

## Research Article

# Factors predictors of residual illness in patient conizadas for lesions micro invaders and of high degree

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## Abstract

In Cuba, the cervical cancer constitutes an important problem of health for its high indexes of morbi-mortality and emotional impact in the population. In the handling of the women with their lesions precursors, the objective consists on preventing the possible progression to cancer invader without sobretratar the lesions with high regression probabilities. Along the time different treatments and protocols have been proven in order to obtaining the best results in the control of this pathology with conservative techniques, in the face of the growing incidence in patient without satisfied parity and minimizing the possibility of residual illness. It was carried out a prospective descriptive study to determine the relationship between the diagnosis of residual illness and clinical-epidemic factors in 428 patients with lesions cervical epithelial of high degree that were conization in the Hospital General Educational Heroes of the Baire during the period 2014-2016. 53% of the studied patients was bigger than 35 years of age, 74% had one or two children, 20% smoked, 38% had an initial cytology of high degree, 46% they had a lesion with an area of 100-199mm<sup>2</sup>, 90% they were conization for handle diathermic and 29% they were conization for not correlation diagnostics. The surgical margins affected by lesion, the carcinoma histology in situ or micro invader, the area of more lesion 199mm<sup>2</sup> and the glandular lesions of the cervical channel constituted factors predictors of residual illness. The presence of these factors predictors meant 79,6% of probability of appearance of residual lesion.

## Introduction

The cancer is at the moment one of the illnesses that awake bigger interest among the investigators to be an important cause of morbidity and of death in the world. THE cervical cancer is the third more frequent gynecological cancer in the world, with a frequency of 9,8% and it is considered that annually in the world they are diagnosed around 500 000 new cases of cancer cervical invader, of which the half is mortals [1]. In Cuba, this illness constitutes an important problem of health for its high indexes of morbi-mortality and emotional impact in the population. In some territories of the country, a stable tendency is observed while in other it spreads to the ascent of its incidence, like it is evidenced in an article of Padilla and collaborators [2] in Ciego de Ávila (2015), the same as in the Isle of Youth where growing values are reported in the last decade [3].

A series published by Lamb and García [4] in the town of San José de the Flagstones among 2011-2012 was also evidenced that it is happening a change in the age of appearance of this tumor type possibly related with the precocity of the first sexual relationships, the promiscuity and the concomitance of other factors of risk. This phenomenon has already been described by authors in diverse counties of the country like León Cruz [5] Rodríguez Salvá [6] and Martínez Pinillo [7].

The patients with lesion intraepithelial of low degree face minimum possibilities to develop a lesion cervical invader, as long as those with lesions of high degree are progression risk on high to cancer. In the handling of the women with NIC, the objective consists on preventing the possible progression to cancer invader without sobretratar the lesions with high regression probabilities [8]. Along the time different treatments and protocols have been proven with the objective of obtaining the best results in the control of this pathology; among these the ablative methods that destroy the lesion in situ and the split that extirpate it are. In the last years, a deep change has taken place in the handling of the pre-wicked processes of the uterine neck.

The cone with handle surgical electro (LEEP) it is an alternative in most from the cases to the cold cone with scalpel, with what a reduction of the bled intra operating has been obtained and of the post-surgical hemorrhage; with the rising reduction of the time of hospitalization or with ambulatory character, like in the context object of this investigation. The biggest difficulty attributed to the conization with handle of LEEP refers to the evaluation histological of the surgical borders for the thermal damage that produce [9]. The recurrence range or persistence of the NIC is located among 5-17%, independently of the type of elected therapy. The high indexes of persistent illness associate to lesions of big dimensions, commitment of glands endocervical, positive margins and continuous positivity to DNA of the virus of the human papilloma.

In the Isle of Youth, the behavior of the morbidity and mortality for cervical cancer and the incidence of its lesions precursors constitutes a serious problem of health. With a global tendency to the increment in the last 15 years, in the triennium 2014-2016 40% of all the cases of the period 2003-2016 and 57% have been diagnosed in patient smaller than 30 years (data of the autor [3,10]) over dimensioned the problem to medical situations not habitual two or three decades behind, as the attention to pregnant and patient without satisfied parity.

For the context where this study the contribution of this investigation is developed it could constitute a vital tool in the taking of decisions before one of the most common dilemmas that faces to newspaper to a kindred doctor to the topic: when to decide for expectant behavior, re-

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cone or hysterectomy. The study of these variables allows to deepen in the knowledge that every day arises in this respect, since they were few studies in the country and none deepens in the prediction diagnostics, which won't only offer a therapeutic contribution but also diagnosis of this pathology. From the methodological point of view, the present investigation will be good as starting point to other investigators to elaborate future studies related with this topic, and it would also allow to this institution to offer them more and better treatment alternatives to the patients that consult for this pathology, diminishing this way its relapse and the high rate of mortality for cancer of uterine neck and for ended, less economic impact on the costs hospital and better quality of the population's life.

## Objectives

General: To identify relationship between the diagnosis of residual illness and clinical-epidemic factors of interest in patient with lesions cervical epithelial of high degree or micro invader that were conics in the Hospital General Educational Heroes of the Baire during the period 2014-2016.

Goals objectives:

1. to describe the distribution of variables as groups age, conization type, diagnosis cytology and time of study post-cone.
2. to identify the presence of factors spreading of residual lesion in the study sample.

## Design methodological

It was carried out a prospective descriptive observational study to determine the statistical relationship between the diagnosis of residual illness and clinical-epidemic factors of interest in patient with lesions cervical epithelial of high degree that were conic in the Hospital General Educational Heroes of the Baire during the period 2014-2016. Universe and it Shows: The universe understood the 779 patients to who were practiced a conization by handle diathermic and it was obtained a lesion epithelial of high cervical degree or a carcinoma micro invader as a result in the period 2014-2016. For the conformation of the sample the range was calculated understood between the 25 and 75 percentile of the stocking of the age for the patients with residual lesion, considering that these 63 patients only represented 8% of the universe and the disproportion among patient con/sin residual lesion could affect the statistical significance. The sample was integrated by 428 patients: 63 with residual lesion and 365 without residual lesion.

Inclusion approaches: Patient conic in the Isle of Youth during the period 2014-2016.

Diagnosis definitive histological of NIC2, NIC3, Carcinoma in situ or Carcinoma micro invader <7mm surface and <5mm depth, at least two studies cytological and colposcópicos post-cone, histological of residual lesion.

Exclusion approaches: Patient with more diagnosis to the stadium that were conic for confirmation histological or estadiamiento.

Gathering of data: The clinical histories of all studied patients, the cytology card, their images colposcópicas and the biopsy tickets were revised. Variables were analyzed as age, diagnosis initial cytological, diagnoses previous histological to the cone and definitive, conization type, time of evolution post-cone free of lesion, glandular lesion in cervical channel, extension of the lesion to the channel according to colposcopy and diagnosis cytological of IVPH confirmed by histology. Specifically, in the studied surgical specimen the state of the borders

of surgical section, state of the cervical channel, area was evaluated affected by lesion and persistence of the IVPH post-cone.

Prosecution of data: For the statistical analysis the applications Epidat 3.1 and SPSS-22 were used. The width and number of intervals for the analysis of the age were determined using the rule of Sturges. The description of categorical variables is carried out with absolute and relative frequencies in percentages. The relationships among categorical variables are analyzed by means of the comparison of proportions with the test of Chi-square of Pearson and the exact test of bilateral Fisher was used in the case of not being able to be applied the Chi-square test of Pearson. To determine the statistical significance 95%, it was used ( $p < 0,05$ ) according to Cornfield, being carried out an analysis initial univariate that also evaluated reasons of disparity (odds ratio). The variables that demonstrated significance were subjected to an analysis multivariate of Binary Logistical Regression, leaving of a maximum model with the variables and moving away variables for approach of statistical significance. The obtained prediction pattern was subjected safe against kindness of adjustment of Hosmer and Lemeshow, besides being determined its Coefficient of determination and the area under the Curve of ROC.

## Analysis and discussion of the results

The distribution for age bracket shows like a similar distribution existed among the four strata, with slight prevalence of the groups among 36-41 years (27%) and bigger than 41 years (26%). however, the comparison among patient with and without alone residual lesion it showed significant statistical relationship in the patients bigger than 41 years ( $OR > 8$ ,  $p < 0,05$ ). The results of this investigation coincide with most of studies published regarding the age of the patients, with stockings that oscillate between 27 and 47 años [11]. The fact of finding a remarkable quantity of cases below 30 years (22%) it denotes the precocity with which they spread to appear these lesions precursors. Examples of this are works like those of Leguevaque *et al.* [12] (it mediate: 38 years); Lubrano *et al.* [13] (it mediate: 37,8) and Söderlund-Strand *et al.* [14] (media: 34 years). The basic explanation is related with the own natural evolution of the infection for the VPH considered necessary cause for the development of a lesion intraepithelial of uterine cervical. After the 30-35 years, the clearing capacity diminishes and the infection for the VPH persists in the cervical epithelium developing its capacity oncogenic and increasing the prevalence of NIC2 + that requires surgical treatment.

38% of the patients had a previous cytology to the conization with a lesion cervical epithelial of high degree and 29%, a lesion cervical epithelial of low degree. 19% of the patients had its last negative cytology and 5% only presented a cytology with cervical cancer. Several bibliographical revisions have valued the accuracy of the one sieved with conventional cytology comparing it with the diagnosis histological. Among 12 studies selected by their best methodology [15], the range of sensibility was of 30-87% and that of specificity of 86-100%. The notables' differences in the sensibility of the cytology among the different publications can be explained by the scarce reproducibility of the cytology or different biases. Some articles like the one presented by Carvajal *et al.* [16] only mentions a disagreement cytological of 24%, while others as Perrotta *et al.* [17] mention 52% of disagreement. In Cuba, a study of it Seasons I Lived and Carlos Moya *et al.* [18] in the Hospital University Martyrs of April 9<sup>o</sup> (Villa Clara) it showed that a direct relationship exists among the infection for VPH and the appearance of the lesions cervical intraepithelial, since in the patients' 72,6% the discovery cytological of the VPH existed, against alone 27,4% of patient with negative cytologists. Similar result shows Lamb Martínez *et al.* [4] in its study in the county of Mayabeque.

As for the parity, 39% of the patients had two children and similar percent (36%) they had a son, while the patient nulíparas only represented 9%. however, a statistical difference was only observed in patient with more than two children (OR=1,9 p=0,049).

The habit of smoking didn't show significant difference among patient with and without residual lesion, in spite of being present in 87 studied patients, with OR=1,7 and p=0,1115. 37% of the patients was conizadas for a previous biopsy with NIC2, while in 22% the biopsy a NIC3 reflected. In 29% he/she was not correlation cytological-colposcópica-histological. However, only in the patients with carcinoma in situ (OR: 2,8 p: 0,014) or carcinoma micro invader (OR: 3,4 p: 0,036) he/she was statistical difference. Diverse studies have demonstrated that even with the use of strict approaches of selection, around 10-20% of patient with confirmed histology of CIN2-3 in the biopsy directed by colposcopy before the surgery, residual CIN doesn't present in the definitive histology of the conization piece. In the study of Livasy *et al.* [19] the percentage of negative cones was of 13,8%, in the series of Ryu *et al.* [20] 17,7% and in that of Rodríguez-Manfredi *et al.* [21] 16%.

46% of the patients had a lesion with an area of 100-199mm<sup>2</sup> and 28% of the patients they had a lesion of 200-299mm<sup>2</sup>. The patients with lesions of 300mm<sup>2</sup> or they only represented less 5%. nevertheless, he/she was statistical difference among patient with and without residual lesion in the patients with an area of more lesion at 199mm<sup>2</sup> (OR=2,6-4,5 p <0,05). 90% of the patients was conizadas for the method of handle diathermic (radiosurgery). In none of the cases with the method of cold scalpel was residual lesion.

With relationship to the diagnosis definitive histological, it is appreciated that almost 50% of the patients presented a NIC3 and 30%, a NIC2. In spite of it, only those that presented a carcinoma in situ (OR: 2,53 p=0,01) or a carcinoma microinfiltrante (OR: 6,42 p=0,00) they showed a different behavior statistically as for the presence or not of residual lesion. It was also observed as three of each four patients without residual lesion they present more than 24 months free of the illness and in the patients' 15%, this period was of 13-24 months.

In the consulted literature, the frequency of margins affections oscillates in 10,8-46% [22,23]. most of the studies demonstrate that

the margins affections increase the risk of illness residual [24,25] significantly. In the study of Houfflin-Debargue *et al.* [26] the patients with positive margins were 36%, in the study of Serati *et al.* [27], 32% of the patients presented margins affections and it was found that this was the factor more important predictor of recurrent illness, the same as in the works of Prato [28] and Baloglu *et al.* [29].

In an analysis univariate of factors related with the surgical specimen, 16% of the studied patients had an infection for VPH diagnosed to the moment of the conization and 13% it maintained this infection during its evolution post-cone. It is attractive also that in 10% of the patients borders of surgical section were evidenced affected by lesion and in 9% of the patients the colposcopy showed that the lesion penetrated the channel endocervical. However, the variables that showed statistical significance were the presence of glandular lesion (OR: 3,5 p=0,0001), the borders of surgical section affected by lesion (OR: 4,3 p=0,0000) and the presence of area of transformation type 3 (OR: 5,0 p=0,0000), in growing order (Table 1).

When carrying out an analysis multivariate of logistical regression with the variables that showed statistical significance it was found that, of the studied factors, only the surgical borders affected by lesion (OR: 7,1), the carcinoma diagnosis in situ or microinfiltrante (OR:6,0), an area of lesion bigger 199 mm<sup>2</sup> (OR: 5,8) and the presence of glandular lesion (OR: 4,0) they behaved as factors predictors of residual lesion, when reflecting an OR>1 and a significance (p <0,05) (Table 2).

The proposed pattern showed a good variability among the prospective value and observed for patient with and without residual lesion to the subjected being to the test of kindness of adjustment of Hosmer and Lemeshow, what demonstrates its validity predictor. This way, when calculating the probability of appearance of residual lesion in presence of the four factors predictors, a p=0,796 is obtained. that is to say, according to the proposed pattern a patient with carcinoma in situ or micro invader, with glandular lesion, a bigger area 199mm<sup>2</sup> and positive surgical borders have 79,6% of probability of having a residual lesion.

## Conclusions

1. The age among 36-41 years, the cytology with lesion epithelial of high degree, obstetric history of one or two children and the lesions

**Table 1.** Distribution of conized patient with LIEAG or micro invader according to factors related with surgical specimen. Island of the Youth, 2014-2016. [Source: individual clinical histories and SPIC 3.0].

Factors of the surgical specimen	WRL	%	wRL	%	Total	%	OR	Prob.
Previous HPV I	21	33,3	103	14,4	124	15,9	1,3 (0,7-2,2)	0,4991
Persistent HPV I	17	27,0	87	12,2	104	13,4	1,2 (0,7-2,2)	0,7047
Embroider positive surgical section	26	41,3	51	7,1	77	9,9	4,3 (2,4-7,7)	0,0000
White Epithelium that channel penetrates	12	19,1	57	8,0	69	8,9	1,3 (0,7-2,5)	0,6182
Transformation área type 3	24	38,1	40	5,6	64	8,2	5,0 (2,7-9,1)	0,0000
Glandular lesion	21	33,3	31	4,3	52	6,7	3,5 (1,9-6,5)	0,0001
Previous conization	2	3,2	35	4,9	37	4,8	0,3 (0,1-1,3)	0,1526

WRL: with residual lesion; wRL: without residual lesion; HPV I: human papilloma virus infection

**Table 2.** Regression logistical multivariate of variables with statistical significance. [Source: Database of the study].

Factores predictivos	E.E	Prob.	OR	Coef.
Embroider positive surgical section	0,3910	0,0000	7,1 (3,3-15,3)	1,9594
In situ/Microinfiltrante carcinoma	0,3876	0,0000	6,0 (2,8-12,9)	1,7942
Area of lesion >199 m2	0,3916	0,0000	5,8 (2,7-12,4)	1,7483
Glandular lesion	0,5908	0,0000	4,0 (1,3-12,8)	3,6928
Age >41 years	0,3903	0,0650	1,4 (0,9-2,4)	1,0956
Transformation area type 3	0,6445	0,1182	0,4 (0,1-1,3)	-1,0068

Quotient of Determination: 0,4269; Quotients of Verisimilitude // Statistical: 155,6 gl:6 p=0,0000; Constant ( $\beta_0$ ): - 4,2295

with area of 100-199 mm<sup>2</sup> was frequent conditions found in the study sample.

- The biggest procedures number was carried out with handle diathermic and it was significant the number of patient conizadas for not correlation diagnostic mention-colpo-histological.
- The surgical margins affected by lesion, the carcinoma histology in situ or micro invader, the area of lesion bigger 199 mm<sup>2</sup> and the glandular lesions of the cervical channel constituted factors predictors of residual illness.

## Recommendations

- To purify the quality of the diagnosis cytological and histological of the study of the cervical channel, for the sensitive thing that it is in the handling of patient with lesion epithelial.
- To demonstrate with the continuity of the study that the pattern possesses a high sensibility, specificity and value predictive will allow to establish more suitable and more pertinent therapeutic rules.
- To study other variables that can be predictors like type of affected surgical border and serotype of papilloma viral present.

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