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Original Research

Impact of endocervical surgical margin in the treatment of dysplastic cervical lesions

Serena Loda[1], Federica Salinaro[1], Claudio Schreiber[1], Giuseppe Ciravolo[1], GiancarloTisi[1], Federico Ferrari[1], Tiziano Maggino[2], Franco Odicino[1], Enrico Sartori[1]

[1]*Department of Gynecology and Obstetrics, Spedali Civili of Brescia, University of Brescia, Brescia*
[2]*Obstetrics and Gynecology Unit, "Dell'Angelo" General Hospital, Mestre, Venice, Italy*

Summary

Aim of the study: To describe the impact of endocervical margin involvement after cervical CO_2 laser conization and to report the risks factors for positive margin and patterns of subsequent management. *Methods*: Clinical and pathological data of 2863 patients who underwent treatment were retrospectively reviewed. Data were obtained from consecutive patients treated from January 1990 to June 2019 at the Department of Gynecology and Obstetrics of Spedali Civili of Brescia. We used Chi-square test with significance defined at $p < 0.05$ to explore the results. Further, we described the "cylindrical" technique for cervical CO_2 laser conization. *Results*: Endocervical margin involvement was found in 152 patients (5.3%), while 1795 patients with negative endocervical margin were available for follow-up (62.7%), the remaining were lost to follow-up. The risk factors for endocervical margin involvement were the grade of the lesion ($p < 0.001$), age ($p < 0.001$), extension to the cervical canal ($p < 0.001$); presence of moderate intraoperative bleeding ($p = 0.04$) and lack of preoperative antibiotic prophylaxis ($p = 0.05$). Among patients with positive endocervical margin, 21 patients (13.8%) with invasive lesion underwent definitive treatment (Group 1), 30 patients (Group 2) underwent hysterectomy or reconization, while intensive follow-up was offered to 101 patients (Group 3). Only 91 patients were available for follow-up in Group 3. The treatment failure/recurrence in the latter group (n = 91) of patients was higher when compared to patients (n = 1795) with negative endocervical margin (14.3% versus 6.7%; $p = 0.01$). *Conclusion*: Endocervical margin involvement after CO_2 laser conization is a predictor of treatment failure/recurrence of disease. Risk factors for endocervical margin involvement should be subject of prospective multicenter studies.

Key words: Cervical dysplasias; Endocervical margin involvement; CO_2 laser conization.

Introduction

In recent years, organized population based cervical cancer screenings at National and Regional levels have produced an increasing detection of dysplastic lesions of the cervix, particularly in young women [1] and especially with the introduction of HPV (Human Papilloma Virus) high risk test as primary step in the screening programs [2]. Low grade squamous intraepithelial lesion (LSIL), also known as cervical intraepithelial neoplasia of grade 1 (CIN1) is now recognized as a histological diagnosis of benign viral replication, with a high proportion of spontaneous regression and consequently is treated only in case of persistent or progressive disease. High grade lesions (HSIL, that includes CIN2 and CIN3) are the forms of intraepithelial lesion which usually require a treatment, even though CIN2 is suitable for surveillance rather than primary treatment under certain conditions [3].

Traditionally, treatment of dysplastic cervical lesion is based on disruptive or excisional technique of the cervix and so far, a Cochrane review failed to identify a superiority of a technique [4]. Nevertheless, excisional procedures are preferred as they allow to report a histological diagnosis to diagnose an eventual invasive disease [5, 6] and hence tailor subsequent treatment [7, 8]. The most common techniques of excisional procedures with comparable results are large loop excision of the transformation zone (LLETZ) and carbon dioxide (CO_2) laser conization, since cold knife conization was progressively abandoned and reserved to selected cases [9–11]. Conservative surgical treatment of dysplastic lesions is a relevant topic, given the rise of the maternal age, the need to prevent adverse obstetrical outcome and minimize the surgical risk. However, more conservative surgical approaches can expose to a higher risk of persistent disease and recurrence and hence subsequent further treatment, consequently the identification of prognostic factors can potentially guide the management of these patients [12, 13].

Some prognostic factors are universally recognized, including the age of the patient, human immunodeficiency virus serological status, smoking habits, the grade and histopathology of the previous disease and persistence of documented HPV infection [14–19]. Surgical margin involvement still has a controversial role in literature as risk factor for persistent or recurrent disease [20–24] and particular attention should be given to which margin is involved. In fact, the surgical excision creates three margins, the exocervical, the deep (along the surface of penetration) and the endocervical margin. Of interest, few studies describe the

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involvement of the endocervical margin as a crucial factor in determining the persistence and the recurrence of the lesion [25, 26], even though the management of women who have had incomplete excision at the apex of the cone remains controversial [27].

The aim of this study is to describe the impact of endocervical margin involvement after cervical CO_2 laser conization and to report the risks factors for positive endocervical margin and the patterns of subsequent management and follow-up.

Materials and Methods

From January 1990 to June 2019 we collected data of all the patients underwent CO_2 laser conization at the Department of Obstetrics and Gynecology of Spedali Civili of Brescia, a tertiary northeastern teaching hospital. We collected baseline characteristics of the patients, including age, menopausal status, preoperative cervical cytological and biopsy, and the type of cervical treatment. We classified the final pathological findings based on the severity of the disease and we considered for analysis only patients with involvement of the endocervical margin. Free margins at pathological report were defined if the lesion was distant at least 0.5 mm; these patients underwent an intensive follow-up with cytological and colposcopic evaluation at 6, 12, 18 and 24 months after surgery.

We defined as a treatment failure the presence of residual disease within one year after CO_2 laser conization, while a treatment recurrence if failure occurred more than one year later. All data of the patients were collected prospectively in a dedicated electronic database and were registered according to the current legislation in terms of privacy. The authors used a Chi-square test to analyze the risk factors for positive endocervical margins and recurrence and the level of significativity was established at $p < 0.05$.

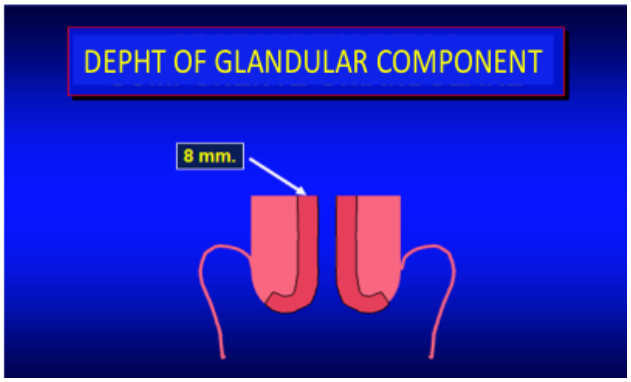

Figure 1. — Depth of the glandular portion of the cervix.

Surgical Technique

All the patients underwent colposcopic evaluation and subsequent biopsy performed on the basis of abnormal cytology prior surgical treatment [28]. The indication for CO_2 laser conization included glandular atypias, CIN2-3, carcinoma in situ (CIS), early invasive disease (FIGO 2018 Ia1 without lymph vascular space invasion), discrepancy between cytology and histology with a colposcopic suspect of greater grade lesion, non-assessable endocervical margins of the lesion, non-visible lesion with atypical cytology, suspected cytological or colposcopic lesion initially or frankly invasive (as reported in Table 1). Commonly, the procedures were performed under local anesthesia while narcosis surgery was used in cases of greater complexity or high risk of bleeding, subjectively assessed during colposcopic evaluation. In all patients, cervical infiltration was performed

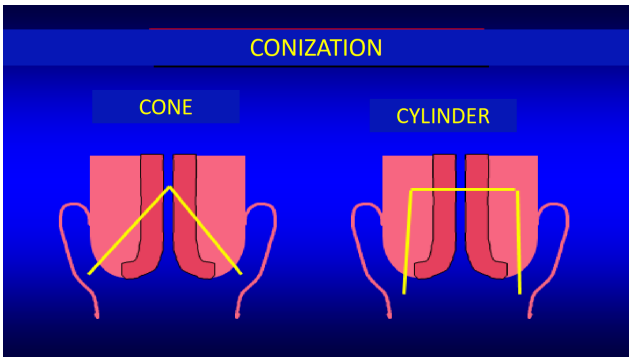

Figure 2. — Planned cylindrical excision of the cervix.

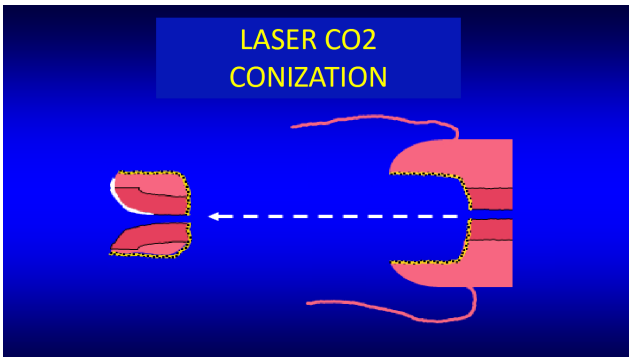

Figure 3. — Cylindrical specimen.

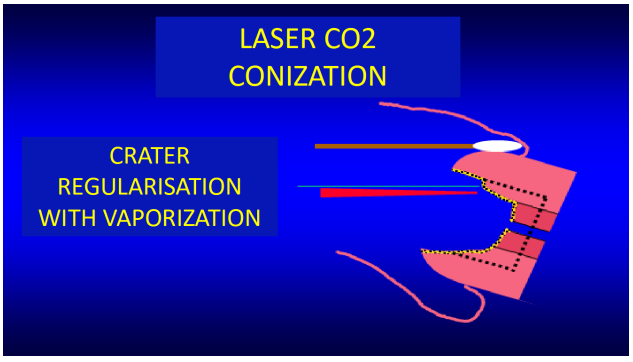

Figure 4. — Regularization of the cervical crater.

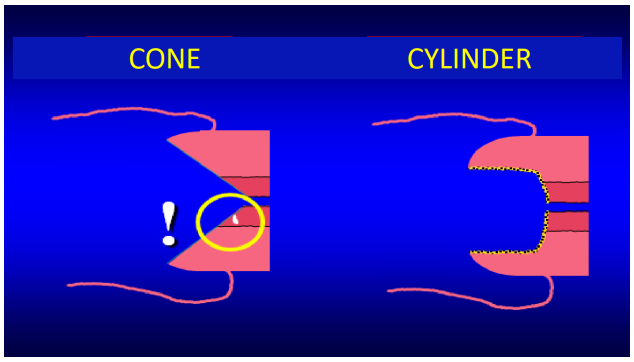

Figure 5. — Different shape of the surgical site.

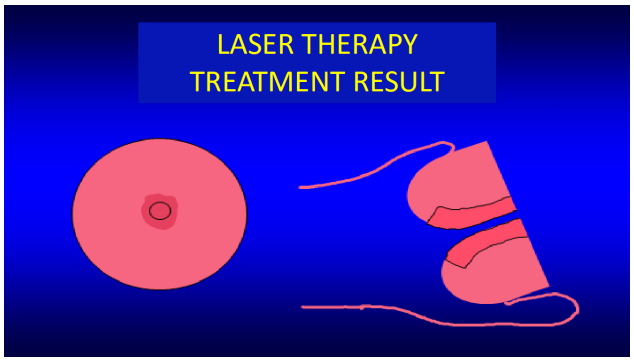

Figure 6. — Anatomical restitution of the cervix.

using 3-4 milliliters of 1% Mepivacaine hydrochloride with 1/200.000 Ephinefrine, for local anesthetic and vasoconstrictor purposes, unless known allergies. We used a CO_2 laser equipment connected with a micromanipulator to the colposcopic device, which permitted to assess the margins of the lesion and hence tailor the size of the excision. We used a 40 to 50 watt power CO_2 laser emission. The aim of the surgical technique adopted is to obtain a specimen suitable both for diagnostic and therapeutic purposes, assuming an 8 millimeters depth of the glandular portion of the cervix (Figure 1). A cylindrical-shaped excision of the exocervix and cervical canal (Figure 2 and 3) with a modulated caudo-cranial extension guided by intraoperative colposcopic evaluation was attempted. The cranial extension along the cervical canal was at least 10 mm or greater up to 3-5 mm of visible endocervical limit respectively for exocervical and endocervical lesions. In case of exocervical spread of the disease exceeding the excision volume, the treatment was further completed with the vaporization up to a depth of at least 8 mm on the cervix and up to 2 mm on the vaginal fornix involved. After the removal of the surgical specimen, the treatment was completed with the vaporization of the cervical crater to enhance the regularity of the cylindrical excision (Figure 4). Finally, 3-4 mm were vaporized at the apex of the cylinder to obtain a safety margin in case of endocervical margin involved at pathological report.

The "cylindrical" technique and the absence of scarring and hemostatic sutures minimize the risk of occult persistence of disease (Figure 5). Further, the containment of the thermal effect on healthy peri-excisional tissues obtainable with the CO_2 laser technique has the advantage to restore a normal structural and functional anatomy of the cervix (Figure 6). The latter is of outmost importance in terms of obstetrical outcomes and to ensure an adequate cytological and colposcopic evaluation (Figure 6) during follow-up.

Table 1. — *Indications for CO_2 laser conization treatment.*

Indication for conization	**n (%)**
Persistent LSIL or HSIL with negative biopsy	80 (2.8%)
Persistent condyloma or CIN1	791 (27.6%)
Pap smear AGC	28 (1%)
Squamous Lesion	
- CIN2	626 (21.9%)
- CIN3/CIS	1283 (44.8%)
AIS	31 (1.1%)
Early invasive	
- Squamous	11 (0.4%)
- Adenocarcinoma	1 (< 0.1%)
Invasive cancer	
- Squamous	8 (0.3%)
- Adenocarcinoma	4 (0.1%)
Total	2863 (100%)

Table 2. — *Phatological report of the cone specimens.*

	n (%)	**Positive endocervical margin**
Negative	180 (6.3%)	0 (0%)
Condyloma or HPV presence	195 (6.8%)	0 (0%)
CIN1	625 (22%)	2 (0.3%)
CIN2	562 (19.6%)	2 (0.3%)
CIN3/CIS	1161 (40.5%)	95 (8.2%)
AIS	34 (1.2%)	7 (20.6%)
Early invasive	75 (2.6%)	25 (33.3%)
- Squamous	60 (2.1%)	22 (36.7%)
- Adenocarcinoma	15 (0.5%)	3 (20%)
Invasive cancer	31 (1.1%)	21 (67.7%)
- Squamous	24 (0.8%)	15 (62.5%)
- Adenocarcinoma	7 (0.2%)	6 (85.7%)
Total	2863 (100%)	152 (5.3%)

Results

We found a total of 2863 patients treated with CO_2 laser conization during the study period (Table 1). The median age was 39.1 (range 16-78) years, most of the patients were nulliparous (48.5%) while only 6.8% had more than two

Table 3. — *Risk factors for positive endocervical margin.*

		N	Positive endocervical margin	*p* value
Age	< 50	2404	110 (4.6%)	0.001
	> 50	459	42 (9.1%)	
Extension to the cervical canal	No	1171	42 (3.6%)	0.001
	Yes, limit visible	1228	69 (5.6%)	
	Yes, limit not visible	464	41 (8.8%)	
Moderate intraoperative bleeding	No	2478	123 (5.0%)	0.04
	Yes	379	29 (7.7%)	
Preoperative antibiotic Prophylaxis	No	683	47 (6.9%)	0.05
	Yes	2174	105 (6.9%)	

pregnancies. CO_2 laser conization was performed under local anesthesia in 2420 cases (84.5%). Endocervical extension was found during colposcopic assessment in 1228 patients and the cranial limit was visualized in 83% of the cases. A concomitant involvement of the vaginal wall with evidence of HPV-related diseases were treated during the same surgery in 257 patients. The depth of the cylindrical-excision was < 10, between 11 and 15, between 16 and 20 and > 20 mm, respectively in 26.3%, 46.4%, 20.3% and 7% of the cases. Pathological report is shown in Table 2 and interestingly, in 375 cases (13.1%) no atypical lesions were detected.

Endocervical margin involvement (at the endocervical apex of the "cylinder") was seen in 152 patients accounting for an involvement rate of 5.3% (Table 2). Involvement occurred rarely (0.3%) in low-medium grade lesions (CIN1 and CIN2). In other cases, the involvement of the endocervical margin was proportional to the severity of the lesion as reported in Table 2. Overall, the risk factors that increase the likelihood of endocervical involvement included the severity of the lesion ($p < 0.001$), age older than 50 years old ($p < 0.001$), extension to the cervical canal ($p < 0.001$), presence of moderate intraoperative bleeding ($p = 0.04$) and omitted preoperative antibiotic prophylaxis ($p = 0.05$), as seen in Table 3. In detail, we took in account for analysis the patients with endocervical margin involvement by dividing them in three groups according to their pathological report and management (Table 4).

Group 1 - Patients treated with non-conservative surgery for invasive disease

Twenty-one patients had an invasive lesion (Stage IA1 with LVSI or greater) and were treated with radical hysterectomy in 20 cases and primary radiotherapy in one case. We found persistence of disease in 14 cases (70%) in the uterine specimen. Unfortunately, no data regarding surgical time neither the oncological outcomes were available, hence no conclusions were available regarding the impact of surgical access [29–31] and lymphadenectomy procedures [32]. All the patients of this group were excluded from subsequent follow-up analyses.

Group 2 - Patients treated with non-conservative surgery for pre-invasive or early invasive disease

In 29 patients, we found a pre-invasive (CIN3/CIS, AIS) or early invasive (FIGO 2018 Ia1 without LVSI) disease and the decision for hysterectomy was based age, parity, surgical risk of major surgery and the presence of associated pathology recommending itself a hysterectomy, as shown in Table 4. Surgical uterine specimens demonstrated residual disease in 44.8% of the cases (n = 13). In details, we found a residual disease respectively in 31.2% and 63.6% of the patients with a previous diagnosis of HSIL (CIN3/CIS) and early invasive squamous lesions; one case of adenocarcinoma in situ (AIS) was confirmed in the hysterectomy specimen (see Table 5). Of note, an additional case of early invasive adenocarcinoma received a subsequent CO_2 laser conization, but without evidence of disease on the cervical specimen. All the patients of this group were excluded from subsequent follow-up analyses.

Group 3 - Patients sent for cytological and colposcopic follow-up

A total of 101 patients were referred to a periodic follow-up. Ten were not assessable because they were lost to follow-up, consequently only 91 patients were available (Table 4) with an average follow-up of 58 months and a median of 43. Seventy-eight patients (85.7%) were free from disease at the last colposcopic follow-up while 13 patients (14.3%) were found with disease at follow-up. Of the latter group of patients, respectively 12 and 1 had a previous diagnosis of CIN3/CIS and early invasive disease (with squamous histology) with a treatment failure rate of 8.7% and a treatment recurrence rate of 5.5%. The treatment of the recurrence was a CO_2 laser vaporization in three cases with a very small and visible low-grade lesion, while the remaining ten patients underwent further CO_2 laser conization. Of the latter group, only one patients had a positive endocervical margin and hence she was submitted to total hysterectomy. Similarly, one of the three patients treated with vaporization showed subsequently a new disease recurrence (CIS) after 18 months and underwent hysterectomy while one other patient removed the uterus for a concomitant benign condition (leiomyomas) without evidence of residual disease.

Table 4. — *Study groups according to pathology of the cone.*

	Total	Group 1	Group 2	Group 3	Lost to follow-up
CIN1	**2 (1.3%)**	0 (0%)	0 (0%)	2 (100%)	0 (0%)
CIN2	**2 (1.3%)**	0 (0%)	0 (0%)	1 (50%)	1 (50%)
CIN3/CIS	**95 (62.5%)**	0 (0%)	16 (16.8%)	72 (75.8%)	7 (7.3%)
AIS	**7 (4.6%)**	0 (0%)	2 (28.6%)	4 (57.1%)	1 (14.3%)
EARLY INVASIVE DISEASE					
- Squamous	**22 (14.4%)**	0 (0%)	11 (50%)	10 (45.5%)	1 (4.5%)
- Adenocarcinoma	**3 (1.9%)**	0 (0%)	1 (lasercono) (33.3%)	2 (66.6%)	0 (0%)
INVASIVE DISEASE	**21 (13.8%)**	21 (100%)	0 (0%)	0 (0%)	0 (0%)
Total	**152 (100%)**	**21 (13.8%)**	**29 (19.1%) + 1 lasercono**	**91 (60%)**	**10 (6.6%)**

Table 5. — *Hysterectomy patients and follow-up patients (excluding invasive lesions).*

Histological examination cone with positive endocervical margin	N°	Operated patients	Positive histology (%)	Evaluable patients at follow up	Recurrence at follow-up (%)
CIN1	2	0	0 (0%)	2	0 (0%)
CIN2	2	0	0 (0%)	1	0 (0%)
CIN3/CIS	95	16	5 (31.2%)	72	12 (16.6%)
AIS	7	2	1 (50%)	4	0 (0%)
Early invasive squamous carcinoma	22	11	7 (63.6%)	10	1 (10%)
Early invasive adenocarcinoma	3	1 (lasercono)	0 (0%)	2	0 (0%)

Comparison of persistence/recurrence

As reported above, from the initial group of 2863 patients, we identified 152 patients (Group 1, 2 and 3) with positive endocervical margin, and of them only 91 patients (Group 3) underwent CO_2 laser conization with an available subsequent follow-up.

Conversely, a total of 1795 patients with negative endocervical margin were available for follow-up analyses after initial CO_2 laser conization. In detail, we found a persistent/recurrent disease rate of 14.2% and 6.7% respectively in group 3 and in the 1795 with negative margin ($p = 0.01$)

Obstetrics outcomes

After CO_2 laser conization the number of known pregnancies was 206 in 138 women; among these two pregnancy suffered cervical incontinence (0.97%).

Discussion

CO_2 laser conization with cylindrical technique modulated on the basis of the intraoperative evaluation of the endocervical extension of the lesion, resulted in a very high rate of negative endocervical margins (94.7%), higher than any other available technique [33–35]. In our series we demonstrated a higher prevalence of recurrence in case of endocervical involvement regardless the type of the lesion when compared to the negative endocervical margins.

Incomplete excision of CIN lesions expose women to a consistent risk of post-conization high-grade disease, as reported in previous literature and meta-analysis [33, 34]. In fact, the most representative works is a comprehensive meta-analysis by Ghaem-Maghami that described the findings in 35109 women of whom 8091 (23%) had at least one margin of the excisional biopsy involved with disease (CIN or any type) [36]. Regardless the type of the excisional procedure, the pooled prevalence of post treatment disease was 16%, 21% and 23 % respectively in patients with involved exocervical margins, endocervical margins and with both margins ($p < 0.001$). Furthermore, a recent meta-analysis confirmed that CO_2 laser conization technique was more effective in terms of complete excision (absence of positive margins) than LEETZ and cold-knife conization [34]. These findings are relevant, given that our case series included not only CIN2 and CIN3, but also AIS and early invasive disease.

The comparison over the time between patients with negative and positive margins confirmed that patients with positive endocervical margins have a greater risk of persistence/recurrence of disease than those with negative margins [25, 37, 38]. In our study the recurrence rate was 8.2% and this is in line with the overall average of 7% found in the most recent meta-analysis [34] and the median proportion of 9% in an earlier meta-analysis [36, 37]. Interestingly, in a study conducted on the determinants of success in treating CIN, the grade of the lesion and the involvement of the endocervical margin were identified as the most important determinants of high-grade post-treatment disease [37]. However, in this study, the extensive vaporization of the crater during the procedure could have reduced the significance of endocervical margin involvement in terms of persistence or recurrence and this further strengthens the role of endocervical margin involvement. In fact, patients with positive endocervical margin involvement had worse

grade lesion at histological examination of the cone, even though the severity of the lesion was not a significant predictor of recurrent disease in our study. This finding implies that the complete excision also in case of CIN3/CIS disease is likely to yield a complete cure. Nonetheless, it is crucial to identify patients requiring immediate second surgery and patients suitable for delayed decision with close follow-up. In the meta-analysis by Ghaem-Maghami [36] some patients received immediate hysterectomy after initial treatment, often in view of the involved margin; however non-conservative treatment was not reported systematically and hence the risk of recurrence is underestimated. The latter can partly justify the wide range of recurrence (median 29% with IQR 14-39) reported in the meta-analysis.

The low percentage of treatment failures in the high grade SIL group of 16,6% in our patients derives from the real incidence of cases followed in a planned way after primary conization.

Further key question is the length of the follow-up, which is crucial to detect persistent disease rather than relapsed pathology. As stated by Ghaem-Maghami [36] and others [39], many studies followed the women for relatively short lengths of time. Only twenty studies in the meta-analysis presented data for an average follow-up of more than two years and the cumulative risk of failures in individual studies rises with increasing length of follow-up. Our patients were evaluable with an average FU of 58 months and a median follow-up of 43 months with only 9.9% of cases lost to follow-up. The adoption of this follow-up schedule identified the treatment failure and recurrence after conization: the majority of cases occurred during the first year (58%), 25% in the second year and 16.7% in the third year. An intensive follow-up can provide the opportunity to retreat these patients with a subsequent CO_2 laser conization.

Several authors published reports describing persistent or progressive disease, after conservative management of adenocarcinoma in situ of the cervix (AIS). In a review of 14 studies including 157 patients, affected by AIS and treated obtaining negative conization margins a prevalence of 26% of patients harbored residual AIS and in 2% of the cases an unsuspected invasive cancer was detected [40]. The diagnostic issues related to cervical AIS reside in the reduced colposcopic accessibility to the cranial border of the lesion, the adequacy of the pathological processing of the cone and the multifocality features of these type of lesions. In the series of Costa et al. the patients affected by AIS were treated conservatively, and interestingly, persistent or recurrent disease was observed in 40.4% of cases, with a relative prevalence of 19% and 65% respectively in patient with free and involved margins after first conization [41]. In our series, we had a similar frequency of persistent/recurrent disease in patients with free margins.

In the group of early invasive squamous lesions the high number of persistent disease and the risk of unrecognized invasive neoplasm, affect the criteria for a conservative approach to patients who wish pregnancy and who can ensure constant cytological and colposcopic control [42].

The vast majority of cervical cancer and their immediate precursors are caused by persistently detectable infection with human papillomavirus (HPV) test and recently, many studies have included the combined test (pap smear and HPV test) not only as a primary screening but also in the follow-up after treatment [43, 44]. In a systematic review [43], the overall sensitivity was significantly higher for HPV testing compared to pap smear at 3 and 6 months; at 9 and 12 months the sensitivity for HPV was still higher, but the difference was not significant. At 24 months the cytological assessment was as sensitive as virology and it the combination of the two tests confers a significant advantage at any interval of time compared to any test applied alone [44]. Recent studies have shown that the combination of HR-HPV at follow-up and positive margins may increase the accuracy in predicting treatment failure and combined results of the margin status and post-treatment HPV status could be used to stratify risk and diversify management [36, 38].

The CO_2 laser conization technique adopted in our Department allows a tailored excision of the lesion in a single specimen and, in case of multiple associated lesions of the fornix or vagina, a complementary treatment in a single surgical attempt. Furthermore, limited thermal damage on the residual cervical tissues reduces the anatomical retraction and permits adequate condition for a correct colposcopic and cytological follow-up. Multiple steps excision procedures and electro thermal derived damage compromise the correct pathological assessment of apical margins and these conditions may justify the wide range of post-treatment failures reported in literature [36, 39]. Our data confirm that the status of the endocervical margin is crucial to define the risk of developing persistence or recurrence of disease.

Meta-analysis on obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions by Kyrgiou [45] revealed an increased risk for preterm delivery, low birthweight and premature rupture of the membrane after cold knife conization and LLETZ. On the contrary, none of the previous clinical condition were relevant after laser ablation, but this may not be true after immediate repetition of conization with further loss of cervical tissue, which is an important variable in determining the risk of negative obstetric outcomes [46]. In literature there is not a uniform protocol for follow-up after CO_2 laser conization of cervical preinvasive lesions, however, our results confirmed the efficacy of semestral cytology and colposcopy during the two years following conization, especially in women with endocervical margin involved.

In conclusion, our case series demonstrated that involvement of endocervical margin after CO_2 laser conization increases the risk for treatment failure/recurrence. However, the “cylindrical” technique allows a relative low rate of recurrence in these patients, even though intensive follow-up is crucial to identify patients ideally candidate to a second

conservative treatment attempt. Risk factors for endocervical margin involvement should be subject of prospective multicenter studies.

Ethics approval and consent to participate

All clinical investigations are conducted according to the Declaration of Helsinki principles. Retrospective observational studies involving the collection of anonymized existing data have been considered exempt from the requirement of an institutional review board (IRB) approval as stated by the Local Ethical Committee of our institution.

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Conflict of Interest

The authors declare no conflict of interest.

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Corresponding Author:
Tiziano Maggino, M.D.
Obstetrics and Gynecology Unit, "Dell'Angelo" General Hospital, Mestre, Venice, Italy
e-mail: tiziano.maggino@aulss3.veneto.it