

## Validation of a Prediction Model for Residual Disease in Patients Conized by Microinvasive and High-Grade Lesions

Dr.C Heenry Luis Dávila Gómez<sup>1\*</sup>, Dr.C Lidia Esther Lorié Sierra<sup>2</sup>, Dr.C Georgia Díaz-Perera Fernández<sup>3</sup>, Dr. Cs Jorge Bacallao Gallestey<sup>4</sup> and Dr. Eliany Regalado Rodríguez<sup>5</sup>

<sup>1</sup>Doctor in Medical Sciences. I and II degree specialist in Gynecology and Obstetrics. Professor and Assistant Researcher at the Faculty of Medical Sciences of the Isla de la Juventud. Cuba

<sup>2</sup>Doctor in Health Sciences. I and II degree specialist in Gynecology and Obstetrics. Full Professor at the Guantánamo University of Medical Sciences. Cuba

<sup>3</sup>Doctor in Medical Sciences. I and II degree specialist in Epidemiology. Professor and Senior Researcher at the University of Medical Sciences of Havana. Cuba

<sup>4</sup>Doctor of Sciences. I and II degree specialist in Biostatistics. Professor and Senior Researcher at the University of Medical Sciences of Havana. Cuba

<sup>5</sup>First degree specialist in Gynecology and Obstetrics. Instructor Professor at the “Leonilda Tamayo Matos” University Polyclinic on the Isla de la Juventud

\***Corresponding Author:** Dr.C Heenry Luis Dávila Gómez, Doctor in Medical Sciences. I and II degree specialist in Gynecology and Obstetrics. Professor and Assistant Researcher at the Faculty of Medical Sciences of the Isla de la Juventud. Cuba, E-mail: heenry@infomed.sld.cu

**Received Date:** September 22, 2024 **Accepted Date:** October 22, 2024 **Published Date:** October 25, 2024

**Citation:** Dr.C Heenry Luis Dávila Gómez, Dr.C Lidia Esther Lorié Sierra, Dr.C Georgia Díaz-Perera Fernández, Dr. Cs Jorge Bacallao Gallestey, Dr. Eliany Regalado Rodríguez (2024) Validation of a Prediction Model for Residual Disease in Patients Conized by Microinvasive and High-Grade Lesions. J Cancer Res Therap Oncol 12: 1-6

### Summary

**Introduction:** The diagnosis and treatment of poscone residual disease is not considered standardized due to the lack of prediction models adjusted to the characteristics and needs of the national context, particularly in young patients, without satisfied parity or not eligible for hysterectomy.

**Objective:** Validate a prediction model of post-cone residual disease.

**Methods:** A prospective descriptive study was carried out in the 209 patients conized by microinvasive and high-grade le-

sions, between the period 2020-2023 as an external validation of the model designed by the authors between 2014 and 2019 and is based on a classification tree that includes three variables: human papillomavirus infection, the state of the surgical edges and the depth of the cone.

**Results:** In this study, the variables showed a significant risk association, with an odds ratio of 6.2; 5.8 and 4.2; respectively. The model showed a sensitivity of 78.1%, a specificity of 93.8% and an efficacy of 91.4%. When including other significant variables such as the presence of glandular lesion and the largest area and degree of lesion, the sensitivity increased to 90.3% and the efficacy to 93.3%.

**Conclusions:** The proposed model is considered relevant for use in clinical practice.

**Keywords:** Residual Disease; Conization; Microinvasive; Cervix; High-Grade Epithelial Lesion

### Abbreviations and Acronyms

CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; HSIL: high-grade epithelial lesion; NHSCSP: National Health Service Cervical Screening Program; OR: odds ratio; RD: residual disease

## Introduction

The evolution of the management of residual disease (RD) of the cervix in conized patients is undergoing an evolution, in line with scientific development. Several investigations reflect the relevance of the state of the surgical margins and other variables in therapeutic decision making, without defining tracer variables that define or protocolize said action [1].

Currently, methodologies are proposed that are based on risk stratifications such as the British National Guidelines that suggest repeating conization or performing hysterectomy in all patients over 50 years of age with a high-grade epithelial lesion (HSIL) and with involvement of the edges. Surgical procedures, based on an ER rate greater than 90% [2]. Furthermore, it highlights the idea that early recurrences, during the first year of post-treatment follow-up, are more related to the positivity of the endocervical margins, when compared to the exocervical, in a direct relationship with the degree of histological alteration [3].

Currently, evidence indicates that involvement of the surgical margins, histology, glandular involvement, persistent HPV infection, age and immunosuppression are the main predictive factors associated with ER [1,2,4-6].

Although American and European Guidelines recommend repeating surgery when the surgical margins are positive in patients with a diagnosis of carcinoma in situ or microinvasive, there is still no consensus among researchers on management when the diagnosis is CIN 2-3 [5,6]. The options management of these patients ranges from cytological and colposcopic follow-up to repeat conization or immediate hysterectomy. NHSCSP recommends excision only in patients over 50 years of age with evidence of glandular involvement or microinvasion [7].

Several RD prognostic methods that currently exist are time-consuming, require pathology specimens, and are often limited to modeling only a particular type of disease, in addition to being inaccessible for low-resource settings, whereas described concentrates the largest number of cases [8,9]. The findings of certain models can simplify post-operative diagnosis and serve as a novel method to use commonly collected operational parameters for ER prediction using machine learning.

This research provides a diagnostic methodology based on the prediction models previously proposed by the authors that would contribute to the optimization of therapeutic behavior for each patient; at the same time that it offers a particular approach to the different moments that the diagnosis and treatment of these injuries and the possible

RD go through, based on self-made diagrams. Therefore, the authors in this article propose to show the results of the validity of the classification tree as a prediction model for RD in conic patients.

## Methodological Design

A prospective descriptive observational study was carried out to determine the validity of a classification tree as a prediction model for RD in conized patients. The prediction model proposed by lead author was used, which consists of a classification tree that includes three variables: the depth of the cone, the state of the surgical edges and the presence of the human papillomavirus. The study went through two stages: a first stage with the 1,090 cases used in the construction of the classification tree (internal validation) in the period 2014-2019 and a second stage, which included the 209 cases between the years 2020 and 2023 (external validation).

To create the study universe, all patients who underwent cervical conization for a microinvasive or high-grade lesion on the Isle of Youth during both stages of the research were considered and no sampling technique was used. In each stage we worked with two groups: with RD or without it. Exclusion criteria were considered not to have at least two poscone cytological and colposcopic studies, the definitive diagnosis greater than stage Ia1 in cone biopsy results and those patients with a degree of fragmentation of the sample that does not allow the evaluation of the surgical margins.

Those with a histological diagnosis of CIN 2, CIN 3, carcinoma in situ or microinvasive carcinoma, a positive result of the post-cone study of the cervical canal, or with cytology or colposcopy suggestive of HSIL, or both, and result were classified in the group of patients with RD. histology of HSIL or microinvasive carcinoma, by punch, cone biopsy or hysterectomy. The exit criterion was considered to be those patients whose diagnostic or therapeutic process was incomplete.

The analysis variables were organized into three dimensions: dependent on the patient, the surgeon and the surgical technique. To collect the data, the medical records of each patient, their cytology cards and the data provided

by the SPIC 3.0 software for processing colposcopic images were reviewed.

For the statistical analysis, version 22 of the SPSS statistical package was used from databases built in Microsoft Excel; using common metric resources of sensitivity, specificity, predictive values and efficacy.

## Analysis of the Results

The frequency of RD did not vary significantly between both study stages, with 12.0% in the model design stage and 15.3% in the validation stage.

Table 1 shows in the construction of the prediction model that all variables, except smoking, showed statistical association, with greater relevance for those included in the classification tree: initial HPV (OR=11.3), positivity of the surgical edges (endocervical: OR=8.5; exocervical: OR=6.8) and the depth of the cone less than 10 mm (OR=4.9).

In the validation group, the behavior of the predictor variables did not vary noticeably and the greatest association of these with RD was maintained: initial HPV (OR=6.2), positivity of exocervical edges (OR=5.8) and endocervical (OR=4.6), with an OR=4.2 for cone depth less than 10 mm.

Other variables that showed statistical association with residual disease in both stages of the study were the lesion area  $\geq 175 \text{ mm}^2$  (OR=6.1), the histological diagnosis of carcinoma in situ or microinvasive (OR=4.7) and glandular involvement (OR=4.0); values obtained in the validation stage.

When the classification rule was applied at the design stage (Table 2), the metric indicators of forecast quality were as follows: sensitivity (61.1%), specificity (96.8%), and effectiveness (92.5%). When performing the same calculation in the validation stage, a sensitivity of 78.1%, a specificity of 93.8%, a positive predictive value (54.0%), a negative predictive value (96.9%) and a test efficiency of 91.4%.

By adding the most significant variables (area, histology, glandular involvement) to the RD prognosis (Table 3), the quality of the prognosis improved, by increasing the

sensitivity to 90.6% (+12.5%), the effectiveness of the test at 93.3% (+1.9%), the positive predictive value at 73.8% (+19.2%) and the negative predictive value at 99.4% (+2.5%).

## Discussion of the Results

Several researchers such as Ayhan [7] and Buskwofie [10] propose that the presence of HPV is the most important risk factor for the development of CIN and its chronic viral persistence is definitive for the progression towards HSIL or invasive cancer. Even so, not all patients with RD had HPV infection, so the multi-causal complex of RD is not reduced to this, but rather involves other factors. However, it is indisputable that HPV has a very high negative predictive value in relation to RD: OR 6.2 [2.1 OR 17.5].

There are studies that show an association between the risk of RD, sample fragmentation and the positivity of the surgical margins, as an expression of the surgeon's skill, although not exclusively dependent on it [11].

Although the American and European Guidelines recommend repeating the surgery if there are positive margins with a diagnosis of microinvasive carcinoma, there is still no consensus for the future management of dysplastic lesions of the CIN 2-3 type [4,7]. Although the indications for the loop electrosurgical electrode procedure cone are clear and its use is highly accepted, there is no consensus regarding the management of patients with CIN and positive margins in the surgical specimen [12]. From another position, several studies do not report differences in RD according to the type of involvement of the surgical edge,<sup>13</sup> facts that differ from the results of this research, which highlights above all the involvement of the endocervical edge, like the Santa-María study [1].

The histological report of the cone piece is not sufficient on its own to consider the presence of residual disease; the probability of involvement of these edges is related to the size and severity of the injury. When deciding on treatment if the lesion persists, greater importance should be given to the positivity of the endocervical margins. If there is suspicion of microinvasive cancer, glandular dysplasia or an unsatisfactory colposcopy, the possibility of per-

forming a new surgery should be considered [1,6-8].

Although the depth of conization is a relevant variable, especially in postmenopausal women who have a greater probability of affecting the cervical canal, the present study does not provide favorable evidence for a fixed or stable relationship between higher-grade disease, extension and depth of the injury. Currently, the general recommendations of the NHSCSP [1,3,7] and the European Guidelines on Colposcopy Department of Health State that diathermic loop treatments should be at least 8 mm deep, which seems reasonable to ensure complete excision of the injury [14].

The relationship between the size and severity of the lesion is neither direct nor linear, so in healthcare practice it is not exceptional to find extensive lesions that can result in low squamous intraepithelial lesion; On the contrary, lesions can be found that are limited to one quadrant of the cervix and result in microinvasive carcinoma. The larger size of a lesion is associated with a greater probability of residual disease to the extent that these dimensions are related to more serious histological changes, or are associated with extension to the cervical canal or the bottom of the vagina.

The increase in the severity of the lesion in terms of its histology is related to an increased risk of RD and there is evidence that also relates it to an increase in the size of the lesions and the possibility of glandular injury [8,15]. Furthermore, as explained in the theoretical references of the research, the severity of the lesion is also related to the presence of high risk-HPV serotypes and the coexistence of several of these serotypes [4].

The diagnosis of glandular disease in the surgical specimen is relevant from a clinical point of view because it informs both the management and prognosis of these lesions. Jones recognizes that glandular injury is related to high rates of RD, independently of the involvement of the surgical margins [16].

The design and application of residual disease prediction models would allow greater objectivity in therapeutic decision-making by being able to measure the probability of risk of each patient, based on previously identified and evaluated conditions, which may have particularities that are related with population characteristics.

## Conclusions

The prediction model based on a classification tree of three variables: HPV infection, positivity of the surgical edges and depth of the cone less than 10 mm is feasible for its application in clinical practice, showing adequate diagnostic quality. The prognostic capacity of the model improves when combined with other predictor variables, such as glandular disease, diagnosis of carcinoma in situ or microinvasive, and lesion area greater than or equal to 175 mm<sup>2</sup>.

## Funding

This research did not receive any funding nor are there any permission conflicts between authors.

## References

- Santa-María-Ortiz J, Álvarez-Silvares E, Bermúdez--González M, García-Lavandeira S, Pato-Mosquera M, Couso--Cambeiro B (2020) Importance of affected surgical margins in cervical uterine conization. *Ginecol Obstet Mex.* 88: 586-97.
- Manchanda R, Baldwin P, Crawford R, Vowler SL, Moseley R, Latimer J, Welton K, Shafi M (2008) Effect of margin status on cervical intraepithelial neoplasia recurrence following LLETZ in women over 50 years. *BJOG.* 115: 1238-42.
- Flannelly G, Bolger B, Fawzi H, De Barros Lopes A, Monaghan JM (2001) Follow up after LLETZ: could schedules be modified according to risk of recurrence? *Br J Obstet Gynaecol.* 108: 1025-30.
- Bottari F, Iacobone A, Passerini R, Preti E, Sandri MT, Cocuzza CE, et al. (2019) Human papillomavirus genotyping compared with a qualitative high-risk human papillomavirus test after treatment of high-grade cervical intraepithelial neoplasia. A systematic review. *Obstetrics & Gynecology*, 134: 452-62.
- Jun-Yu C, Zhi-Ling W, Zhao-Yang W, Xing-Sheng Y (2018) The risk factors of residual lesions and recurrence of the high-grade cervical intraepithelial lesions patients with positive-margin after conization. *Medicine*, 97: 41-8.
- Marth C, Landoni F, Mahner S, McCormack M, Gonzalez Martin A, Colombo N (2017) Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 28: 72-83.
- Ayhan A, Aykut Tuncer H, Haberal Reyhan N, Kuscu E, Dursun P (2016) Risk factors for residual disease after cervical conization in patients with cervical intraepithelial neoplasia grades 2 and 3 and positive surgical margins. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 201: 1-6.
- Cheung L, Egemen D, Chen X, Katki H, Demarco M, Wisner A, et al. (2019) ASCCP risk-based management consensus guidelines: methods for risk estimation, recommended management, and validation. *J Low Genit Tract Dis.* 24: 90-101.
- Ganguli R, Franklin J, Yu X, Lin A, Heffernan D (2022) Machine learning methods to predict presence of residual cancer following hysterectomy. *Scientific Reports*, 12: 2738.
- Buskwofie A, David-West G, Clare CA (2020) A Review of Cervical Cancer: Incidence and Disparities. *J Natl Med Assoc.* 112: 129-32.
- Chambo Filho A, Garbeloto E, Rodrigues Arrabal Guarconi J, Pereira Partele M (2015) Positive Endocervical Margins at Conization: Repeat conization or colposcopic follow-up? A Retrospective Study. *J Clin Med Res.* 7: 540-4.
- Hecken JM, Rezniczek GA, Tempfer CB (2022) Innovative diagnostic and therapeutic interventions in cervical dysplasia: A systematic review of controlled trials. *Cancers*, 14: 2670.
- Venegas Rodríguez G, Cardoza Jiménez K, Alvarez M, Santos C, Mariátegui JC, Velarde C, et al. (2017) Recurrence/persistence of cervical intraepithelial neoplasia after LEEP cone at the National Institute of Neoplastic Diseases. *Horiz Med.* 17: 6-10.
- Petry KU, Nieminen PJ, Leeson SC, Bergeron CO-MA, Redman CWE (2017) Update of the European Federation for Colposcopy (EFC) performance standards for the practice of colposcopy. *Eur J Obstet Gynecol Reprod Biol.*

2018: 137-41.

15. Bogani G, Lalli L, Sopracordevole F, Ciavattini A, Ghelardi A, Simoncini, T, et al. (2022) Development of a nomogram predicting the risk of persistence/recurrence of cervical dysplasia. *Vaccines*, 10: 579.

16. Jones R, Dale F, Fite J, Cowan M, Williamson B, DeLuca J, et al. (2020) Endocervical glandular involvement is associated with an increased detection rate of high-grade squamous intraepithelial lesions on the Papanicolaou test. *Journal of the American Society of Cytopathology*, 9: 137-45.

**Submit your manuscript to a JScholar journal and benefit from:**

- ¶ Convenient online submission
- ¶ Rigorous peer review
- ¶ Immediate publication on acceptance
- ¶ Open access: articles freely available online
- ¶ High visibility within the field
- ¶ Better discount for your subsequent articles

Submit your manuscript at  
<http://www.jscholaronline.org/submit-manuscript.php>