

LEEP IN THE TREATMENT OF CIN AND ITS IMPACT ON THE REDUCTION OF MORTALITY OF CERVICAL CANCER

A CIRURGIA DE ALTA FREQUÊNCIA NO TRATAMENTO DA NEOPLASIA

INTRAEPITELIAL CERVICAL E SEU IMPACTO NA REDUÇÃO DA MORTALIDADE POR CÂNCER CERVICAL

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ABSTRACT

Introduction: The adequate treatment of cervical intraepithelial neoplasia (CIN) is an important component of cervical cancer prevention programs and its inadequate management may increase the future risk of neoplasia. **Objective:** To evaluate the role of loop electrosurgical excision procedure (LEEP) conization in the treatment of CIN, in an important state capital in southern Brazil, and to determine the impact on reducing cervical cancer mortality in the next 20 years. **Methods:** A retrospective cohort study was conducted in patients who underwent CIN treatment from January 1999 to December 2007 at Erasto Gaertner Hospital, analyzing the treatment morbidity and recurrence rate of the disease, using the χ^2 test for statistical analysis and $p \leq 0.05$. **Results:** A total of 1,550 women, between 14 and 93 years of age (35 ± 11.42) were evaluated. Recurrence rate was 6.8%. The postoperative complications were 5.8% bleeding, 2% cervical stenosis and 2% infection. The cervical cancer mortality rate decreased from 12 to 3.8/100,000 women and there was an increase in the incidence of the lesion in situ as opposed to the reduction of other clinical stages. **Conclusion:** LEEP conization was proven to be a highly effective tool in CIN treatment, substantially contributing to the reduction of mortality from cervical cancer, justifying its use in a systematic way in prevention programs.

Keywords: cervical intraepithelial neoplasia; conization; electrosurgery; mortality; recurrence.

RESUMO

Introdução: O adequado tratamento da neoplasia intraepitelial cervical é um importante componente dos programas de prevenção do câncer cervical, e seu manejo inadequado pode aumentar o risco futuro de progressão para neoplasia. **Objetivo:** Avaliar os resultados da cirurgia de alta frequência no tratamento da neoplasia intraepitelial cervical em uma importante capital do Sul do país e o impacto na redução da mortalidade por câncer cervical nos 20 anos subsequentes. **Métodos:** Estudo tipo coorte retrospectivo de pacientes submetidas a tratamento da neoplasia intraepitelial cervical, no período de janeiro de 1999 a dezembro de 2007, no Serviço de Patologia Cervical do Hospital Erasto Gaertner, Curitiba, Brasil, analisando a morbidade do tratamento e o risco de recorrência da doença utilizando o teste das proporções (χ^2) e valor $p \leq 0,05$, relacionando esses dados às taxas de mortalidade no período dos últimos 20 anos. **Resultados:** O número de 1.550 pacientes, com idade entre 14 e 93 anos ($35,3 \pm 11,42$). A taxa de recidiva foi 6,8%. As complicações pós-operatórias foram 5,8% de sangramento, 2% de estenose de colo e 2% de infecção. A taxa de mortalidade para câncer de colo na cidade de Curitiba caiu de 12 para 3,8 casos/100mil mulheres, ocorrendo o aumento da incidência da lesão in situ em contraposição à redução dos demais estádios clínicos. **Conclusão:** a cirurgia de alta frequência mostrou-se um instrumento relevante e de alta eficácia no tratamento da neoplasia intraepitelial cervical, contribuindo de forma efetiva para a redução da mortalidade por câncer de colo uterino, justificando seu uso de maneira sistemática dentro dos programas de prevenção.

Palavras-chave: neoplasia intraepitelial cervical; conização; eletrocirurgia; mortalidade; recorrência.

INTRODUCTION

Cervical cancer is an important public health problem in adult women in developing countries, which is the second or third most common cancer among women, depending on the place⁽¹⁾. Cervical cancer is mostly caused by persistent infection with certain subtypes of HPV (*Human papillomavirus*), a sexually transmitted disease that infects cells and can lead to precancerous lesions and invasive cancer⁽¹⁾.

With about half a million new cases and 270,000 deaths every year in the world, the incidence of cervical cancer is twice as high in the least developed countries, and the high mortality rates could be reduced through effective screening programs of signal lesions of cervical intraepithelial neoplasia (CIN)⁽¹⁾.

Screening programs for cervical cancer is a public health intervention in a target population to detect signal lesions, to decrease incidence and mortality. However, to achieve this goal, an organized program involves, besides the application of screening examinations, a complex structure for diagnosis and treatment of these lesions, along with appropriate follow-up⁽¹⁾.

The adequate treatment of CIN is an important component of the cervical cancer prevention program. The inadequate handling of CIN may increase the risk of progression to a future invasive neoplasm, on the one hand, and future obstetric complications, on the other⁽²⁾.

Up to the 1960s, aggressive methods such as conization and hysterectomy were used for the treatment of all grades of CIN. The introduction of a more conservative approach, such as destruction or excision of the abnormal transformation zone (LEEP/CAF/EZT), developed by Cartier in 1981, and subsequently refined by Prendiville in 1987, represented important progress for women with premalignant cervical disease⁽³⁻⁵⁾.

Since the 1990s, high-frequency surgery has been the method of choice for removing high-grade CIN and has demonstrated some

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advantages over other approaches. However, persistent or recurrent disease after conization by this technique varies from 5 to 30%, requiring appropriate follow-up and new treatment of lesions that can be identified⁽⁶⁾.

Based on these data, this study aimed to evaluate LEEP in the treatment of CIN, analyzing its efficacy as a therapeutic method, recurrence rate, data on the morbidity of treatment and, above all, the reduction in mortality from invasive neoplasia in the subsequent 20 years in a state capital of southern Brazil, in the context of an organized and qualified program for screening for cervical cancer.

METHODS

A retrospective cohort study was carried out in patients who underwent surgical conization by LEEP and/or conization by the SWETZ technique, at the Cervical Pathology Service of Hospital Erasto Gaertner (HEG) in Curitiba, in the period from January 1999 to December 2007. This study was previously reviewed and approved by the Ethics Committee of the aforementioned service under Protocol No. 1742.

Sample selection

Women attended at the HEG Cervical Pathology Service with a confirmed diagnosis of CIN 2 and 3, endocervical canal CIN 1 or persistent CIN 1 for more than one year, and who underwent LEEP conization in the aforementioned service, and had a minimum clinical follow-up of 3 years were selected for the study.

Exclusion criteria were the presence of invasive neoplasia, loss of clinical follow-up before 3 years of follow-up and insufficient data in the patient's medical records.

Data collection

Physical and/or electronic medical records of the selected patients were investigated, including: age, initial anatomopathological diagnosis, intra- and postoperative surgical complications, anatomopathological result of the conization specimen, disease recurrence rate and follow-up time.

The data related to the general mortality rate for cervical cancer were obtained from the Health Department of the Municipality of Curitiba, Epidemiology Sector.

The data related to the incidence of cervical cancer by clinical stage were provided by the Epidemiology Sector of Hospital Erasto Gaertner.

Conization technique

The LEEP conization technique was performed under local anesthesia, with demarcation of the area to be resected using Lugol's iodine, with removal of 1 or 2 samples, followed by hemostasis performed by cauterization of the margins and placement of a vaginal tampon for 24 hours.

The Swetz technique was performed with a procedure similar to that of the classic cone, using local anesthesia with blockade of the paracervical points, combined with sedation. The demarcation of the colposcopic margin of the lesion was made with Lugol's

iodine, and instead of the cold scalpel, the straight electrode of the electrocautery probe was used without ligation of the paracervical arteries for removal of a single specimen of conical lesion, followed by cauterization of the margins and placement of a vaginal tampon for 24 hours.

In both techniques, the conization specimen was marked with China ink on the true ectocervical and endocervical margins, before sending samples in formaldehyde to the pathological anatomy service.

After surgery, the patients' follow-up was carried out through cytology, colposcopy and, when necessary, cervical biopsy, every 4 months in the first year. After the first year, follow-up was every six months for two more years.

After the third year of follow-up, the patients were discharged by the HEG Cervical Pathology Service, with a medical report for subsequent follow-up by the primary health care service.

Anatomopathological study of biopsy specimens

The study of the biopsy specimens and conization sample was carried out by the pathological anatomy team at the hospital, by conventional hematoxylin-eosin (HE) staining. Serial sections of the entire length of the tissue piece was examined at up to 400x magnification, with determination of the presence of residual disease in the true margins (marked with China ink).

Data statistical analysis

Statistical evaluation was done using Excel and database software SPSS version 12.0, using univariate analysis and proportions test (χ^2), having as reference value a significance level of 5% ($p \leq 0.05$) and 95% confidence interval.

RESULTS

We evaluated 1,550 women, aged between 14 and 93 years (35 ± 11.42), with diagnosis of CIN 2 and 3, CIN 1 of endocervical canal and/or persistent CIN 1, who underwent treatment, and subdivided by evolutionary potential into 2 groups: clinical cure and recurrence of the disease. Of these women, 1,410 (91%) were subjected to LEEP for CIN treatment, 77 (5%) to the Swetz technique and 62 (4%) to other procedure (reconization). Of the 1,550 patients treated, 1,254 did not show prior history of CIN treated at another moment in life (first diagnosis of CIN at the time of this study) and the others had persistent or recurrent disease.

Among the 1,254 submitted to first CIN treatment in this service, 139 were CIN 1 cases, and 1,115 CIN 2 and 3 cases; 1,197 underwent conization and 57 the Swetz technique.

Of the 1,550 patients treated, 105 had recurrence of the disease after treatment in this service, with a recurrence rate of 6.8%. The epidemiological data of the study population is shown in **Table 1**.

In the intraoperative period, there were only 1.2% cases of complications ($n=18$) as follows: 1.1% bleeding ($n=17$) and 0.1% bladder lesion ($n=1$). The postoperative period showed the following complications: 5.8% bleeding ($n=90$), 2.1% infection ($n=32$) and 2.1% cervical orifice stenosis ($n=32$).

Analysis of the conization sample showed that margins were disease-free in 77% (n=1,197) of cases, involved in 16% (n=243), exiguous in 4% (n=63) and not evaluable in 3% (n=45).

There was no statistical difference in recurrence with regard to either the technique used for conization (p=0.75) or the surgeon who performed it, whether head surgeon or resident (p=0.629).

When both margins were disease-free, through the analysis of the conization specimen, there was 5% of recurrence, and when they were involved, recurrence was 16%, showing that involved appearance of the conization specimen margins was a statistically relevant factor for recurrence (p<0.001).

When the Swetz technique and LEEP were compared, there was a 10.5% recurrence rate in patients subjected to the Swetz technique and 6.4% in those who underwent LEEP, showing no statistical difference regarding the risk of recurrence and the surgical technique. Data related to the surgical treatment are shown in **Table 2**.

The anapathological results of the conization specimen did not show a statistical difference between CIN grade and the risk of disease recurrence or the presence of glandular extension and recurrence (**Table 2**).

From these data, the evolution of the incidence of cervical cancer screening protocol program was introduced in Curitiba, as shown in **Figure 1**.

Simultaneous to the evolutionary curve of the clinical stages of cervical cancer over the years, the mortality rate of uterine cervix cancer was plotted, as shown in **Figure 1**.

Figure 1 shows a clear decrease in the incidence of invasive carcinoma, conversely to the increased incidence of carcinoma *in situ*, during the years in which the organized protocol was in operation, and it displays the progressive decrease in the mortality rate of cervical cancer in the city of Curitiba since 1998, even with the population increase in the city over the years.

Table 1 – Epidemiological data of the population studied.

Classification	N	Group		p CI95%
		Clinical cure	Recurrence	
AGE*	1,550	1,445 35±10.9	105 35±14	p=0.927
SMOKING**	NO	666 (93.5%)	46 (6.5%)	p=0.126 (CI95% 18–163)
	YES	522 41 (91%)	46 (9%) 4 (9%)	
ALCOHOLISM**	YES	45 1020 (93%)	4 (9%) 73 (7%)	p=0.503 (CI95% 10–18)
	NO	1093 828 (92%)	71 (8%) 13 (8%)	
METHOD ACO**	YES	899 159 (92%)	71 (8%) 13 (8%)	p=1.0 (CI95% 21–24)
	NO	172 20 (71%)	8 (29%) 90 (8%)	
DM**	YES	28 1048 (92%)	8 (29%) 90 (8%)	p=0.01 (CI95% 3–9)
	NO	1138 29 (83%)	6 (17%) 83 (8%)	
HIV	YES	35 891 (92%)	6 (17%) 83 (8%)	p=0.07 (CI95% 5–107)
	NO	974		

Source: Cervical Pathology Service, HEG/BRAZIL.

*Student t-test; **Fisher exact test; ACO: contraceptive method; DM: diabetes mellitus; HIV: human immunodeficiency virus; CI95%: confidence interval of 95.

Table 2 – Data related to the surgical procedure and cervical intraepithelial neoplasia recurrence risk.

Variable	Classification	N	Group		p (95%CI)
			Clinical cure	Recurrence	
Type of Surgery	LEEP	1,197	1,106 (92%)	91 (8%)	p=0.07 (CI95% 7–138)
	SWETZ	57	49 (86%)	8 (14%)	
Cone AP	CIN 1	83	73 (88%)	10 (12%)	p=0.20 (CI95% 10–44)
	CIN 2	466	427 (92%)	39 (8%)	
	CIN 3	548	505 (92%)	43 (8%)	
	BOTH+	37	31 (84%)	6 (16%)	
Cone Margins	ECTOCERVICAL+	92	72 (78%)	20 (22%)	p<0.001 (CI95% 6–12)
	ENDOCERVICAL+	137	118 (86%)	19 (14%)	
	FREE	1197	1133 (95%)	64 (5%)	
Glandular Extension	ABSENT	545	501 (92%)	44 (8%)	p=0.47 (CI95% 30–35)
	PRESENT	690	636 (92%)	54 (8%)	
Surgeon	HEAD	622	568 (91%)	54 (9%)	p=0.408 (CI95% 7–17)
	RESIDENT	639	592 (92%)	47 (8%)	

Source: Cervical Pathology Service, HEG/BRAZIL.

*Fisher exact test; ** χ^2 test; LEEP: loop electrosurgical excision procedure; CIN: cervical intraepithelial neoplasia.

Note: Control Group = clinical cure/Study Group = with CIN recurrence.

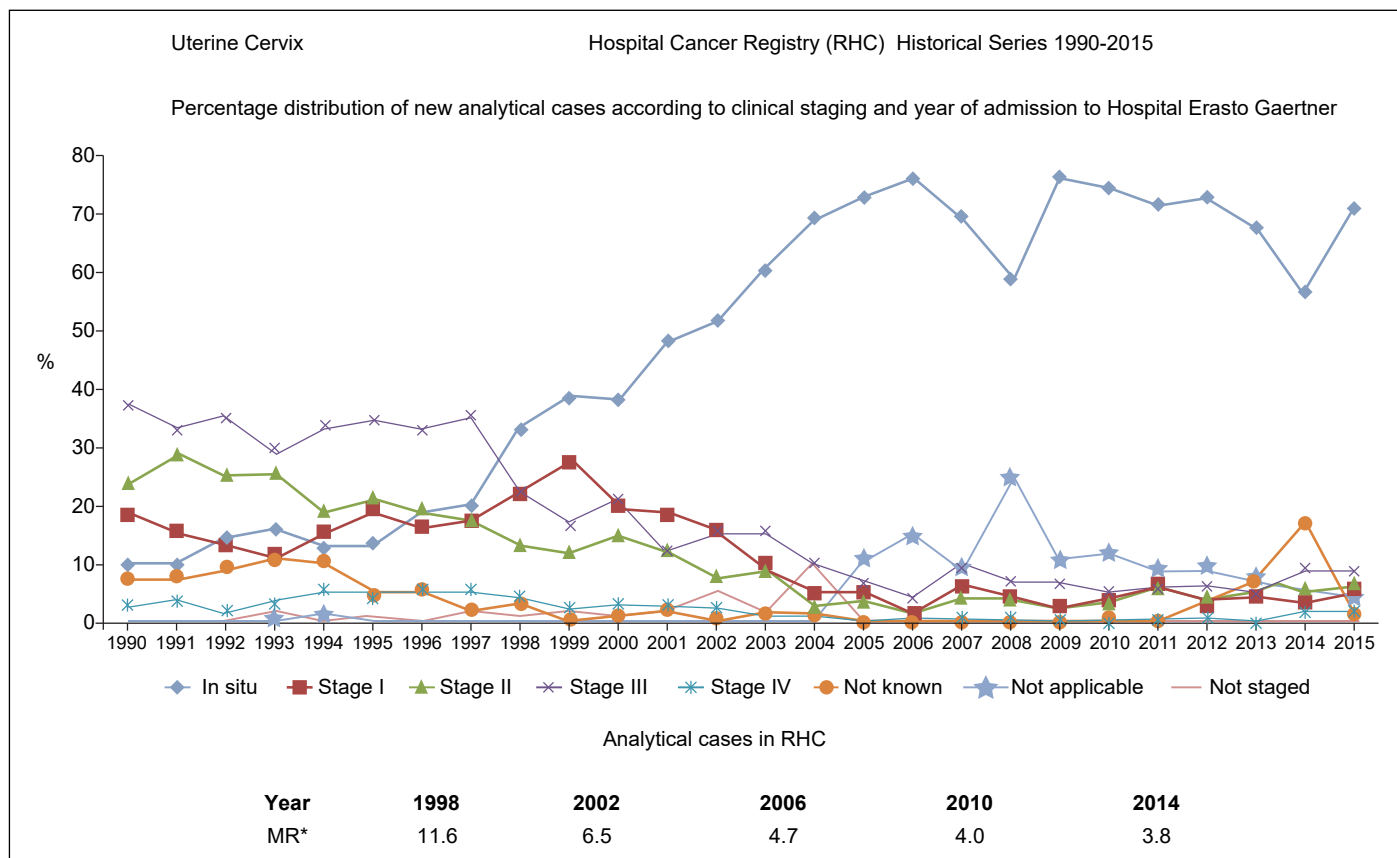


Figure 1 – Data correlate the clinical staging of cervical cancer and mortality rate for cervical cancer in the city of Curitiba (data provided by the Municipal Health Department). Source: Cervical Pathology Service, Hospital Erasto Gaertner and Municipal Health Department. *MR: mortality rate from cervical cancer for every 100,000 women.

DISCUSSION

Every year more than 2 million women around the world are diagnosed with breast cancer or cervical cancer, and the quality of life and the socioeconomic condition of each woman will determine the type of cancer she will develop⁽⁷⁾.

In less economically favored regions, where health conditions are precarious, cancer contributes to the "cycle of poverty". These inequalities show the urgent need, especially in underdeveloped or developing countries, for sustainable investments for the control of cancer⁽⁷⁾.

Cervical cancer develops from a neoplasia with the greatest preventive potential among human cancers of greatest incidence. The genesis of this tumor depends essentially on an infection of the uterine cervix by HPV, which needs to persist for many years to cause cellular transformation⁽⁸⁾.

These peculiarities make it easier for both primary prevention through vaccination, and secondary prevention through diagnosis and treatment of precursor lesions⁽⁸⁾.

The treatment of women with CIN reduces the risk of invasive carcinoma up to 95%. LEEP has been the preferred method in both the USA and the United Kingdom, due to being associated with low morbidity and high effectiveness in the short term⁽⁹⁾.

LEEP shows advantages over cold conization: it is an ambulatory procedure, done under local anesthesia, with low risk of complications, and it is easy to learn and perform. The technique initially only consisted of the use of a strap to remove the transformation area, but over time the use of a second strap was introduced to cover the deeper lesions, although with increased risks to the reproductive future of treated women⁽⁵⁻¹²⁾.

The findings of this study are comparable to those of the vast majority of studies over the years⁽¹⁰⁻¹⁵⁾, since they indicated a low rate of residual disease and/or recurrence and very low morbidity, and demonstrated low rates of surgical complications, both in the early and later postoperative period, like in most studies of good quality⁽¹⁰⁻¹⁵⁾.

Duggan et al.⁽¹⁰⁾, in their study comparing cold conization and LEEP, obtained 8 to 9% compromise of the margins of the conization specimen, 1% postoperative infection and 9 to 10% intraoperative bleeding. Also, these authors found no difference between the efficacy of the two techniques in the prevention of disease recurrence and in the rates of postoperative complications, which is comparable to the findings with our sample, both in the efficacy of the conization technique and in the rate of complications.

Several authors⁽⁹⁻¹⁵⁾ have evaluated the persistence and/or recurrence of the disease, and found recurrence rates between 8 and 40% of the cases, using cold laser and LEEP techniques.

A recent meta-analysis⁽¹¹⁾ on CIN treatment demonstrated that LEEP treatment had a recurrence rate of around 5.3% after 12 months and a low rate of complications, one of them being premature birth.

Similarly, another recent meta-analysis⁽¹²⁾ concluded that LEEP is as effective as the "gold standard" in the treatment of CIN, with regard to the risk of residual disease, risk of recurrence, compromised margins, secondary bleeding and cervix stenosis after surgical treatment. However, women who had undergone LEEP had a significantly lower percentage of deeper conizations and, consequently, lower preterm birth risk.

Since the 1970s, the incidence and mortality of cervical cancer have been decreasing in Northern Europe and North America countries. This decline is related to the introduction of screening programs in asymptomatic women. While in many parts of the third world, this type of cancer still leads prevalence and incidence statistics, determining a severe loss of years of life and quality of life⁽⁸⁾.

Mortality analysis studies in the last decade⁽¹⁶⁻¹⁸⁾ identified that the decline in the mortality rate of cervical cancer is directly proportional to the investment in and the extent of screening and prevention programs for each place.

The epidemiological and evolutionary data collected here show that the application of the prevention program over 20 years resulted in a clear inversion in the clinical stages of cervical neoplasia, with gradual increase in the incidence of carcinoma *in situ*, and a decrease in the more advanced stages, with a progressive reduction of mortality rates.

Analyzing the evolutionary chart by clinical stage of cervical cancer, we see almost no change in the incidence of stages III and IV, which probably reflects that group of women who, because of system precariousness, cannot access screening programs. However, a limitation of this study was that we analyzed data related to the implementation of a screening program, since this research was carried out only at the level of tertiary activities of the local health system.

CONCLUSION

LEEP proved to be a highly useful tool in CIN treatment, contributing effectively to the reduction of mortality from cervical cancer, justifying its use in a systematic way in of cervical cancer prevention programs, even in places with few resources.

Participation of each author

All authors participated actively in this work and gave final approval of the manuscript version submitted.

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Conflict of interests

There is no conflict of interests to be reported.

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