Loop Electrosurgical Excision Procedure in Vulvar Intraepithelial Neoplasia Treatment

Anne-Thérèse Vlastos, MD,[1] Larry B. Levy, PhD,[2] Anais Malpica, MD,[3] and Michele Follen, MD, PhD[4]

[1]*Département de Gynécologie et Obstétrique, Hôpitaux Universitaires de Genève, Geneva, Switzerland;* [2]*Department of Biomathematics, The University of Texas M. D. Anderson Cancer Center, Houston, TX;* [3]*Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; and* [4]*Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX*

■ **Abstract**

Objective. Our objective was to compare by response rate the therapeutic options of loop electrosurgical excision procedure (LEEP), laser therapy, and wide local excision in managing high-grade vulvar intraepithelial neoplasia in a pilot study for a randomized clinical trial.

Materials and Methods. Between 1995 and 1999, 109 patients presenting with vulvar lesions were registered at a comprehensive cancer center and 2 associated colposcopy clinics. From these 109, we identified 74 patients with lesions histologically proven to be vulvar intraepithelial neoplasia who underwent treatment with CO_2 laser, wide local excision, or LEEP. Clinical and pathological features were reviewed retrospectively. Wilcoxon rank sum test and life table analyses were used to compare groups. Response rates for this retrospective study will be used to calculate the sample size for a prospective clinical trial.

Results. Our population was similar to others reported in the literature in age, range of diagnoses, and follow-up. Only 1 of 74 patients (1%) had invasive cancer. In a subset of 62 patients treated for the first time, LEEP and wide local excision were equal in their ability to achieve complete response. Laser ablation was the least successful of all methods (10/20 with laser, 3/20 with LEEP, and 2/22 with wide local excision experienced recurrences [$p = .04$]). No statistically significant differences among the 3 were noted in time to recurrence ($p = .24$). Age, age at first intercourse, and number of sexual partners were not correlated with recurrence and did not confound the results. Using a χ^2 approximation, an alpha error of 0.05, and a power of 0.80, researchers should enroll 25 patients per arm if improvement over standard therapy is expected to be 40%, 45 if expected to be 30%, and 95 if expected to be 20%.

Conclusions. Because of differences in recurrence rate and length of hospital stay and indications of potential differences in cost found in this pilot, LEEP merits comparison in a prospective randomized clinical trial with wide local excision and laser therapy in which recurrence rate, patient treatment preference, and cost-effectiveness are evaluated. Patients entered in such a trial should be stratified according to their risk of invasion. If the risk of invasion is high, then the laser should be used to excise a sample rather than ablate. ■

Key Words: vulvar intraepithelial neoplasia, loop electrosurgical excision procedure, laser surgery

The incidence of vulvar intraepithelial neoplasia (VIN) is increasing, and analysis indicates that age at diagnosis is decreasing [1–3]. VIN, a well-defined pathologic entity, may be associated with invasive vulvar cancer [4, 5] in 1% to 22% of cases (Table 1) [6–16]. The therapy for VIN has evolved over the last 40

Reprint requests to: Michele Follen, MD, PhD, Department of Gynecologic Oncology and the Biomedical Engineering Center, Box 193, The University of Texas M. D. Anderson Cancer Center, 1515 M. D. Anderson Boulevard, Houston, TX 77030. E-mail: mfollen@mdanderson.org

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Table 1. Summary of Case Series Reporting VIN Associated with Invasive Vulvar Cancer

Author (y)	No. of patients in series and disease	Mean or median age (y)	Patients with invasive cancer	
			n	%
Buscema et al. 1980 [6]	106 CIS	47	4/106	4
Crum et al. 1984 [7]	41 VIN	49	5/41	12
Powell et al. 1986 [8]	50 CIS	43	4/50	8
Rettenmaier et al. 1987 [9]	108 VIN	40	6/48	13
Chafe et al. 1988 [10]	69 VIN	45	13/69	19
Woodruff 1991 [11]	101 VIN	~40	1/101	1
Jones and Rowan 1994 [12]	113 VIN	36	11/113	10
Hording et al. 1995 [13]	73 VIN	48	12/73	17
Herod et al. 1996 [14]	133 VIN	38	9/133	7
Modesitt et al. 1998 [15]	73 VIN	45	16/73	22
Husseinzadeh and Recinto 1999 [16]	78 VIN 3	47	16/78	21
Present article 2002	74 VIN	45	1/74	1

VIN, vulvar intraepithelial neoplasia; CIS, carcinoma in situ.

years from vulvectomy and radiation therapy to wide local excision, laser ablation, chemotherapy with 5-fluorouracil, and cryotherapy. Case series show similar long-term cure rates for these therapies of 70% to 80% [17]. Retrospective reviews cannot answer the question of how well a therapy performs. Only prospective randomized trials can answer those questions. The purpose of this retrospective review was to examine differences in response rates as an exercise in planning a prospective randomized trial.

Laser ablation provides a cosmetically appealing treatment with a cure rate comparable with that of wide local excision, but it has the disadvantage of not providing a specimen for pathological analysis [18–21]. The loop electrosurgical excision procedure (LEEP) provides an alternative to laser ablation and wide local excision with 2 advantages: provision of a specimen and avoidance of the operating room and general anesthesia.

Ferenczy et al. [22] reported a series of 28 patients with VIN lesions. They treated half of each lesion with a laser and used LEEP on the other half. Patients with lesions > 6 cm^2 (16) underwent general anesthesia, and those with lesions < 6 cm^2 (12) underwent local anesthesia. All procedures were performed in an outpatient clinic. Researchers followed 25 of 28 patients (89%) for 9 months. A complete response was obtained in 12 of 25 (48%) after a single treatment. They reported no significant differences between the laser or loop excised areas with respect to recurrence of disease, healing time, postoperative discomfort, or complications. Because the patients were taken to the operating room based on lesion size, not on intervention characteristics, cost by procedure cannot be assessed in this series. This case series, though small, is provocative and suggests a clinical trial is necessary.

The assessment of new technologies involves several steps, including assessing technical feasibility, clinical effectiveness, patient satisfaction, and cost-effectiveness [23]. LEEP has been conclusively demonstrated to be technically feasible, and its use is widespread in patients with cervical intraepithelial neoplasia. Its use in patients with VIN has been more limited. Successful expertise, however, is the product of experience and the practice of safeguards. Clinical effectiveness, patient satisfaction, and cost-effectiveness are now being evaluated. As part of planning for a clinical trial to evaluate clinical effectiveness and patient satisfaction, we conducted a retrospective review of patients who underwent LEEP and other vulvar procedures. We report here the clinical characteristics of this experience and generate data necessary in planning a clinical trial.

MATERIALS AND METHODS

Cases were identified using the institutional databases from 1995 to 1999 and the search term *VIN*. The cases were treated by 1 of the authors (M.F.) at 1 of 3 sites: The University of Texas M. D. Anderson Cancer Center, The University of Texas Health Science Center at Houston, or the Lyndon Baines Johnson Hospital District Center in Houston. The charts were abstracted by 1 of the authors (A.T.V.) for the following variables: name, date of birth, race, marital status, education level, work environment, use of alcohol, use of tobacco, use of drugs, history of medical problems and surgical procedures, previous cancers, history of hysterectomy, pres-

ence of lichen sclerosis, age at menarche, gravidity, parity, age at first intercourse, number of sexual partners, contraception, history of sexually transmitted diseases, HIV testing, last Pap smear, history of abnormal Pap smear findings, human papillomavirus testing, history of genital warts, history of VIN, presenting symptoms, colposcopic findings, localization of disease, history of concomitant disease in the vagina or cervix, history of treatments for VIN, pathologic findings (including presence of invasive cancer and margin status of excised specimens), recurrences of VIN, and length of follow-up. The pathology was reviewed by 1 of the authors (A.M.) to confirm the diagnosis, review margin status, and confirm the presence or absence of invasive cancer.

All surgical procedures were carried out under the supervision of 1 attending physician (M.F.). Surgical assistants included fellows in gynecologic oncology and residents in obstetrics and gynecology from the 3 institutions. The techniques of wide local excision and vulvectomy, which were combined in the analysis, have been described in detail by Mitchell [17]. Laser vaporizations were carried out using the CO_2 laser and the technique described by Reid [18]. The laser group included patients treated only with the laser. Institutional policy required vulvar laser procedures to be performed in an operating room. Loop excisions, which include excision, fulguration, ablation, and eschar removal, were carried out as described by Ferenczy et al. [22] and others [17, 18]. In LEEP, excision of VIN and perianal skin is accomplished using a square loop and microneedle powered by an electrosurgical generator. Fulguration requires a 5-mm ball electrode and a 1-mm needle electrode. The surgeon uses saline-soaked cotton-tipped applicators to remove the hard eschar that forms after fulguration. Postprocedure instructions advise patients to apply a 1% silver sulfadiazine cream topically, perhaps along with a 5% benzocaine cream, twice a day. Patients are advised to have only protected intercourse for 6 weeks following the procedure. Some patients underwent both wide local excision and laser vaporization, usually when lesions on the clitoris were preferably treated with laser. In this analysis, wide local excision was considered to have failed when patients in the group experienced recurrences on the labia. Clitoral recurrences did not occur and were not part of the final analysis of the failure rate for wide local excision. Complete response was defined as no evidence of disease on visual inspection and on biopsy at all colposcopic examinations postsurgery.

Data were analyzed using SAS software (SAS Institute, Cary, NC). Frequencies were calculated for all variables, and *t* test and analysis of variance measures were used to compare continuous variables. Pearson's and χ^2 tests were used to compare nominal variables. The log-rank test was used to compare Kaplan-Meier plots of time to recurrence for the 3 treatments. Logistic regression and Cox proportional hazards methods were used to compare the significance of variables for predicting response. Statistical analyses were carried out by 3 of the authors (L.B.L., A.T.V., M.F.).

RESULTS

A total of 109 patients with vulvar pathology were identified at the 3 clinical sites; of these, 74 had histologically proven VIN. Their 74 charts were abstracted and make up the basis for this case series. Charts and pathology specimens were available for all patients. Review of Table 2 indicates that the patients were comparable with other groups of patients with vulvar neoplasia reported in the literature.

Table 2. Demographic Characteristics of Patients

Characteristic	*n*	%
Age		
Mean: 44.5 y		
Range: 23–72 y		
Race or ethnicity		
White	49	66
African American	16	22
Hispanic	4	5
Unknown	5	7
Marital status		
Married	38	51
Single, divorced, widowed	36	49
Education		
Graduated from college	8	11
Graduated from high school	26	35
Without high school diploma	40	54
Tobacco use		
Smokers	54	73
Nonsmokers	20	27
Drug and alcohol use		
History of drug use	6	8
Alcohol use	23	31
Reproductive history		
Multigravid	50	70
Primigravid	7	10
Nulligravid	15	20
STD		
History of STD	34	46
History of genital warts	28	38
History of hysterectomy	33	45
History of dysplastic cervical lesion	11	15
Diagnosis at referral		
VIN 1	3	4
VIN 2–3	49	66
Vulvar carcinoma in situ	22	30

STD, sexually transmitted disease; VIN, vulvar intraepithelial neoplasia.

As Table 2 shows, most patients had VIN 2 or VIN 3 (66%). A total of 127 procedures were performed: 49 CO_2 laser vaporizations, 26 wide local excisions, 12 combined CO_2 laser vaporizations and wide local excisions, and 36 LEEPs. Of the 127 cases, histologic diagnosis identified 11 as VIN 1, 14 as VIN 2, 58 as VIN 3, 43 as vulvar carcinoma in situ, and 1 as invasive carcinoma. (Carcinoma in situ is part of VIN 3, but the pathologist separated those cases out to make the categorizations comparable with those used previously in the literature.) Almost all procedures, except the LEEPs, were performed in the operating room with the patient under general anesthesia. Eighty-four of 91 instances (92%) in which patients underwent general anesthesia resulted in overnight stays in the hospital of 1 to 2 days. In contrast, only 2 of 36 LEEPs (6%) were performed with the patient under general anesthesia. These patients were treated early in the series, and both had large lesions. All other LEEPs (94%) were performed in an outpatient gynecology clinic using local anesthesia (lidocaine). None of these patients was hospitalized overnight.

Using the χ^2 test, we found no statistically significant differences in clinical presentation ($p = .314$), pathology ($p = .309$), or positive margins ($p = .215$) between patients treated by LEEP and those treated by other procedures. There was also no statistically significant difference in age (analysis of variance F test [$p = .378$]). The postoperative complication rate was 6% for the 127 procedures. There were no statistically significant differences in complication rates among procedures (numbers were very small). There were 4 patients treated with the laser with complications: 3 patients had infections and required outpatient antibiotic therapy, and 1 patient with prolonged pain required additional prescriptions for pain medicine. Two patients had complications following wide local excision: 1 with delayed healing after wound breakdown and 1 who required additional pain medicine. One patient returned after LEEP with bleeding, which cauterization resolved in the emergency room. Median follow-up after treatment was 37 months (range, 1–175 months). There was no statistically significant difference between the groups in time to recurrence (log-rank test of equality of strata [$p = .194$]).

A subgroup of patients was identified for whom there were no previous treatments. Clinical characteristics of these 62 patients are shown in Table 3. There were no significant differences among the 3 groups in age, race, smoking habit, marital status, number of sexual partners, or age at first sexual intercourse or in history of sexually transmitted disease, genital warts, or cervical intraepithelial neoplasia (see Table 3 for p values). Lesions indicated VIN 2 to VIN 3 and were multifocal in all patients. No invasive lesions were found in this subset.

Table 3. Summary of 62 Patients with No Previous Treatment

Variable	Treatment			p value
	LEEP ($n = 20$)	Wide local excision ($n = 22$)	CO_2 laser ($n = 20$)	
Median age (y)	44.4	48.3	43.5	.44
Race: white	11	15	16	.25
Smoker	12	18	16	.23
Married	9	8	14	.09
Nulligravid	5	10	4	.15
First intercourse < 18 y	10	12	10	.99
History of STD	6	3	4	.46
Genital warts	6	8	13	.07
Cervical intraepithelial neoplasia	6	11	9	.43
Multifocal VIN	10	15	15	.27
Positive margins	3	2	NA	.26
Local anesthesia	18	2	3	.0001
Hospital stay	0	9	18	.0001
Complications	0	2	1	.76
Follow-up (mo)	20	32	51	.02
Recurrences	3	2	10	.04
Time to recurrence (mo)	16	15	25	.24

LEEP, loop electrosurgical excision procedure; STD, sexually transmitted disease: VIN, vulvar intraepithelial neoplasia; NA, not applicable.

Recurrences after the first procedure were significantly fewer with LEEP and wide local excision than with the other procedures ($p = .04$). Complete response as a nominal variable was compared using the χ^2 test. Complete response was achieved after 1 treatment in 17 of 20 (85%) LEEP procedures, 17 of 22 (77%) wide local excision procedures, and 10 of 20 (50%) laser procedures. When the rate of complete response in LEEP and that in wide local excision are compared, the difference is not statistically significant ($p = .52$). In contrast, the complete response rate associated with LEEP is significantly different from that associated with laser procedures ($p = .02$).

Although the laser group was followed longer, the duration of follow-up did not account for the differences in recurrence rates. This was assured using a Cox proportional hazards analysis, which uses time to recurrence as an end point. Follow-up for the LEEP group was 20 months, that is, 83% of the time generally acknowledged as a minimum follow-up period (24 months). Time to recurrence for each procedure was compared using the log-rank test to compare Kaplan-Meier curves. There were no statistically significant dif-

ferences among the therapies for time to recurrence, whether compared as LEEP, laser, and wide local excision, or as LEEP versus wide local excision, LEEP versus laser, or laser versus wide local excision. A Cox proportional hazards analysis showed that none of the following predicted recurrence: age, age at first intercourse, or number of sexual partners.

DISCUSSION

The findings in this case series seem similar to others in the literature. The prevalence of invasive cancer in our series was lower than that of many and similar to that of Woodruff [11]. The incidence of invasion is very important to trial design. If the investigator is worried about a high rate of invasion, ablative therapies that produce no specimens would not be analyzable treatment. The low rate in this study may represent referral bias, as all patients referred to the institution have histopathologic diagnoses at the time of referral; thus, one would expect to see less incidental invasive cancer in our series. This same bias may have applied to the series by Woodruff et al. Inasmuch as the associated rate of invasion varies between 1% and 22%, obtaining a specimen should be an objective of a clinical trial.

Patient satisfaction was not assessed in this study, so patient preference is unknown. Although no formal cost analysis was performed, we can probably safely assume that LEEP was less expensive than the other procedures in this series because operating room charges and anesthesiology fees were usually avoided with it. Though policy may differ elsewhere and thereby reduce cost, policy at the institution where the study was performed requires (and in some cases lesion dimensions also demand) general anesthesia for wide local excision. On the other hand, we cannot probably safely assume that all practitioners will perform LEEP with equal skill. Even though LEEP has been conclusively demonstrated to be technically feasible, successful expertise is the product of experience and the willing practice of safeguards. Training and experience are necessary to maintain low rates of positive margins and to ensure technique fosters healing.

This retrospective study examines the results of treatment of 2 groups: 74 patients with pathologically proven VIN and a subgroup of 62 previously untreated patients. Previous treatment, when received, had been based on clinician judgment. Although recognizing that it is better to compare patients who share similarities, a consideration that, in fact, prompted the analysis of the 62, we also recognized that we would introduce a bias were we to limit the analysis only to that group. By including previously treated patients in the initial analysis, we avoided introducing a bias favoring the laser and LEEP procedures, knowing that with them there is less chance of postintervention microinvasion than there is with wide local excision.

Another bias, that of treatment selection, could not be overcome. Because this is not a prospective study, providing randomization and blinding, selection bias is an inescapable but not fatal limitation. Our purpose was not to identify definitively the best technology but to examine past work to determine what guideposts it could yield for future clinical studies that can answer that question. Retrospective reviews produce data for use in determining sample sizes, a critical part of study design.

A randomized clinical trial will afford an unbiased assessment of the technologies used to treat VIN. Because obtaining a specimen may be important, a clinical trial comparing wide local excision with LEEP is warranted. In such a prospective study, patient preference and cost could be addressed. Clinical variables of interest would include specimen quality, healing time, and complication rates (bleeding, infection, pain). Lesion size might be used to stratify patients to the operating room or outpatient gynecology clinic, as in the case series by Ferenczy et al. [22]. Alternatively, a strategy for using LEEP for large lesions might be to excise the lesions in segments. Up to a 4-by-4–cm area can be excised in the gynecology clinic without undue pain or complications, and larger lesions could be removed in 2 appointments, perhaps 1 to 2 months apart. No matter the design, the clinical trial should be stratified by lesion size and site of treatment to minimize bias in the final analysis.

VIN incidence is rising and younger women are most affected. LEEP seems to be a clinically effective treatment for VIN and also the most cost-effective. Case series are important in the planning of well-designed prospective trials. It is time for a prospective randomized clinical trial to compare wide local excision with LEEP. Laser therapy may have a role in a clinical trial of patients expected to be at very low risk of invasion, such as patients younger than 40 years of age with multifocal disease, but this would only be true if laser ablation works as well as wide local excision or LEEP in this population.

The similar cure rates for the procedures and the 10% to 30% regression of VIN 2 to VIN 3 lesions must

be taken into account in planning trials. If one uses a χ^2 approximation as a basis for sample size calculation and assumes an alpha error of 0.05 and a power of 0.80, a treatment that produced a 20% improvement over the standard would require 95 patients per arm, a treatment that produced a 30% improvement over the standard would require 45 patients per arm, and a treatment that improved 40% over the standard would require 25 patients per arm. The investigator needs to identify a clinically meaningful difference in response. Inasmuch as the cure rates are expected to be similar and the complication rates low, a large trial should be planned that follows patients for 2 to 5 years. Such a trial would need to account for losses to follow-up in the estimate of sample size.

CONCLUSION

Given the results of this retrospective review, a randomized clinical trial of LEEP is warranted. If a study could be performed at many institutions, a randomized trial of all these procedures with patients stratified by age would be ideal. If the studies were to be performed at smaller medical centers, then other study designs might be necessary. In a well-screened, young population, in which prevalence of invasion is expected to be low, LEEP could be compared with another ablative therapy like laser vaporization. In a population less well screened, in whom the prevalence of invasion might be more than 1% or in patients older than 45 to 50 years in whom the prevalence of invasive cancer is expected to be higher, LEEP could be compared with wide local excision.

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