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Original Research

LaserCo$_2$ role in the treatment of vaginal intrepithelial neoplasia (VAIN) retrospective study involving 587 patients

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Summary

Aim of the Study: To evaluate the presentation features of intraepithelial vaginal neoplasia, the clinical outcome in LaserCO$_2$ vaporization treated patients, the therapeutic results, the procedure-associated complications, and the risk factors for recurrence. *Materials and Methods:* This was a retrospective study of 587 consecutive patients diagnosed with vaginal intraepithelial neoplasia (VAIN) and treated by laserCO$_2$ vaporization at Spedali Civili of Brescia between January 1990 and June 2018. All the patients underwent cytological and colposcopic follow-up. Recurrences were evaluated in terms of clinical features and association with risk factors. Chi-Square was used to establish the correlation between the two groups. *Results:* Mean age was 40.9 years. Most lesions were localized at the vaginal superior third (94.4%), 55.3% were multifocal, and 49.5% were associated with synchronous intraepithelial cervical neoplasia (CIN). In 8% of cases, VAIN affected the vaginal vault in hysterectomized patients. In 84,4% among the 282 evaluable cases, a vaginal swab was positive for HPV. HR-HPV was more frequent in high-grade lesions. No intraoperative complications were registered and the treatment was well tolerated. Follow-up was available for 428 patients with a mean duration of 56 months. Complete regression of VAIN after treatment was 85.3% with a recurrence rate of 14.7%. HR-HPV has been identified as a significant risk factor for recurrence. *Conclusions:* LaserCO$_2$ vaporization is a safe, low impact, and effective technique for VAIN therapy with a high success rate. HR-HPV must be considered an independent risk factor for recurrence.

Key words: Vaginal intraepithelial neoplasia; Laser vaporization; Human papillomavirus; Colposcopy.

Introduction

Intraepithelial vaginal neoplasms (VAIN) are a rare disease, which represents 0.5% of all intraepithelial neoplasia of the lower female genital tract [1-4]. It affects women from 40 to 50 years of age [5]. Histology is characterized by an altered cellular maturation that gradually extends from the deeper layers (VAIN1) towards more superficial layers (VAIN2), up to completely involving the vaginal epithelium (VAIN3). Published data show that first and second grades of disease are more common than the third ones [6-11]. VAIN may present alone or with associated intraepithelial cervical neoplasia (CIN) or vulvar intraepithelial neoplasia (VIN), or in anatomical continuity with cervical dysplastic lesions. It may affect the vaginal vault in hysterectomized women. VAINs are often associated with other pre-invasive or invasive pre-existing or synchronous pathologies of the lower genital tract; in 40-80% of cases they are associated with neoplasms of the cervix [6, 9, 12], less frequently with vulvar neoplasms [6, 12]. Hysterectomized patients have a higher risk of VAIN [9, 13], and of recurrence [14]. VAINs are diagnosed with colposcopy that follows an abnormal Pap test [5]. They are often asymptomatic [15, 16]; in rare cases they present bleeding or abnormal vaginal spotting. The colposcopic examination is crucial to identify white epithelium or mosaic structures [13, 17]. Although HPV infection is necessary for the development of vaginal and cervical dysplasia, the incidence of CIN is 100 times greater than VAIN [4], with an anticipated incidence peak of ten years [18]. The difference in incidence and age is due to embryological and histological differences between cervical and vaginal epithelium as cervical neoplasia develops in metaplastic squamous epithelium (more active than the original one) while vaginal neoplasia arises from the original type [19, 20]. The literature reports a mean progression rate from VAIN to invasive neoplasia of 4% (range 0-20%) [9, 21, 22]. However, these results mainly derive from cases related to follow-up of treated VAIN, thus do not provide accurate information on their spontaneous progression capacity. The progression without treatment is around 9% in dating cases [23]. Data on high grade VAIN's spontaneous regression are unknown, while low-grade VAIN's spontaneous re-

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gression was observed in 48% to 90% cases [3, 9, 24].

Literature reports a variable association between HPV infection and VAIN [8, 25, 26]. Authors agree to consider the upper-third of the vagina the elective site for VAINs, reporting its involvement in over 80% of cases [2, 3, 9, 13, 27, 28]. Treatment options range from excisional treatments (total or partial vaginectomy, local excision), with high morbidity to more conservative and flexible therapies (laserCO_2 vaporization, diathermocoagulation, topical 5-fluorouracil, trichloroacetic acid, imiquimod, etc.). Vaporization of vaginal mucosa with laserCO_2 has an international diffusion. There are several types of lasers with different wavelengths lights depending on the active medium used. LaserCO_2 (carbon dioxide) has proved to be the most suitable in the gynecological field.

Materials and Methods

Five hundred eighty-seven cases of VAIN were treated with laserCO_2 from January 1990 to June 2018 at the 1st and 2nd Division of Gynecology and Obstetrics of the Hospital Spedali Civili of Brescia. VAINs extensively involving the vaginal walls were excluded from laser treatment in favour of topical 5-fluorouracil, while VAINs extensively involving vaginal vault were treated with surgical excision. Estrogen therapy before the procedure was prescribed to all postmenopausal women. Inclusion criteria are: recent Pap test, colposcopy (or vulvoscopy), bioptical histology of vaginal lesions (or cervical, vulvar, perineal, if present), blood tests, sierological tests (antibodies to HIV, HCV, TPHA or VDRL, and HBsAg), detailed anamnestic history, and informed consent.

The authors provided indications on the appropriate behavior in postoperative time to minimize possible complications. The authors performed treatment on outpatient access or Day-Hospital procedure (for narcosis). They used laser CO_2 equipment connected to an operating colposcope with a series of articulated arms. A special fume extractor completes the technical equipment, connected by flexible tube to metal vaginal speculum and with suction cannula. The authors made a new colposcopy examination before treatment. Local anesthesia was used only in case of cervical involvement with 2-3 ml of 1% mepivacaine hydrochloride and 1/200000 adrenaline. General anesthesia was performed in case of extensive involvement of the low genital tract or of the patient's pronounced reactivity. Vaporization of the vaginal lesions with laserCO_2 affected the dysplastic epithelium to a depth of 1-1.5 mm, extending to 3-5 mm of adjacent healthy mucosa as well. The power of the laser beam was 10-15 W for vaginal lesions and 40-50 W for cervical lesions. Depending on the operator's preference, the authors used laser in continuous or superpulsed mode. On average, the laser session lasted 10-15 (range 3-20) minutes. Patient were immediately discharged at the end of operation. Only in case of general anesthesia the discharge took place after a few hours. The follow-up required Pap test and colposcopy 6, 12, and 24 months after treatment.

HPV testing was completed in the certified diagnostic laboratory Unit of this Hospital using Hybrid Capture 2 (HC 2) test by a nucleic acid hybridization assay with signal amplification that utilizes microplate chemiluminescent detection. This test allows to detect the 13 HPV subtypes described as high risk (HR) for cervical cancer, as well as the low risk (LR) subtypes.

All patients' data were collected in an Excel database and were processed according to the current legislation in terms of privacy. The authors also used the Chi square test, the level of significance was established at $p < 0.05$ to test the correlation between groups.

Table 1. — *Distribution of VAIN based on histological degree and localization.*

	Extension of CIN		Isolated		Dome		*Total*
	N°	%	N°	%	N°	%	
VAIN 1	64	22.1	225	77.8	20	6.9	289
VAIN 2	26	13.6	165	86.4	13	6.8	191
VAIN 3	41	38.3	66	61.7	14	13.1	107
Total	131	22.3	456	77.6	47	8.0	

Table 2. — *Anatomical localization of isolated lesions.*

Location	N° cases	%
Vaginal arches	407	69.3
Upper vagina	147	25
Medial vagina	9	1.5
Lower vagina	9	1.5
Dome	47	8
More than one site	32	5.5

Table 3. — *Pre-treatment.*

Pre-treatment	N° patients
Laser	97
Laser portio	87
Laser vagina	6
Laser vulva	4
Diathermocoagulation (DTC)	31
DTC portio	22
DTC vagina	3
DTC vulva	6
Interferon	1
Cold-knife conization	15
Loop diathermy	17
5FU	1
Other	39
Total	201 (34.2%)

Results

The authors examined 587 patients who underwent laserCO_2 vaporization treatment for VAIN. The pre-operative biopsy examination showed: 289 VAIN1 (49.2%), 191 VAIN2 (32.5%), and 107 VAIN3 (18.2%). The patients' median age was 40.9 years, the mean age compared to the pathological grade was: 38.8 in VAIN1 (persistent lesions at interval of 12-24 months), 41.6 in VAIN2 and 45.0 in VAIN3. The relationship between mean age and grade of the lesion was statistically significant ($p < 0.05$). The difference between the mean age of cases with exclusive vaginal pathology and the mean age of cases with associated CIN was also statistically significant ($p < 0.05$) (respectively 44.4 *vs*. 38.1 years).

Evaluating the site and the extension of dysplastic lesion, there were: 131 (22.3%) cases in which vaginal dysplasia was an extension of cervical dysplasia on the vagina and in 456 (77.6%) cases, the vaginal lesion was isolated. In this

Table 4. — *HPV (LR/HR) on vaginal swab and histological grade of VAIN.*

	LR-HPV		LR-HPV only		HR-HPV		χ^2
	N°	%	N°	%	N°	%	L *vs.* H
VAIN 1	36	75.0	20	41.7	28	58.3	$p < 0.05$
VAIN 2	20	46.5	10	23.3	33	76.7	L only *vs.* H
VAIN 3	10	41.7	4	16.7	20	83.3	$p < 0.05$
Total	66	57.4	34	29.6	81	70.4	

Table 5. — HPV (LR/HR) on cervical swab compared to the histological grade of VAIN.

	LR-HPV		LR-HPV only		HR-HPV		χ^2
	N°	%	N°	%	N°	%	L *vs.* H
VAIN 1	34	54.0	13	20.6	50	79.4	0.078807
VAIN 2	22	48.9	5	11.1	40	88.9	L only *vs.* H
VAIN 3	8	24.2	1	3.0	32	97.0	p=0.047994
Total	64	45.4	19	13.5	122	86.5	

Table 6. — *Recurrence vs. globally considered HPV swabs.*

	Relapse		Evaluable	χ^2
	N°	%		Neg *vs.* pos
Negative	0	0.0	36	$p = 0.022983$
Low risk	12	26.7	45	L only *vs.* H
High risk	21	12.6	167	$p = 0.037285$

group there were vaginal lesions associated with CIN (160) and not associated with CIN (296). Among vaginal lesions not associated with CIN, there was a group of 47 (8% of the total) cases in which the dysplasia affected the vaginal dome in hysterectomized women. Table1 describes the distribution of VAIN in relation with histological degree and site. Table 2 describes the distribution of VAIN in relation with anatomical site of the isolated lesions. The isolated lesions on the vagina were unifocal in 204 (44.7%) cases and multifocal in 252 (55.3%); 201 (34.2%) patients were previously treated for genital tract diseases with various methods (Table 3).

HPV-DNA swabs were collected in 282 patients. The number was limited because in the Division the use of swabs ended in 2005. In 134 cases the site of the sampling was a vaginal lesion, in 168 cases a cervical one, and in 20 cases both. Of the 134 vaginal swabs: 115 (85.8%) were positive for HPV and 19 (14.2%) were negative.

The relationship between vaginal swab result and degree of vaginal lesion was: 48 (82.8%) VAIN1 with positive swab, ten (17.2%) negative, 43 (84.3%) VAIN2 with positive swab, eight (15.7%) negative, and 24 (96%) VAIN3 with positive swab, one (4%) negative The correlation between vaginal swab positivity and VAIN grade was not statistically significant ($p = 0.2630$).

Of the 168 cervical swabs, 141 (83.9%) were positive for HPV and 27 (16.1%) were negative. The relationship between cervical swab result and degree of vaginal lesion was 63 VAIN1 with a positive swab (78.8%), 17 with a negative one (21.3%), 45 VAIN2 with positive swab (88.2%), six with a negative one (11.8%), 33 VAIN3 with positive swab (89.2%), and four with a negative one (10.8%). The correlation between cervical swab positivity and VAIN grade was not statistically significant ($p = 0.217517$).

The authors were able to distinguish HPV with high or low oncogenic risk (HR-HPV and LR-HPV, respectively) with the Hybrid Capture swab. Among the 115 HPV positive vaginal swabs, 34 (29,6%) were only LR-HPV and 81 (70,4%) were HR-HPV. Table 4 describes the distribution of HR/LR-HPV on vaginal swabs in relation to the degree of vaginal lesion. The relationship between oncogenic risk of HPV and degree of vaginal lesion was statistically significant ($p < 0.05$). Among the 141 HPV positive cervical swabs, 19 (13.5%) were only LR-HPV and 122 (86.5%) were HR-HPV. Table 5 describes the distribution of HR/ LR-HPV on cervical swabs in relation with associated vaginal lesion. The relationship between oncogenic risk of HPV (cervical lesion swab) and the degree of vaginal lesion was statistically significant ($p < 0.05$).

Evaluating smoking habits, vaginal deliveries, HIV infection, estrogen-progestin contraceptive pill use, and focal lesions in relation to HPV positive swabs, the authors did not find any statistically significant correlation, either for vaginal or cervical swabs. Anesthesia was local in 496 (84.5%) patients and general in 91 (15.5%).

There were 428 (72.9%) patients at follow-up (56 months/1,698 days), while 134 patients were lost. No patient formally refused to undergo the planned follow-up program. Relapse affected 63 (14.7%) patients out of 428 evaluable at follow-up.

In relation to the histological grade, the 63 relapses were distributed as follows: 33 VAIN1, 21 VAIN2, and nine VAIN3.

In order to identify risk factors for recurrence, the authors analyzed the following criteria in relapsed patient: 1) degree of the primary lesion, 2) cervical lesion associated, 3) type of lesion (vault, isolated, in continuity with cervical lesion), 4) uni/multifocality (only for isolated lesions), 5) smoking habit, 6) parity (only vaginal deliveries), 7) estro-progestinic pill, and 8) HIV infection. The correlation of all these risk factors with the relapse was not statistically significant.

Considering all vaginal and cervical swabs the authors also evaluated the positivity of HPV (LR or HR) in relapsed patients. There was no case of recurrence in patients with negative swabs;, 12 (26.7%) cases of recurrence in patients with only LR-HPV swab, and 21 (12.6%) cases of recurrence in patients with HR-HPV swab.

The correlation between recurrence and positive swab was statistically significant ($p < 0.05$) and among positive swabs, the correlation between recurrence and HR-HPV was significant ($p < 0.05$) (Table 6).

Discussion

The series of 587 VAIN treated at the Spedali Civili of Brescia from January 1990 to June 2018 is one of the widest among international literature. All the patients were asymptomatic and came to observation following an abnormal Pap-test. The mean age was 40.9 (range 19-76) years, consistent with the incidence age reported by the majority of authors [5-7,17, 29]. Since VAINs affect also young women, it is important to propose a treatment that guarantees a preservation of sexual function. The authors observed an increase of the histological grade along with patient age ($p < 0.05$). This suggests that VaINs tends to progress over time. The authors cannot make any consideration regarding natural history of VAINs, because all the patients were treated. They also treated VAINs1 in case of not spontaneous regression after a follow-up of 18/24 months. In cases where VAIN was associated with CIN, patients' mean age was significantly lower according to the literature [18].

The authors found VAINs with synchronous CIN in 49.6% of cases and 20.4% (120) of patients had a previous CIN treated with another method. This suggests that colposcopy examination should be extended to vaginal mucosa in toto. This is also supported by the frequent multifocality of the lesions: in this series, 55.3% of the isolated lesions are multifocal [6]. Dysplasia affected the vaginal arches or the upper-third of the vagina in most cases (94.4%), according to the literature [2, 8]. It is accepted that these anatomical sites are more traumatized during sexual activity and that they remain in touch with etiologic agents/risk factors longer than other vaginal sites. The number of cases treated on vaginal dome (47 cases, 8%) are much lower than those reported in the literature [8, 9, 13]. In the present hospital, cervical cytology is always required before performing a hysterectomy: if CIN is present, the lesion is limited to colposcopy in the preoperative period. This attention can justify the low risk observed of incomplete excision of atypical areas involving vaginal arches.

Only one of the VAINs presented synchronous VIN, a lower association than previously reported [8]. Swabs were positive for HPV in 84.8% of cases. Among positive swabs, both vaginal and cervical, HR-HPV had a high prevalence in high-grade lesions and the correlation between high-risk viral type and vaginal lesion degree was statistically significant. The results obtained confirm the wide prevalence and the etiopathogenic role of HPV in vaginal dysplasia [8, 9]. It should be emphasized that the presence of only LR-HPV was higher in swabs performed on the vaginal lesion than those on cervical ones: 29.6% *vs*. 13.5%, respectively. The different susceptibility of the two epithelia to HPV can justify this observation [30]. At the vaginal level, a "lytic" infection would prevail, with a high turn-over of HR-HPV, while at the cervical level, the infection would be "persistent". It can be hypothesized that in the vaginal epithelium, HPV would replicate more effectively, lysing the cell and favoring the regression of the lesion.

The laserCO_2 procedure was quick and flexible, allowing treatments in Day-Hospital regimen. The procedure was always well-tolerated: the only reported discomfort was related to the speculum; only in the case of associated treatment of the cervix, the patients reported mild abdominal cramps, secondary to reflex uterine contractions. There were no intraoperative complications and the blood loss was none or totally negligible. During early follow-up, the authors achieved a complete return to the integrity of the treated tissues. In three patients there were minimal outbreaks of vaginal adenosis. The authors observed 63 (14.7%) relapses: it is a good result since the reported success rate of VAIN laser treatment varies between 50% and 90% [4, 6, 8, 14, 31].

In order to achieve a good prognosis, it is necessary to select patients through accurate colposcopy examination with biopsy, which identifies and characterizes the lesions by site, number, extension, and type. It is also necessary to have correct criteria of radicality during treatment. Demolition treatments must be reserved for selected cases, in which the lesion is not completely viewable or in case of other diseases associated with VAIN that require a demolitive surgical approach.

The grade, location, focal length, type of lesion, smoking habits, HIV infection, parity, and use of estroprogestinics were not significantly correlated with recurrence. However according to some authors, recurrences after treatment would be more frequent in multifocal lesions [2], extensive and high-grade lesions [32, 33], and in the presence of other intraepithelial or invasive neoplasia related to HPV of the low genital tract [4, 27]. Relapse was significantly more frequent in HR-HPV positive swabs ($p < 0.05$). HR-HPV was identified as an independent risk factor for relapse [8, 9]. The authors did not detect a greater incidence of recurrence in the hysterectomized patients and in those where VAIN affected the vaginal vault, as indicated by some authors [7, 8, 32]. There is uncertainty about the possible risk factors for relapse, so the authors recommend a cytological and colposcopic follow-up (at 6, 12, and 24 months) in the first two years for high-grade VAIN.

LaserCO_2 is highly effective in the treatment of VAIN for the absence of intra and post-operative complications, the low rate of relapse, the precision of the procedure, and the possibility of treatment of several anatomical sites (cervix, vulva, perineum, anorectum) in the same operative session.

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