

# Outcome after treatment of high-grade squamous intraepithelial lesions: Relation between colposcopically directed biopsy, conization and cervical loop excision

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## Summary

**Purpose of investigation:** The hypothesis that cold-knife conization performed in women with high-grade squamous intraepithelial lesions (HSIL) and unsatisfactory colposcopy is a better procedure than the loop electrosurgical procedure (LEEP) is tested.

**Methods:** A retrospective study was conducted in conization specimens of women submitted to LEEP (n = 102) or conization (n = 245) due to HSIL. Age, biopsy, compromised surgical margins in conization, and recurrence were analysed.

**Results:** The frequency of invasion, non-compromised margins, and recurrence in conization and LEEP were, respectively, 7.7% versus 2.9%, 64.1% versus 48% (p = 0.008), and 33.8% versus 24.1%. Eight (42.1%) and five (26.3%) of 19 women submitted to conization where invasion was found in surgical specimens were, respectively, menopausal or had unsatisfactory colposcopy. Twenty-five (96.2%) of 26 and 23 (95.8%) of 24, respectively, undergoing conization and LEEP had recurrence in the first five years.

**Conclusion:** We recommend the use of cold-knife conization in cases where the lesion is located deep in the cervical canal.

**Key words:** Loop electrosurgical excision procedure; Conization; Cervical intraepithelial neoplasia; Outcome.

## Introduction

The incidence of cervical cancer can be reduced with screening by Papanicolaou smears and together with treatment of precancerous lesions [1]. Colposcopy with directed biopsy has been the standard for diagnosis and management of cervical cancer precursors for more than three decades [2]. Different treatments have been proposed over the years, including conization, hysterectomy or close follow-up schedules, and more recently, the loop electrosurgical excision procedure (LEEP) [2-5].

The development of LEEP allows outpatient excision of the cervical transformation zone with histologic evaluation of the entire transformation zone [5, 6]. It is now a widely used procedure for diagnosing and treating cervical intraepithelial neoplasia (CIN) [6, 7]. Low cost, local anaesthesia, and low perioperative complications are the advantages of LEEP [7, 8]. Cold-knife conization is an older procedure than LEEP, which is performed with the patient under regional anaesthesia in a hospital setting, requires surgical training, and is more expensive [9-11]. Although LEEP was implemented in selected patients as an alternative method to conization, long-term morbidity and treatment outcome have not been completely assessed [7, 8].

Another problem is a significant underdiagnosis of high-grade squamous intraepithelial lesion (HSIL) and cervical invasive carcinoma by colposcopically directed biopsy can be detected [2]. The literature shows that the

degree of discrepancy varies between 18-55% [2, 12-14], depending on whether LEEP is performed without prior colposcopically directed biopsy [14]. Consequently, women with more advanced disease may receive inadequate treatment.

To our knowledge, very few studies have yet analysed the factors influencing the reliability of colposcopically directed biopsy and its relationship with LEEP or conization treatment and clinical follow-up. The aim of this study was to compare the histologic and clinical outcome of cold-knife conization with those of LEEP in patients with HSIL. We tested the hypothesis that cold-knife conization performed in women with HSIL and unsatisfactory colposcopy is a better procedure than LEEP.

## Material and Methods

### Patients

A retrospective study was conducted on the cytology and/or surgical specimens of women submitted to LEEP or conization due to HSIL from 1 January 1981 to 31 December 1999 at the Gynecologic and Obstetrics Outpatient Service of our Institution. The project was approved by the Research Ethics Committee.

Three hundred and forty-seven patients had been referred because of presence of CIN II or III (HSIL) in biopsy specimens. All patients were submitted to triple collection of material for cytological examination and colposcopically directed biopsies. The clinical data, cytology and biopsy evaluations are shown in Table 1. LEEP and conization were performed in 102 (29.4%) and 245 (70.6%) women, respectively.

Table 1. — *Distribution of clinical data, cytology and biopsy of patients undergoing conization (n = 245) and LEEP (n = 102).*

Clinical data	Conization		LEEP	
	n	%	n	%
Average age (years)	37.3 ± 9.4		31.6 ± 7.3	
Parity	n	%	n	%
Nuliparous	13	5.3	12	11.7
Pauciparous	105	42.8	56	54.9
Multiparous	127	51.8	34	33.3
Pregnancy	17	6.9	9	8.8
Cytology				
LSIL	2	0.8	9	9.7
HSIL	243	99.2	93	91.2
Biopsy				
CIN II	26	10.6	29	28.4
CIN III	219	89.4	73	71.9

#### *LEEP and conization management, and follow-up criteria*

LEEP and conization were performed by residents supervised by board-certified attending obstetrician-gynecologists. LEEP was performed in 102 (29.4%) women with the LEEP WEM machine with the power set at 50 watts. After application of Lugol iodine, cervical anaesthesia was performed with 2% lidocaine containing a solution of 1:1000 epinephrine (4-6 ml, approximately 1 ml per cervical quadrant). Loop size was 10 mm x 10 mm and current was blended to cut and coagulate. After the procedure, all cases underwent roller ball coagulation (50 watts) with the aim of haemostasis. The main criteria for LEEP in the majority of cases were small lesion, visible squamocolumnar junction (SCJ), and desire of future gestation.

Cold-knife conization was performed in 245 (70.6%) women in the operating room after spinal anaesthesia. After the Schiller test, a surgical margin of 2 mm was done by bistoury and the cone specimen was extirpated. Sturmdorf points were performed.

Follow-up criteria after conization or LEEP consisted of cytology and colposcopy every six months for five years and afterwards annually. The minimum time of follow-up was two years. From the total of 245 and 102 women submitted to conization or LEEP, respectively, 108 and 71 in each group respected the above criteria and comprised the groups for recurrence analysis.

#### *Cytohistological techniques*

The cytological material was processed to Papanicolaou's technique and reading was performed by doctors trained as cytologists.

The biopsy was guided by colposcopic exam carried out by supervised residents, and the material was fixed in 4% formaldehyde. There was no standard number of histological cuts for each biopsy and they varied from one to ten successive cuts as judged necessary by the pathologist for each case.

The cone biopsy specimens were marked with sewing thread at the 12 o'clock position and fixed in 4% formaldehyde. The cone biopsy was cut into pieces of about 1 mm in thickness, perpendicular to the surface of the endocervical mucosa and the material was processed for inclusion in paraffin. One histological cut of each block was stained with hematoxylin-eosin. Additional cuts were made when necessary.

The results of the histopathological exams (guided biopsy and surgical-removed tissue) were compared. In cases with discordance, the histological preparations were reviewed by two

pathologists to try to evaluate the causes of errors.

#### *Statistical analysis*

Comparisons between groups were made with the Mann-Whitney test and chi-square test with Yates' correction or the Fisher's exact test, depending on the conditions of validity of the chi-square test. Risk relative (RR) and 95% confidence interval (CI) were shown. The differences were considered significant with  $p < 0.05$ .

#### **Results**

The frequency of invasion in conization and LEEP was, respectively, 7.7% and 2.9% (Table 2). The surgical margins were not compromised in 64.1% of conization and 48% of LEEP. Nine (47.4%) and six (31.6) of 19 women submitted to conization showed micro-invasion or invasion in the surgical specimen, and were, respectively, menopausal or had unsatisfactory colposcopy. From the total of 19 women, 11 women with micro-invasion were treated with hysterectomy, three women with invasion were treated with Wertheim-Meigs and five were treated at other services. All women with micro-invasion in LEEP specimens had satisfactory colposcopy and were premenopausal. From the total of four women, two underwent conization, one was submitted to hysterectomy and one was treated at another service.

Table 2. — *Distribution of histology and margin evaluation of patients undergoing conization (n = 245) and LEEP (n = 102).*

Histology	Conization		LEEP	
	n	%	n	%
(surgical specimen)				
Normal	15	6.1	7	6.8
CIN I	4	1.6	5	4.9
HSIL	207	84.5	87	85.3
Microinvasion	15	6.1	3	2.9
Invasion	4	1.6	0	0
Margins of surgical specimen				
Non compromising*	157	64.1	49	48
Compromising	61	24.9	34	33.3
Not analysed	27	11	19	18.6

\*  $p = 0.0081$ , RR and CI 1.221 (1.052 to 1.418).

One hundred and eight and 71 patients submitted to conization and LEEP, respectively, had follow-up of two years or more. Table 3 shows the unsatisfactory colposcopy results and frequency of menopausal women who were more frequent in the conization group. Recurrence was more frequent in the LEEP group. Twenty-five (96.2%) of 26 and 23 (95.8%) of 24, respectively, who underwent conization and LEEP had recurrence in the first five years. Twenty (76.9%) of 26 and 20 (83.3%) of 24 women with recurrence treated with conization or LEEP were submitted to other treatments in our service. After conization or LEEP, five, six, nine and nine, ten, one women underwent, respectively, LEEP, reconization and hysterectomy. The only case of microinvasion was found in the hysterectomy specimen.

Table 3. — Distribution of patients undergoing conization (n = 108) and LEEP (n = 71) with recurrence or without recurrence (WR) after two or more years of follow-up in relation to unsatisfactory colposcopy and menopausal status during the first treatment, and cytology, biopsy, histology of surgical specimens of the second treatment, number of cases and time of recurrence (years) during the follow-up.

Follow-up	Conization (n = 108)				LEEP (n = 71)			
	Recurrence (n = 26)		WR* (n = 82)		Recurrence (n = 24)		WR* (n = 47)	
Colposcopy	n	%	n	%	n	%	n	%
Unsatisfactory	10	38.55**	16	19.6#	3	12.5	2	4.3
Menopause	5	19.2	15	18.3##	1	0.04	2	0.04
Cytology	n		%		n		%	
Without SIL	—		—		1		4.2	
ASCUS	—		—		2		8.3	
LSIL	2		7.7		1		4.2	
HSIL	24		92.3		20		83.3	
Biopsy##	n		%		n		%	
Without CIN	3		16.6		2		10.5	
CIN I	3		16.6		3		15.8	
HSIL	12		66.7		14		73.7	
Without biopsy	8		—		5		—	
Histology (surgical specimen)	n		%		n		%	
Without CIN	4		16.6		2		10	
CIN I	3		12.5		4		20	
HSIL	12		50		14		70	
Microinvasion	1		4.2		—		—	
Recurrence	26		24.1		24		33.8	
Time of recurrence (years, median and range)	1 (1-6)				1 (1-9)			

\* WR= without recurrence, \*\* p = 0.0003, # p = 0.0173, ## p = 0.0292, RR and CI, respectively: 0.3148 (0.1926 to 0.5144), 0.6689 (0.5345 to 0.8371) and 1.475 (1.171 to 1.858), compared to LEEP.

## Discussion

Disappearance of HSIL after colposcopic biopsy may occur. After a short time (2-3 months) between the biopsy and conization or LEEP, our results showed that regression occurred in approximately 6.3% and 2.6%, respectively, to normal and LSIL at histology of surgical specimens. The regression of HSIL may be related to local trauma following the biopsy, mainly, in very localised lesions [2].

This study found that 6.3% of women submitted to biopsy under colposcopy who underwent LEEP or conization had invasive lesions identified in histological specimens. This is consistent with data found in the literature [15]. Nonetheless, we observed that in patients submitted to LEEP, the micro-invasion rate was lower than in patients treated with conization. It must be emphasised that both groups submitted to conization or LEEP were heterogeneous with respect to the clinical data and indications of each procedure, as reported in the methods section. This may explain the different findings of invasive lesions between the groups. The results of our study showed that colposcopically directed biopsy presents limitations of accurate diagnoses of CIN or invasive cervical lesions. This occurred for both conization and LEEP, nonetheless, it was a more common finding in the

first procedure. The number of unsatisfactory colposcopies and menopausal women was higher in the group submitted to conization and explains the discrepancy in relation to the LEEP group. This discrepancy suggests that patients with unsatisfactory colposcopy should be managed with caution and that performing conization is indicated. Our results confirmed previous observations regarding the relation between age and unsatisfactory colposcopy with the probability of a non diagnosis of invasive carcinoma in biopsy [16]. A careful histological evaluation and close follow-up is mandatory. Recent studies have shown that frozen section examination of conization is effective and reduces residual or recurrence of disease [17, 18].

Histopathological results of surgical specimens required histologic accuracy with assessment of the depth and width of stroma. Patients with microinvasive (< 3 mm) carcinoma of the cervix can be treated by extrafacial hysterectomy [19] or conservatively by conization alone in young women with the desire of future gestation [20]. Women with deeper invasion (> 3 mm) were treated with hysterectomy and lymphadenectomy [21]. An accurate evaluation of surgical specimens may be difficult due to incomplete or destructive surgical margins or the transformation zone [22-24]. A disadvantage of LEEP, mainly when small loops were used, is the high frequency of tissue fragmentation with damage in the margins or transformation zone. Consequently, inadequate treatment due to incomplete histological evaluation may occur.

Compromised surgical margins are more common in women submitted to LEEP than conization. This is a not surprising for two reasons. First, we utilised a loop size of 10 mm x 10 mm and larger lesions were not completely excised. Second, LEEP sometimes cuts across the lesions and it is impossible for the pathologist to identify the correct face of the specimen if it is not identified. Although compromising margins were more frequently found in the LEEP group, apparently this did not influence recurrence rates, because no statistical difference was found between the LEEP and conization procedure. Our results confirm other studies that did not show a difference in recurrence rates between conization and LEEP [25]. The time of recurrence is similar and the majority of cases occurred during the first year of follow-up in both groups. The risk of developing recurrence is highest in the first year and rare beyond the third year of follow-up [26]. Our findings showed that more than 95% of recurrences in both groups occurred in the first five years. Thus close follow-up during the first five years after treatment is recommended.

Our results demonstrated that compromised or damaged margins were more frequent with the LEEP and that invasive carcinoma may occur after a combination of cytology, colposcopy and biopsy. LEEP is best indicated in young women with a satisfactory colposcopy. Conization of the uterine cervix is performed with the goal of entirely removing an epithelial lesion. This constitutes a strong argument for conization in cases of unsatisfactory colposcopy. Moreover, in cases of early invasive cervical

carcinoma, conization can be the definitive treatment. We therefore recommend using cold-knife conization in cases where the lesion is located deep in the cervical canal.

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