

Clinicopathologic outcomes of laser conization for high-grade cervical dysplasia

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Summary

Purpose of investigation: To evaluate the incidence of thermal artifact and rates of persistent disease and recurrence in laser conization for cervical dysplasia.

Methods: A retrospective study examined the cases of 110 patients who underwent carbon dioxide laser conization for high-grade cervical dysplasia at our institution between January 1999 and March 2002. Rates of thermal artifact, persistent disease, recurrence, hemorrhage and cervical stenosis were investigated. Dysplasia severity and recurrence rates in smokers were also evaluated.

Results: One hundred and five (95.5%) of 110 laser cones had negative margins, and only five (4.5%) had significant thermal artifact, with two (1.8%) noted to interfere with adequate evaluation of margins. Seventy-eight patients returned to Roswell Park Cancer Institute (RPCI) for follow-up with a mean follow-up period of 15.7 months. Fourteen (12.7%) patients had persistent disease detected within two visits, and one (0.9%) patient had a recurrence of dysplasia at ten months. One (0.9%) patient had same-day postoperative hemorrhage requiring hemostatic suturing. There were no cases of cervical stenosis detected at follow-up. Smokers had an increased incidence of high-grade lesions on cone biopsy when compared to non-smokers (46/57 and 30/53 patients, 80.7% and 56.7%, respectively; $p = 0.008$). The rate of persistent disease or recurrence was 8/57 (14%) in smokers and 7/53 (13.2%) in non-smokers ($p =$ not significant).

Conclusion: Laser conization is an efficacious and safe procedure for the treatment of high-grade cervical dysplasia, with a very low incidence of thermal artifact and postoperative complications, and a relatively low rate of persistent disease. Smokers had a significantly increased incidence of high-grade lesions on cone biopsy.

Key words: Laser conization; Thermal artifact; Postoperative complications; Persistent disease.

Introduction

Laser conization has been recognized as a diagnostic and treatment modality for cervical dysplasia since 1979 [1]. In contrast to ablative techniques, conization offers the advantage of providing a specimen for definitive diagnosis and determination of margin status. Several studies have compared this method to cold-knife conization and the loop electrosurgical excisional procedure (LEEP), with the potential of thermal artifact identified as a diagnostic difficulty in both laser conization and LEEP [2-4]. In the past several years, laser conization has been the most commonly performed excisional procedure for patients referred to our institution for cervical dysplasia.

Although it is now well recognized that infection with the human papillomavirus (HPV) is responsible for the majority of cervical dysplasia and cancer [5], co-factors such as cigarette smoking [6-8], number of sexual partners [9] and host immunogenetic factor [10] determine the risk of persistence, progression or recurrence of dysplasia. In this regard, cigarette smoking impairs the local cervical immune microenvironment by reducing the number of Langerhans' cells, leading to impaired ability to eradicate HPV [11].

The goal of this study was to examine the rate of persistent disease and recurrence, incidence of significant thermal artifact, and rates of hemorrhage and cervical

stenosis in these cases. In addition, the lesion severity and recurrence rate in smokers was compared to non-smokers, and the diagnostic value of preoperative endocervical curettage was evaluated.

Materials and Methods

One hundred and ten patients with cervical dysplasia underwent laser conization of the cervix at our institution between January 1999 and March 2002 and were included in a retrospective study. The study protocol was approved by the Roswell Park Cancer Institute Institutional Review Board. Indications for conization included biopsy-proven cervical intraepithelial neoplasia (CIN) 2-3, discrepancy between cytology and histology, unsatisfactory colposcopy, dysplastic endocervical curettage (ECC), and suspicion of invasive disease. In accordance with the Bethesda system, results were classified as mild dysplasia in cases of CIN 1 or moderate-to-severe dysplasia in cases of CIN 2-3. All patients underwent preoperative colposcopy to define the extent of the lesion.

The procedure was performed under local anesthesia in all except two cases in which the patient was unable to tolerate the procedure without general anesthesia. After the lesion was visualized under colposcopy, the cervix was infiltrated with a 2% lidocaine with epinephrine solution 1:100,000. Using a CO₂ laser set at power between 15 and 30 watts, a circular incision was made outside the transition zone and margins of the lesion, cutting approximately 1 cm deep toward the periphery and 1.5 cm deep towards the endocervical canal. All specimens were analyzed by the pathology department at our institution.

Patients were followed-up with Papanicolaou (Pap) tests and

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clinical examination at three-month intervals for a period of one year, then at six-month intervals thereafter. Endocervical curettage and colposcopy were performed at follow-up visits at the discretion of the examining physician based on clinical examination and cytology results. Additional ablative or excisional procedures were performed as indicated. Dysplasia that was detected at the first or second follow-up visit was considered to be persistent disease; recurrence was defined as dysplasia detected after two negative postoperative Pap tests occurring three months apart.

Information regarding cigarette smoking and hormone use was obtained from patient questionnaires routinely collected at our institution and included in patients' charts. Statistical analysis was performed using the Fisher's exact test (two-tailed) for statistical significance.

Results

One hundred and ten patients underwent laser conization. Epidemiologic characteristics of the patient population are presented in Table 1.

Table 1. — Patient characteristics ($n = 110$).

Mean age	30.6 years (range 15-78, median 27.5)
Postmenopausal	8 (7.3%)
Prior history of dysplasia > 1 year	42 (38.2%)
Suggested HPV effects noted on pathology	71 (64.5%)
Smokers	57 (51.8%)
Hormone use	OCP 50, HRT 3 (48.2%)

The preoperative diagnosis was CIN 2-3 in 93 patients (84.5%), squamous cell carcinoma in situ in 16 patients (14.5%), and adenocarcinoma in situ in one patient (0.9%). The postoperative cone pathology reported adenocarcinoma in situ in one (0.9%), squamous cell CIS in 15 (13.6%), CIN 2-3 in 58 (52.7%), CIN 1 in 12 (10.9%), and no evidence of dysplasia in 22 (20%). Two cases (1.8%) of microinvasive squamous cell carcinoma were identified, classified as Stage Ia1 and Ia2 cervical cancer. There was only one case of postoperative bleeding that occurred within hours of the procedure and was treated with hemostatic suturing of the cervix. There were no cases of postoperative cervical stenosis manifested by hematometria or dysmenorrhea requiring cervical dilatation.

Twenty-three cones had positive margins (Table 2). Twelve of these involved the endocervical margin only, nine involved the ectocervical margin only, and two cones had CIN extending to both margins. Eight of the 14 (57%) positive endocervical margins had a CIN on pre-

Table 2. — Positive margins ($n = 23$, 20.9%).

Cone pathology	Number	% of all positives
Microinvasive carcinoma	2	8.7
CIS	5	21.8
CIN 2-3	12	52.2
CIN 1	3	13.0
Immature squamous atypia	1	4.3

operative ECC. One patient with Stage Ia2 cervical cancer underwent radical hysterectomy, with no residual disease found. Five (21.7%) of these 23 patients had persistent disease detected at the first follow-up Pap smear.

One hundred and five (95.5%) of 110 laser cones had evaluable margins, and only five (4.5%) had significant thermal artifact, with two (1.8%) noted to interfere with adequate evaluation of margins. Significantly denuded epithelium interfering with complete margin evaluation was reported in two cases.

Seventy-eight patients returned for at least one visit, with a mean follow-up period of 15.7 months. Fifteen patients (13.6%) had dysplasia identified at follow-up. Twelve of these were CIN 1, two were CIN 2-3 and one was adenocarcinoma in situ. Five (33.3%) of these occurred in patients with positive margins, and ten (66.7%) occurred after negative margins. Fourteen were detected at the first or second follow-up visit (mean time to detection 4.6 months). In one case (0.9%), with negative margins on cone biopsy, CIN 1 was detected after two negative follow-up Pap tests, with a time to recurrence of ten months.

Eighty-five patients had preoperative ECC performed, with 35/85 (41.2%) positive for dysplasia. Twenty-six of 28 (92.9%) patients with high-grade ECC and 4/7 (57.1%) patients with low-grade ECC had high-grade lesions on biopsy.

Fifty-seven patients (51.8%) reported regular cigarette smoking. This group had an increased incidence of CIN 2-3 or CIS lesions on cone biopsy when compared to non-smokers (46 and 30 patients, 80.7% and 56.7%, respectively; $p = 0.008$). Forty patients attended at least one follow-up visit, with a mean follow-up period of 13.2 months, versus 12.9 months in non-smokers. The rate of persistent disease and recurrence was 8/57 (14%) in smokers vs 7/53 (13.2%) in non-smokers ($p =$ not significant).

Discussion

The technique of laser conization has been the mainstay of treatment for high-grade cervical dysplasia at our institution for the past several years. Since our institution is a major referral center, our study group had a greater prevalence of persistent recurrent and severe dysplasia than the general gynecologic population, and many patients had undergone previous procedures elsewhere. Some patients return to their primary physicians for follow-up and are referred back to RPCI for complications or persistent disease.

A number of randomized controlled trials have compared laser conization to cold-knife cone biopsy or to LEEP. No trial showed a statistically significant difference in the rate of persistent or recurrent disease, with rates for laser conization ranging from 2.7-16.7% with various follow-up periods [2, 3, 12, 13]. The literature contains differing opinions regarding the definition of recurrent versus persistent disease. Our results indicated that a total of 15 patients had dysplasia detected during the follow-up period. Fourteen of these were detected at

the first or second follow-up visit, including five with positive margins on cone biopsy. With a mean time to detection of 4.6 months, these patients represent persistent disease (12.7%). The remaining patient had a low-grade lesion detected at ten months, after two negative postoperative Pap tests. According to our definition, this represents a true recurrence rate of 0.9%.

Laser conization has been shown to produce significantly less cervical stenosis and a higher adequate colposcopy rate at follow-up when compared to cold-knife conization [2, 13-15]. Our data supports this finding, with none of the patients developing cervical stenosis requiring dilatation. However, when compared to LEEP, the laser conization procedure has been reported to result in greater incidence (17-38%) and depth of significant thermal artifact [2-4]. The incidence of significant thermal artifact with LEEP has been reported to be 3.3-31% [2, 3]. Our data indicated that only five laser cones had significant thermal artifact noted by the pathologist, and only two (1.8%) of these were deemed sufficient to preclude adequate evaluation of the margins. Our data clearly contrasts previous reports and suggests that the incidence of thermal artifact in laser conization is comparable to or less than LEEP.

There were 23 cases with positive margins, but only five of the 18 patients who returned for follow-up were found to have persistent disease. While immune factors may play a role, it is probable that the remaining dysplasia in the crater was ablated by the increased depth of thermal injury and inflammation created by the laser.

Our data support previous assertions that preoperative ECC is a valuable diagnostic tool [16]. Detection of high-grade dysplasia on ECC was a strong predictor of the presence of a high-grade lesion on cone biopsy. We recommend that ECC be performed routinely during the preoperative colposcopic examination.

Cigarette smoking is a known risk factor for the development of cervical cancer, with an associated increase in DNA adducts found in cervical mucus [6-8]. Approximately one-half of our study population reported regular smoking. These patients had a statistically significant increase in the rate of high-grade lesions on cone biopsy. This suggests that cigarette smoking predisposes to increased severity of dysplasia and more extensive lesions that are less likely to be removed entirely on colposcopic-directed biopsy. Our data did not show a significant increase in rates of persistent disease or recurrence in smokers. This may be related to the fact that there was a very low recurrence rate overall, and may have reached significance in a larger sample size.

In conclusion, CO₂ laser conization as an outpatient procedure is a safe procedure and can be performed obtaining negative margins with a thermal artifact in less than 5% of the patients. High-grade lesions are more commonly found in women with a history of regular cigarette smoking, although their recurrence rate of dysplasia was not significant. A larger sample would be necessary to show if a high rate of persistent dysplasia results in regular smokers.

Patients with positive margins who do not have invasive disease can be followed safely as the majority of patients will not require additional treatment as seen in this study. This may be as a result of thermal injury as well as inflammation produced by the laser and possibly immune factors playing a role in these patients.

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