Loop electrosurgical excision procedure in Greek patients with vaginal intraepithelial neoplasia and history of cervical cancer

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Summary

Objective: The aim of our study was to evaluate the therapeutic effectiveness of loop electrosurgical excision procedure (LEEP) in Greek patients with vaginal intraepithelial neoplasia (VAIN) and history of cervical cancer. *Materials and Methods*: Between January 2002 and January 2009, eight women with histologically confirmed VAIN and history of cervical cancer were included in our study. For the LEEP procedure we used a high frequency Electrosurgery Unit with at least 80 W output. *Results:* Complete response rate, at 12 months of follow-up, was 75%. Recurrence rate, at 12 months of follow-up, was 25%. Complete response rate, at 24 months of follow up, was 62.5%. Recurrence rate, at 24 months of follow up, was 37.5%. *Conclusion:* LEEP may constitute a valuable excisional method for the treatment of VAIN in cases with a history of cervical cancer. It provides an interpretable specimen of the whole lesion within a few minutes. It needs a short period of training and has low cost.

Key words: Electrosurgery; LEEP; Vaginal intraepithelial neoplasia; VAIN; Cervical cancer.

Introduction

Vaginal intraepithelial neoplasia (VAIN) is uncommon, representing 1% of lower genital tract intraepithelial neoplasias [1, 2]. The median age at diagnosis of VAIN is 41 years (range 16-87 years) [3-5]. However VAIN is now being diagnosed in younger women and this rise seems to be associated with the increased incidence of human papilloma virus (HPV) infections of the lower genital tract [6].

Generally, most patients are asymptomatic. If present, symptoms may include postcoital spotting, vaginal bleeding, unusual vaginal discharge and odor [3, 4, 7]. The majority of lesions are located in the upper one-third of the vagina and are often multifocal [3-5].

The natural history of VAIN is little known but is thought to be similar to that of cervical intraepithelial neoplasia (CIN) [3, 5]. VAIN is classified in a similar manner to CIN and HPV is the primary initiator of these lesions [6, 7]. In women with VAIN: 78% may regress, 13% may persist and 9% may progress to invasive vaginal cancer [3].

The management of women with VAIN remains controversial. Treatment protocols use topical medical therapy (5% 5-fluorouracil, imiquimod), immunotherapy (interferon), surgical procedures (local excision, partial vaginectomy, total vaginectomy, loop electrosurgical excision procedure (LEEP), laser surgery, cavitational ultrasonic surgical aspiration), chemosurgery (preoperative 5-fluorouracil followed by laser surgery or LEEP) or radiation therapy [4, 5, 8-17].

The aim of our study was to evaluate the therapeutic effectiveness of LEEP in Greek patients with VAIN and history of cervical cancer.

Material and Methods

Between January 2002 and January 2009, eight women with histologically confirmed VAIN and a history of cervical cancer were referred to the 2nd Department of Gynecology of St. Savvas Anticancer-Oncologic Hospital of Athens. Among them, three had been treated for cervical cancer Stage 1A1 with hysterectomy and five had been treated for cervical cancer Stage 1b with radical hysterectomy, lymphadenectomy and radiotherapy.

LEEP was performed in the operating room, with the patient placed in the dorsal lithotomy position. For regional anaesthesia we used lidocaine solution 2% diluted with normal saline (2:1), to infiltrate the vaginal lesion and separate vaginal epithelium from underlying tissue.

In all women the lesional tissue was treated with LEEP, 3 mm away from lesion margins (2 mm for free lesion margins and 1 mm for thermal effect). Tissue specimens consisted of the vaginal mucosa and a portion of the submucosal tissue. Excision depth was ≥ 1 mm and controlled by performing procedures at high magnification.

For LEEP a high frequency electrosurgery unit with at least 80 watts output was used. For electroexcision a 10 x 4 mm or a 5 x 2 mm loop electrode was used and we selected blend cut mode with 50 watts power output. For electrofulguration a 5 mm ball electrode was used and we selected blend coag mode with 60 watts power output.

All patients were advised to avoid intercourse during the first four to six weeks following the procedure and return for follow-up at six weeks. Post-treatment follow-up protocol included physical examination, vaginal smear and colposcopic assessment at three, six, nine and 12 months for the first year and yearly there after.

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Complete response was defined as no cytologic and colposcopic evidence of any VAIN lesion. Recurrence was defined as cytologic and colposcopic evidence of a new VAIN lesion in complete responders.

When patients had more than one grade of VAIN, they were assigned the highest grade. Patients with one focus of VAIN were identified to have unifocal and those with two or more areas were identified to have multifocal disease.

The study was approved by the Ethical Committee of the Hospital. Informed consent was obtained from each woman. Statistical analyses were performed using the SPSS-13 for Windows.

Results

The median age at diagnosis of VAIN was 49 years (range 41-56 years). The median follow-up was 46.2 months (range 29-62 months). The demographics of women are shown in Table 1.

The median operating time was 15 min (range 10-20 min) depending on multifocal and extent of the lesion. The median healing time was five weeks (range 4-6 weeks) depending on the extent of the wound. All tissue specimens had free surgical margins. In our study population we had: three VAIN 2 and five VAIN 3.

Complete response rate at 12 months of follow-up was 75%. Recurrence rate at 12 months of follow-up was 25%. Complete response rate at 24 months of follow-up was 62.5%. Recurrence rate at 24 months of follow-up was 37.5%. None of the treated patients progressed to invasive vaginal cancer during a mean follow-up of 46.2 months. These data are shown in Tables 2 and 3.

Table 1. — *Women's demographics (n = 8).*

		No. of patients (n = 8)	Percentage (%)
Age	< 40	0	0%
	40-60	8	100%
	> 60	0	0%
VAIN	VAIN 1	0	0%
	VAIN 2	3	37.5%
	VAIN 3	5	62.5%
History of cervical cancer	Yes	8	100%
	No	0	0%
History of radiotherapy	Yes	5	62.5%
	No	3	37.5%
History of immunosupression	Yes	0	0%
	No	8	100%

Table 2. — *Response at 12 months of follow-up (n = 8).*

	Complete response	Recurrence
VAIN 2 (n = 3)	3 (100%)	0 (0%)
VAIN 3 (n = 5)	3 (60%)	2 (40%)
Total	6 (75%)	2 (25%)

Table 3. — *Response at 24 months of follow-up (n = 8).*

	Complete response	Recurrence
VAIN 2 (n = 3)	3 (100%)	0 (0%)
VAIN 3 (n = 5)	3 (40%)	3 (60%)
Total	5 (62.5%)	3 (37.5%)

Discussion

VAIN has histopathology similar to CIN [18]. VAIN development, following HPV infection, may require a greater period of time and may occur less frequently because of the different type of epithelium from which VAIN arises [4, 19]. HPV types with a preference for infection of vaginal tissue may be less oncogenic [20]. The vagina lacks an active transformation zone with immature epithelial cells susceptible to HPV infection [18, 21]. However, HPV entry may result from vaginal mucosal abrasions (from coitus or tampon use) and reparative metaplastic squamous cell activity [18].

VAIN may occur as an isolated lesion or as a lesion associated with CIN (65%) or vulvar intraepithelial neoplasia (VIN) (10%) [5]. These lesions may arise at the same time (synchronous lesions) or up to several years after the initial CIN lesion (metachronous lesions) [5, 22]. Most VAIN lesions occur on the vaginal vault after hysterectomy for CIN or invasive cervical cancer [3, 5, 23, 24]. The time interval from an initial diagnosis of CIN 3 to a current diagnosis of VAIN 3 varies from 2-17 years [7, 16, 24-27]. This shows the protracted, delayed onset of VAIN, requiring long-term cytological follow-up after hysterectomy [7, 10, 26, 27]. In our study three patients had VAIN lesions on the vaginal vault after hysterectomy for cervical cancer Stage 1A1 and five patients had VAIN lesions on the vaginal vault after radical hysterectomy, lymphadenectomy and radiotherapy for cervical cancer Stage 1B.

The majority of VAIN (82%) occur in the upper one-third of the vagina [5, 7, 28]. The middle and lower thirds of the vagina are involved by less than 10% of lesions [5, 28]. The majority of VAIN (61%) are also multifocal [3, 5, 25]. The upper one-third of the vagina and especially the angles of the vaginal vault must be carefully examined after hysterectomy [4, 28]. In our study, all women had VAIN lesions in the upper one-third of the vagina. Among them, three women had unifocal VAIN lesions and five women had multifocal VAIN lesions.

The most important risk factors for developing VAIN are previous abnormal Papanicolaou smear, HPV infection, genital warts, CIN or cervical cancer, immunosupression, radiation therapy, history of diethylstilbestrol exposure, low education, low family income, smoking and early hysterectomy [5, 29]. In our study three patients had VAIN lesions on the vaginal vault after hysterectomy for cervical cancer Stage 1A1 and five patients had VAIN lesions on the vaginal vault after radical hysterectomy, lymphadenectomy and radiotherapy for cervical cancer Stage 1B. None of the women had any history of immunosupression or diethylstilbestrol exposure.

Vaginal intraepithelial neoplasia is a rare disorder that, in most instances, will regress after initial treatment. VAIN lesions not associated with CIN or VIN tended to show a higher rate of spontaneous regression (91%) than

VAIN lesions associated with CIN or VIN (67%) [3]. However, patients with VAIN require careful monitoring because of the risk of recurrence and even progression to invasion [3, 4]. Risk factors for recurrence of VAIN are multifocality, association with anogenital neoplastic syndrome, histologic grade, immunosupression and treatment modality [3, 4, 5, 30]. In our study three women treated for VAIN 3 recurred after initial treatment. None of the women in our study progressed to invasive vaginal cancer during a mean follow-up of 46.2 months.

The choice of treatment modality for patients with VAIN was influenced by the number of lesions, location of lesions, length of vagina, sexual activity, previous radiation therapy, previous VAIN treatment, patient preference and operator experience [5, 11]. Multifocal lesions are more difficult to treat because some lesions can be missed during treatment [4, 5, 12].

LEEP for VAIN lesions has been proposed with excellent results in selected groups of patients [5, 12, 13, 14]. There are potential advantages of LEEP for treating VAIN lesions. These include: low cost of equipment, avoidance of operating room, avoidance of general anaesthesia, limited tissue damage, provision of a specimen, reduced bleeding and discomfort [12, 13, 14]. LEEP may be more accurate than laser CO_2 in uncovering foci of early invasion (LEEP uses excision rather than ablation) [13]. In our study all tissue specimens had free surgical margins. The operating time ranged from 10-20 min depending on multifocal and extent of the lesion. We believe that every gynaecologist is capable of performing LEEP on VAIN after 10-15 supervised applications with a high index of confidence [12].

There are potential complications of LEEP for treating VAIN lesions. These include: bleeding, infection, vaginal perforation, bladder injury, rectal injury, vesicovaginal and rectovaginal fistulae [12, 13, 14, 31, 32]. In our study population there were no complications. Only a few cases had spot bleeding during the operation. The newly formed vaginal epithelium, after a mean period of five weeks, presents excellent topography. None of the women complained about post-treatment sexual dysfunction.

It is clear that current treatments for VAIN are suboptimal and continue to represent a clinical challenge. The best approach is individualized management based on clinical presentation, extent of disease and patient preference [12]. LEEP may constitute a valuable excisional method for the treatment of VAIN in cases with a history of cervical cancer. It provides an interpretable specimen of the whole lesion within a few minutes [12, 33]. The procedure needs a short period of training and has low cost [12, 33].

References

[1] Sillman F.H., Sedlis A., Boyce J.G.: "A review of lower genital intraepithelial neoplasia and the use of topical 5-fluorouracil". *Obstet. Gynecol. Surv*., 1985, *40,* 190.

[2] Timonen S., Numers C., Meyer B.: "Dysplasia of the vaginal epithelium". *Gynaecologia*, 1966, *162*, 125.

[3] Aho M., Vesterinen E., Meyer B., Purola E., Paavonen J.: "Natural history of vaginal intraepithelial neoplasia". *Cancer,* 1991, *68,* 195.

[4] Sillman F.H., Fruchter R.G., Chen Y.S., Camilien L., Sedlis A., McTigue E.: "Vaginal intraepithelial neoplasia: risk factors for persistence, recurrence, and invasion and its management". *Am. J. Obstet. Gynecol*., 1997, *176,* 93.

[5] Dodge J.A., Eltabbakh G.H., Mount S.L., Walker R.P., Morgan A.: "Clinical features and risk of recurrence among patients with vaginal intraepithelial neoplasia". *Gynecol. Oncol*., 2001, *83*, 363.

[6] Sugase M., Matsukura T.: "Distinct manifestations of human papillomaviruses in the vagina". *Int. J. Cancer,* 1997, *72*, 412.

[7] Boonlikit S., Noinual N.: "Vaginal intraepithelial neoplasia: a retrospective analysis of clinical features and colpohistology". *J. Obstet. Gynaecol. Res*., 2010, *36*, 94.

[8] Krebs H.B., Helmkamp B.F.: "Chronic ulcerations following topical therapy with 5-fluorouracil for vaginal human papillomavirus-associated lesions". *Obstet. Gynecol*., 1991, *78,* 205.

[9] Haidopoulos D., Diakomanolis E., Rodolakis A., Voulgaris Z., Vlachos G., Antsaklis A.: "Can local application of imiquimod cream be an alternative mode of therapy for patients with high-grade intraepithelial lesions of the vagina?". *Int. J. Gynecol. Cancer,* 2005, *15*, 898.

[10] Murta E.F., Neves Junior M.A., Sempionato L.R., Costa M.C., Maluf P.J.: "Vaginal intraepithelial neoplasia: clinical-therapeutic analysis of 33 cases". *Arch. Gynecol. Obstet*., 2005, *272*, 261.

[11] Indermaur M.D., Martino M.A., Fiorica J.V., Roberts W.S., Hoffman M.S.: "Upper vaginectomy for the treatment of vaginal intraepithelial neoplasia". *Am. J. Obstet. Gynecol*., 2005, *193,* 577.

[12] Terzakis E., Androutsopoulos G., Zygouris D., Grigoriadis C., Derdelis G., Arnogiannaki N.: "Loop electrosurgical excision procedure in Greek patients with vaginal intraepithelial neoplasia". *Eur. J. Gynaecol. Oncol*., 2010, *31,* 392.

[13] Fanning J., Manahan K.J., McLean S.A.: "Loop electrosurgical excision procedure for partial upper vaginectomy". *Am. J. Obstet. Gynecol*., 1999, *181*, 1382.

[14] Patsner B.: "Treatment of vaginal dysplasia with loop excision: report of five cases". *Am. J. Obstet. Gynecol*., 1993, *169,* 179.

[15] Diakomanolis E., Rodolakis A., Boulgaris Z., Blachos G., Michalas S.: "Treatment of vaginal intraepithelial neoplasia with laser ablation and upper vaginectomy". *Gynecol. Obstet. Invest*., 2002, *54*, 17.

[16] Robinson J.B., Sun C.C., Bodurka-Bevers D., Im D.D., Rosenshein N.B.: "Cavitational ultrasonic surgical aspiration for the treatment of vaginal intraepithelial neoplasia". *Gynecol. Oncol*., 2000, *78,* 235.

[17] Woodman C.B., Mould J.J., Jordan J.A.: "Radiotherapy in the management of vaginal intraepithelial neoplasia after hysterectomy". *Br. J. Obstet. Gynaecol*., 1988, *95*, 976.

[18] Woodruff J.D.: "Carcinoma in situ of the vagina". *Clin. Obstet. Gynecol*., 1981, *24*, 485.

[19] Androutsopoulos G., Adonakis G., Ravazoula P., Kourounis G.: "Vaginal cancer in patient treated for Cervical Intraepithelial Neoplasia (CIN 3): a case report". *Eur. J. Gynaecol. Oncol*., 2006, *27,* 638.

[20] Castle P.E., Schiffman M., Glass A.G., Rush B.B., Scott D.R., Wacholder S. *et al*.: "Human papillomavirus prevalence in women who have and have not undergone hysterectomies". *J. Infect. Dis*., 2006, *194,* 1702.

[21] Schneider A., De Viliers E.M., Schneider V.: "Multifocal squamous neoplasia of the female genital tract: significance of human papillomavirus infection of the vagina after hysterectomy". *Obstet. Gynecol*., 1987, *70,* 294.

[22] Vinokurova S., Wentzensen N., Einenkel J., Klaes R., Ziegert C., Melsheimer P. *et al*.: "Clonal history of papillomavirus-induced dysplasia in the female lower genital tract". *J. Natl. Cancer Inst*., 2005, *97,* 1816.

[23] Diakomanolis E., Stefanidis K., Rodolakis A., Haidopoulos D., Sindos M., Chatzipappas I. *et al*.: "Vaginal intraepithelial neoplasia: report of 102 cases". *Eur. J. Gynaecol. Oncol*., 2002, *23*, 457.

[24] Rome R.M., England P.G.: "Management of vaginal intraepithelial neoplasia: a series of 132 cases with long-term follow-up". *Int. J. Gynecol. Cancer,* 2000, *10*, 382.

[25] Hummer W.K., Mussey E., Decker D.G., Dockerty M.B.: "Carcinoma in situ of the vagina". *Am. J. Obstet. Gynecol.,* 1970, *108*, 1109.
[26] Frega A., French D., Piazze J., Cerekja A., Vetrano G., Moscarini M.: "Prediction of persistent vaginal intraepithelial neoplasia in previously hysterectomized women by high-risk HPV DNA detection". *Cancer Lett*., 2007, *249,* 235.
[27] Schockaert S., Poppe W., Arbyn M., Verguts T., Verguts J.: "Incidence of vaginal intraepithelial neoplasia after hysterectomy for cervical intraepithelial neoplasia: a retrospective study". *Am. J. Obstet. Gynecol*., 2008, 199, 113.e1.
[28] Audet-Lapointe P., Body G., Vauclair R., Drouin P., Ayoub J.: "Vaginal intraepithelial neoplasia". *Gynecol. Oncol.,* 1990, *36,* 232.
[29] Brinton L.A., Nasca P.C., Mallin K., Schairer C., Rosenthal J., Rothenberg R. *et al*.: "Case-control study of in situ and invasive carcinoma of the vagina". *Gynecol. Oncol*., 1990, *38*, 49.
[30] Kim H.S., Park N.H.., Park I.A., Park J.H., Chung H.H., Kim J.W. *et al*.: "Risk factors for recurrence of vaginal intraepithelial neoplasia in the vaginal vault after laser vaporization". *Lasers Surg. Med*., 2009, *41,* 196.
[31] Harroch J., Siegler E., Bornstein J.: "Vesicovaginal fistula resulting from loop electrosurgical excision in a woman with intraepithelial neoplasia of the cervix and vagina: a case report". *J. Low Genit. Tract. Dis.,* 2004, *8,* 205.
[32] Powell J.L., Asbery D.S.: "Treatment of vaginal dysplasia: just a simple loop electrosurgical excision procedure?". *Am. J. Obstet. Gynecol*., 2000, *182,* 731.
[33] Terzakis E., Androutsopoulos G., Derdelis G., Zygouris D., Grigoriadis C., Apostolikas N.: "Loop electrosurgical excision procedure in Greek patients with vulvar intraepithelial neoplasia". *Eur. J. Gynaecol. Oncol*., 2010, *31,* 191.

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