

CO₂ Laser Cylindrical Excision or Standard Re-conization for Persistent-recurrent High-grade Cervical Intraepithelial Neoplasia (HG-CIN) in Women of Fertile Age

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Abstract. *Aim: To investigate the therapeutic efficacy of cylindrical or cone-shaped excision performed by laser CO₂ in the conservative management of persistent-recurrent high-grade cervical intraepithelial neoplasia (HG-CIN) in women of fertile age. Patients and Methods: Ninety-four premenopausal patients with persistent-recurrent HG-CIN had undergone re-conization or cylindrical excision according to the time of reappearance of the disease. The length of the procedures, intra- and postoperative complications, height of the excised specimens, final histological findings and follow-up data were retrospectively evaluated. Results: Fifty-five (58.5%) persistent and 39 (41.5%) recurrent cases had undergone cylindrical excision and standard re-conization respectively. All the treatments were successfully performed in an out-patient setting under local anesthesia with no differences in term of operative time, height of removed specimens, intra- and postoperative complications between the two groups. Definitive histology confirmed HG-CIN in 95.7% of the cases and FIGO Stage Ia1 cervical cancer (negative lymph vascular space involvement, LVSI) in 4.3% of the cases. The endocervical margins were involved in 3.6% of the cylindrical (persistent) and in 17.9% of the cone-shaped (recurrent) specimens ($p=0.03$). The overall cure rate after a median follow-up time of 54 months (range 10-196) was 91.5%. A third excisional procedure was performed in 8 cases of persistent-recurrent HG-CIN with a disease-free subsequent follow-up of 38 months (range 6-108). Conclusion: Cylindrical or conical re-excision performed by CO₂ laser according to the time of*

reappearance of the disease seems to be a promising conservative approach for persistent-recurrent HG-CIN even though further randomised prospective studies are needed to confirm the long-term efficacy and reproductive outcomes.

There is general agreement that treatment of high-grade cervical intraepithelial neoplasia (HG-CIN) reduces the incidence and mortality caused by invasive cervical cancer in women with these lesions (1-3).

Multiple techniques have been used for the conservative treatment of HG-CIN (4-7). These include ablative methods (e.g. cryotherapy, laser vaporization and cold coagulation) for women with satisfactory colposcopic examination in whom invasion has been ruled out, and excisional methods (e.g. the loop electrosurgical excision procedure (LEEP), laser conization and cold-knife conization) for women who have an unsatisfactory colposcopic examination. Hysterectomy is an unacceptable option as a primary therapy for HG-CIN women of a fertile age.

Although the reported primary cure rates of conservative treatment for HG-CIN exceed 95%, a significant number of patients have persistence or recurrence of disease during the follow-up (4-9).

The appropriate management of persistent-recurrent HG-CIN after conservative treatment in women of fertile age is still a matter of debate. The last consensus guidelines for the management of CIN provided by the American Society for Colposcopy and Cervical Pathology (ASCCP) provide only weak support for clinical decisions, considering both a repeat diagnostic excision or hysterectomy acceptable options for women with a histological diagnosis of persistent-recurrent HG-CIN (10).

The aim of the present study was to investigate the therapeutic efficacy of cylindrical or cone-shaped excision performed by CO₂ laser in a large series of fertile patients presenting with persistent-recurrent HG-CIN after a previous excisional treatment.

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Patients and Methods

A retrospective review of the clinical database was conducted to identify all the pre-menopausal patients submitted to a CO₂ laser cervical excision from January 1992 to June 2007 for persistent-recurrent HG-CIN after a previous excisional treatment initially performed at the Authors' institution or elsewhere.

The personal history (age, parity, smoking, oral contraception) was available for every patient. The clinical and pathological details concerning the first excisional treatment were extracted including pre-operative findings, type of procedure (LEEP, CO₂ laser or cold-knife conization), final histology and margin status. Post-operative follow-up was conducted according to the standard protocol of each institution.

Persistent disease was defined as a high-grade cytological and/or histological lesion detected within 12 months of the initial treatment and recurrence as disease detected more than 12 months after therapy with negative findings on at least one preceding follow-up examination. Margin status did not represent a relevant criterion for defining persistent or recurrent disease.

Before laser re-excision all the patients had undergone pap smear, colposcopy and cervical biopsy when necessary. The cytological diagnosis was formulated in agreement with the Bethesda System (11), reinterpreting all the smears performed before 2001, while colposcopic examination was interpreted according to the International Nomenclature (12). All the laser procedures were planned in a day-surgery setting and performed by two skilled laser surgeons (C.P. and M.G.F.). All the treated patients provided informed consent. The laser instrument used and the local anesthesia administered to perform the second procedures were the same as previously described for standard CO₂ laser conization (13).

The CO₂ laser excision procedures were modulated according to the recurrent or persistent behaviour of the disease. In cases of recurrent HG-CIN a standard therapeutic re-conization was performed. Patients with persistent disease were submitted to a laser cylindrical excision according to our technique previously described for the treatment of cervical adenocarcinoma *in situ* (AIS) (14).

The length of the procedures, intra- and postoperative complications, height of the excised specimens, final histological findings and margins status were documented for each patient. Only the involvement of endocervical margins of the excised specimens was considered significant.

Follow-up examinations were performed every 3 months for the first year after re-treatment, every 6 months during the second year and once every year thereafter. At each visit cervical cytology and colposcopic examination were performed in all cases and a cervical biopsy was carried out in the event of colposcopic abnormalities. In cases of reappearance of disease during follow-up, a further treatment was performed following the same procedures.

The results were expressed as median (range) for the discrete variables and mean±standard deviation (SD) for the continuous variables. The statistical analysis was conducted by estimated difference between means with 95% confidence interval (ED; 95% CI) for the continuous variables and by Fisher's exact test for the discrete ones considering $p < 0.05$ as significant.

Results

During the study period, a total of 1,306 CO₂ laser excisions for CIN were carried out at the Authors' institution. Out of these, 94 (7.2%) were performed in pre-menopausal patients

Table I. Anamnestic, clinical and pathological variables of patients submitted to a second procedure by CO₂ laser.

value	Persistence (N=55)	Recurrence (N=39)	P
Age at procedure (median; range)	39 (23-45)	39 (20-45)	
Age at menarche (median; range)	13 (10-17)	12 (10-16)	
Age at coitarche (median; range)	17 (14-26)	18 (13-23)	
Smokers	35	26	ns
Oral contraceptives users	37	28	ns
Smokers and oral contraceptives users	24	16	ns
Parity ≥1	36	17	ns
First treatment			
Laser conization	17	18	ns
LEEP	33	13	0.01
Cold-knife conization	5	8	ns
Involved margins at first treatment	21	7	0.04

LEEP: loop electrosurgical excision procedure.

for persistent-recurrent HG-CIN after a previous excisional treatment. Fifty-five (58.5%) of these patients exhibited persistent HG-CIN and were scheduled for laser cylindrical excision (Figure 1), while the remaining 39 (41.5%) developed recurrent disease for which they underwent a standard laser re-conization.

Table I summarizes the main anamnestic, clinical and pathological variables of the treated patients. Univariate analysis revealed that the LEEP procedure and involved endocervical margins at first treatment were associated with persistence rather than recurrence of disease ($p < 0.05$).

The re-interventions for persistent and recurrent disease were performed a median time of 6 (range 3-12) and 22 (range 13-120) months after the initial treatment, respectively. The cytological and colposcopic findings observed before the second and the third procedure along with the histological results on punch biopsy are detailed in Table II. All the second treatments were successfully performed in an outpatient setting with local anesthesia. The mean length (±SD) of the procedure was 12±5.3 minutes for laser re-conization and 16±6.5 minutes for cylindrical excision (ED=4; 95% CI 1.58-6.42) (ns). The mean height (±SD) of the excised specimens was 14±4.3 mm in cases of re-conization and 19±5.2 mm in cases of cylindrical excision (ED=5; 95% CI 3.1-6.9) (ns).

No major hemorrhages requiring additional sutures were recorded. Eleven patients (28.2%) in the re-conization group and 18 (32.7%) in the cylindrical excision group ($p=ns$) presented minor intraoperative bleeding fully controlled by defocalized laser beam and diathermal coagulator. In all cases, a menstruation-like bleeding that spontaneously cleared up was experienced a week after the treatment and none of the patients required hemostatic treatment.

Definitive histological analysis of the excised specimens revealed HG-CIN in 90 cases (95.7%) and FIGO Stage Ia1 squamous cervical cancer without lymph vascular space involvement (LVSI) in four (4.3%) cases.

The endocervical margins were involved in 2 (3.6%) out of the 55 persistent cases and in 7 (17.9%) out of the 39 recurrent cases ($p=0.03$). All the cases of involved margins were HG-CIN on definitive histology.

After the second procedure, all the patients underwent regular checks with a median time of follow-up of 54 months (range 10-196). Cytological and biopsic histopathological findings observed during follow-up (Table II) led to a third excisional procedure in 8 cases. Six patients re-developed HG-CIN after standard re-conization and two patients after cylindrical excision ($p=0.04$). Table III details the main clinical, pathological and operative data of the patients submitted to the third procedure. Six persistent cases underwent cylindrical excision after a median time of 7 months (range 3-12) from the second procedure and two recurrent cases underwent standard re-conization after 60 and 94 months, respectively. The mean operative times did not differ between the two groups and no significant intra- or postoperative complication was observed. The mean heights (\pm SD) of the conical and cylindrical specimens after the third procedure were 11 ± 1.3 and 13 ± 5.7 mm, respectively. Definitive histological analysis revealed HG-CIN in all the 8 excised specimens, with one case of endocervical margin involvement in each group. During a median follow-up time of 38 months (range 6-108), no case of persistent-recurrent disease was observed among the patients submitted to the third excisional procedure.

Discussion

At present, evidence-based recommendations for the management of women with persistent-recurrent HG-CIN are lacking since in the past relatively few studies have investigated the effectiveness of repeating conservative treatment. Milojkovic (15) found 23 cases of persistent-recurrent disease out of 934 treated HG-CIN (2.5%) and concluded that another operation was recommended for those patients but the specific indications as to conservative management or total hysterectomy remained to be specified. Jeng *et al.* (16) treated 20 cases of persistent-recurrent HG-CIN after LEEP by the excision of the vaginal part of the uterine cervix (partial trachelectomy) under general anesthesia. During an average follow-up of 48 months, no recurrent dysplasia was observed. Das *et al.* (17) recently proposed restricting hysterectomy for persistent-recurrent HG-CIN to patients where repeat loop treatment was considered not to be technically possible because of insufficient remaining cervical tissue.

In our practice, in cases of persistent-recurrent HG-CIN the shape of the excision (conical or cylindrical) was modulated according to the recurrent or persistent behaviour of the disease, considering the time of reappearance as the main differentiating criterion. Positive cyto-histological findings observed within 12 months from a conservative therapy should be considered the only definitive signs of a residual CIN, even though some studies have shown that HG-CIN positive margins on conization specimens correlated with an increased risk of persistent disease (4, 5, 8, 9, 18). According to the literature and as shown in the present series, involved margins at first treatment were associated with persistence rather than recurrence of disease. However, negative margins at histological analysis of the removed cone do not exclude the possibility that a skip lesion might remain within the surviving cervical tissue. In our experience, more than half of the persistent cases (61.8%) revealed free margins after the initial procedure. At the same time, positive margins of the removed cone might not correspond to persistent disease since remaining traces of disease might be destroyed by the vaporization generally used as an adjuvant step at the end of the excision.

Besides the significance of involved margins, the main reason for choosing a cylindrical excision after a primary incomplete treatment is the deep localization of the residual disease within the cervix, topographically corresponding to the apex of the cone initially removed. This choice is supported by a previous study where cylindrical excision provided a high clearance rate in the treatment of cervical adenocarcinoma *in situ* which notoriously arises deeply within the endocervical canal and is complicated by a higher persistence rate than its squamous counterpart after conservative treatment (14).

Conversely, in cases of recurrence after a disease-free period, the lesion could reasonably be presumed to have developed *de novo* within the transformation zone nearly to the external uterine orifice. A standard conization with the removal of the entire transformation zone seems to be an adequate re-intervention in these patients.

The retrospective descriptive feature of the present study significantly limited the value of the obtained results and further trials randomising the two laser procedures among recurrent and persistent cohorts of patients is advocated to definitively establish the most appropriate type of excision. However, in our experience, the adopted strategy for managing persistent-recurrent HG-CIN led to a 91.5% cure rate after a single treatment, with a 100% overall cure rate after two excisional treatments over relatively long-term follow-up. Even if the cylindrical excision technique might require a longer learning curve, in experienced hands the surgical times and operative complication rate were not significantly affected by the type of procedure. Due to the relative infrequency of persistent-recurrent CIN requiring

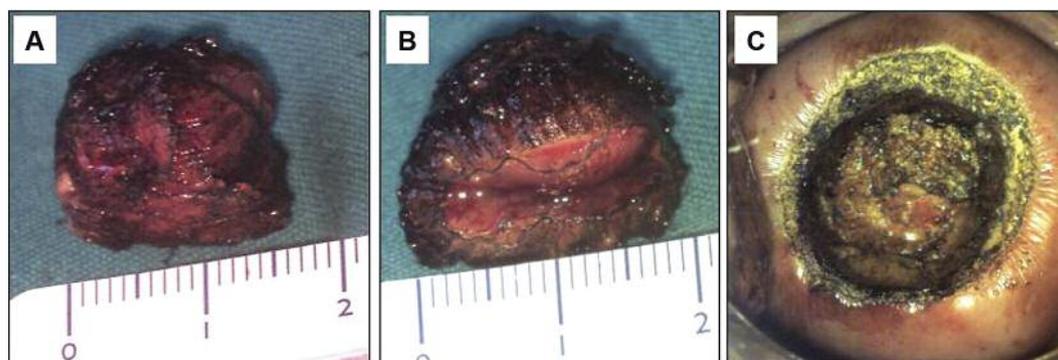


Figure 1. A 17×20 mm laser cylindrical specimen. (A) Lateral view; (B) Frontal view; (C) Surgical field at the end of the procedure.

Table II. Cytological, colposcopic and histological results on punch biopsy observed before and after the second procedure.

	Cytology					Colposcopy				Punch Biopsy	
	Negative	ASC-US	ASC-H	L-SIL	H-SIL	Negative	G1	G2	Unsatisfactory	Not performed	HG-CIN
Before 2nd treatment (number of patients)	-	8	12	8	66	-	24	46	24	24	70
After 2nd treatment (number of patients)	86	-	1	-	7	47	1	2	44	91	3

Table III. Clinical and pathological data of patients submitted to a third procedure by CO₂ laser.

Case no.		2nd Procedure	Final Histology	Margin status		3rd Procedure	Final Histology	Margin status
1	Persistence	Cylindrical	HG-CIN	Negative	Recurrence	Re-conization	HG-CIN	Positive
2	Persistence	Cylindrical	HG-CIN	Positive	Persistence	Cylindrical	HG-CIN	Negative
3	Recurrence	Re-conization	HG-CIN	Negative	Recurrence	Re-conization	HG-CIN	Negative
4	Recurrence	Re-conization	HG-CIN	Positive	Persistence	Cylindrical	HG-CIN	Positive
5	Recurrence	Re-conization	HG-CIN	Negative	Persistence	Cylindrical	HG-CIN	Negative
6	Recurrence	Re-conization	HG-CIN	Positive	Persistence	Cylindrical	HG-CIN	Negative
7	Recurrence	Re-conization	HG-CIN	Positive	Persistence	Cylindrical	HG-CIN	Negative
8	Recurrence	Re-conization	HG-CIN	Negative	Persistence	Cylindrical	HG-CIN	Negative

local re-intervention, all cases should be referred to experienced centres where the procedures can be properly performed by skilled operators.

The surgical instruments employed for the cylindrical excision are an essential issue. Our present and past experience (14) demonstrated that the laser beam should be considered ideal for tailoring the excision to the distribution of a lesion within the cervix or specifically for obtaining a cylindrical specimen. Unfortunately the CO₂ laser methodology is not available worldwide due to its high cost and the requirement for a high level of operator skill.

Excision by LEEP on an out-patient basis has gained widespread use for the diagnosis and/or treatment of patients

with CIN and several studies have shown this procedure to be at least as efficacious as the traditional cold-knife conization for primary intervention (4, 7, 19). However, it is an inflexible instrument able to remove only a fixed amount of tissue predetermined by the size and shape of the loop. This makes cylindrical excision unrealizable even when specimens are removed in more than one piece. Furthermore, during the procedure, the loop itself tends to hide the deepest cutting edges leading to poor results when dealing with disease inside the cervical canal.

Hand-guidable alternatives to the laser beam, allowing modulated excision, are the cold knife or the diathermy needle. The cold-knife procedure has the potential to allow a

cylindrical excision, but it has been widely dismissed because it requires general anaesthesia and is characterized by a high rate of intra-operative, such as haemorrhage, and post-operative complications, among which obstetrical negative outcomes are considered the worst (20). Conversely the needle procedure can be performed in an out-patient setting under local anaesthesia. Even though some surgeons have reported that the use of a diathermy needle was difficult and often increased bleeding compared with the loop, this technique seems to reflect the flexibility of laser to tailor the shape of the excision according to the requirements of a specific lesion (21).

Conclusion

For women of fertile age with persistent-recurrent HG-CIN, the repetition of a local excisional treatment is an adequate option. Cylindrical or conical re-excision performed by CO₂ laser according to the persistent or recurrent behaviour of the disease seems to be a promising approach, even though further randomised prospective studies are needed to confirm long-term efficacy and contraindications.

References

- McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW and Skegg DC: Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 9(5): 425-434, 2008.
- Soutter WP, Sasieni P and Panoskaltis T: Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer* 118(8): 2048-2055, 2006.
- Strander B, Andersson-Ellström A, Milsom I and Sparén P: Long-term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population-based cohort study. *BMJ* 335(7629): 1077, 2007.
- van Hamont D, van Ham MA, Struik-van der Zanden PH, Keijser KG, Bulten J, Melchers WJ and Massuger LF: Long-term follow-up after large-loop excision of the transformation zone: evaluation of 22 years treatment of high-grade cervical intraepithelial neoplasia. *Int J Gynecol Cancer* 16(2): 615-619, 2006.
- Ueda M, Ueki K, Kanemura M, Izuma S, Yamaguchi H, Nishiyama K, Tanaka Y, Terai Y and Ueki M: Diagnostic and therapeutic laser conization for cervical intraepithelial neoplasia. *Gynecol Oncol* 101(1): 143-146, 2006.
- Fallani MG, Penna C, Fambrini M and Marchionni M: Laser CO₂ vaporization for high-grade cervical intraepithelial neoplasia: a long-term follow-up series. *Gynecol Oncol* 91(1): 130-133, 2003.
- Mathevet P, Chemali E, Roy M and Dargent D: Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP. *Eur J Obstet Gynecol Reprod Biol* 106(2): 214-218, 2003.
- Ghaem-Maghani S, Sagi S, Majeed G and Soutter WP: Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol* 8(11): 985-993, 2007.
- Skjeldestad FE, Hagen B, Lie AK and Isaksen C: Residual and recurrent disease after laser conization for cervical intraepithelial neoplasia. *Obstet Gynecol* 90(3): 428-433, 1997.
- Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ and Solomon D; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia or Adenocarcinoma *In Situ*. *Am J Obstet Gynecol* 197(4): 340-345, 2007.
- Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M *et al*: The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 287(16): 2114-2119, 2002.
- Staffl A and Wilbanks GD: An international terminology of colposcopy: report of the Nomenclature Committee of the International Federation of Cervical Pathology and Colposcopy. *Obstet Gynecol* 77: 313-314, 1991.
- Fambrini M, Penna C, Pieralli A, Bussani C, Fallani MG, Andersson KL, Scarselli G and Marchionni M: PCR detection rates of high-risk human papillomavirus DNA in paired self-collected urine and cervical scrapes after laser CO₂ conization for high-grade cervical intraepithelial neoplasia. *Gynecol Oncol* 109(1): 59-64, 2008.
- Fambrini M, Pieralli A, Taddei GL and Penna C: Laser cylindrical excision for cervical adenocarcinoma *in situ*. *Int J Gynaecol Obstet* 95(3): 292-293, 2006.
- Milojkovic M: Residual and recurrent lesions after conization for cervical intraepithelial neoplasia grade 3. *Int J Gynaecol Obstet* 76(1): 49-53, 2002.
- Jeng CJ, Shen J and Huang SH: Partial trachelectomy: a new treatment choice for persistent or recurrent high grade cervical intraepithelial neoplasia. *Gynecol Oncol* 100(2): 231-232, 2006.
- Das N, Naik R, Jackson S, De Barros Lopes A, Monaghan JM, Godfrey KA and Hatem MH: Recurrent smear abnormalities where repeat loop treatment is not possible: is hysterectomy the answer? *Gynecol Oncol* 97(3): 751-754, 2005.
- Zaitoun AM, McKee G, Coppen MJ, Thomas SM and Wilson PO: Completeness of excision and follow-up cytology in patients treated with loop excision biopsy. *J Clin Pathol* 53(3): 191-196, 2000.
- Paraskevaidis E, Koliopoulos G, Malamou-Mitsi V, Zikopoulos K, Paschopoulos M, Pappa L, Agnantis NJ and Loli DE: Large loop excision of the transformation zone for treating cervical intraepithelial neoplasia: a 12-year experience. *Anticancer Res* 21(4B): 3097-3009, 2001.
- Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W and Paraskevaidis E: Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 367(9509): 489-498, 2006.
- Panoskaltis T, Ind TE, Perryman K, Dina R, Abrahams Y and Soutter WP: Needle *versus* loop diathermy excision of the transformation zone for the treatment of cervical intraepithelial neoplasia: a randomised controlled trial. *BJOG* 111(7): 748-753, 2004.

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