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CO_2 laser vaporization for the treatment of vaginal intraepithelial neoplasia: effectiveness and predictive factors for recurrence

E. Piovano[1], C. Macchi[1], L. Attamante[1], L. Fuso[2], G. Maina[3], L. Pasero[3], R. Volante[3], P. Zola[1]

[1] Gynecological Oncology Unit, Department of Surgical Sciences, University of Turin, Sant'Anna Hospital, Turin
[2] Gynecology and Obstetrics, AO Mauriziano Umberto I, Turin
[3] SSCVD Colposcopy and Laser Surgery, A.O.U. Sant'Anna Hospital, Turin (Italy)

Summary

Objective: To evaluate the outcome of vaginal intraepithelial neoplasia (VaIN) treatment with CO_2 laser vaporization in terms of local recurrence and progression to vaginal carcinoma. Additionally, the authors investigated the predictive factors for first recurrence. *Materials and Methods:* The medical records of all patients treated for VaIN with CO_2 laser vaporization at Sant'Anna Hospital in Turin (1995-2012), were retrospectively reviewed. A univariate logistic model was applied to evaluate selected clinical features as predictive factors for recurrence. A multivariate logistic regression analysis was then carried out including significant risk factors after univariate analysis ($p < 0.05$). *Results:* The analysis included 285 out of 302 patients. Seventy-one (25%) women relapsed; of these 24 VaIN 1 (22%), 37 VaIN 2 (27%), and ten VaIN 3 (26%). The median time to the first recurrence was 5.2 months (1.4−127.8) for VaIN 1, 6.6 months (1−85.2) for VaIN 2, and 3.6 months (1.2−62) for VaIN 3. Sixty-one out of 71 patients were retreated with CO_2 laser vaporization. At the last follow-up visit, 273 (96%) women were free from VaIN. No patients progressed to vaginal carcinoma. The multivariate model showed a higher risk of VaIN recurrence in the case of previous hysterectomy (HR 3.3, 95% CI 1.7−6.3, $p < 0.001$) and concomitant H-SIL on the Pap smear (HR 1.9, 95% CI 1.2−3.1, $p = 0.008$). *Conclusion:* CO_2 laser vaporization is an effective low impact treatment for VaIN. Despite this, VaIN recur, in particular in cases of previous hysterectomy and concomitant H-SIL on the Pap smear. An intensive follow-up is proposed for women with a high risk of VaIN relapse.

Key words: CO_2 laser vaporization; Predictive factors; Relapses; Vaginal intraepithelial neoplasia.

Introduction

The vaginal intraepithelial neoplasia (VaIN) was first reported by Hummer in 1933 as "squamous cell atypia without stromal invasion" [1]. VaIN represents 0.4−1% [2, 3] of all intraepithelial neoplasias of the lower genital tract with an incidence of 0.2−0.3 new cases out of 100,000 women per year [3]. The incidence of VaIN is higher among patients aged 40 to 61 years [4], and recent data suggest an increasing incidence in patients aged 30-35 years [4, 5].

Human papillomavirus (HPV) plays a critical role in the development of anogenital neoplasia and has been found in 93.6−98.8% [6, 7] of VaIN cases. Other risk factors for VaIN are a history of hysterectomy [8-10], diagnosis of cervical intraepithelial neoplasia (CIN) or vulvar intraepithelial neoplasia (VIN) [6-9], previous pelvic radiotherapy [11], immunosuppression [12], and smoking [13].

VaIN most commonly affects the upper third of the vagina [3, 4] and lesions are often multifocal [2, 10, 14]. Since most cases are characterized by asymptomatic disease, the diagnosis is often driven accidentally by a Pap smear [4, 7] or during a colposcopy performed for other reasons. The biopsy of all colposcopic abnormalities is, however, mandatory to confirm the presence of VaIN and to map its extension.

The increasing incidence of VaIN, especially in young women, the frequent relapses of VaIN after treatment (10−42%) [5], and the desire to maintain sexual function have prompted gynecologists to identify new ways of treating this disease, in order to balance radical treatment and the incidence of complications. For these reasons, treatment has changed from upper or total vaginectomy along with hysterectomy to a more conservative and tailored procedure, related to the clinical, morphological and topographical features of the lesion [16]. As far as the excisional procedures are concerned, options include wide local excision (WLE) with a combination of sharp and gauze dissection, a loop electrosurgical excision procedure (LEEP), cold knife excision, and CO_2 laser excision. In addition, we must also consider ablative treatments (electrosurgery, cryotherapy, CO_2 laser vaporization and cavitational ultrasonic surgical aspiration [CUSA]), medical therapies (with 5-fluorouracil (5-FU), imiquimod or trichloroacetic acid), and brachytherapy.

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CO_2 laser vaporization can be considered an excisional and ablative technique. It is easy to repeat if needed, with few side effects, high precision, and a minimal impact on psychological and sexual function [2, 17, 18]. Hoffman *et al.* [19] described this technique, reporting a mean operative time of 42 minutes, with five ml of blood loss and an 8% complication rate. Benedet *et al.* [20] analyzed some biopsies from patients with VaIN and found epithelial involvement from 0.1 mm to 1.4 mm in thickness; epithelial destruction to a depth of 1.5 mm should therefore be sufficient to destroy the VaIN-containing epithelium without damaging the normal surrounding structures. Surgical specimens, however, are not available after CO_2 laser vaporization, the equipment is very expensive, and a long training period is needed for the operator [21].

The aim of this study was to review a large cohort of patients with VAIN treated with CO_2 laser vaporization in the present institution and to evaluate the outcome of this treatment in terms of local recurrence and the rate of progression to vaginal carcinoma. Additionally, the authors attempted to investigate the predictive factors for the first recurrence of VaIN.

Materials and Methods

A retrospective review of the medical records of all patients treated for VaIN with CO_2 laser vaporization at the Colposcopy and Laser Surgery unit at Sant'Anna Hospital of Turin, between 1995 and 2012 was performed. All patients included in the analysis had a histological confirmation of VaIN (after cytology and colposcopy examination) and at least three months of follow-up.

Patient data were collected from colposcopic registers and hospital records. For each woman, the authors have reported the age and parity at first diagnosis, the result of the colposcopic examination, grade and site of the lesion, association with CIN or VIN, HPV cytopathic effect, state of immunosuppression, previous hysterectomy, the date of treatment, the first and other recurrences, the grade of recurrence, and other vaginal therapies. In cases of multiple simultaneous lesions of different grades, the authors considered the worst grade.

The extent of the vaginal lesion was determined by a colposcopic examination after application of 3% acetic acid and Lugol iodine to the vaginal mucosa. The authors used a satinized metal speculum to prevent laser reflection, linked to a suction system of developed gas. Laser vaporization was performed without anesthesia at 25−43 Watts of power, until a depth of 1.5−2 mm. The beam size was two to three mm, with a continuous energy distribution. The mean operation time was ten minutes and the patients were discharged on the same day. VaIN 1 was treated if it persisted for at least two rounds, while VaIN 2 and 3 were treated at the first diagnosis.

A univariate logistic model was applied to evaluate the potential of a number of clinical features as predictive factors for the first recurrence of VaIN: age at first diagnosis, HPV cytopathic effect, grade of VaIN, the result of the Pap smear performed when VaIN was diagnosed, vaginal vault location, association with CIN or VIN and previous hysterectomy. A multivariate logistic regression analysis was then fitted including significant risk factors after univariate analysis. A variable was considered prognostically significant when the p-value was < 0.05. All statistical analyses were carried out using SPSS version 17.

This study was approved by the local ethical committee. Data processing, the formulation of any epidemiological analysis, and the prognostic correlation between biological and clinical data was strictly anonymous.

Table 1. — *Patient features.*

Median age (years)	38 (14-76)	
Grade of vaIN	VaIN 1	110 (38.6%)
	VaIN 2	136 (47.7%)
	VaIN 3	39 (13.7%)
Parity	Nulliparous	102 (35.8%)
	1 child	41 (14.4%)
	≥ 2 children	36 (12.6%)
	Unknown	106 (37.2%)
Location	Right vaginal wall	54 (18.9%)
	Left vaginal wall	22 (7.7%)
	Ant-post vaginal wall	11 (3.9%)
	Fornix	72 (25.3%)
	Vaginal vault	5 (1.8%)
	Multiple	121 (42.4%)
Colposcopy	Aceto-white epithelium	238 (83.5%)
	Punctation	6 (2.1%)
	Mosaic	2 (0.7%)
	Condylomatosis	9 (3.2%)
	Multiple	23 (8.2%)
	Various	5 (1.8%)
CIN association	CIN 1	33 (11.6%)
	CIN 2	36 (12.6%)
	CIN 3	14 (4.9%)
	Total	83 (29.1%)
VIN association	VIN 1	2 (0.7%)
	VIN 2	4 (1.4%)
	VIN 3	3 (1.1%)
	Total	9 (3.2%)
HPV cytopathic effect		38 (13.3%)
Pap smear performed at vaIN diagnosis	ASCUS	12 (4.2%)
	ASC-H	1 (0.4%)
	L-SIL	151 (53%)
	H-SIL	83 (22.1%)
	Negative	26 (9.1%)
	Inadequate	26 (4.2%)
Immunosuppression*		10 (3.5%)
Previous hysterectomy	Benign disease	9 (3.2%)
	Malign disease	6 (2.1%)
	Unknown	3 (1.1%)
	Total	18 (6.3%)

*One patient had a selective immunoglobulin A (IgA) deficiency (SIGAD), one patient had acute myeloid leukemia (AML) treated with chemotherapy drugs, six patients underwent immunosuppressive therapy for autoimmune diseases, and two patients underwent immunosuppressive therapy to avoid rejection after organ transplantation.
VaIN: vaginal intraepithelial lesion; Ant: anterior; post: posterior; CIN: cervical intraepithelial lesion; VIN: vulvar intraepithelial lesion; HPV: human papillomavirus; ASCUS: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion; L-SIL: low grade squamous intraepithelial lesion; H-SIL: high grade squamous intraepithelial lesion.

Table 2. — *Median time to first recurrence of VaIN and concordance of VaIN grade at diagnosis and VaIN grade at first recurrence.*

Grade of lesion at first diagnosis	Median time at first recurrence (months)	Grade of lesion at first relapse			
		Concordant	Superior	Inferior	Total
VaIN 1	5.2 (1.4−127.8)	18	6	\	24
VaIN 2	6.6 (1−85.2)	22	\	15	37
VaIN 3	3.6 (1.2−62)	3	\	7	10
Total	6.0 (1−127.8)	43	6	22	71

VaIN: vaginal intraepithelial lesion.

Results

From 1995 to 2012, 302 women were diagnosed with VaIN in the present unit. Among them, 285 women were included in the study according to the inclusion criteria (11 patients were excluded because of a follow-up shorter than three months, VaIN regressed spontaneously in four patients, one woman was treated with LEEP, and another patient was treated with topical 5-FU followed by radiotherapy). Patient features are summarized in Table 1.

The median age at VaIN diagnosis was 38 years (14−76). Most cases of VaIN were low or intermediate grade: 110 (38.6%) VaIN 1 , 136 (47.7%) VaIN 2 , with only 39 (13.7%) cases of VaIN 3. The median age for women with VaIN 1 was 35 years (14−64), 38 years (22−76) for VaIN 2, and 43 years (22−70) for VaIN 3. This difference, however, was not statistically significant ($p = 0.10$).

Association with CIN was found in 83 (29.1%) women; among them, 16 had a previous diagnosis of CIN, while 67 had diagnosis of CIN concomitant to VaIN diagnosis. Association with VIN was found in nine women (3.2%), while an association with both CIN and VIN was confirmed in only one woman (0.4%), who had concomitant VaIN 2, CIN 2, and VIN 3.

Eighteen women (6.3%) had a history of hysterectomy. The median time between uterine surgery and VaIN laser treatment was 219 months (3.1−365.7); in particular, women who underwent hysterectomy for benign disease developed VaIN after a median time of 135 months (4.6−365.7), while in women who underwent hysterectomy for malignant disease, the median time to VaIN was reduced to 62 months (3.1−280.4) ($p = 0.76$). Median follow-up time was 58 months (3−204).

Among the 285 women affected by VaIN, 71 (25%) relapsed; in particular, 24 (22%) VaIN, 37 (27%) VaIN 2, and ten (26%) VaIN 3 recurred. Eighteen (75%) cases of VaIN 1, 22 (59%) VaIN 2, and three (30%) VaIN 3 relapsed with the same grade of previous lesion; six (25%) VaIN 1 and no VaIN 2 relapsed with a superior grade; 15 (40.5%) VaIN 2 and seven (70%) VaIN 3 relapsed with an inferior grade compared to the initial lesion. The median time to the first recur-

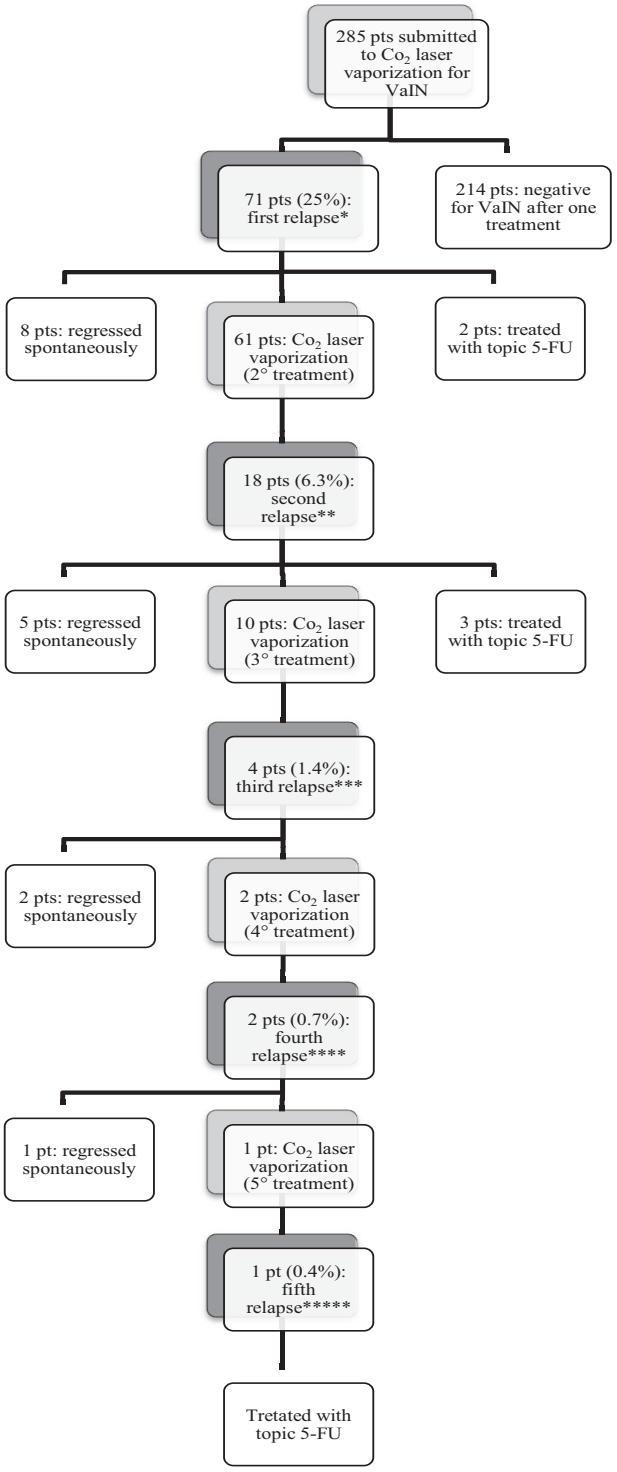

Figure 1. — VaIN relapses in the present series and their treatments. Multiple relapses of VaIN occurred in this series, but they were successfully retreated.

* According to the original VaIN grade: 24 (22%) VaIN 1, 37 (27%) VaIN 2 and 10 (26%) VaIN 3. ** According to the original VaIN grade: 6 (5.5%) VaIN 1, 8 (5.9%) VaIN 2 and 4 (10.3 %) VaIN 3. *** According to the original VaIN grade: 2 (1.8%) VaIN 1, 1 (0.7%) VaIN 2 and 1 (2.6%) VaIN 3.
**** According to the original VaIN grade: 1 (0.9%) VaIN 1 and 1 (0.7%)VaIN 2. ***** According to the original VaIN grade: 1 (0.7%) VaIN 2. VaIN: vaginal intraepithelial neoplasia; Pt: patients; 5-FU: 5-fluorouracil.

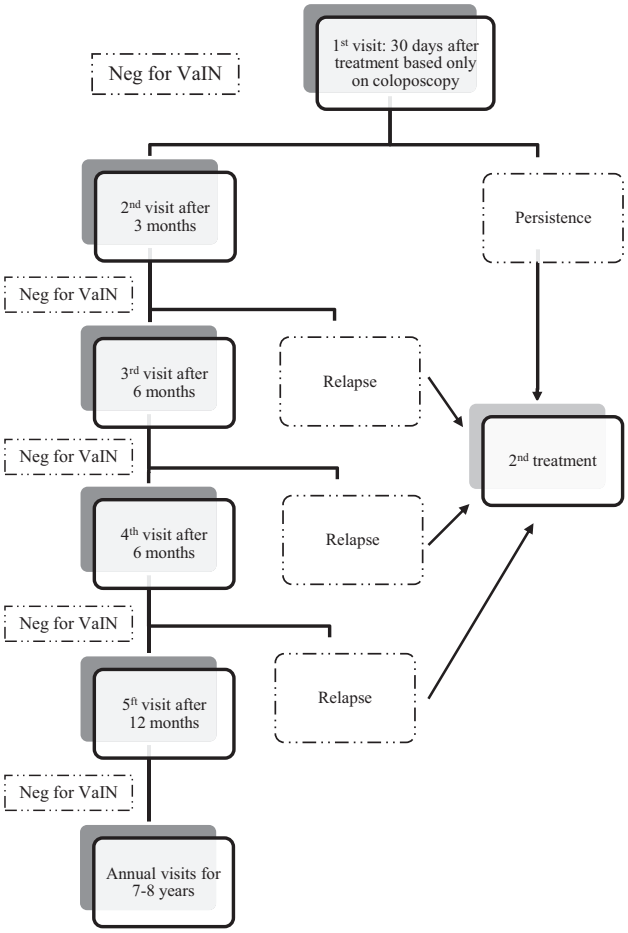

Figure 2. — Algorithm of follow-up for the patients with VaIN treated with CO_2 laser vaporization with a high risk of recurrence. VaIN: vaginal intraepithelial neoplasia; Neg: negative.

rence was six months (5.2 months if lesion at first diagnosis was VaIN 1, 6.6 months for VaIN 2, and 3.6 months for VaIN 3) (Table 2). Figure 1 reports the features of multiple recurrences in the present series and their treatment. At the last follow-up visit, 273 (96%) women were free from VaIN and no patients progressed to invasive vaginal carcinoma.

In the univariate logistic model, VaIN grade 2-3 (versus grade 1) (HR 1.3, 95% CI 0.8−2.1, $p = 0.4$), CIN-VaIN association (HR 1.4, 95% CI 0.8−2.3, $p = 0.3$), and VIN-VaIN association (HR 2.1, 95% CI 0.8−5.6, $p = 0.2$) were not statistically significant predictive factors for recurrence of VaIN. Vaginal vault site (versus other sites) (HR 4.2, 95% CI 1.5−11.8, $p = 0.006$), high grade squamous intraepithelial lesion (H-SIL) on the Pap smear (versus other results) (HR 1.7, 95% CI 1.1−2.8, $p = 0.03$), and previous hysterectomy (HR 3.4, 95% CI 1.8−6.5, $p < 0.001$) proved to be statistically associated with an increased risk of VaIN recurrence (age ≥ 38 years *vs.* < 38 years) (HR 1.7, 95% CI 1.0−2.8, $p = 0.05$) and the HPV cytopathic effect (HR 1.7, 95% CI 1.0−3.1, $p = 0.05$) suggested a trend for higher risk of VaIN recurrence.

The multivariate model confirmed a higher risk of VaIN recurrence only in cases of previous hysterectomy (HR 3.3, 95% CI 1.7−6.3, $p < 0.001$) and concomitant H-SIL on the Pap smear (HR 1.9, 95% CI 1.2−3.1, $p = 0.008$).

Discussion

Patient and lesion features drive treatment in patients affected by VaIN [16]. In particular, the topography of VaIN, the size, the presence of an erosion area, grading, multifocality, the association with CIN and VIN, and the opportunity to evaluate by colposcopy the extension of the lesion are the main factors to be taken into account [21]. In the case of a single lesion not situated on the vaginal vault and completely visualized during colposcopy, the best treatment is CO_2 laser vaporization, with few complications and the possibility of repeated treatment [2]. Yalcin *et al.* [22] reported no intraoperative or early post-operative complications in 24 women treated with CO_2 laser vaporization; only one case of stricture of the upper vagina after multiple rounds of laser treatment was observed. In the case of a single lesion situated on the vaginal vault or not completely visualized during the colposcopy, laser surgery has demonstrated a higher failure rate, therefore an excisional technique or topical 5-FU application are the best choices [23]. 5-FU is useful in the case of multiple lesions and in the case of lesions which are difficult to reach and after radiotherapy [14].

The age of the patient, co-morbidities, the desire to preserve sexual function, and previous vaginal therapies have to be taken into account in the choice of VaIN therapy. In sexually active young women, minimally invasive and repeatable techniques, like CO_2 laser vaporization or topic application of 5-FU, would be the best first choice. In the case of persistence or multiple recurrence of VaIN, more aggressive techniques such excisional therapy should be considered. For older women, however, the literature suggests direct excisional therapy or radiotherapy [21].

In the present authors' experience, CO_2 laser vaporization has proven to be an effective technique: 75% of women were free from VaIN after the first application and 93% after the second treatment. This study confirms data from a previous study [24] that reported a global effectiveness of 94.4% for CO_2 laser vaporization in 36 patients treated for VaIN (all grades). Among the present patients, none progressed to vaginal carcinoma, similar to studies by Massad *et al.* [23] and Zeligs *et al.* [25]. In the present series, VaIN 3 (which progresses more frequently to vaginal carcinoma [2, 19]) was less frequent than VaIN 1 and 2, and the patients were closely followed up. Moreover, most vaginal cancers occur in elderly women, with the peak incidence during the sixth and seventh decades (older than the mean age of this series), and less than 10% of these tumors are diagnosed in patients less than 40 years of age [26]. These reasons seem to explain the lack of progression to invasive vaginal cancer in the present study. One out of four of the

present patients relapsed; this is consistent with the literature showing a global recurrence rate of 20-40% [17, 18, 21].

The median age of women with VaIN in the present study (38 years, range 14-76) was lower compared to the literature (range 40-61 years) [4, 27], and the authors suggest a trend of a higher risk of VaIN recurrence in women aged ≥ 38 (HR 1.7, 95% CI 1.0−2.8, $p = 0.05$).

Most authors suggest that patients with low grade lesions should be followed up because most of these lesions regress spontaneously [14]; however, other authors affirm that this practice is not safe, because of the frequent association of these lesions with high risk HPV infection [28]. Patients with high grade VaIN must always be treated [1, 14, 29] because a high risk of progression to invasive vaginal cancer has been observed (20% without treatment within three years [2] and 8-11.5% after treatment [14, 19]). In the present unit, the authors treated low grade lesions persisting for at least two rounds and high grade lesions at the first diagnosis.

In contrast to the results of a study by Hoffman *et al.* [19] (recurrence rate of 42% for high grade VaIN), more recent studies have supported the use of CO_2 laser vaporization for the treatment of high grade VaIN, reporting a long term relapse rate of 20-30%, especially for multifocal lesions [17, 18]. These data are consistent with the present study, with a recurrence rate for VaIN 2-3 of 26.9%.

The median time for the first recurrence after treatment of VaIN 3 was 3.6 months *vs.* 5.2 months after VaIN 1 (Table 2): this difference was not statistically significant (HR 1.1, 95% CI 0.5−2.2, $p = 0.8$). Most of VaIN 1 (75%) and VaIN 2 (59%) cases relapsed with the same grade of the initial lesion; most VaIN 3 (70%) cases relapsed with an inferior grade compared to the previous lesion, and no VaIN progressed to invasive vaginal carcinoma. Therefore, the present authors observed early but indolent relapses after CO_2 laser therapy; hence women should be clearly informed and offered a careful follow-up.

When the lesion is localized on the vaginal vault scar or hidden in the recess of its angles, it is difficult to reach with CO_2 laser vaporization or other ablative techniques; therefore, excisional treatment is suggested [21, 30]. As shown in Table 1, the present authors treated five lesions localized on the vaginal vault: they were single, completely visualized during colposcopy, and not within the vaginal vault scar. By stratifying the present patients according to the different site of the lesion, a statistically significant difference in the risk of recurrence was not found ($p = 0.9$), nor was stratifying the patients according to lesions in the upper third of the vagina versus other sites, as analyzed by Dodge *et al.* [5]. Comparing VaIN on the vaginal vault post hysterectomy versus other sites, the present authors noted that lesions on the vaginal vault had a higher risk of recurrence (HR: 4.2, 95% CI 1.5−11.8, $p = 0.006$), confirming that CO_2 laser vaporization on the vault is not an effective treatment.

Regarding the association of VaIN with cervical or VIN, the literature reports a VaIN-CIN association in 37-65% of patients [4, 5], a VaIN-VIN association in 10% of patients [10], and a CIN-VIN-VaIN association in 9% of patients [5]. In the present study, the association of VaIN with CIN and VIN was lower (29.1% and 3.2% of patients, respectively) and only one patient (0.4%) had concomitant CIN-VIN-VaIN. The presence of intraepithelial lesions in at least two different sites of the lower genital tract (vagina, cervix, vulva, and anus) is called lower genital tract syndrome. While this syndrome is considered an important risk factor for the development of VaIN relapses [5, 15], the presence of concomitant single CIN or VIN is not considered a significant risk factor for VaIN recurrence [5, 15, 22]. The present study reports an association with CIN in 20.5% of VaIN relapses and an association with VIN in 44.4%, confirming that single CIN or VIN association is not a statistically significant factor for VaIN recurrence (CIN: HR 1.4, 95% CI 0.8−2.3, p=0.3; VIN: HR 2.1, 95% CI 0.8−5.6, $p = 0.2$).

Cervical cytology performed differently if compared to cervical histology, with H-SIL as a statistically significant factor for VaIN relapse. Out of 83 patients with VaIN and concomitant H-SIL on the Pap smear, 29 (34.9%) developed a VaIN relapse, versus 41 (21.6%) relapses among 190 patients with other Pap smear results (ASCUS, ASC-H, L-SIL, and negative) (HR 1.7, 95% CI 1.1−2.8, $p = 0.03$). H-SIL on the Pap smear may have arisen directly from high grade VaIN in vaginal cells collected by the Pap smear, without the involvement of any cervical cells.

Finally, the present authors examined the role of previous hysterectomy. As is known, this is an important risk factor for the development of VaIN, especially in the case of hysterectomy performed for CIN or cervical carcinoma with a rate of VaIN diagnosis of 4-55% [9]. For this reason, some authors suggest these patients should have cytology and colposcopy included in their follow-up [15]. The data regarding VaIN after hysterectomy for benign disease are very contrasting [8]. In the present study, 18/285 patients (6.3%) with VaIN had a history of hysterectomy, and 11 of them (61.1%) relapsed (HR 3.4, 95% CI 1.8−6.5, $p < 0.001$). The present numbers were too small to stratify the data in terms of the indication for the previous hysterectomy. However, the multivariate model confirmed the role of two negative predictive factors for the recurrence of VaIN: previous hysterectomy (HR 3.3, CI 1.7−6.3, $p < 0.001$) and concomitant H-SIL on the Pap smear (HR 1.9, 95% CI 1.2−3.1, $p = 0.008$).

Some limitations of the present study include its retrospective and monocentric nature and the lack of some data regarding the demographic features of women (i.e. parity). Moreover, the authors analyzed HPV co-infection only by the observation of cytopathic effects and not by an HPV DNA test.

The strengths of the present study include the large number of patients with VaIN treated with a standardized technique by the same experts (R.V., L.P. and G.M.) and a long median time of follow-up, i.e. 58 months.

Figure 2 provides a suggestion for the scheduled follow-up for women with a high risk of VaIN relapse. A colposcopy should be performed 30 days after treatment, followed by scheduled visits (including colposcopy, cytology, and eventually histology) after three months, then every six months, and then annual visits. Based on the present data, recurrences could occur after a long period of time (127.8 months), therefore the present authors consider it worthwhile to continue follow-up until ten years after treatment.

The present data suggest that CO_2 laser vaporization can be used successfully as a low impact treatment for high and low grade VaIN completely visualized by colposcopy. Careful counseling regarding frequent VaIN relapses and long-term follow-up are needed for these patients because VaIN often recurs, especially in women with a history of hysterectomy or concomitant H-SIL on the Pap smear. The first recurrence could occur quite early, and multiple sequential relapses could also occur, but most of them can be successfully retreated with laser.

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Address reprint requests to:
C. MACCHI, M.D.
Via Ventimiglia, 3
10126 Turin (Italy)
e-mail: chia.macchi@gmail.com