

Research Article

# Positive Margins for High-Grade Intraepithelial Lesion after Cervical Conization - A Five-Year Retrospective Study

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## Abstract

**Overview and aim:** Women treated for high-grade squamous intraepithelial lesions (HSIL) may be at increased risk for recurrent intraepithelial lesions and cervical cancer for up to 25 years. The presence of positive margins after cervical conization is a well-defined predictor of persistent/recurrent disease, however management of these patients is controversial. The aim of this study was to evaluate woman with HSIL affected margins after conization, the type of approach that was used and follow-up.

**Study design, population and methods:** Retrospective study that included women who underwent cervical conization between 2016 and 2020. Only cases with positive margins for HSIL were included. Clinical records were reviewed.

**Results:** 71 (7.7%) patients presented HSIL positive margins. The endocervical margin was affected in 49, ectocervical margin affected in 19 and both margins were affected in 2 cases. In patients with involvement of endocervical margin, 16 received follow-up, 27 underwent a second conization and 6 underwent total hysterectomy. In patients who received follow-up, regression of disease was achieved in 8 (50%) and 2 HSIL cytology were described. In patients

who underwent repeat conization, surgical specimen showed HSIL in 6. Regression of disease was seen in 20 patients. All women with isolated involvement of ectocervical margin underwent follow-up. So far regression of disease was seen in 9 patients and 3 remain under surveillance with negative HPV test at 12 months.

**Conclusion:** Management of positive margins after conization should be individualized and based on affected margin, age and reproductive desire. Women treated for HSIL have an increased risk for invasive cervical cancer and long-term surveillance is essential, regardless margin excision status.

**Keywords:** Conization; Margins of excision; Squamous intraepithelial lesions

## Introduction

Despite significant advances in screening, diagnosis and treatment of premalignant cervical lesions, cervical cancer remains one of the most frequent malignant tumors of the female reproductive system. High-grade squamous intraepithelial lesion (HSIL), also designated as cervical intraepithelial neoplasia (CIN) 2/3, is a well-defined precursor lesion of cervical invasive squamous cell carcinoma [1-3]. Cervical cancer can be prevented by early detection and proper treatment of HSIL. Cervical conization is the standard procedure for treatment of HSIL as it allows histological confirmation of the lesion, evaluation of the resection margins, exclusion of invasive and glandular disease and preservation of fertility [3-6].

Women treated for HSIL may be at increased risk for recurrent intraepithelial lesions and cervical cancer for up to 25 years [7]. Certain factors appear to be associated with a greater risk of persistence/recurrence of disease after treatment like age, histological grade of the conization specimen, incomplete excision and infection by high-risk Human Papillomavirus (HPV) [3,8-10]. The presence of positive margins after cervical conization represents one of the most relevant risk factors for persistence/recurrence of disease, however the optimal management of these women remains controversial. While some authors state that short-term surveillance is preferable, others suggest performing a secondary conization [3-6]. The aim of this study is to analyze the clinical data of women undergoing cervical conization with HSIL at the margins of the surgical specimen, the type of approach that was used and follow-up.

## Methods

This was a retrospective study of women who underwent cervical conization between January 2016 and December 2020 in Centro Hospitalar Universitário do Porto in Portugal. In this analysis only cases with positive margins for HSIL (CIN 2 and 3) were considered. Cases with negative margins, margins impossible to evaluate, low-grade squamous intraepithelial lesion (LSIL) involved margins, diagnosis of invasive disease and/or cervical adenocarcinoma were excluded.

Clinical data extracted from medical records included patients characteristics (age at surgery, parity, menopause status, use of oral contraception, smoking habits), preoperative cervical cytology and

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high-risk HPV test results (if available), histologic findings before initial conization, details regarding initial conization (method, laser vaporization of surgical site), location of involved margin sections, cervical cytology and high-risk HPV findings during follow-up and histology from the second conization or hysterectomy. Regarding preoperative cervical cytology, low grade abnormalities included negative for intraepithelial lesion and malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US) and LSIL. High grade abnormalities included atypical squamous cells cannot exclude a high-grade lesion (ASC-H), HSIL and atypical glandular cells (AGC). Choice of conization method (electrosurgical conization or laser conization) depended on several factors, namely doctor's experience and material available at the time of the procedure. Whenever possible cervical conization was followed by laser vaporization of the cervical crater and margins.

Post conization management options included follow-up, secondary conization or total hysterectomy. Decision between close follow-up or surgical intervention (secondary conization or hysterectomy) was made individually, considering patient's age, comorbidities, affected margin, reproductive desire and personal preferences. Follow-up procedures included gynecologic examination, liquid-based cytological testing, detection of high-risk HPV and/or colposcopy, according to portuguese current protocols. Hysterectomy was carried out when repeat cervical conization was technically impossible. Disease regression was defined by negative cytology and high-risk HPV test 24 months after surgery.

This study is in accordance with the Declaration of Helsinki, as revised in 2013. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 26.

## Results

A total of 924 women underwent cervical conization in our institution during the period of study. Of the potentially eligible women, exclusions were as follows: 722 negative margins, 104 LSIL positive margins, 13 for missing data on margin status, 6 for invasive disease and 8 for cervical adenocarcinoma. Thus, the final study sample included 71 women with HSIL positive margins and the rate for HSIL positive margins after cervical conization was 7.7%. The patient demographic and clinicopathologic characteristics are summarized in table 1. The age of the patients ranged from 23 to 77 (median: 39) years. Regarding parity, about 19 patients were nulliparous, 22 patients had one child and 20 patients had more than one child. Only 9 (12.7%) women were in menopause and about 35 (49.3%) had present or past smoking habits. The cytology before first cervical conization showed low grade abnormalities in 20 (28.2%), high grade abnormalities in 47 (66.2%) and squamous cell carcinoma in 3 (4.2%) patients. The pre-cone high-risk HPV showed that 23 patients had HPV 16, 1 had HPV 18 and 26 had other high-risk HPV (not 16 or 18). Cervical biopsy performed prior to cervical conization revealed HSIL in 64 (88.7%) cases and LSIL in 5 (7%) cases; in 2 (2.8%) cases it didn't describe dysplasia. The reason for cervical conization in cases where cervical biopsy was LSIL or did not reveal dysplasia was great discordance between cytology, colposcopy and/or histology. Initial cervical conization was performed by laser in 45 (63.4%) and electrosurgery (loop electrosurgical excision procedure or using a needle electrode) in 26 (36.6%) patients. Laser vaporization of cervical crater and margins was made in 59 (83.1%) cases.

Characteristics	N (%) / range (M)
Age range, y (median)	23 - 77 (39)
<b>Parity</b>	
Nulliparous	19 (26.7)
Para 1	22 (31)
Multiparous (>1)	20 (28.2)
No data	10 (14.1)
<b>Oral contraception*</b>	
No	33 (53.2)
Yes	29 (46.8)
<b>Menopause</b>	
No	62 (87.3)
Yes	9 (12.7)
<b>Smoking habits (past/present)</b>	
Yes	35 (49.3)
No	36 (50.1)
No data	17 (23.9)
<b>Cytology</b>	
Low-grade**	20 (28.2)
High-grade***	47 (66.2)
SCC	3 (4.2)
No data	1 (1.4)
<b>High-risk HPV</b>	
16	23 (32.4)
18	1 (1.4)
Others (not 16 or 18)	26 (36.6)
<b>Cervical biopsy</b>	
No dysplasia	2 (2.8)
LSIL	5 (7)
HSIL	64 (88.7)
<b>Method of cervical conization</b>	
Electrosurgery	26 (36.6)
Laser	45 (63.4)
<b>Laser vaporization</b>	
No	12 (16.9)
Yes	59 (83.1)
<b>Location of positive resection margins</b>	
Endocervical	49 (69)
Ectocervical	19 (26.8)
Both	2 (2.8)
Uncertain which margin	1 (1.4)

**Table 1:** Patient demographic and clinicopathologic characteristics.

M: median; HSIL: high-grade cervical intraepithelial neoplasia; LSIL: low-grade cervical intraepithelial neoplasia;

SCC: squamous cell carcinoma; HPV: human papillomavirus; \*Women of reproductive age; \*\*Included: NILM (negative for intraepithelial lesion and malignancy), ASC-US (atypical squamous cells of undetermined significance), LSIL (low grade squamous intraepithelial lesion); \*\*\*Included: ASC-H (atypical squamous cells, cannot exclude a high-grade lesion), HSIL (high-grade squamous intraepithelial lesion), AGC (atypical glandular cells).

Of the 71 women that presented HSIL positive margins, 49 (69%) had positive endocervical margins, 19 (26.8%) had positive ectocervical margins and 2 (2.8%) had positive endocervical and ectocervical margins. In one case the affected margin was not discriminated. Among patients with involvement of endocervical margin, 16 (31.4%) received follow-up only, 27 (52.3%) underwent a second cervical conization and 6 (11.8%) underwent a total hysterectomy; in 2 patients there was a loss of follow-up right after initial conization. In the follow-up patients there was one case of nonadherence to surveillance that later underwent a second cervical conization, one case that ended in hysterectomy due to benign gynecological pathology and two cases of loss of follow-up before 24 months (both had a negative cytology and high-risk HPV test at 12 months after initial treatment). The disease regression rate in this group of women was 50% (8/16). There were two cases (12.5%) of persistence/recurrence of disease with HSIL cytology. One of these cases was a 35-year-old woman and she underwent a secondary cervical conization 6 months after initial treatment; surgical specimen confirmed HSIL. The other case was a 77-year-old woman with multiple comorbidities and in this case it was decided to keep under surveillance after evaluating the risks of a new surgical intervention. In patients with involvement of endocervical margins that underwent a second cervical conization, so far disease regression rate is 74.1% (20/27). The histological diagnosis of surgical specimen showed persistence of HSIL in 6 (22%), LSIL in 10 (37%) and no dysplasia in 11 (40.7%) cases. In patients that underwent hysterectomy, the surgical specimen showed persistence of HSIL in 2 (33.3%) and no dysplasia in 3 (50%) cases. Main reason for hysterectomy was technical impossibility for new conization.

Among patients with isolated involvement of ectocervical margin, all of them received follow-up with cytology plus high-risk HPV testing. So far disease regression was seen in 9 (47.2%) patients and 3 (15.8%) patients are still under surveillance (all of them presented a negative high-risk HPV test at 12 months follow-up). There were no cases of persistence/recurrence of HSIL in this group of patients.

## Discussion

High-grade squamous intraepithelial lesion (HSIL) is considered to be the precursor of cervical cancer. Due to its unpredictability, surgical excision is the most common treatment modality for the majority of HSIL [2]. Cervical conization is the recommended treatment as it is a relatively safe, low-cost outpatient procedure that can be performed under local anesthesia. It can be done using different techniques such as electrocauterization (loop electrocauterization procedure or using a needle electrode), laser conization or cold-knife conization [11-13]. As HSIL is frequently multifocal and lesions are not contiguous the risk of incomplete excision after cervical conization is not negligible [4].

Data regarding the rate of positive margins after cervical conization varies widely in the literature (7.2 to 42.5%), which can possibly be attributed to the different definition of positive margins in different publications [3-6]. The rate of HSIL positive margin in our study was 7.7%, which is consistent with published literature. A positive margin after cervical conization is closely associated with persistence/recurrence of HSIL [3-5,9,14]. Ghaem-Maghani et al., reported high-grade post-treatment disease occurred in 18% of women who had incomplete excision versus 3% of women who had complete excision [14]. Yet, optimal treatment for patient with HSIL positive margins remains controversial. While some authors state that a secondary surgery should be applied to reduce the risk of recurrence/persistence

of disease, others state that follow-up is preferred in order to prevent overtreatment, especially in younger patients. Currently, the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines state that in the presence of HSIL positive margins follow-up with HPV-based testing 6 months after initial treatment or a secondary cervical conization are both acceptable, depending on factors such as patient's age and fertility desire [15]. However, in addition to the factors mentioned by ASPPC, the affected margin is also an important factor to take into consideration. Some authors state that women with positive endocervical margins have higher risk of recurrent disease than women with isolated involvement of ectocervical margins [6,7]. In our study, the affected margin was in fact one of the main factors that we took into account when discussing the type of management of each patient. When analyzing cases of positive endocervical margins, we found that women that underwent follow-up only with cytology plus high-risk HPV testing had a low rate of recurrence/persistence of disease and a high percentage of these women remained disease free during follow-up. One of the cases that initially was under surveillance missed some consultations and ended up being proposed to a secondary conization, as the conservative approach requires a high compliance by the patients. In women with positive endocervical margins that underwent secondary surgical procedures, we also found a higher rate of surgical specimens without dysplasia. On the other hand, all cases of isolated involvement of ectocervical margins were managed conservatively and remained under surveillance. So far, we didn't find any case of recurrence/persistence of disease. This spontaneous resolution of the majority of cases of positive margins could be partly explained by the necrosis and intense inflammatory reaction that occurs in the site of initial treatment and the release of numerous immunological mediators which could destroy the residual process [4,8,16]. In addition to that, laser vaporization of the crater base and side walls can also contribute to the reduction of affected margins and lesion recurrence as it can destroy potential isolated foci of abnormal cells left behind after initial treatment [17]. In our institution, laser vaporization after conization is a routine procedure, regardless conization method. However, during the COVID pandemic, laser surgery was replaced by electrosurgery, which may explain the percentage of women who did not undergo vaporization of the cervical crater and margins after conization.

Even though HSIL margins are associated with higher rates of persistence/recurrence of disease, patients should be informed about treatment options. Not all patients with positive margins will have residual lesions and the majority of cases with positive margins will regress spontaneously. Approach of these patients should be individualized based of affected margin, high-risk HPV status, fertility desire, age and patient's preference. Regardless excision status, as women treated for HSIL may be at increased risk for invasive cervical cancer, long-term surveillance is essential.

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