



The efficacy of long term follow-up and CO₂ laser conization as conservative management in patients with cervical cancer stage FIGO IA1

Maria Grazia Fallani[†], Annalisa Pieralli^{*}, Virginia Lozza[†], Serena Tarani[†], Claudia Bianchi[†], Sepideh Sadat Peyrov Sajad[†], Massimiliano Fambrini[†] and Carlo Penna[†]

*Correspondence: pierallannalisa@virgilio.it

[†]These authors contributed equally to this work.

Department of Woman and Child Health, Section of Gynecology and Obstetrics, University of Florence, Largo Brambilla 3, 50144 Florence, Italy.

Abstract

Background: Patients with FIGO (International Federation of Gynaecologists and Obstetricians) stage IA1 cervical squamous carcinoma can be treated conservatively with conization only as alternative to a hysterectomy. The aim of this study was to evaluate the efficacy of laser CO₂ excision as therapeutical method for stage IA1 cervical squamous carcinoma.

Methods: Sixty patients were submitted to CO₂ laser conization with histologic diagnosis of squamous carcinoma stage FIGO IA1 and then submitted to follow-up with PAP smear, colposcopy and biopsy. Prognostic risk factors for relapse were evaluated with univariate analysis.

Results: Conservative management with laser therapy was effective in more than 90% of the patients. When disease persistence was detected (7%), patients underwent repeated laser CO₂ conization and followed-up without demolitive intervention. The risk of disease progression in the case series was 1.8%. Univariate analysis revealed that only depth of stromal invasion was a significant risk factor for relapse ($P < 0.04$). Moreover, depth of stromal invasion between 1-3 mm was the only prognostic factor for relapse with specificity 78%, sensitivity 75% and likelihood positive ratio 3,47.

Conclusion: Laser CO₂ conization alone appeared to be an effective and safe treatment for patients with Cervical Cancer Stage FIGO IA1 if careful post-treatment follow-up was guaranteed. The depth of stromal invasion has been confirmed as the most important risk and prognostic factor to be evaluated for disease relapse.

Keywords: Cervical cancer, conservative therapy, conization, microinvasive, stromal invasion

Introduction

Cervical cancer is the seventh most common cancer in the World and the second neoplasia in incidence among women [1].

The percentage of invasive tumors decreased progressively over the years, mainly due to the improved of screening methods. However, early diagnosis produced an increasing number of cervical intraepithelial neoplasia (CIN) and microinvasive forms of carcinoma [2].

The classification of FIGO defines stage IA1 of cervical cancer as a microinvasive lesion with a stromal invasion less than 3 mm in depth and a horizontal spread less than 7 mm [3]. The best treatment for patients with cervical cancer stage IA1 is still discussed [4-7].

Historically, the gold standard of treatment for microinvasive cervical cancer is by simple or modified hysterectomy. Pelvic lymphadenectomy is considered taking into account the fact that the risk of lymph node metastases in cervical cancer with invasion less than 1 mm is insignificant in absence of lympho-vascular space invasion (LVSI); the risk increases to 0.8% in case of stromal invasion between 1 and 3 mm and to 8.2% in presence of lympho-vascular space invasion [8-11].

However, in relation to patients' age, good prognosis and low risk of lymph node metastases, a conservative treatment

performed by conization is a recent proposal as unique therapeutic presidium in women in their fertile age and strongly wishing to conceive [4,12-16].

The authors present a retrospective cohort study to evaluate laser CO₂ excision associated to a strict long term follow up as a definitive treatment for women with stage IA1 cervical cancer.

Methods

Using data from the archive of Colposcopy and Laser Therapy Unit of University of Florence, a retrospective analysis of laser conization cases performed between 1998 and 2010 was conducted.

The patients' inclusion criteria in the study group were the presence of a histological diagnosis of squamous cervical cancer stage IA1 on the surgical specimen, according to 2010 FIGO classification (all the specimens obtained before 31 December 2010 were re-analyzed according to the new classification) and a clinical management of treatment and follow-up entirely conducted at the Colposcopy and Laser Therapy Unit of Careggi. All patients with glandular histology were excluded from the study group.

Each patient's medical history was collected with particular attention to demographic risk factors for HPV-related disease,

such as age, diabetes, seropositivity for HIV, HCV or HBV, autoimmune diseases, cigarette smoking, past or current chemotherapy treatment, previous treatment for HPV-related disease.

Laser procedures were performed in day-surgery regimen under local anesthesia, in an outpatient setting. Up to 2002 the conization was performed by a Sharplan 733A CO₂ laser (ESC Sharplan. Yokneam, Israel) with maximum power output of 40 Watt, used in continuous mode. The beam spot diameter ranged from 0.5 to 1 mm with an irradiance ranging from 2500 to 3500 W/cm², guided by a micromanipulator. However, laser procedures carried out after 2002 were performed by a SmartXide 50HS (Deka Inc. Italia) CO₂ laser with maximum power output of 50 Watt, used in super-pulsed mode at 25 Watt. The beam spot diameter ranged from 0.5 to 1 mm with an irradiance ranging from 3500 to 4000 W/cm², guided by a micromanipulator.

The CO₂ laser was connected to a Zeiss OPMI colposcope (Carl Zeiss. Oberkochen, Germany).

After delineating the transformation zone of the cervix with Lugol's iodine solution, local anesthesia was administered performing at the 3-, 6-, 9- and 12-o'clock site of the cervix injections of 3.6-5.4 mL of a 2% lidocaine mixed with epinephrine 1:100.000.

The first step of laser conization procedure was to direct the laser beam perpendicularly to the cervical surface achieving an initial 0.5-1 cm deep circular section and then to guide it obliquely by manipulating the on-going excised specimen using a small steel hook. To assure the complete clearance of the lesion, after the excision the crater base and the walls were vaporized with defocused laser beam. Generally, the laser beam was sufficient to obtain satisfactory haemostasis; some cases required the use of a diathermal coagulator for a dot haemostasis of a single bleeding vessel.

Cervical cones were subjected to histological examination at the Institute of Pathology of the University of Florence. The diagnostic report was considered complete if it contained histological type, stage of disease, involvement of endocervical margins of resection and eventual lympho-vascular space invasion.

According to the depth of the tissue invasion, the diagnostic reports were divided into cervical cancer stages IA1 less or equal than 1 mm and cervical cancer stage IA1 less or equal to 3 mm, but greater than 1 mm.

After the conization and the diagnosis of Stage IA1 squamous cell cervical carcinoma, the patients were counselled about the possibility of a conservative management with careful post-treatment follow-up as an alternative to the conventional treatment proposed by guidelines [9].

Patients, giving their informed consent were directed to follow-up, which provided visits every 3 maximum 6 months in the first 2 years and then once a year up to at least 5 years after treatment. Each visit consisted in a Pap smear, a colposcopy and eventually a biopsy of evident lesions.

Table 1. Demographic risk factors.

Sieropositivity for HIV, HCV or HBV*	3
Past or actual chemotherapy treatment	2
Diabetes	0
Autoimmune diseases	1
Smoking*	5

*risk factor in recurrent patients.

Recurrent disease was defined as the histological diagnosis of CIN II/III or more advanced lesion in one of the biopsies taken during the follow-up.

Every patient with relapsing CIN II/III was sent to a second treatment of laser conization; patients with a diagnosis of invasive carcinoma, however, were sent to major surgery.

Univariate analysis by Fisher's Exact test was conducted on the risk factors for disease recurrence known in literature to identify those which had influence in the series. P values < 0.05 were considered statistically significant. Sensitivity, specificity and likelihood ratio were calculated for each of the risk factors resulted significant at univariate analysis.

Results

From 1998 to 2010, a total of 1108 patients were submitted to a diagnostic laser CO₂ conization with a bioptical diagnosis of CIN II/III (high-grade cervical intraepithelial neoplasia) at Colposcopy and Laser Therapy Unit of the University of Florence. Of those, 60 patients were diagnosed stage IA1 squamous cell carcinoma of the cervix and respecting inclusion criteria for the study built up the initial study group and were asked to undergo a strict follow up as alternative to standard treatment.

These patients had a mean age of 43 years at the time of conization (range 25-76 years); 14 of them had already experienced HPV-related benign disease, no patient had been previously treated for CIN of any grade.

In the history of 11 patients, there were one or more demographic risk factors for HPV-related disease and for cervical cancer (Table 1).

No major intraoperative complications occurred such as trauma of adjacent organs (bladder or rectum) or major bleeding (> 500cc).

9.6% of treated patients experienced a minor bleeding during the procedure, spontaneously solved by the application of a vaginal tampon at the end of treatment and removed the day after.

In histological reports of 17/60 (28.3%) conizations, the stromal invasion was greater than 1mm, but less than or equal to 3mm; in the remaining 43/60 (71.7%) conizations the invasion was less than 1mm. A total of 31/60 (51.7%) reports described the presence of intraepithelial neoplasia on endocervical margins of resection and only 3/60 (5%) reports reported the presence of lympho-vascular space invasion (LVSI); all of these patients were followed-up without repeating conization or demolitive intervention.

Table 2. Follow-up of treated patients.

Treatment's year	Number of patients	Follow-up < 2 years	2 years ≤ follow-up < 5 years	5 years ≤ follow-up < 10 years	Follow-up ≥ 10 years
1998	5	-	-	-	5
1999	5	-	-	-	5
2000	5	-	1	4	-
2001	2	-	-	2	-
2002	4	-	1	3	-
2003	4	-	-	4	-
2004	4	-	-	4	-
2005	3	-	3	-	-
2006	5	-	5	-	-
2007	3	-	3	-	-
2008	5	-	5	-	-
2009	3	3	-	-	-
2010	7	7	-	-	-
Tot.	55	10	18	17	10
%	-	18%	33%	31%	18%

Table 3. Recurrence rate according to analyzed risk factors.

	Relapse	No relapse	P
Depth of stromal invasion (mm)			
≤1	0/4	40/51 (78%)	NS
1-3	3/4 (75%)	11/51 (21%)	<0.04
Positive resection margins	1/4 (25%)	30/51 (59%)	NS
Positive LVSI [†]	0/4	2/51 (4%)	NS
Demographical risks [‡]	2/4 (50%)	9/51 (18%)	NS
Previous HPV	1/4 (25%)	13/51 (25%)	NS

[†]Lymph-Vascular space infiltration

[‡]such as age, diabetes, seropositivity for HIV, HCV or HBV, autoimmune diseases, smoking, past or actual chemotherapy treatment.

The 8.3% of patients (n=5) were excluded from the study because they couldn't follow a conservative management: 2 of these patients (40%) underwent simple hysterectomy for not oncological disease (Abnormal Uterine Bleeding); the remaining patients (3/5, 60%) voluntarily chose to undergo hysterectomy because they presented, as a complication of conization in menopause, a stenosis of external uterine orifice that would not allow a complete cytological follow-up. The cone histological reports of these patients presented margins affected by CIN in 3/5 cases (60%); in any of them lympho-vascular space invasion (LVSI) was reported and 3/5 cases (60%) reported stromal invasion greater than 1 mm but less than or equal to 3 mm. In none of the surgical specimen of 5 hysterectomies residual cervical dysplasia after conization was found.

Of the 60 originally enrolled patients, 55 (91.7%) constituted the final study group. These patients represented the younger ones of the series with a mean age of 38 (range 25-47 years).

The mean time of follow-up was 4.8 years (range :1-12 years). For 49% (27/55) of patients, the time of follow-up was ≥ 5 years, while for 33% (18/55) of patients was < 5 years and

≥ 2 years. For the remaining 18% (10/55) of women follow-up period was < 2 years. The shorter time of follow-up in these patients was mainly due to the year in which the treatment was done. In fact these patients were submitted to laser CO₂ conization between 2009 and 2010 and they are still doing the regular follow-up checks (Table 2).

During follow-up time, 4/55 (7.2%) disease recurrences occurred: 3 (5.45%) CIN III, which were sent to a second laser conization, and 1 (1.8%) invasive cervical carcinoma, which was sent to major surgery (radical hysterectomy - Piver III class - with pelvic lymphadenectomy) and the histological reports confirm the diagnosis of invasive cervical cancer. In the personal history of these patients, two were smokers and one was HCV positive (Table 1).

Of all recurrences, 2 (50%) occurred more than 5 years after laser conization (6 and 8 years, respectively), while the remaining 50% cases occurred within the first year of follow-up, so we can not exclude that they could be a persistence of disease.

All 3 patients who underwent a second laser treatment accepted to be followed-up with cyto-colposcopic examinations at the Colposcopy and Laser Therapy Unit of University of Florence and they are currently free from disease after a time of 4, 6 and 11 years, respectively.

From the statistical analysis that we carried out, only the depth of stromal invasion was found to be a significant risk factor (p < 0.04) for recurrent disease after laser conization (Table 3). The stromal invasion up to 3 mm can be considered a prognostic factor with discrete diagnostic accuracy because it presents in our series a sensitivity of 75%, a specificity of 78% and a statistically significant positive likelihood ratio of 3.47 (95% CI 1.6 to 7.5).

Discussion

The National Comprehensive Cancer Network (NCCN) recommends, through the establishment of clinical practice guidelines, that the treatment for cervical cancer stage IA1 always includes simple extra-fascial hysterectomy in case where the diagnosis is achieved through a cervical conization whose resection margins result negative or modified radical hysterectomy (Piver II) with pelvic lymphadenectomy in case where resection margins result positive or there is evidence of lympho-vascular space invasion (LVSI).

The waiting management after diagnostic excision is expected only in those patients who voluntarily express a strong desire to preserve their anatomical integrity for reproductive purposes. This choice, however, is not recommended in case of positive resection margins.

Regardless of the aforecited international protocol drawn up in 2008, treatment strategies for cervical cancer stage IA1 are still debating in the scientific community and they are often chosen independently by each health center according to patients' expectations, physicians' ability and accordance with the protocols of the individual institution.

Conservative approaches for cervical cancer stage IA, proposed by Litterature, include conization alone or trachelectomy according to Dargeant [17].

The trachelectomy according to Dargeant is considered by the international community of gynecologists as an alternative treatment to radical hysterectomy or radio-chemotherapy in patients in childbearing age with stage IA2 or IB1 cervical cancer and it is generally associated with pelvic lymphadenectomy performed laparoscopically. However it is considered an overtreatment by most clinicians in case of stage IA1 cervical cancer, for the aggressiveness that the intervention produces on the anatomical and functional integrity of the female genital tract [17].

The possibility of considering staging conization as the definitive treatment for patients with stage IA1 cervical carcinoma derives from the observation of previous studies showing how this stage of disease can be considered a unique and distinct histological entity according to diagnostic behavior.

Burgardt *et al.*, [18] reported that among over 429 women analyzed with < 3 mm stromal invasion, 80% didn't develop disease recurrence within 5 years after diagnostic intervention. Later Ostor [19] isolated, among over 2274 women, patients with minimal stromal infiltration (< 1 mm) and declared them as a sub-category with better prognosis, characterized by a 0.1% risk of pelvic lymph node metastases and a 0.4% risk of local recurrence.

The results of our survey completely confirm that stromal invasion in the histological report of the excised cone represents the only risk factor for recurrence disease and it can be used with appropriate diagnostic accuracy as a tool in planning follow-up of patients conservatively treated. Many gynecologists still consider positive conization resection margins as a significant prognostic factor for disease relapse. Published studies demonstrated that only a small amount of cases with positive margins developed recurrent CIN II/III. The most frequent explanation provided for this phenomenon recalls the thermodynamic effect that electric cutting tools develop on the removed surface and the inflammatory response associated with wound healing [20,21].

Our study, in addition to being an important confirmation of these data, points out that conservative treatment can be considered effective even in cases of stage IA1 carcinoma with positive margins of resection. In fact, at the expense of a high incidence of positive resection margins (52%), this factor didn't appear statistically significant in influencing the prognosis of patients.

The presence in our study of a high rate of positive margins (> 50%), despite of a recurrence rate equal to that described in literature (< 8%), is justifiable considering the characteristics of the technique used by the working group of the University of Florence, already described in previous studies [22]. The CO₂ laser, instead of LEEP, allows to tailor the treatment according to the size of the lesion and to minimize

the volume of the excised cone, because the intervention always includes a second destructive moment characterized by vaporization of the crater base and walls, reaching more millimeters of depth.

In laser treatment, therefore, we don't invoke the inflammatory process as a probable cause of eradication of disease from the margins of excision, but we make a real cleaning of the margins through a destructive treatment of vaporization of the tissue, ensuring maximum success with minimum volume excised and thermal effect.

The exact definition of disease stage cancer should be considered the most important prognostic factor for stage IA1 cervical cancer. In fact in previous studies on invasive stage IA2 cervical cancer [23], where staging criteria appeared to be rigid and strictly observed during diagnostic time, it was demonstrated that patients who had been submitted to radical hysterectomy and pelvic lymphadenectomy did never present parametrial or lymph node involvement or recurrence of disease at 5 years from treatment. This evidence should therefore be as true as for stage IA1.

Present Authors' analysis of relevant literature discover that published studies include cases that don't satisfy criteria for definition of stage IA1 cervical cancer such as included patients with clinically evident lesions or patients in whom diagnosis of microinvasion was reached by target biopsy and in whom we can't exclude a frank invasion, so to be more properly classified as stage IB1. In Authors' opinion, this causes the erroneous indication to use demolitive treatment in case of stage IA1 cervical cancer.

This is also confirmed by the great difference between the incidence of lympho-vascular space invasion reported in literature (10-30%) [24,17] compared with our one (only 5%). Moreover, about lympho-vascular space invasion, the present study (which strictly adheres to diagnostic criteria of stage IA1 with more than 50% of cases characterized by a stromal invasion lower or equal than 1 mm in depth), not only confirms that it can't be described as an additional risk factor of lymph node metastasis, recurrence and mortality [25], but represents a query whether a solid invasion of such spaces can be really measurable.

The 92.7% of our patients followed during a maximum follow-up of 12 years did not develop recurrent disease, so Authors can state that conservative management of stage IA1 cervical cancer, in this series, was effective in more than 90% of cases.

No patient in the study group underwent demolitive surgery in case of recurrent disease, with total absence of overtreatment and with a theoretical risk of disease progression of 1,8% (1 only case of invasive cervical cancer among 55 patients).

This finding furtherly confirms that conservative treatment by laser conization represents a safe and effective therapeutic option for stage IA1 cervical cancer, in whatever form it manifests (initial, persistent or relapsing disease). However,

conservative treatment must be accompanied by a satisfying post-treatment follow-up because it is not completely risk-free.

In our study, 5% of the total series (3 women) had a tight stenosis of external uterine orifice so the conservative management was not possible. This complication has to be considered the worst since it jeopardise post-operative follow-up and therefore compromises the effectiveness of treatment. Several authors attempted to identify risk factors for cervical stenosis. Baldauf *et al.*, [26] reported the association of cervical canal stenosis with the height and size of cone specimen and with the location of the lesion. Suh-Burgmann *et al.*, [27] correlated the risk of stenosis with eventual previous loop excision (LEEP) and with the volume of tissue removed. The incidence of stenosis according to a study of Mathevet *et al.*, [28] does not depend on the used conization technique: LEEP, laser conization and cold knife conization do not show significant differences in the risk of stenosis. Another risk factor is patient's age at the time of the intervention which represents, according to some authors [29], the only independent factor associated with the risk of stenosis, independently from the presence or not of others factors. This observation leads to assume that menopausal and post-menopausal age at the time of conization represents a risk factor, also due to involution of cervical tissue for the lack of sexual hormones. The correlation between patient's age at the time of treatment and the stenosis of cervical canal was also recognized by the working group of University of Florence and was described in previous works [30]. Considering our series, patient's age appears the main risk factor for stenosis: patients (3/60) in which this complication occurred were respectively 49, 52 (both in menopausal phase) and 72 years old (post-menopausal phase). Cervical stenosis, resulting in unsatisfactory cyto-colposcopic follow-up, is ultimately an important risk factor for unseen relapses; for this reason these patients, according to their clinical conditions and their will, underwent major surgery.

Our final study group submitted to therapeutical conization and strict follow up ranging in age from 25 to 47 matched the theoretical target of population who gained major benefits from such as conservative treatment. In fact the Italian cancer registry on 2012 reported that women aging in the range 25-40 years are the population in which the national screening program produced a cumulative increase in incidence of microinvasive forms of cervical cancer of 8.7% for year despite a cumulative reduction of the invasive forms in the general female population [31].

Moreover the Italian institute of the statistical analysis on demographics stated on their 2008 report that the mean age of Italian women for their first pregnancy is 32,4 years with a rate of first pregnancy over 40 years up 5%.

Conclusions

In conclusion although the restrospectivity of the present study together with the paucity of the study group due to the

non-multicenter nature of the project represents two biases which may influence the importance of findings, Authors support with evidence that laser CO₂ conization alone can be an effective and safe treatment for patients with stage IA1 microinvasive squamous cell carcinoma of the uterine cervix if careful post-treatment follow-up is guaranteed, for patients in their fertile age and with strong desire to conceive or respect their anatomical integrity.

The depth of stromal invasion has been confirmed as the most important risk factor and prognostic factor to be evaluated for disease relapse.

Authors are planning to realize a multicentric prospective study to confirm this initial and promising evidence and to evaluate performance status of treated cervix on subsequent pregnancies.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Fallani MG: laser surgery and study planning
Pieralli A: clinical follow up, statistical analysis of data, manuscript revision, corresponding Author
Lozza V: clinical follow up, manuscript writing
Bianchi C: data collection, manuscript writing
Peyrov Sajad SS: data collection, manuscript writing
Fambrini M: statistical analysis of data and manuscript revision
Penna C: laser surgery and manuscript revision.

Acknowledgement

We thank DEKA M.E.L.A. srl for technical support.

Publication history

Received: 22-Mar-2013 Revised: 03-May-2013
Accepted: 14-May-2013 Published: 16-May-2013

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Citation:

Fallani MG, Pieralli A, Lozza V, Tarani S, Bianchi C, Peyrov Sajad SS, Fambrini M and Penna C: **The efficacy of long term follow-up and CO2 laser conization as conservative management in patients with cervical cancer stage FIGO IA1.** *Gynecology* 2013, **1**:3.
<http://dx.doi.org/10.7243/2052-6210-1-3>