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A Randomized Clinical Trial of Cryotherapy, Laser Vaporization, and Loop Electrosurgical Excision for Treatment of Squamous Intraepithelial Lesions of the Cervix

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***Objective*: To compare cryotherapy, laser vaporization, and loop electrical excision for treatment of squamous intraepithelial lesions (SILs).**

***Methods*: Women at least 18 years old with biopsy-proven SIL, negative pregnancy tests, negative findings on endocervical curettage, satisfactory colposcopy examinations, and congruent Papanicolaou smear and biopsy results were assigned randomly to treatment after stratification by SIL grade, endocervical gland involvement, and lesion size; they were evaluated 1, 4, 8, 12, 16, 20, and 24 months after treatment. Data were analyzed using χ^2 statistics, logistic regression analysis, and the Cox proportional hazards model.**

***Results*: Of 498 patients assigned, 108 were excluded (most because of inadequate follow-up), leaving 390 (139 cryotherapy, 121 laser vaporization, 130 loop excision) for analysis. All were followed 6–37 months (mean 16). There were no statistically significant differences in complications, persistence (disease present less than 6 months after treatment), or recurrence (disease present more than 6 months after treatment). Risk of persistent disease was higher among women with large lesions (risk ratio [RR], 18.9; 95% confidence interval [CI], 3.2, 110.6). Recurrence risk was higher among women aged 30 years and older (RR, 2.1; 95% CI, 1.2, 4.3), those with human papillomavirus type 16 or 18 (RR, 2.1; 95% CI, 1.1, 4.0), and those who had had prior treatment (RR, 2.1; 95% CI, 1.1, 3.9).**

***Conclusion*: The data support a high success rate with all three modalities. No significant difference in success rates was observed between the three treatments in our population. Additional attention and research should be directed toward the higher risk patients identified above. (Obstet Gynecol 1998;92:737–44. © 1998 by The American College of Obstetricians and Gynecologists.)**

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Table 1. Previous Trials of Cryotherapy, Laser, and Loop Excision for Cervical Intraepithelial Neoplasia

First author	Reference no.	Year	Total patients	Treatment	Range of follow-up (mo)	No. with recurrence or persistence (%)
Nonrandomized						
Wright	5	1981	334	152 cryotherapy	12–42	22 (14)
				131 laser		4 (3)
Townsend	6	1983	200	100 cryotherapy	12	7 (7)
				100 laser		11 (11)
Ferenczy	7	1985	294	147 cryotherapy	12–48	13 (9)
				147 laser		6 (4)
Gunasekera	8	1990	199	98 LLETZ	6	5 (5)
				101 laser		8 (8)
Randomized						
Kirwan	9	1985	98	35 cryotherapy	17–24	6 (17)
				71 laser		8 (11)
Kwikkel	10	1985	101	50 cryotherapy	3–18	7 (14)
				51 laser		15 (30)
Berget	11	1987	204	101 cryotherapy	3–23	9 (9)
				103 laser		10 (10)
Berget	12	1991	187	93 cryotherapy	12–80	4 (4)
				94 laser		8 (8)
Alvarez	13	1994	375	195 LLETZ	3	13 (7)
				180 laser		8 (4)

LLETZ = large loop excision of the transformation zone.

Ablation of the transformation zone has been the standard of care for several decades for patients with biopsy-proven squamous intraepithelial lesions (SILs) of the cervix who have negative findings on endocervical curettage, a satisfactory colposcopy examination, and congruent Papanicolaou smear and biopsy results. Several techniques for ablation are available: cryotherapy, laser ablation, and loop excision of the transformation zone, also called the loop electrosurgical excision procedure.

Each of the three techniques has advantages and disadvantages.[1] Cryotherapy remains a trusted tool because of its reliability, ease of use, and low cost. Major disadvantages include the lack of ability to tailor the treatment to the size of the lesion and the lack of a tissue specimen. Laser vaporization has the advantage of being easily tailored to the size of the lesion of interest; its disadvantages are that it requires an expensive piece of equipment, requires a moderate amount of training to perform properly, produces toxic effects (eg, burns and eye injuries), and, again, yields no specimen. The loop electrical excision procedure is reasonably reliable, is easy to use, can be tailored to the size of the lesion, and produces a tissue specimen. The potential advantage of a specimen is underscored by the finding of unsuspected adenocarcinoma in situ and microinvasive squamous carcinoma in 2–3% of specimens.[2–4] The disadvantage of loop excision is its high cost.

The three therapies have had similar cure rates (80–90%), and similar complication rates (bleeding in 1–5% of cases, cervical stenosis in 1–3%, and infection in 1–9%) have been seen in case series.[1–4] Four nonrandomized trials and five randomized trials have shown no statistically significant differences in cure rates between cryotherapy and laser treatment or between laser and loop excision (Table 1). In these studies, three prognostic variables have been associated with persistent or recurrent disease: high lesion grade, endocervical gland involvement, and large lesion size.[1]

No previous randomized clinical trial has assessed the effectiveness of all three treatment modalities in the management of SIL. Our central hypothesis was that there was not a 10% statistically significant difference in complication rates or a 20% statistically significant difference in failure rates among the three treatments. We therefore conducted a randomized clinical trial to compare differences in the rates of complications and persistent and recurrent disease among the treatment modalities and to identify predictive factors for persistent and recurrent disease in women with SIL. To ensure the validity of the comparison, before randomization patients were stratified by the prognostic variables listed above.

Materials and Methods

Study Protocol

The study population was drawn from women referred to the University of Texas M. D. Anderson Cancer

Center Colposcopy Clinic with the diagnosis of SIL, then called cervical intraepithelial neoplasia (CIN), between March 1992 and April 1994. Patients were eligible if they 1) were at least 18 years of age, 2) were using contraception, 3) had a negative pregnancy test, 4) had a biopsy-proven CIN lesion, 5) had negative findings on endocervical curettage, 6) had a satisfactory colposcopy examination (visualization of the squamocolumnar junction and the entire lesion), and 7) had congruent Papanicolaou smear and biopsy results. Exclusion criteria were as follows: 1) suspicion or evidence of invasive lesions on Papanicolaou smear, biopsy, or colposcopic examination, 2) positive pregnancy test, 3) current pelvic inflammatory disease, cervicitis, or other gynecological infection, and 4) past poor compliance (patient had missed visits or rescheduled twice previously). The institutional review board approved the study.

Once evaluated for eligibility, patients were asked to participate and sign an informed consent document. They then were stratified by lesion characteristics and assigned randomly to undergo cryotherapy, laser vaporization, or the loop electrosurgical excision procedure. Patients were contacted and informed of their treatment assignment. Treatments were scheduled within 1–3 weeks of diagnosis. Once treated, patients were asked to return 1, 4, 8, 12, 16, 20, and 24 months after treatment. The outcome measures of interest were complications (infection requiring oral or intravenous antibiotics, bleeding requiring a hospital visit, or cervical stenosis requiring dilation), persistent disease (disease present within 6 months of treatment), and recurrent disease (disease found more than 6 months after treatment). A sample size was set to detect a 10% difference in complications and a 20% difference in persistent or recurrent disease at a $P = .05$ level of significance.

Evaluation

All patients had their referral pathology specimens reviewed at M. D. Anderson, gave a complete medical history, and had a physical examination followed by pan-colposcopy of the vulva, perineum, vagina, and cervix. Colposcopically directed biopsies and human papillomavirus (HPV) testing using the ViraPap/ViraType assay (Digene Corp., Beltville, MD) were performed. On average, 1–2 biopsy specimens measuring 1 × 2 mm were taken with the Tischler biopsy forceps. A visible lesion was present after the biopsy.

Assignment

Patients were stratified in 18 blocks by grade of CIN (1, 2, or 3), lesion size (less than or equal to a third of the cervix surface area, between a third and two-thirds of the surface area, and two-thirds or more of the surface area), and the presence or absence of endocervical gland involvement. For example, for CIN 1, there were six blocks: ≤ ⅓ with endocervical gland involvement; ≤ ⅓ with no involvement; ⅓–⅔ with involvement; ⅓–⅔ with no involvement; ≥⅔ with involvement; ≥ ⅔ with no involvement. Each patient gave informed consent at the initial visit and was assigned to a treatment once biopsy results were available. For each of the 18 blocks, the Department of Biomathematics generated a randomized list of treatments. A physician assistant who was not involved in treatment used the computer-generated list to assign the random treatment and scheduled the patient. The providers performed the assigned treatment. For follow-up cytologic and histologic evaluation, data on patients were abstracted from the chart, and the pathology department was blinded as to which treatment had been performed under the direction of one of the authors (GTL).

Treatment Procedures

All patients returned to the outpatient clinic for the procedures, which were performed using local anesthesia. The cervix was colposcopically visualized to identify the lesion and the transformation zone, and Lugol solution was applied to outline the squamocolumnar junction and lesions. Colpophotographs were taken of the lesion. The cervix was swabbed with 1% benzocaine gel for all procedures, and for laser vaporization or loop excision, the cervix was injected with 4 mL of 1% lidocaine with epinephrine.

The Cryomedics machine (Cabot Medical Corp., Langhorne, PA) was used for cryotherapy. A large Graves speculum was placed in the vagina, and a nipple-tipped probe of appropriate size to cover the lesion and transformation zone was selected. KY Jelly (Johnson & Johnson Medical Inc., Arlington, TX) was applied to the probe, and the probe was applied to the cervix. Tongue blades were used along the vaginal walls for protection. The cervix was treated for 3 minutes, thawed, and treated again for 3 minutes so that an ice ball extended 5 mm beyond the lesion and transformation zone.

The Leisegang carbon dioxide laser colposcopy unit (Leisegang Medical Inc., Boca Raton, FL) was used for laser ablation. The procedure included the placement of a large ebonized Graves speculum with suction attachment. The laser was set at 20 W on continuous mode,

and the spot size was 1 mm. Small dots were made around the lesion and the transformation zone, and the laser was then used to ablate an area 8 mm deep around the canal and 6 mm deep at the edge. Rulers were used to check the depth; the procedure was continued until the appropriate depth was achieved. Homeostasis was achieved by increasing the spot size and defocusing the beam. Ferric subsulfate solution (Monsel's solution) was applied at the end of the procedure.

For loop excision, machines from Cooper Medical Gynemed Division (Boulder, CO), Leisegang Medical Inc., Valleylab Inc. (Boulder, CO) and Cabot Medical Corp. (Longhorne, PA) were used at the appropriate setting indicated by each company. The procedure included the placement of a large plastic Graves speculum and a plastic vaginal retractor. The 20 × 8–mm loop was used to remove the lesion and entire transformation zone, in one piece if the cervix was 4 cm or smaller. If the cervix was larger than 4 cm, the tissue was removed in two sections. The bed was coagulated with the ball electrode, and ferric subsulfate solution was placed in the bed.

Training Procedures

The three gynecologists, two family practitioners, and two nurse practitioners performing the procedures were trained at the same institution (M. D. Anderson), performed ten procedures of each type together, and designed and attended an intensive 1-day training program to ensure that similar techniques were used for the procedures. Similarly, all providers observed 30 colposcopies together and drew lesions on patients' charts documenting size and type of vascular atypia. The colpophotographs were scanned into the computer and surface areas were generated for the lesions. Good agreement among observers was obtained for drawings and estimation of lesion size compared with the colpophotographs (data not shown). The head nurse and two licensed vocational nurses attended extensive in-service training in the use of all three devices, and the clinic manager made certain that sufficient supplies of the same kind were available for the entire trial period. A physician assistant served as a research monitor and attended all procedures to be certain that the procedures and data collection were carried out in similar fashion.

Pathology Review

The study pathologist (ES) trained the providers to ink the loop excision specimens in the clinic room to ensure proper orientation. Ectocervical and endocervical margins were inked in different colors, and a suture was placed at the 12-o'clock position. In all cases, the entire transformation zone was removed, along with 8 mm of the endocervical canal. All specimens were submitted for pathologic evaluation of permanent sections.

Specimens were reviewed routinely by the Department of Pathology and again by the study pathologist. The presence or absence of endocervical gland involvement was noted. Margins were considered to be evaluable if the pathologist could discern the presence or absence of disease in the margins. Thermal damage was defined as marked distortion of the cells that precluded the identification of each cell. Denudation was defined as partial or total fractionating of the specimen that prevented an adequate pathologic diagnosis.

Follow-up

Women were encouraged to seek emergency care, if needed, at our hospital. All patients were scheduled for follow-up examinations 1, 4, 8, 12, 16, 20, and 24 months after treatment. At each follow-up visit, all women had a complete physical and pelvic examination, colposcopic exam, and Papanicolaou smear, as well as colposcopically directed biopsies if lesions were present. Women were asked about complications such as bleeding, infection (fever, vaginal discharge), visits to the emergency room, and use of pain medication (within 24 hours after treatment or later). In addition, women were evaluated for the presence of cervical stenosis. By phone or certified mail, an attempt was made to contact patients who missed a scheduled appointment and to schedule a new appointment. After three unsuccessful attempts to contact a woman, she was considered lost to follow-up and excluded from analysis.

Responses (persistent and recurrent disease) were assessed on the bases of cytologic and histologic evaluation. Persistent disease was defined as the cytologic or histologic presence of CIN at the time of the second follow-up visit (within 6 months after treatment). Recurrent disease was defined as the cytologic or histologic presence of CIN diagnosed at a subsequent follow-up visit (at least 6 months after treatment) in a patient who had had at least one negative cytologic smear after treatment.

Statistical Analysis

The relevant estimated difference in treatments was assessed to be 20% with an α error of .95 and power of .80; 104 evaluable patients per group would identify a 20% difference and 152 a 10% difference in outcomes. SPSS for Windows (SPSS Inc, Chicago, IL) was used to analyze the data. Descriptive statistics and Pearson χ^2 statistic were used to compare the distribution of de-

mographic and clinical characteristics among treatment groups. Differences in persistence and recurrence rates among treatment groups were assessed by the Pearson χ^2 statistic. Univariate and multivariate logistic regression models were used to estimate the relative risk and 95% confidence intervals (CIs) for persistent and recurrent disease associated with treatment modality and other covariates (age, HPV status, smoking habits, grade of disease, glandular involvement, size and location of lesion, and history of prior treatment for CIN). Differences in disease-free interval (date of treatment to date of recurrence) among treatment groups were estimated by the log-rank test. Univariate and multivariate logistic regression and Cox proportional hazard models were used to estimate the risk and 95% CI of recurrence associated with treatment modality and other covariates. Statistical significance was defined as $P < .05$.

Results

Four hundred ninety-eight patients were assigned randomly to receive one of the three treatments. A total of 108 were excluded from analysis (four because they did not present for treatment, one because of other illness, one because of physician error in assignment, and 102 because they did not complete 4 months of follow-up), leaving 390 patients for analysis (139 cryotherapy, 121 laser vaporization, 130 loop electrosurgical excision procedure). No differences in age ($P = .88$) or grade ($P = .37$), size ($P = .46$), or location ($P = .60$) of lesion were observed between evaluable and inevaluable patients.

Table 2. Baseline Characteristics by Treatment Group

Characteristic	No. (%) of patients by treatment group*		
	Cryotherapy ($n = 139$)	Laser therapy ($n = 121$)	LEEP ($n = 130$)
Diagnosis			
CIN 1	42 (34)	41 (33)	40 (33)
CIN 2	50 (40)	31 (25)	43 (35)
CIN 3	47 (33)	49 (34)	47 (33)
Presence of EGI	38 (34)	39 (35)	36 (32)
Lesion size†			
<⅓	104 (36)	91 (31)	98 (33)
⅓–⅔	23 (33)	23 (33)	24 (34)
>⅔	12 (44)	7 (26)	8 (30)
Location			
One quadrant	18 (35)	15 (29)	19 (37)
Two quadrants	38 (33)	41 (35)	37 (32)
Three quadrants	22 (33)	22 (33)	22 (33)
Four quadrants	61 (39)	43 (28)	52 (33)
Age (y)			
<25	54 (32)	59 (35)	58 (34)
25–29	40 (38)	33 (31)	32 (31)
>29	45 (40)	29 (25)	40 (35)
HPV positive	76 (35)	70 (32)	70 (32)
HPV 16/18 positive	49 (36)	39 (29)	48 (35)
History of prior treatment	21 (37)	18 (32)	18 (32)
History of smoking	57 (32)	58 (33)	61 (35)
Current smoking	51 (33)	53 (34)	52 (33)

LEEP = loop electrosurgical excision procedure; CIN = cervical intraepithelial neoplasia; EGI = endocervical gland involvement; HPV = human papillomavirus.

* Percentages are calculated by characteristic. Their relative uniformity demonstrates that the treatment groups were similar in makeup.

† Proportion of the surface area of the cervix involved by the lesion.

Table 3. Complications by Treatment

Complication	No. of patients by treatment group		
	Cryotherapy	Laser	LEEP
Infection	1	1	1
Bleeding <24 h after treatment	0	0	1
Bleeding >24 h after treatment	0	3	6
Stenosis requiring dilation in the office	2	1	1
Pain requiring medication	0	0	1
Total	3 (2%)	5 (4%)	10 (8%)*

LEEP = loop electrosurgical excision procedure.

* $P = .09$ for comparison of total complications by group.

The mean age of evaluable patients was 27.2 years; 59% were white, 17% black, 22% Hispanic, and 2% Asian. Fifty-five percent of the patients were HPV positive; of these, 63% were positive for HPV 16 or 18. Fifteen percent had received prior treatment for CIN, and 45% had a history of smoking. There were no statistically significant differences between treatment groups with regard to demographic characteristics, HPV positivity, history of prior treatment, or smoking status (Table 2). The patients were followed for 6–37 months; the mean follow-up was 16 months, and median was 15.1 months. Seventy-five percent of patients completed at least two follow-up visits (8 months follow-up), 50% completed at least four follow-up visits (16 months follow-up), and 25% completed at least five follow-up visits (20 months follow-up).

There were no statistically significant differences between treatment groups with regard to the variables by which patients were stratified (Table 2). Of the 390 evaluable patients, 123 had CIN grade 1, 124 had CIN grade 2, and 143 had CIN grade 3. More than 32% of lesions in each treatment group had evidence of endocervical gland involvement, and 75% of the lesions involved one-third or less of the surface area of the cervix. All loop excision specimens were adequate for review; there were no inevaluable margins and no specimens in which denudation precluded adequate reading. The final pathology results for the 130 patients in this group were as follows: 15 negative specimens, two cases of atypia, 18 cases of HPV, 27 cases of CIN 1-HPV, 35 cases of CIN 2-HPV, 30 cases of CIN 3-HPV,

Table 4. Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Persistence of Cervical Intraepithelial Neoplasia

	Risk ratio (95% CI)	
	Univariate	Adjusted*
Treatment		
Cryotherapy	Reference	Reference
Laser therapy	0.81 (0.25, 2.63)	0.70 (0.19, 2.54)
LEEP	0.60 (0.17, 2.09)	0.50 (0.13, 2.00)
Diagnosis		
CIN 1	Reference	Reference
CIN 2	1.85 (0.60, 5.68)	1.60 (0.47, 5.48)
CIN 3	0.33 (0.06, 1.76)	0.16 (0.02, 1.17)
EGI		
No	Reference	Reference
Yes	0.81 (0.26, 2.57)	1.14 (0.32, 4.15)
Lesion size		
<⅓	Reference	Reference
⅓–⅔	1.41 (0.37, 5.36)	1.80 (0.40, 8.0)
>⅔	5.49 (1.57, 19.19)†	18.91 (3.23, 110.6)†
Location		
One quadrant	Reference	Reference
Two quadrants	2.29 (0.26, 20.11)	0.63 (0.26, 1.53)
Three quadrants	2.42 (0.25, 23.99)	0.81 (0.31, 2.10)
Four quadrants	2.39 (0.29, 19.89)	0.88 (0.37, 2.06)
Age (y)		
<25	Reference	Reference
25–29	0.23 (0.03, 1.86)	0.12 (0.01, 1.31)
30+	1.77 (0.62, 5.02)	2.32 (0.72, 7.50)
HPV positive‡		
No	Reference	
Yes	0.79 (0.29, 2.16)	
HPV 16/18 positive		
No	Reference	Reference
Yes	0.42 (0.12, 1.49)	0.38 (0.09, 1.63)
History of prior treatment		
No	Reference	Reference
Yes	0.38 (0.05, 2.91)	0.32 (0.04, 2.84)
Smoking history		
No	Reference	Reference
Yes	1.59 (0.59, 4.35)	1.22 (0.39, 3.76)

CI = confidence interval; LEEP = loop electrosurgical excision procedure; CIN = cervical intraepithelial neoplasia; EGI = endocervical gland involvement; HPV = human papillomavirus.

* Adjusted for all other variables in the model.

† $P < .05$.

‡ Excluded from multivariate model.

one case of microinvasive cancer, and two cases of ungraded dysplasia. For the 15 negative cases, specimens were recut, and no CIN was found in the blocks.

There were no statistically significant differences in complication rates among groups (Table 3). Three patients developed infections and associated fever for which they required antibiotics. One patient was treated as an outpatient with amoxicillin/clavulanate potassium for 2 weeks; the other two patients developed symptoms compatible with a flare-up of pelvic inflammatory disease and were hospitalized for 2 weeks of intravenous antibiotic treatment. Ten patients (2%) were evaluated for bleeding—one within 24 hours and nine after 24 hours. In all cases, patients were seen in the emergency room, and bleeding stopped after ferric subsulfate solution was applied. Four patients (1%) underwent dilation in the clinic for cervical stenosis. One patient called in for pain medication and was given a prescription for acetaminophen with codeine.

A slightly higher, but non–statistically significant, overall failure rate (persistent disease and recurrent disease combined) was observed among women in the cryotherapy group (24%) than among women in the laser ablation (17%) and loop excision (16%) groups

Table 5. Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Recurrence of Cervical Intraepithelial Neoplasia

	Risk ratio (95% CI)	
	Univariate	Adjusted*
Treatment		
Cryotherapy	Reference	Reference
Laser therapy	0.66 (0.34, 1.30)	0.77 (0.38, 1.59)
LEEP	0.65 (0.34, 1.27)	0.68 (0.34, 1.38)
Diagnosis		
CIN 1	Reference	Reference
CIN 2	1.22 (0.59, 2.55)	1.08 (0.49, 2.39)
CIN 3	1.60 (0.80, 3.18)	1.37 (0.62, 3.03)
EGI		
No	Reference	Reference
Yes	0.73 (0.38, 1.39)	0.63 (0.31, 1.27)
Lesion size		
<⅓	Reference	Reference
⅓–⅔	1.24 (0.61, 2.50)	1.30 (0.59, 2.84)
>⅔	1.36 (0.49, 3.78)	1.40 (0.46, 4.21)
Location		
One quadrant	Reference	Reference
Two quadrants	0.66 (0.26, 1.63)	0.65 (0.24, 1.75)
Three quadrants	0.85 (0.32, 2.28)	0.82 (0.28, 2.41)
Four quadrants	0.96 (0.42, 2.20)	1.00 (0.39, 2.57)
Age (y)		
<25	Reference	Reference
25–29	1.63 (0.78, 3.38)	1.51 (0.71, 3.23)
>29	2.68 (1.38, 5.20)†	2.61 (1.28, 5.31)†
HPV positive‡		
No	Reference	
Yes	1.69 (0.94, 3.01)	
HPV 16/18 positive		
No	Reference	Reference
Yes	1.86 (1.06, 3.25)†	2.02 (1.08, 3.80)†
History of prior treatment		
No	Reference	Reference
Yes	2.62 (1.35, 5.08)†	2.58 (1.25, 5.35)†
Smoking history		
No	Reference	Reference
Yes	1.36 (0.77, 2.37)	1.13 (0.66, 1.94)

CI = confidence interval; LEEP = loop electrosurgical excision procedure; CIN = cervical intraepithelial neoplasia; EGI = endocervical gland involvement; HPV = human papillomavirus.

* Adjusted for all other variables in the model.

† $P < .05$.

‡ Excluded from multivariate model.

($P = .24$). There were no statistically significant differences in persistence rate among the three therapies (cryotherapy, 5%; laser ablation, 4%; loop excision, 3%; $P = .72$). There were also no statistically significant differences in recurrence rate among the three therapies after follow-up of 6–37 months (cryotherapy, 19%; laser ablation, 13%; loop excision, 13%; $P = .34$). The mean disease-free interval (time from treatment to recurrence) was 31.9 months for the study population as a whole, and there were no statistically significant differences by treatment group: cryotherapy, 28.9 months (95% CI, 26.9, 30.8); laser therapy, 30.9 months (95% CI, 28.7, 33.0); and loop excision, 32.7 months (95% CI, 30.7, 34.7) (log-rank test = 2.04, $P = .36$).

Using logistic regression analysis, persistent disease was statistically significantly associated with lesion size after controlling for other covariates, including treatment group, grade of lesion, glandular involvement, lesion location, age, HPV status, and smoking history (Table 4). Women with lesion size greater than two thirds of the surface of the cervix were 19 times more likely to have persistent disease than women with smaller lesions (relative risk [RR], 18.9; 95% CI, 3.2, 110.6). No other factor was associated with the risk of persistent disease. Recurrent disease was statistically significantly associated with three variables after controlling for other covariates (Table 5); a two-times higher risk of recurrence was observed among women aged 30 years and older (RR, 2.61; 95% CI, 1.3, 5.3), women positive for HPV type 16 or 18 (RR, 2.02; 95% CI, 1.1, 3.8), and women with prior history of treatment for CIN (RR, 2.6; 95% CI, 1.3, 5.4). Results for persistent and recurrent disease using the Cox proportional hazards model were similar (data not shown).

Discussion

Previous nonrandomized and randomized studies of these treatments in the literature were not stratified by prognostic variables; thus, differences in these variables could have accounted for differences in failure rates. The case series that have reported on patients treated with these modalities have high dropout rates, and none were analyzed using statistical methods accounting for the amount of time patients were followed. The nonrandomized and randomized studies have short follow-up (Table 1) with the exception of the study of Berget et al, [12] for which the average follow-up was 50 months. This is the first randomized trial of the three therapies, stratified for important prognostic variables, using time-sensitive statistical methods, and having a mean of 16 months of follow-up with disease-free intervals of 30 months. As seen in Table 1, many of the studies have had short follow-up periods. The similar failure rates seen with the longer follow-up in our study attest to the comparability of these treatments; however, relative failure rates may change if patients are observed for 5, 10, or 20 years.

The three therapies had similar rates of success and complications in the treatment of SIL for the period of follow-up. Because this was a randomized trial, we were able to compare the therapies on the basis of persistence alone, recurrence alone, and the two combined. The rates of persistence and recurrence were consistent with the findings of prior studies. This study was carried out in a tri-ethnic population largely referred to the medical center from the surrounding county. The results may be extrapolated to similar populations.

Our results support the comparable safety of loop excision. Loop excision was associated with a slightly higher rate of bleeding in this study than was seen for the other two therapies, as in other studies in the literature.[2–4] Overall, however, complication rates were not statistically significantly different among the therapies in this study. These data also refute the reports in the literature that the cure rate following loop excision might be higher than that for cryotherapy or laser ablation.

The charges associated with these procedures vary; in our institution, cryotherapy is much less expensive than laser or loop excision. However, the potential advantage of loop excision in producing a specimen must be considered. Because 2–3% of specimens in other studies showed unsuspected adenocarcinoma in situ and microinvasive squamous carcinoma, there is adequate reason for concern about not having a specimen for pathologic review. In our study, only one of 130 patients undergoing loop excision had unsuspected microinvasive squamous cancer. If patients are compliant with follow-up, recurrences following ablation would be detected. For compliant patients, the potential advantage of loop excision in producing a specimen, given the potential for undetected adenocarcinoma in situ and microinvasive squamous carcinoma, should be evaluated in a cost-effectiveness model.

If patients are noncompliant with follow-up, however, recurrences might go undetected. The eligibility criteria for our study excluded noncompliant patients (those who had already missed two appointments). We routinely perform a cone biopsy in patients with SIL who have been noncompliant with follow-up in the past; because a cone biopsy removes tissue higher in the canal and has a higher diagnostic and cure rate, we believe this to be a safer course in this group of patients.

Additional attention and research should be directed toward studying the relationship between HPV and the immune system and how it is affected by treatment. It is

possible that one of these treatments better primes the humoral or cell-mediated immune response. Viral load may be an important predictor of which patients form lesions, respond to therapy, or experience recurrence.

In this study, patients with large lesions were more likely to have persistent disease. This persistence occurred despite our attention to treating not only the lesion but also the entire transformation zone. It may be that additional strategies to reduce the risk of persistent disease in these patients should be considered; these might include the addition of a second treatment, such as 5-fluorouracil or a chemopreventive agent. Our results also suggest that additional measures might be considered in patients 30 years and older, patients whose lesions are HPV-positive, and patients with a history of prior treatment, all of whom were more likely to have a recurrence.

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