of multicentric intraepithelial neoplasia of the cervical (6/21: 28.6%) and vaginal areas (1/4: 25.0%) but was significantly higher when the perianal area was involved (9/14: 64.3%), compared to non-multicentric VIN (18/75: 24.0%, $p = 0.003$).

Marginal status was a major risk factor affecting relapse rate. Thus five out of the seven cases treated by the excisional conservative mode in whom surgical margins were involved, recurred (71.4%) compared to a significantly lower relapse rate of the non-involved cases (10/31: 32.3%, $p = 0.055$).

Management of relapsing VIN was based on the location of the lesion, the grade of the disease and the age of the patients. Thus from 34 relapsing cases (17 VIN_I and 17 VIN_{II-III}), laser CO_2 treatment was applied in ten VIN_I and surgical excision in the remaining 24 cases.

A second intraepithelial disease recurrence was also noted in nine patients (7.9%), six of these being VIN_I and the remaining 3 VIN_{II-III}. Four VIN_I cases were managed by laser CO_2 vaporization and the remaining five by local excision. Long-term follow-up of our patients revealed a third recurrence in five patients (4.4%) who were managed by local excision (Table 8).

Table 8. — *Association of VIN grading between primary and relapsing disease.*

	Relapsing disease								
	1st relapse			2nd relapse			3rd relapse		
	VIN_I	VIN_{II-III}	Total	VIN_I	VIN_{II-III}	Total	VIN_I	VIN_{II-III}	Total
Non treated VIN_I (n = 25)	10	2	12	–	–	–	–	–	–
Treated VIN_I (n = 24)	4	1	5	3	1	4	1	1	2
Treated VIN_{II-III} (n = 64)	5	12	17	3	2	5	2	1	3

On the other hand long-term follow-up showed that four out of 113 (3.5%) initially recruited patients developed invasive vulvar carcinoma (Table 9).

The mean age of these patients at the time of invasive Ca diagnosis was 48.2 years (range 26-65). Invasive vulvar carcinoma was diagnosed within a mean follow-up time of 45.5 months after primary treatment for VIN (range 28-64 months). Three patients had a primary histology showing VIN_{III} and the fourth VIN_I with a lichen sclerosus surrounding the epithelial pattern (Table 9). Thus the invasive potential of VIN_{II-III} lesions (3/64: 4.6%) was greater in our study than that of VIN_I lesions (1/49: 2% ($p = 0.45$).

Two of these cases had multicentric disease with an AIN_3 lesion in one and AIN_3-CIN_3 lesions in the other, respectively. All four cases were primarily recorded as multifocal.

Primary treatment consisted of laser CO_2 in two and local excision in the remaining women. None of the these women was immunosuppressed or had another systemic disease.

Three women were followed-up regularly (every 3-6 months) for the first two years and every 12-18 months thereafter. The fourth patient (case no. 3, A.L.) had two visits at the third and sixth postoperative month and was subsequently lost to follow-up.

All cases were histologically squamous cell carcinomas located in the vulvar area in three cases and in the vulvar-perianal areas in the fourth (case no. 3).

Modified radical vulvectomy with the 3-incisions technique was applied in three cases. The fourth patient (case no. 2) with a large perianal-vulvar lesion was managed

Table 9. — *VIN patients progressing to vulvar carcinoma.*

	Case 1	Case 2	Case 3	Case 4
Initials	Z. V.	E. D.	A. L.	I. L.
Primary histology	Lichen sclerosus-VIN_I	VIN_{III}-AIN_{III}	VIN_{III}-CIN_{III}-AIN_{III}	Lichen sclerosus-VIN_{III}
Age	59	26	43	65
Primary treatment	No treatment	Laser CO_2, skinning vulvectomy	Local excision	Local excision
Secondary treatment	Laser vaporization	–	–	Hemivulvectomy + ipsilateral IFLND
Follow-up	- Regular x 36 ms - Intermittently thereafter	- Regular x 20 ms - Intermittently thereafter	- Regular x 6 ms - Lost thereafter	Regular
Timing of invasive Ca diagnosis	49 ms	64 ms	28 ms	46 ms
Histology of invasive disease	Squamous Ca Grade II	Squamous Ca (warty) Grade I	Squamous Ca Grade I	Squamous Ca Grade III
Management of invasive disease	Radical Vulvectomy + IFLND	- Preoperative RT (interstitial) - Radical Vulvectomy + IFLND	Radical Vulvectomy + IFLND	Radical Vulvectomy + IFLND
Follow-up	27 ms	6 ms	26 ms	31 ms
Outcome	Alive-NED	Alive-NED	Alive-NED	Alive W.D. (Local recurrence re-excised)

* IFLND = Inguinofemoral lymph-node dissection; ** NED = No evidence of disease; *** WD = With disease.

with preoperative radiation treatment and subsequently underwent radical vulvectomy with the 3-incisions technique [14]. Bilateral inguinofemoral lymphadenectomy was also performed and in all cases lymph nodes were negative for metastatic disease.

All four patients were alive after a mean follow-up period of 22.5 months (range 6-31 months). Three of them have no evidence of disease and the fourth one suffered a local recurrence amenable to re-excision.

Discussion

Vulvar intraepithelial neoplasia (VIN) is a disease seen with increasing frequency. Although the progressive potential of the disease from VIN_I through VIN_{III} to invasive squamous cell carcinoma has not been clearly demonstrated, it is obvious that it does occur [1]. There is a lack of satisfactory prospective studies which would elucidate the natural process of this disease. The retrospective nature of our study does not allow firm statements, nevertheless the relatively large number of cases analyzed and the close and effective follow-up, helped us to draw some conclusions.

The marked increase in the incidence of VIN reported in other studies was also confirmed by ours [2, 5, 6, 10]. There was a 23.8% increase of VIN reported cases in the latter part of our study compared to the former one (70 cases vs 43) and that was seen in both VIN_I and VIN_{II-III} patients. This absolute increase in the incidence of the disease was accompanied by a shift of the mean age at presentation towards younger ages. It has been reported that from a mean age at presentation of 52.7 years before 1980, a fall to 35.8 years has been recently observed [5]. That shift towards younger age was also confirmed in our study for both VIN_I and VIN_{II-III} patients with no significant variation between these two groups.

Diagnosis of VIN is often difficult since the overwhelming majority of women will be asymptomatic or have non specific symptoms [1]. A total of 38 patients (33.6%) in our study were asymptomatic whereas symptoms like pruritus, soreness or dyspareunia and vaginal discharge were non specific, with the suspicion arising only by colposcopic inspection of the vulva. Only patients with a warty lesion (17.6%) or a vulvar discoloration (24.7%) were considered as highly suspicious.

A thorough colposcopic assessment of the entire lower genital tract in women with a known history of the HPV infection, preinvasive or invasive genital disease, is necessary to identify a multicentric disease [1, 10]. The recorded high prevalence of multifocal disease in our study (56.6%) may reflect an increase in the recognition of HPV-infection related changes and a true increase in HPV incidence which is also reported in some other studies [15].

The association between VIN and anogenital neoplasia in our cases confirms the findings of others and emphasizes the importance of careful examination of the vulva as well as during follow-up of women with such history [5].

Management of vulvar intraepithelial neoplasia represents a great challenge of current gynecologic practice. Radical surgical procedures especially when performed on younger patients are today considered as overtreatment, resulting in considerable psychological distress without ensuring a better local control [6, 14]. The ultimate goal of treatment is to provide effective disease control, preserving the same functionality of the vulva. Thus minimally invasive therapeutic techniques are generally recommended for VIN since they provide adequate effectiveness and minimal morbidity for the patient [6-8, 16-18].

Wide local excision and laser CO_2 therapy are the most popular modalities used under proper circumstances. Wide local excision allows for adequate removal of the lesion and thorough histopathologic examination to exclude the presence of occult invasive carcinoma. The major drawback of this conventional approach is that it is not performed under colposcopic guidance. Thus despite the removal of up to 1 cm of normal-appearing surrounding skin and mucosa, the margins will be involved with intraepithelial neoplasia. The recurrence rate of VIN under these circumstances has been reported as high as 50% [1].

On the other hand the CO_2 laser is also effective in eradicating VIN when properly utilized. The effectiveness of this approach in treating both unifocal and multifocal lesions has been reported by many authors [7, 16, 19]. The fact that laser CO_2 treatment is always performed under colposcopic guidance and the excellent aesthetic result with no compromise of the anatomic integrity of the vulva, represent the advantages of laser CO_2 treatment [1].

Although the carbon dioxide laser has been proven successful for lesions involving the clitoris and the perianal area, the eradication of disease involving hairy surfaces was reported to be poor [16, 19].

In our Department, both methods are equally applied for treatment of VIN. There is a trend to use laser CO_2 especially for multifocal lesions involving the clitoris or perianal area. Histologic examination by multiple biopsies is always a prerequisite if laser vaporization is the modality chosen. High expertise in laser surgery is also an absolute prerequisite if that form of treatment is chosen [1].

Laser CO_2 treatment was applied in our study for any VIN lesions irrespective of extension, focality or increased probability for invasion. Among our patients Laser CO_2 and surgical treatment were proven equally effective to control VIN_I lesions with no significant difference in recurrence rates ($p = 0.77$).

When treating VIN_{II-III} lesions, laser CO_2 was proven less effective than surgical treatment but this difference was not statistically significant (30.0% vs 20.8% relapsing rates, $p = 0.42$). Considering the role of different factors that could influence the effectiveness of treatment it has been shown that focal and geographic distribution of the disease as well as the marginal status of the excised VIN area, affect relapse rates [1, 19].

Multifocal lesions were more likely to recur in our study (28/64 = 43.7%) than unifocal (6/49 = 12.2%) ($p < 0.001$) confirming results of other studies [1].

It is generally accepted that widespread disease is the most demanding to manage. It has been shown that irrespective of the method of treatment used these patients will experience considerable morbidity, a compromising vulvar function and a high recurrence rate [1, 10]. On the other hand multicentric disease was proven in our study to have a significantly higher recurrence rate only when the perianal area was involved (9/14: 64.3%) compared to non-multicentric VIN (18/75: 24.0%), (p = 0.003).

It is generally accepted that excision either by cold knife or Laser CO_2 provides increased security in terms of completeness or removal of the lesion and exclusion of early invasive disease [5]. The assessment of resection margins seems to be important, affecting the relapse rate [1]. Intraopeartive assessments of the marginal status by frozen sections were not performed in our study. All patients chosen to be managed by excisional treatment had a colposcopic assessment either intraoperatively for laser treatment or preoperatively for cold knife procedures. By delineating the margins and removing of up to 1 cm of normal-appearing surrounding skin, there was no evidence of disease noted along the edges of the removed specimen except in seven cases. Recurrence rate of these cases was as high as 71.4% (5/7) compared to the 32.2% rate of the "non-involved" cases (10/31) (p = 0.055).

The neoplastic potential of VIN has not been clearly determined since the reported progression rates to invasive vulvar cancer do not reflect the true natural history of the lesion, because most studies reported the outcome after treatment [5]. Our study confirms previous reports and development of invasive carcinoma from our treated cases (3.5%) is within the reported range of 3-5% [1, 3, 5, 10]. It is thus reasonable to assume that the invasive potential of VIN_{III} in untreated patients is high and seems greater that that of CIN_{III} [11]. What has also been shown from our series is that VIN_{II-III} lesions have a greater invasive potential (3/64 = 4.6%) that VIN_{I} (1/49 = 2.0%) (p = 0.45).

Close follow-up of VIN patients who have been treated is essential for earlier diagnosis of disease recurrence and the development of invasive carcinoma. This follow-up should be long-term since progression to invasive disease occurred within a time interval varying from two to eight years [5, 20]. In our study we found that the mean time between VIN diagnosis and development of invasive disease was 45.5 months.

Although the retrospective nature of our study does not allow us to consider these results as proof, the relative large number of the patients involved and the close follow-up helped us to draw some useful conclusions.

Vulvar intraepithelial neoplasia represents a heterogeneous disease with diagnostic and management difficulties. The treatment modality to be chosen should depend on the location, the size of the lesion and the physician's expertise. Whatever therapeutic approach is chosen, preservation of the anatomic integrity and function of the vulva is of paramount importance. Eventually close surveillance of VIN patients by colposcopy and histology, on a long-term basis is necessary to prevent the development of invasive vulvar cancer.

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