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Positive margins in cervical H-SIL conization: Can we predict them?

Abstract

Background: Cervical cancer is the second most common gynecological cancer in the female population. Cervical cancer screening includes cytology and tests for oncogenic subtypes of human papillomavirus (HPV), impacting on a significant decrease in mortality.

In patients with a diagnosis of high-grade squamous intraepithelial lesion (HG SIL), the recommended management is excisional treatment (ET). The higher rate of persistent disease is associated with a positive margin status, larger lesion size, endocervical involvement and HPV positive test six months after treatment, especially HPV 16 subtype.

Objective: To identify clinical and/or pathological features capable of predicting the compromise of the margins in the excisional treatment specimens.

Methods: It is an observational, retrospective study carried out in Sanatorio Güemes between September 2017 and June 2020. All those patients with HG SIL who underwent excisional treatment were analyzed.

The variables considered were the pre-treatment status of the endocervical canal, the size of the specimen (height), the type of transformation zone, the presence of greater pathology in the definitive specimen, the delay in consultation and the smoking habit. The relative risk of presenting compromised margins for each of the variables was analyzed.

Findings: Our study shows 124 patients who received excisional treatment for HG SIL, 32 had compromised endocervical margins of the resection specimen. The delay in consultation between the biopsy and the ET has a significant impact on the state of the margins (RR 2,26; IC95 1,27-4; p 0,009). The presence of greater pathology (microinvasive carcinoma or higher stage) in the group with compromised margins (34,4% vs. 5,4%) highlights the importance of a comprehensive pre-treatment advisement to the patient concerning the diagnostic role of the ET in our population.

Keywords: positive margins, cervical cancer, human papillomavirus, H-SIL

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Introduction

Cervical cancer is the second most frequent gynecological cancer in the female population and in Argentina, around 4,000 new cases are diagnosed each year and approximately 1,800 women die from the disease.[1] Cervical cancer screening includes cytology and tests for oncogenic subtypes of the human papillomavirus (HPV) impacting on a significant decrease in mortality.[2]

In patients with a diagnosis of high-grade squamous intraepithelial lesion (H-SIL), the recommended management is excisional treatment (ET) according to the colposcopic lesion and the type of transformation zone.[3] The objective of treatment is to prevent possible progression to cancer in addition to obtaining sufficient histological information to rule out invasion and compromise in the margins of the piece.[4] The serial anatomopathological analysis of the ET piece affects the subsequent conduct in terms of follow-up or reoperation of the patient.

The highest rate of persistent disease is associated with a positive margin state,[5] larger lesion size,[6] involvement of the endocervical canal, and viral DNA positivity 6 months or more after treatment, especially HPV 16.[7–9]

Patients with positive margins after an excision procedure have been shown to be at significantly higher risk of developing residual or recurrent disease, compared with negative margins.[10,11]

Recurrence can occur years after treatment; the mean time reported by Manchanda was four years.[12] On the other hand, Sadaf et al. in 2007 they published a review of 125 articles including 35,109 patients with a 23% rate of affected margins in the ET specimen. In this group of patients, the relative risk for recurrence was 5.47 in contrast to the patients who presented free margins.[13]

Consequently, the management of women who present with a marginally involved excision is controversial and is the subject of debate. However, it has been widely shown that having suffered from H-SIL increases the risk of suffering from cervical cancer in long-term follow-up.[14–16]

H-SIL treatment demonstrated a positive impact in reducing the incidence of cervical cancer. We consider it relevant to identify factors in patients with a diagnosis of H-SIL capable of predicting the compromise of the margins in the excisional treatment piece. In the present study, clinical and pathological variables were analyzed to determine their impact on the finding of compromised margins.

Objective

To identify the impact of clinical and pathological factors in patients who presented compromised endocervical margins in excisional procedures due to H-SIL.

Materials and methods

This is an observational, retrospective study carried out in a single institution. All those patients who underwent cervical conization with electrocautery as treatment for H-SIL at the Sanatorio Güemes in the period between September 2017 and June 2020 were analyzed.

In the Lower Genital Tract Pathology Section, the variables were systematically recorded. Patient clinics. These include, among others: age, smoking, contraceptive method, parity, initiation of sexual relations, number of sexual partners, presence of other sexually transmitted infections, and delay between cervical biopsy and excision.

The information was classified in an electronic database designed specifically for the study and 2 groups were created: those with compromised endocervical margins and those with negative margins.

The variables of the present study that were considered are the positivity of the pre-surgical endocervical curettage, the size of the piece (height), the type of perioperative transformation zone, the presence of greater pathology in the final piece, the delay in the consultation and the smoking.

Data were obtained from 127 patients who underwent ET at our institution in the time period of study analysis. Of these, 3 patients who did not meet the exclusion criteria were excluded (Figure 1).

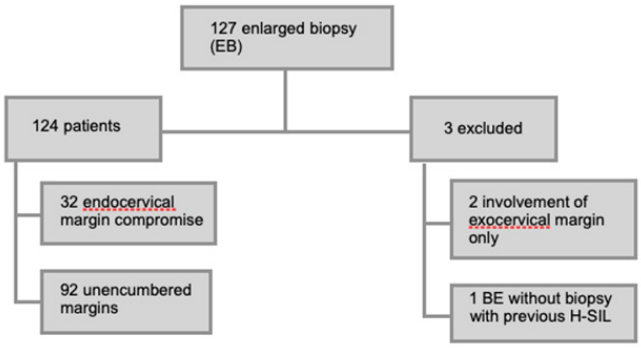

Figure 1 Patient selection flowchart.

Statistical analysis was performed with the Epi Info program and a p value less than 0.05 was considered significant.

Results

Of a total of 124 patients, 32 (26%) presented compromised endocervical margin and 92 (74%) did not present margin compromise. Two groups were divided, those with compromised margins formed group 1 and those without compromised margins group 2 (Table 1).

Table 1 Patient characteristics

	Group 1	Group 2
Age	39 (22-75)	31 (20-68)
ISI	16,8 (14-23)	16,9 (13-28)
NSP	8,0 (1-30)	8,8 (1-60)
Conization height	1,82 (0,8-2,5)	1,63 (0,3-4,3)

ISI, initiation of sexual intercourse; NSP, number of sexual partners

The mean age was 39 and 31 years for the group with compromised and no margins, respectively. In both groups, the average age of initiation of sexual intercourse was 16 years and the average number of sexual partners was 8. In group 1, 43% of the patients were smokers, while in group 2, 32%.

On the other hand, the delay in performing the enlarged biopsy was evaluated, understanding it as a period greater than 4 months between the biopsy date and the surgery date. In group 1, 37% underwent ET with a delay greater than 4 months from the result of the first biopsy. In group 2, on the other hand, only 15% presented this delay (RR 2.26; IC95 1.27-4; p 0.009).

Regarding the study of the endocervical canal, it was positive in 46% of patients with compromised margins and in 42% of those without compromise, with an RR 1.04 (95 CI 0.54-1.99 p 0.16). There was no study of the canal in 15% of the patients with compromised margins and 21% of those with free margins.

The types of transformation zone (TZ) in pre-surgical colposcopy were analyzed, grouping them according to whether TZ is visible (type 1 and 2) or not visible (TZ type 3). In group 1, 15.6% of the patients had non-visible TZ, while in group 2 7.6% (RR 1.7; CI95 0.81-3.64; p 0.16).

Regarding the pathology study of the surgical specimen from the enlarged biopsy, a diagnosis of cancer was reached in 34.4% in the group of patients with compromised margins in contrast to 5.4% in those without compromised margins. (RR 3.5 IC95 2.1-5.8; p 0.0001), being able to interpret that the presence of greater pathology is a predictive factor of compromised margins (Table 2).

Table 2 Variables between both groups

	Group 1		Group 2		RR (IC95%)	p
	n	%	n	%		
Greater pathology	11	34,4	5	4,5	3,5 (2,1-5,8)	0,0001
Non-visible TZ	5	15,6	7	7,6	1,7 (0,81-3,64)	0,16
Delay greater than 4 months	12	37,5	14	15,2	2,26 (1,27-4)	9
Positive endocervical canal	15	46,9	39	42,2	1,04 (0,54-1,99)	0,52

Of the group of patients with compromised margins, 81% underwent another surgical procedure, either reconization, extrafascial hysterectomy, or extended radical, as appropriate. Of these, 53% presented residual lesion in the pathology analysis of the second procedure. 16% of patients with compromised margins were lost to follow-up, and one patient was a candidate for concurrent chemoradiotherapy after ET.

Discussion

Our study shows that of a total of 124 patients who received excisional treatment for high-grade cervical lesions, 32 presented compromised margins of the resection piece. Compared with the meta-analysis carried out by Arbyn, M. published in 2017 where 97 studies were reviewed including 44446 patients, with a proportion of compromised margins of 23%[17] similar to our series. The recurrence rate in the population with compromised margins is significantly higher, as reported by Vedel et al. in 1993 with a recurrence rate of 16.3% in the group with compromised margins in contrast to 3.9% in patients with free margins.[18]

The behavior taken with respect to the compromised margins of re-operating (re-cone, simple hysterectomy or radical hysterectomy) is based on the finding of 53% residual disease in the analysis of the second resections. Likewise, Filho demonstrated it in 2015, reporting a 53% rate of disease persistence in the second procedures carried out after verifying affected endocervical margins in the cone pieces.[19]

In all cases, the method used in our study was excision with electrocautery, varying the depth of excision depending on the

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transformation zone. The preoperative transformation zone did not show significant differences between the two groups analyzed. The fixation of the piece and the sending to pathological anatomy is standardized for its correct analysis, always referencing the pieces in the same way.

Although it is not part of the analysis of this study, in the Lower Genital Tract section of the Sanatorio Güemes, the compromised endocervical margins underwent second procedures, either re-cone or hysterectomy based on the recommendations of the international literature, including Johnson et al. who in 2003 published a series of 702 women followed for 30 months after an excisional procedure, noting twice the risk of presenting CIN2+ cytology in the group with positive endocervical margins without objectifying this impact with the compromised exocervical margin.[20]

It is worth mentioning that the analysis of each procedure did not take into account whether it was performed by professionals in training or by an experienced medical specialist. Although the operators in each of the parts are professionals in training, they operate supervised by an experienced gynecologist using the same regulated and standardized technique. Regarding this variable, Montanari et al.[21] in 2018 he published a series of 912 ET comparing those performed by residents and by trained gynecologists. No differences were found in the volume of the spin-off or in the rate of committed margins between the two operators.[21]

A variable that has not been analyzed in previous series is the delay in patient care and that represented the greatest impact in terms of predicting endocervical margin compromise with a relative risk of 2.26 in contrast to those patients who did not present said delay.

This finding has multiple edges to analyze; our population comes from multiple peripheral centers located in the AMBA (Buenos Aires metropolitan area), which are the ones who refer patients with a diagnosis of H-SIL. Once entered in our section, the time until its excision is 3 weeks on average. Currently, this same working group is carrying out a detailed analysis of the causes of delays in the consultation, given that 30% present delays greater than 4 months and in this group, 5% present delays greater than 12 months, evidencing certain socioeconomic deficiencies that are part of the adverse outcomes.

The variable that showed the greatest impact in our analysis is undoubtedly the finding with the greatest pathology in the pieces analyzed (34.5% versus 5.4%), significantly affecting the margin compromise reported in this series. This finding highlights the importance of understanding enlarged biopsies (conization, LEEP, LLETZ, etc.) as diagnostic/statistical methods and secondly as therapeutic. It is possible that pathologists from less complex centers find it difficult to establish a precise diagnosis in the face of suboptimal samples taken in non-specialized clinics.

Although the effectiveness of HPV tests to predict recurrence in post-treatment follow-up has been demonstrated,[22] the state of the margins is a valid tool to guide conduct in the absence of such technology in the development setting of our practice.

We understand that one of the weaknesses of our study is the absence of the HPV test, since given the population treated and the low resources we find ourselves limited in performing HPV tests on all patients who underwent conization. As we do not have this test, we cannot clarify the final post-conization cure. Apart from this comment, our work focuses on the state of the margins, not on the definitive cure of the patient, understanding this by the disappearance of HPV assessed with a test.

Today we do not have free access to HPV tests for all our patients, we are working to make it so, the biggest difficulty is the costs. It would have been very useful to have an HPV test to perform it 6-12 months after conization in patients with unencumbered margins, as well as in patients with compromised margins.

Conclusion

Much of the published work dealing with this topic is focused on the risk of disease recurrence after incomplete excision without addressing predictive factors for this eventuality. According to our findings, the delay in the consultation between the biopsy and the ET has a significant impact on the state of the margins. The presence of more pathology (microinvasive carcinoma or higher stage) in the group with compromised margins highlights the importance of the pre-surgical dialogue, highlighting the diagnostic importance in the first place of said procedures in our specific population.

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Conflicts of interest

All authors declare any financial interest with respect to this manuscript.

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