Laser Excisional Treatment for Vaginal Intraepithelial Neoplasia to Exclude Invasion: What Is the Risk of Complications?

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Objective: We undertook a retrospective analysis of the incidence of complications of carbon dioxide (CO_2) laser excision for high-grade vaginal intraepithelial neoplasia (HG-VaIN).

Materials and Methods: Retrospective large case series on 128 CO_2 laser excisions for HG-VaIN in 106 women treated at the Department of Gynecologic Oncology, Oncologic Referral Center, Aviano, Italy. These procedures were performed under local anesthesia with a 20-W continuous laser beam focused to a 0.2-mm spot size. Complications were defined as "minor" when limited to vagina, and "major" when surrounding organs were injured or the vaginal vault was opened.

To identify possible factors associated with surgical complications, we performed a univariate analysis with the t test for continuous variables and χ^2 or Fisher exact test for qualitative variables as appropriate.

Results: The overall rate of complication was 7.8% (10/128); nine of them were vaginal bleeding, and only one (0.8%) was a major complication with vaginal vault perforation.

A greater number of previous destructive treatments and of two or more previous laser vaginal excisional treatments was present in patients with complications compared with ones without complications (10% vs 3.9 %, $p = .92$, and 30% vs 15.2%, $p = .44$, respectively), although these differences were not statistically significant. A total of 10.5% (6/57) of occult vaginal cancer was detected in women with initial diagnosis of VaIN3 (HG-VaIN) on biopsy.

Conclusions: Carbon dioxide laser excision for HG-VaIN seems to be a safe approach with low rate of complications, probably because of the better accuracy achieved by CO_2 laser resections, and permits diagnosis of occult invasive disease.

Key Words: surgical complications, VaIN, vaginal cancer, vaginal excision, occult cancer, laser excisional treatment, laser CO_2

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Vaginal intraepithelial neoplasia (VaIN) is a rare human papillomavirus (HPV)-related preinvasive lesion.[1] It is now classified as "low-grade VaIN" (LG-VaIN) or vaginal LSIL and "high-grade VaIN" (HG-VaIN) or vaginal HSIL, according to the 2012 revised Lower Anogenital Squamous Terminology.[2]

Low-grade VaIN, formerly known as VaIN1 or mild dysplasia, has a high rate of spontaneous regression[3,4]; otherwise, HG-VaIN, VaIN3, and VaIN2 (or severe and moderate dysplasia respectively in the past classification) have a malignant potential to evolve into invasive cancer.[5] Former VaIN2 is not present in the revised Lower Anogenital Squamous Terminology because it is not a reproducible histopathologic category among pathologists.[2]

Despite the incomplete knowledge of the natural history of VaIN, a rate of 4.6% of occult invasive vaginal cancer has been found in women previously diagnosed with HG-VaIN and up to 10.6% in women with VaIN3,[6] but some studies have reported even higher rates.[7,8] Thus, excisional treatments are considered the treatment of choice, especially if occult invasion cannot be excluded or if patients present risk factors for the upgrading of lesions, such as previous hysterectomy for HPV-related diseases and the use of tobacco.[6,9]

However, surgical excision of vaginal lesions is technically more difficult to perform than destructive treatments and is burdened by a higher rate of complications, which may cause adjacent pelvic organ damage.[8,10,11]

On these bases, excisional treatments should be used only in patients with a high risk of invasive cancer, such as those previously treated with hysterectomy for HPV-related disease, those with VaIN3 (HG-VaIN) in the vaginal vault or with recurrent lesions after destructive therapy, and whenever an invasive lesion is suspected by colposcopy and cytology.[6]

A carbon dioxide (CO_2) laser may be used both as a destructive method and as an excision method and is considered the treatment of choice by several authors.[3,12–14] Julian et al.[15] found that the use of a CO_2 laser simplified vaginectomy produced a low rate of complications, an excellent diagnostic specimen, and superior healing.

Using data derived from one tertiary care oncologic center, we undertook a retrospective analysis of the incidence of complications of CO_2 laser excision for HG-VaIN and of the possible main risk factors for their development.

MATERIALS AND METHODS

A large case series on the medical records of patients who underwent excisional treatments for high-grade VaIN at the gynecologic oncologic unit, Department of Gynecologic Oncology, Centro di Riferimento Oncologico (C.R.O.) – National Cancer Institute Aviano, (Italy) were retrospectively analyzed.

From January 1991 to June 2016, data were collected from a total of 128 procedures performed on 106 patients. Data obtained included information regarding pertinent medical and surgical history as well as sociodemographic characteristics of each woman. Ethics approval for the review of case records was obtained from the Clinical

Research Ethics Committee of the Centro di Riferimento Oncologico – National Cancer Institute of Aviano (CRO 2013-17), and a written informed consent for use of personal data was obtained from each woman. A specific informed consent for use of personal images was obtained.

Clinical data were retrieved, including incidence and types of complications, age at initial diagnosis, interval from the onset of menopause to the excisional treatment, number and types of previous gynecological surgical treatments, previous radiotherapy, location of disease, and histopathological data.

Complications were divided into major and minor. The first were defined as complications, which resulted in the injury of surrounding organs or the opening of the vaginal vault. The latter consist of complications limited to vagina.

In all cases, the preoperative diagnosis was obtained with a colposcopic-guided biopsy. Every postmenopausal woman was treated with topical estrogen gel for at least 20 days before the procedure, if no contraindications were present, to improve iodine reactivity and to increase the trophism of the vaginal mucosa.[16]

All treatments were performed in a day surgery setting with a colposcopic-guided, hand-directed CO_2 laser (Sharplan CO_2 Laser System, Laser Ventures Inc, Woodstock, GA) by a gynecologist specialized in lower genital tract pathology (F.S.). Each patient was administered local anesthesia with 2 mL of mepivacaine 2%. When it was necessary, an additional 2 to 4 mL of saline solution was injected in the submucosa of the lesion to raise the epithelium from connective tissue below, creating a wheal. The spot size was focused to 0.2 mm, using a continuous laser beam of 20-W output; laser wavelength was 10.600 nm and the focal spot was placed at 25 to 30 cm. Before the procedure, a colposcopy was performed to confirm the presence and the location of the lesions. After the procedure, a vaginal pack was inserted and removed after 2 hours. If no bleeding or other complications were found, the patient was discharged within 3 hours after the procedure.

All continuous variables were tested for normality with the D'Agostino-Pearson test. Normally distributed variables were expressed as mean(SD), whereas skewed variables were reported as median and interquartile range. Qualitative variables were expressed as proportions. To identify factors associated with surgical complications, we performed a univariate analysis with the t test for continuous variables and χ^2 or Fisher exact test for qualitative variables as appropriate. All the variables that were significant at the univariate analysis were included in a logistic multivariate model. A p value of less than .05 was considered statistically significant. MedCalc for Windows version 12.7.0 (Medcalc, MedCalc Software bvba, 2013, Ostend, Belgium) was used for data analysis.

RESULTS

The mean age of the 106 patients was 45.2 years (range = 18–78 years). Fifty-seven patients (53.8%) were in postmenopausal status, and the mean time from the menopause to laser excisional treatments for VaIN was 9.2 years (range = 1–33 years). One hundred twenty-seven (99.2%) of 128 procedures were performed for lesions located in the upper third of the vagina or at the vaginal vault, whether or not associated with a lesion of the middle third. One procedure was carried out for a lesion located in the middle third alone. The mean operative time was 21 minutes, with a range of 14 to 49 minutes, depending on the extension and the number of vaginal lesions. Among the 128 CO_2 laser excisions for HG-VaIN, 6 cases (4.7%) of occult vaginal cancer were detected; all of them in women previously diagnosed with former VaIN3 (HG-VaIN) on biopsy (6/57 cases: 10.5%).

The length of hospital stay was less than 12 hours in 105 procedures (82.0%). In 11 (8.6%) and 7 (5.5%) cases, the discharge was in the first postoperative day and in the second or third postoperative day, respectively. The hospital stay was longer than 3 days in five cases (3.9%).

In our series of 128 procedures, we had 10 complications with an overall rate of 7.8%; nine of them were defined as minor complications, and only one (0.8%) as a major complication with vaginal vault perforation.

In nine cases (7%), the complications were intraoperative or within 2 hours from the procedures; only one patient (0.8%) developed a modest vaginal bleeding in the first postoperative day, and she was treated with hemostatic suture and discharged during the second postoperative day.

All minor complications consisted of vaginal bleeding and occurred in patients with vaginal vault involvement. Bleeding was promptly resolved with an intraoperative hemostatic suture; no patients required blood transfusions.

The only major complication was a vaginal vault perforation with herniation of the epiploic fringes in a 63-year-old woman, in postmenopausal status who underwent CO_2 laser vaporization because of HG-VaIN 2 years ago. The patient had, 3 years ago, a total extrafascial hysterectomy (type A sec. Querlew and Morrow)[17] for endometrioid endometrial cancer pT1aN0 sec. Tumor Node and Metastasis staging system,[18] G1 sec. WHO at the age of 58 years. After 28 months, she had a recurrent multifocal HG-VaIN on the vaginal vault. Because of the recurrence of the disease, she underwent a CO_2 laser skinning vaginectomy of the vault. She could not be treated with vaginal estrogenic therapy, because of the history of breast cancer.

During the CO_2 laser excisional procedure, a vaginal wall perforation was noticeable, located in the left corneal recess on the vaginal vault. The diameter of the iatrogenic lesion was 1.5 cm.

Having assessed the absence of bleeding, a vaginal suture with laparoscopic abdominal visual inspection was performed under general anesthesia to control the closing of the vaginal vault and the bowel integrity. The patient was discharged in the third postoperative day, in good condition.

After histopathological examination of the excisional sample (which was 0.8 mm thick), the lesion was confirmed intraepithelial (see Figures 1A, B). Microscopically, a cleft through the vaginal wall was also evident, and this was surrounded by a rim of fibrotic tissue, showing morphologic features consistent with the laser procedure. Rare mesothelial cells lining the cleft (and thus confirming the perforation) were entrapped by the fibrous tissue and could be highlighted only by immunohistochemical positive staining for Pancytokeratin (see Figure 1C), Calretinin (see Figure 1D), and for D2-40 (not shown).

Twenty-eight procedures (21.9%) were performed after one or more previous CO_2 laser excisional and/or destructive vaginal treatments, whereas the single first procedures were 100 (78.1%). In six cases (4.7%), the laser excisional treatment was performed after one or more previous laser vaginal destructive procedures.

Forty-five procedures (35.1%) were performed in 36 women who had undergone a previous hysterectomy because of cervical cancer or cervical intraepithelial neoplasia (33 patients), benign uterine pathology (1 patient), and endometrial cancer (2 patients); all the hysterectomized patients had a history of HPV-related diseases of the lower female genital tract, and all but one were postmenopausal. In this group, there were only three complications with a rate of 6.7%. The three complications occurred in patients who had a previous laser excisional or destructive vaginal procedure (100%), and in one case, there was a vaginal vault perforation with a rate of 2.2% of major complications.

Four patients had received adjuvant radiotherapy after cervical cancer; among these, no cases of complications were recorded.

At the univariate analysis, no significant differences were observed between patients with complications and ones without complications with respect to age at diagnosis [48.3(11.1) years vs
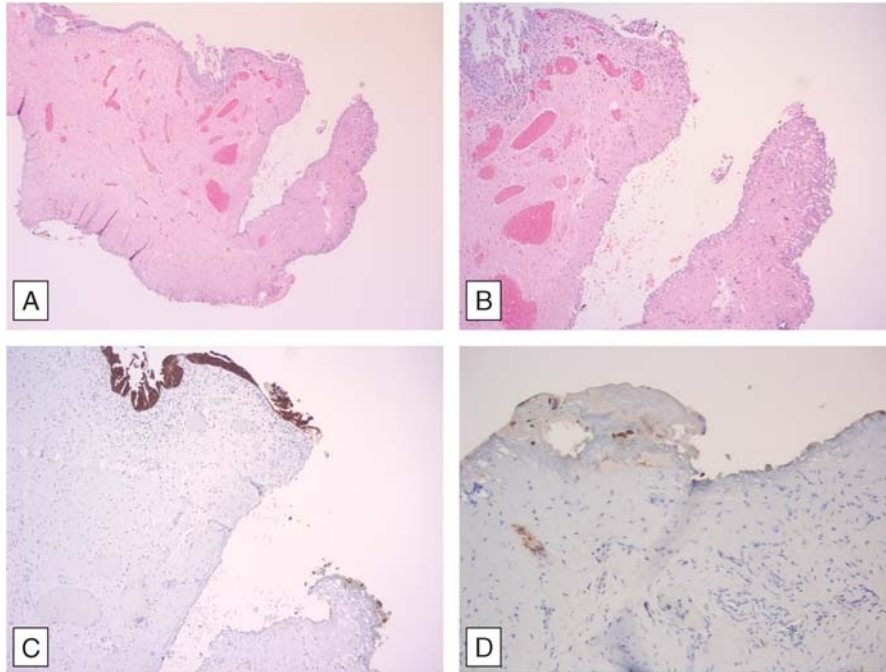
FIGURE 1. Histological specimen of vaginal wall with vaginal intraepithelial neoplasia, in patient with vaginal vault perforation. C, Pancytokeratin. D, Calretinin.

45.2 (10.9)years, $p = .39$], postmenopausal status (9.6% vs 7.0%, $p = .84$), previous hysterectomy (6.6% vs 8.4%, $p = .98$), number of previous treatments of two or more (18.75% vs 7.8%, $p = .36$), and previous destructive treatments (16.6% vs 9.0%, $p = .92$). All but one complication occurred in patients with the site of the lesion at the upper third of the vagina ($p = .11$). A greater number of previous destructive treatments and of two or more previous laser vaginal excisional treatments were present in patients with complications compared with ones without complications (10% vs 3.9%, $p = .92$, and 30% vs 15.2%, $p = .44$, respectively), although these differences were not statistically significant. None of the considered variables was included in the multivariate analysis.

During the follow-up period, no cases of adhesions, shortening, stenosis, or deformity of the vagina were recorded.

DISCUSSION

Surgical treatment for high-grade VaIN can be either destructive or excisional. Destructive treatments, such as electrosurgery, CO_2 laser vaporization, and photodynamic therapy, are easy to perform and have a lower rate of complications than excisional ones. Conversely, excisional treatments, performed with a CO_2 laser, electrosurgery, or cold knife, are burdened with more frequent complications, with a rate of 10%, including life-threatening complications,[8,10,11] but allow doctors to obtain a histopathologic specimen. The rate of occult invasive cancer from a specimen of HG-VaIN was reported as ranging from 4.6% to 28%.[6–8,19] Thus, the choice of an excisional treatment is justified only by the need to identify invasive lesions, to treat them adequately.[1] Moreover, Pap smear and colposcopic view are not specific enough for vaginal evaluation, with a more frequent disparity with histology than for cervical intraepithelial neoplasia.[6,20]

An intraoperative complication rate of 10% was reported for loop electrosurgical excision procedure, which includes hemorrhagic complications and bladder injuries.[8] Powell and Asbery[11] described a life-threatening complication of a loop electrosurgical excision procedure performed on the vagina, consisting of

sigmoid perforation with sepsis and consequent adult respiratory distress syndrome.

We report an overall rate of complications of 7.8% in a series of 128 procedures performed for laser excision of HG-VaIN compared with an incidence of occult vaginal cancer of 4.7%, which increases to 10.5% in women with initial diagnosis of VaIN3, using the former classification.

Our rate of complications is slightly lower than that present in the literature on electrosurgical excision[8,10]; it is fair to assume that the lower rate is due to the better accuracy achieved by CO_2 laser excision procedures, monitoring step by step the depth of excision.

By analyzing our data, no risk factors for complications have been identified. This suggests that risk factors for complications, such as hormonal status and involvement of the upper third of the vagina, may be obviated by the experience of the surgeon performing the procedure.

The only characteristics associated with a slightly increased incidence of complications were related to the number of previous vaginal treatments, to which patients with persistent HPV infection may experience. All the hysterectomized patients had a history of HPV-related diseases of the lower female genital tract with recurrences, repeated procedures, and therefore more uncommon clinical presentations requiring more intervention.

Considering only the patients who underwent a previous hysterectomy, 6.6% of them developed a surgical complication. However, in this group, the rate of major complications was 2.2%.

On the other hand, a lower incidence of vaginal bleeding (minor complications) could be due to the reduced vascularization of the vagina after the blood vessel section during hysterectomy.

This is true if the procedure is performed in a tertiary gynecology oncology service, because the vaginal vault and its recesses, which are frequently the location of HG-VaIN and vaginal cancer, are difficult to explore and to treat.

Regarding the only major complication in our series, this occurred in a previously hysterectomized patient who had been in postmenopausal status for a long time, who had had previous destructive treatment on the vault for HG-VaIN, and in which vaginal

estrogenic therapy was not used because of her history of breast cancer. The treatment was performed for recurrent disease on very thin tissue from the vagina to the peritoneum, this being only 0.8 mm on fixed sections. Fortunately, no damage was done to the adjacent organs, despite herniation of the epiploic fringes. This is probably due to the step-by-step, colposcopic-guided, resection with CO_2 laser.

We recognize that there are some study limitations; our study was retrospective and single-surgeon and, despite the extensive historical records, other risk factors such as the size of the lesion cannot be analyzed.

However, given the rarity of the disease, 106 patients treated homogeneously, by the same surgeon, and who underwent laser excisional treatment, represent a viable population for the study of the complications.

CONCLUSIONS

In the literature, our series is the largest undertaken regarding complications of CO_2 laser excisional treatment for HG-VaIN. The only other published study, on ten partial laser vaginectomies, described a low rate of complications and the same intraoperative complications present in our series.[15] Neither in this other study, there were any injuries to the adjacent organs, supporting the hypothesis of a greater safety in the use of the laser rather than electrosurgery.

In our series, excisional treatments are burdened by a higher rate of complications in case of previous destructive procedures, which should be performed only by experienced operators, graduating the ablation depth.

In our opinion, women diagnosed with HG-VaIN could be treated with excisional procedures, in order to find an occult invasive disease. In our series, we found that the incidence of occult invasive disease is higher than the incidence of major complications.

In conclusion, CO_2 laser excisional treatments for vaginal preinvasive lesions are safe procedures when performed by expert and trained physicians in a tertiary gynecology oncology service. However, they are not devoid of complications. Given the improved accuracy of the CO_2 laser compared to electrosurgery, most of the complications are rapidly solved, with rare damage to the adjacent structures, which did not occur in our series.

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