Universitat de Girona
Facultat de Medicina

RE-CONIZATION VERSUS CLOSELY FOLLOW-UP TO WOMEN WITH AFFECTED EXOCERVICAL MARGINS AFTER CONIZATION FOR H-SIL OR L-SIL, A CLINICAL TRIAL

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I want to thank the department of Gynaecology and obstetrics of Josep's Trueta Hospital to give me the opportunity to learn day by day, and all the professionals involved.
I also want to thank my tutors: Ester Vila for the counselling and the proximity I have received during this time; and Teresa Puig for the time she spent helping us.

Medicine there is only one, and it is effective when you have scientific evidence behind it. (J.M. Mulet)

ABREVIATIONS

- CIN: Cervical Intraepithelial Neoplasia

- LAST: Lower Anogenital Squamous Terminology

- SIL: Squamous Intraepithelial Lesion

- LSIL: Low-grade Squamous Intraepithelial Lesion

- HSIL: High – grade Squamous Intraepithelial Lesion

- AGC: Atypical Glandular Cells

- ASC-H: Atypical Squamous Cells cannot exclude HSIL

- ASC-US: Atypical Squamous Cells of Undetermined Significance

- CIN: Cervical Intraepithelial Neoplasia

- HPV: Human Papilloma Virus

- HR - HPV: high risk HPV

- LEEP: Loop Electrosurgical Excision Procedure.

- LLETZ: Large Loop Excision of the Transformation Zone

- SEGO: Sociedad Española de Ginecología y Obstetricia.

- TZ: Transformation Zone

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1. ABSTRACT

BACKGROUND

Cervical cancer is the third neoplasia among worldwide. It is known, that cervical carcinogenesis is based on the persistence of HPV infection. Fortunately, screening protocols have been recently applied. Those protocols showed great results reducing invasive cancers and offering less invasive techniques due to early detection. The screening with cytology should be performed to women between 25 and 30 years, every 3 years. It's done by HPV tests every 5 years in women between 35 and 60 years old. Treating precancerous injuries is effective, although, the number of women treated is increasing. The main techniques applied to find out precancerous lesions such us L-SIL and H-SIL are cytology, colposcopy and HPV detection. The main technique to treat them is the conization (LEEP procedure). Once a precancerous lesion is confirmed a resection procedure must be done to avoid the progression of the lesion. After that, if the histological margins aren't affected the patient should be followed-up among 20 years. But if the results show affected margins, either the patient can be followed-up or the conization can be repeated.

OBJECTIVE

The aim of this study is to compare the local recurrence between follow-up procedures and re-conization, in women with positive exocervical margins after conization (either for HSIL or LSIL).

STUDY DESING AND POPULATION

A randomized controlled clinical trial will be done. It will be a multicentric study performed on the Province of Girona between the 2019 and 2023. The sample size will be of 144 patients who meet inclusion criteria.

METHODS

The main variables will be: local recurrence confirmed by histology and following-up or re-conization. The following covariables will be considered: age, gravidity, tobacco, alcohol, IMC, HPV, HPV vaccination, STD and number of sexual partners. The patients with LSIL will be classified in two groups randomly: the follow-up group and the re-conization group. The same distribution will be applied for the HSIL patients. Those patients will be followed-up for two years and the local recurrence will be analysed and compared in the two different groups.

KEYWORDS

HSIL, LSIL, Conization, Positive margins, Local Recurrence, Cervical Cancer, CIN.

2. INTRODUCTION

2.1 CERVIX CANCER

Cancer is common in older people but cancer of the uterine cervix primarily affects young women, with the majority of cases appearing between the ages of 35 and 50 as it is said in the European guidelines. (1)

It is the third neoplasia in order of frequency in women around the world and its pathology is well known and the main factor to develop this cancer is the Human Papillomavirus. Luckily the incidence of this cancer is decreasing due to the multiple techniques and treatments stablished lately:

- Vaccination as for primary prevention
- Screening for secondary prevention
- Treating the precancerous injuries as tertiary prevention.

As it occurs with other diseases in the developing countries this cancer is affecting more women, and almost 9 in 10 cervical cancer deaths (87%) occur in the less developed regions. (2)

Women living with HIV are at increased risk of developing cervical cancer and experience more rapid progression of the disease.

2.2 EPIDEMIOLOGY

The cervical cancer is the third neoplasia in the world. In the European Union (EU) 34 000 new cases and more than 16 000 deaths due to cervical cancer are reported annually.(1) You can see the distribution among the world in the Figure 1.

The incidence in Spain for the cervical cancer in the 2017 was of 2584, from GLOBOCAN 2012 extrapolated for the population given by the INE. And the mortality was 620 in 2016 for malignant neoplasia. (3)

In Girona the incidence of cervical cancer is 21 cases per year, with a middle age at diagnosis of 55 years old, as it was seen in the CanGir Study done between 2010-2012. But it was also seen that the carcinoma in situ was more common in younger ages as you can see in the table 1. (4)

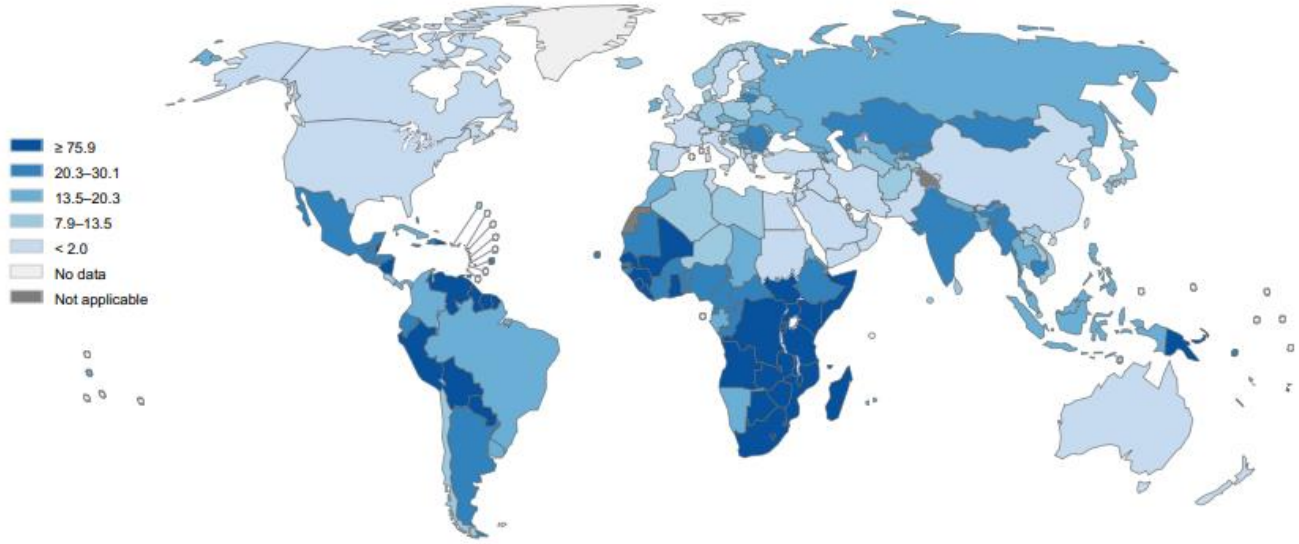

Figure 1: *Estimated age-standardized rates of incidence cases, females, cervical cancer, worldwide in 2012 (2)*

Table 1*: incidence of carcinoma in situ in Girona between 2003-2012(4)*

Cervix cancer in Women in Girona										
Age	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
0-14	0	0	0	0	0	0	0	0	0	0
15-24	8	10	13	8	17	10	8	8	5	8
25-49	88	86	91	96	109	129	125	95	96	75
50-69	8	7	12	8	10	14	8	13	7	10
>70	0	3	1	3	0	2	1	0	2	2

2.3 EVOLUTION

It is known that most of all the cervical cancers are an evolution from precancerous injuries caused by the HPV (Human Papilloma Virus). Here in the Figure 2 you can see the progression of the injuries, that's why it is so relevant to treat the precancerous states before they turn into invasive cancer.(5)

The squamous intraepithelial lesions (SIL) caused by HPV are morphologically identical in all the localizations of the lower anogenital tract in both sexes (cervix, vagina, vulva, anus, perianal region and penis). In 2012, the American College of Pathologists (ACP) and the American Society of Colposcopy and Cervical Pathology (ASCCP) have established a histopathological terminology denominated LAST (Lower Anogenital Squamous Terminology). This terminology has been described in the last classification of the World Health Organization (WHO) for tumours of the female genital tract published in 2014.(6)

The LAST terminology classifies histological SIL associated with HPV into two grades: "low-grade" (LSIL) and "high-grade" lesions (HSIL). The classification therefore uses the same terminology for the cytological result in the Bethesda system and uses similar criteria. The histological criteria defining these lesions are:

- **LSIL:** Proliferation of squamous or metaplastic cells with abnormal nuclear characteristics (increase in nucleus size, irregular nuclear membrane, and increase in the nucleus-to-cytoplasm ratio). There is little maturation of the cytoplasm in the lower third of the epithelium. Also, mitotic figures are only present in the lower part of the epithelium. Koilocytosis may be observed and is characterized by multinucleation, nuclear enlargement and pleomorphism accompanied by perinuclear halos without the characteristics of a high-grade lesion. This term includes the LSIL/CIN1 lesions (cervical intraepithelial neoplasm grade 1) of the Richart/WHO 2004 classification.
- **HSIL:** Proliferation of squamous or metaplastic cells with abnormal nuclear characteristics (increase in nucleus size, irregular nuclear membrane and increase in the nucleus/cytoplasm ratio, accompanied by mitotic figures). There is little or non-cytoplasmatic differentiation in the middle thirds and surface of the epithelium. Mitotic figures may be found in the middle part or surface of the epithelium. HSIL includes: HSIL/CIN2 and HSIL/CIN3 lesions of the Richart/WHO 2014 classification, as you can see in Figure 2.

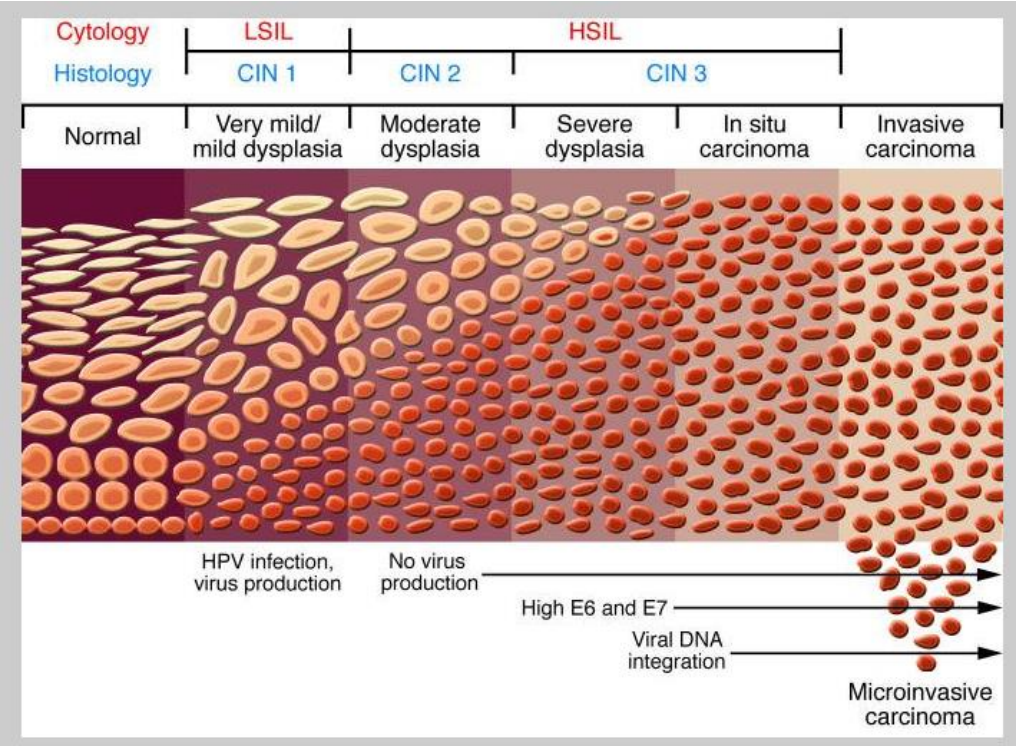

Figure 2: *Progression from a benign cervical lesion to invasive cervical cancer. (5)*

It is accepted that LSIL/CIN1 lesions represents the histological expression of a productive, self-limited HPV infection that usually regress spontaneously. Strict follow-up of women with these lesions minimizes the risk related to the lack of initial detection of HSIL (CIN3).
HSIL/CIN3 lesions are considered real intraepithelial lesions with an elevated potential of progression and are the precursor lesion of CC. In contrast, the biological significance of HSIL/CIN2 lesions is poorly defined since they may regress or progress.
Immunohistochemical determination of p16 allows better categorization of lesions which are borderline between low and high-grade.(7) P16-positive HSIL/CIN2 lesions are included in the HSIL category because of their greater risk of progression, and p16-negative HSIL/CIN2 lesions are re-classified as LSIL due to their benign nature and low risk of progression. It has been estimated that the use of the p16 marker to clarify the significance of a HSIL/CIN2 is only necessary in less than 10% of all biopsies. (1)

2.4 CYTOLOGY AND COLPOSCPY TECHNIQUES

CYTOLOGY METHOD:

First, the patients should empty their urinary bladder. After that, they should lay on the examination table in dorsal position. A speculum is introduced into the vagina to expose the cervix. Usually the cytobrush is used, as you can see in figure 3. The brush must be rotated by 180º, maintaining the contact with the cervical canal. The sample must be unrolled onto the slide in the opposite direction from which it was collected by twirling the handle of the brush. The slide is fixed immediately in 95% ethyl alcohol.

Next, the pointed end of the spatula is introduced into the cervical os and rotated 360° about the circumference of the os maintaining constant contact with the ectocervix. Both surfaces of the spatula were smeared on a new slide and fixed immediately. After this, using the blunt end of the spatula, sample was taken from the posterior fornix and the material obtained was spread on a next slide and fixed immediately.

After fixing, the slides must be sent to the Pathology Department so that the correct evaluation can proceed.

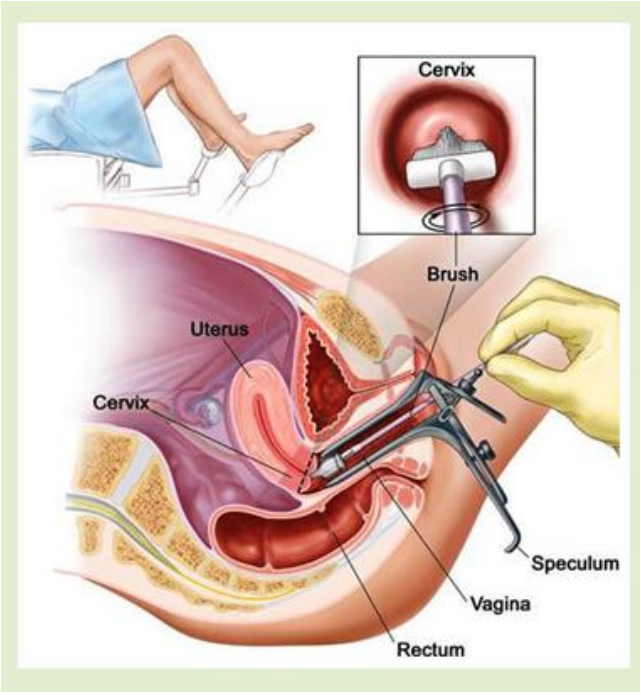

***Figure 3**: Image of the cytology technique(8)*

COLPOSCOPY TECHNIQUE:

Firstly, a speculum is introduced in the vagina. The speculum holds open the walls of the vagina so that the cervix can be easily seen. A colposcope is used because of the lents it contains, allow us to examine the TZ and the sub-epithelial vascular structures. Usually, 5% of acetic acid solution is applied. The solution helps highlight any areas of suspicious cells.(9) You can se the procedure in the Figure 4 below this this text.

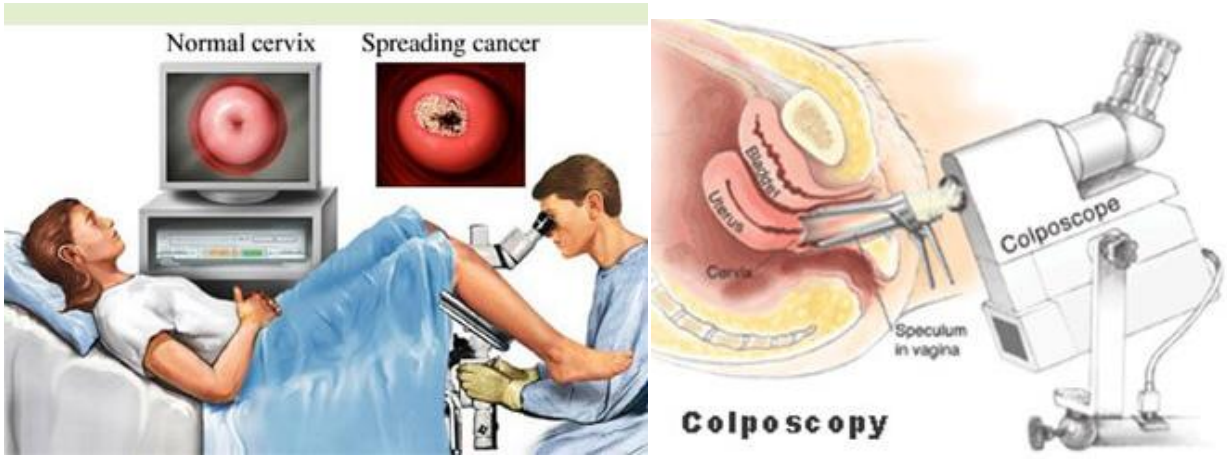

Figure 4: *Image of the colposcopy technique on the left. A colposcpe is on the right side*

2.5 EXCISIONAL TECHNIQUES

The treatment of choice for premalignant cervical lesions aims to eradicate the lesions and prevent the development of invasive carcinoma while also minimizing the possible adverse effects and avoiding over-treatment. Procedure technique:

- **Loop electrosurgical excision:** Different acronyms are used in reference to different electrosurgery procedures such as the loop electrosurgical excision procedure (LEEP) or large loop excision of transformation zone (LLETZ). This technique is simple, rapid and inexpensive. Terminals with different loop sizes and shapes may be used. The loop and the type of excision chosen should be adapted to the characteristics of the lesion. Excisions of one single piece are recommended, avoiding fragmentation. This is currently the technique most widely used. A wire loop electrode on the end of an insulated handle is powered by an electrosurgical unit. The current is designed to achieve a cutting and coagulation effect simultaneously. Power should be enough to excise tissue without causing a thermal artefact. The procedure can be performed under local analgesia.(10)

- **Laser conization**: the technique requires more complex and expensive equipment. Its application requires a longer learning curve. In general, this procedure produces a greater thermal artefact than loop electrosurgery. It is not frequently used.
- **Cold-knife conization**. This procedure allows the excision of extensive lesions and optimal evaluation of the resection margins (important in cases with suspicion of invasion or with glandular disease). This is a less conservative method which often produces greater excision of the cervical tissue and consequently greater anatomical distortion. This technique is practically in disuse and has been substituted by conization by loop electrosurgery.

Destructive treatments:

- **Cryotherapy**: simple, economic and an accessible technique in settings with low resources. Although the probes are of different sizes and shapes, this treatment is not very selective.
- **CO_2 laser vaporization**: complex and expensive technique requiring a longer learning curve. Its use under colposcopic control allows selective destruction of the tissue and adequate control of the depth of the tissue destroyed.(1)

We can conclude that the excisional procedures including loop electrosurgical excision procedure (LEEP) are well known for the diagnosis and treatment of CIN. Moreover, ablative methods such as laser ablation, cryotherapy and cold coagulation are also known to be effective for treating CIN but there are no longer used. Among them, cold coagulation has been used to destroy an abnormal transformation zone, and thereby to treat non-invasive cervical lesions since 1996. Although cold coagulation has some advantages such as less pain requiring minimal analgesia, short time for treatment and rare complications, it is not used widely anymore since the introduction of LEEP providing histologic information.

However, the resection margin status after LEEP is still important because residual dysplastic cells can increase the risk of disease recurrence and progression to invasive cancer. Thus, repeated conization is considered whenever resection margin of specimen is positive after LEEP for obtaining specimen without residual dysplastic cells.

Nevertheless, repeated conization is discouraged for young women who want pregnancy because it increases the risk of preterm birth, and for women who show no residual cervix because repeated conization increases post-procedure complications such as vesicovaginal fistula.(11)

The primary advantage of excisional as compared to ablative treatments is the ability to submit the abnormality in the excised specimen for pathological examination thereby confirming the diagnosis, excluding an occult malignancy and obtaining information on the completeness of excision.(12)

For young women who desire pregnancy, the surgeon should carefully balance complete excision of the lesion and minimal cervical damage to reduce the risk of obstetric complications. This poses a challenge for doctors to avoid incomplete excision during conization(13).

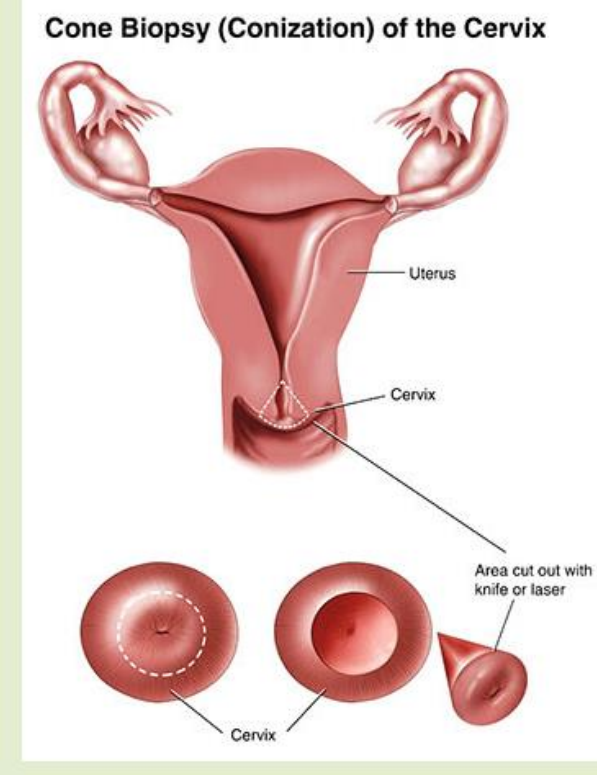

Figure 5: *Image of the conization of the cervix*

2.6 SCREENING, DIAGNOSIS AND MANAGEMENT

The actual guidelines show the following screening recommendations:

-Screening of women from 25 to 30 years old: cytology, and in the case of a negative result, repeat the cytology every 3 years up to the age of 30.

- Screening of women from 30 to 65 years old: clinically validated HPV test every 5 years. The algorithm for the screening results (after HPV test) recommended by the European Guideline can be seen in the Figure 6.

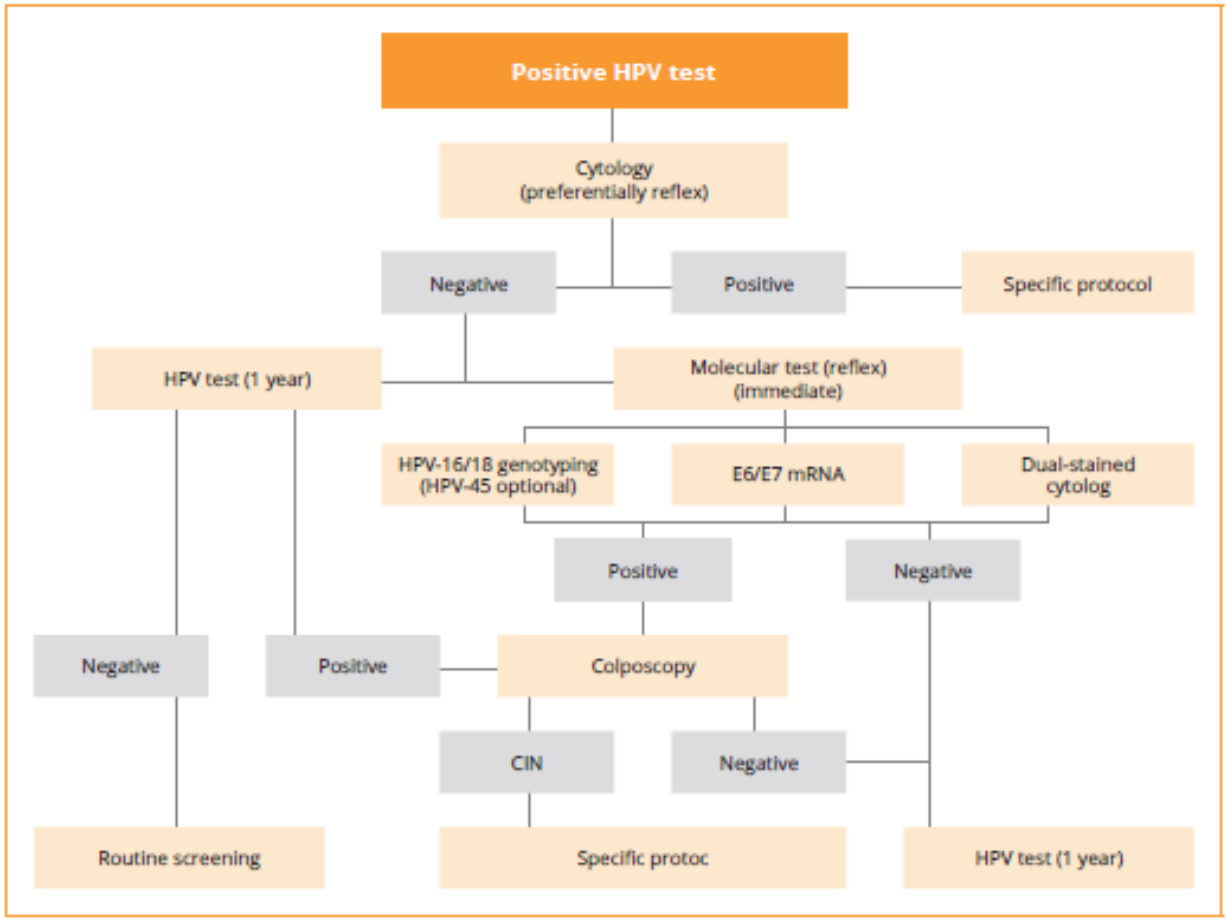

***Figure 6**: Algorithm for procedures recommended after cytology results, taken from the European Guideline*(1)

SPECIFIC MANAGEMENT FOR LSIL

Low-grade squamous intraepithelial lesions (LSIL) represent 2-3% of all cytologies. More than 70% of women with LSIL cytology present a positive HPV test and between 12-16 % of these women have a lesion ≥ HSIL/CIN2 after colposcopy and biopsy. The main recommendation is to do an immediate colposcopy as it's referred in **Figure 7**. The following procedures are showed in the algorithm. (1)

Table 2: *L-SIL risk at 5 years according to initial cytology(1)*

RISK AT 5 YEARS			
Initial Cytology	≥ a HSIL/ CIN2	HSIL/CIN3	Invasive carcinoma
LSIL	16%	5,2%	0,16%
LSIL VPH negative	5,1%	2%	–
LSIL VPH positive	19%	6,1%	–

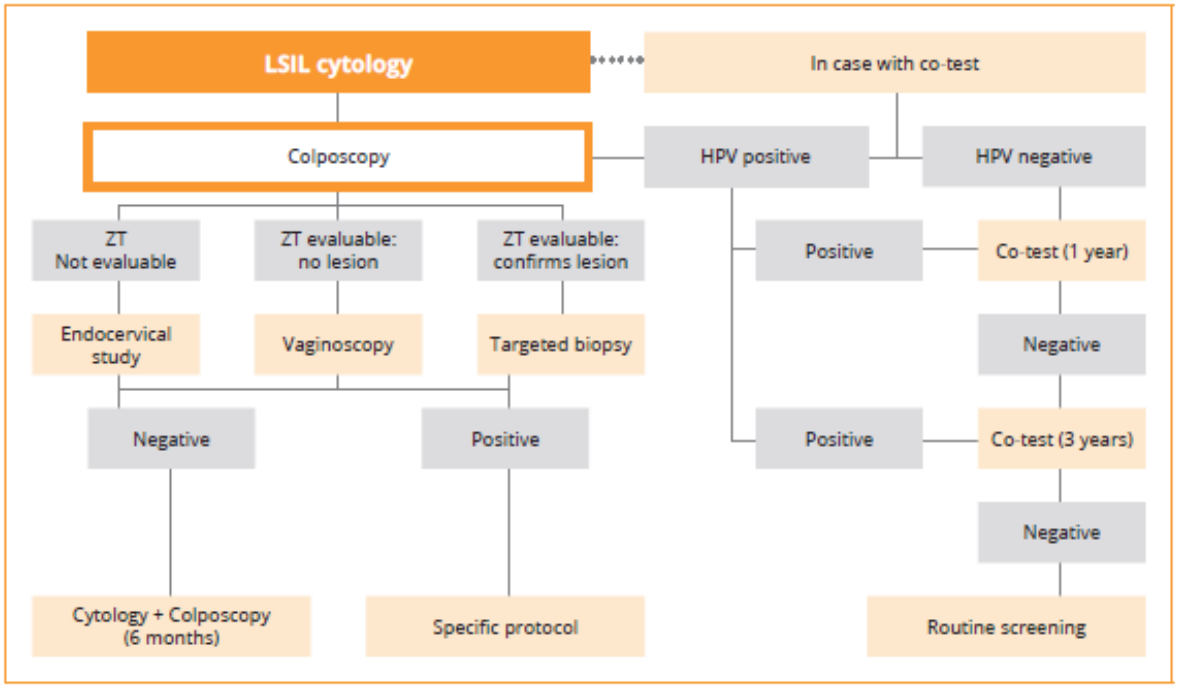

Figure 7: *Algorithm for L-SIL cytologies procedures, taken from the European Guideline(1)*

SPECIFIC MANAGEMENT FOR HSIL

High-grade squamous intraepithelial lesions (HSIL) represent between 0.5 and 1% of all screening cytologies. The prevalence is higher in women from 20-29 years of age (0.6%) than in those from 40-49 years of age (0.2%) and between 50-59 years (0.1%). As you can see in the algorithm showed below (Figure 8), there are two options. The first one, and most accepted, is doing a colposcopy. The other option is direct see-and-treat treatment with conization and it's only recommended if grade 2 injuries or in those in whom there's no possibility of follow-up(1).

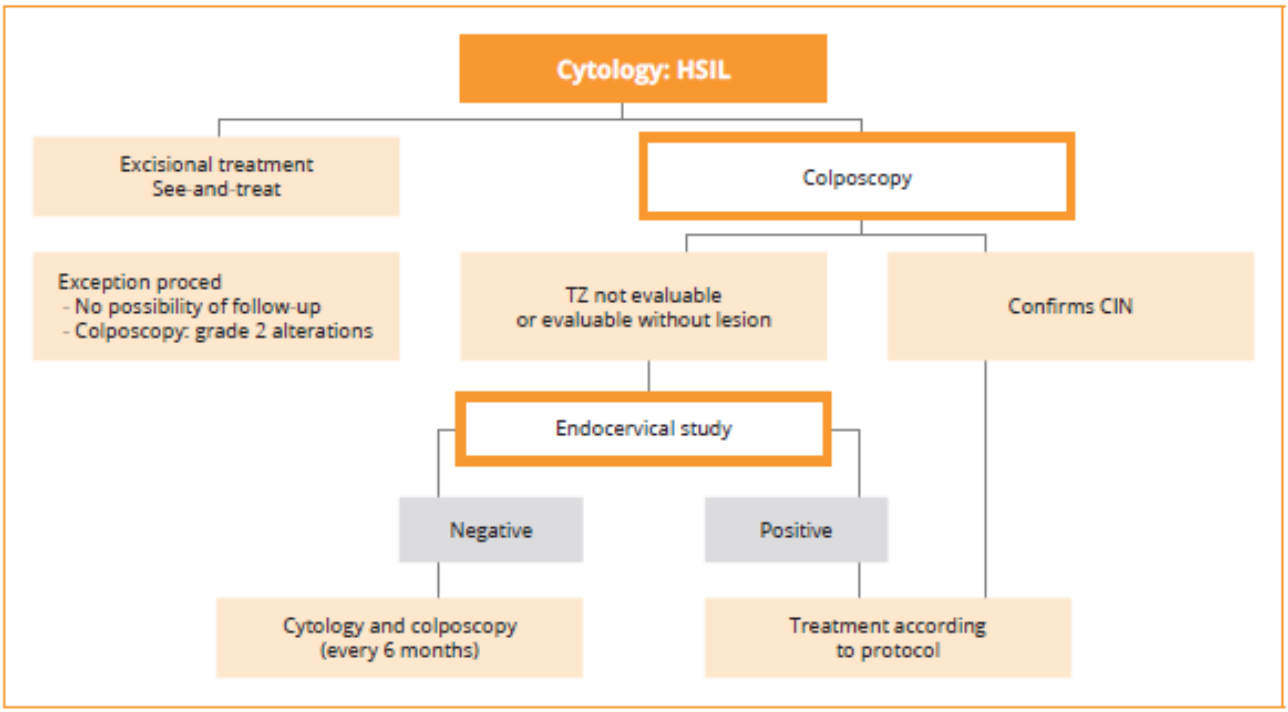

Figure 8: *Algorithm for H-SIL citologies procedures, taken from the European Guidelines*(1)

2.7 POST-TREATMENT FOLLOW UP

Approximately 15% (range: 5-25%) of treated women are newly diagnosed with an intraepithelial lesion within the following 2 years post-treatment. An incompletely resected injurie is called persistent, but if it is detected in the follow-up after one year it is called recurrent (1). Balancing the risk of adequate treatment with iatrogenic harm is challenging. As it was seen in 12 study, where it confirms that the risk of residual/recurrent CIN2+ is significantly greater with positive excision margins. However, high risk HPV test, post-treatment predicts more failure (12).

There is a considerably high proportion of patients who have incomplete excision after conization. Incomplete excision is undoubtedly associated with an increased risk of residual/recurrent disease being found at subsequent follow-up of women treated by conization.(13) So, the objective of post-treatment follow-up is to diagnose lesion persistence or recurrence early and avoid progression to cancer.

After a **conization with negative margins** a co-test must be done at 6 months. Then the patients are revaluated:

- If there are any positive test results a colposcopic examination with biopsy and endocervical study should be done.

- If there are negative another co-test at 24 months should be done.
    - After one year if any positive test results are found: A colposcopic examination with targeted biopsy and endocervical study should be done.
    - After one year if all the results are negative a co-test should be done after 3 years and then routine screening for at least 20 years, independently of the age of the patient.

After a **conization with positive margins** (multiple choices):

- Control at 4 months by cytology, colposcopy and endocervical study.
    - If any test is positive and persistent injurie is confirmed: specific treatment
    - If it is negative: co-test at 12 and 24 months
    - If Any positive test result: colposcopy. If it turns to be negative: co-test at 3 years and then routine screening for at least 20 years.

- Repeat excisional treatment. In women with persistent or recurrent HSIL/CIN2-3 that:
    - Over 50 years of age.
    - Involvement of the endocervical resection margin.
    - Involvement of more than one margin (exocervical, deep, endocervical).
- Hysterectomy is an exceptional procedure in women with persistent or recurrent HSIL/CIN2-3 who meet the following criteria:
    - Desire to become pregnant fulfilled.
    - Impossibility to perform a new excisional procedure.

In the last years the HR-HPV test has been introduced in the post-treatment control protocols and is currently considered a standard test. The HPV test is more accurate than cytology in the follow-up to predict cure or lesion persistence/recurrence.

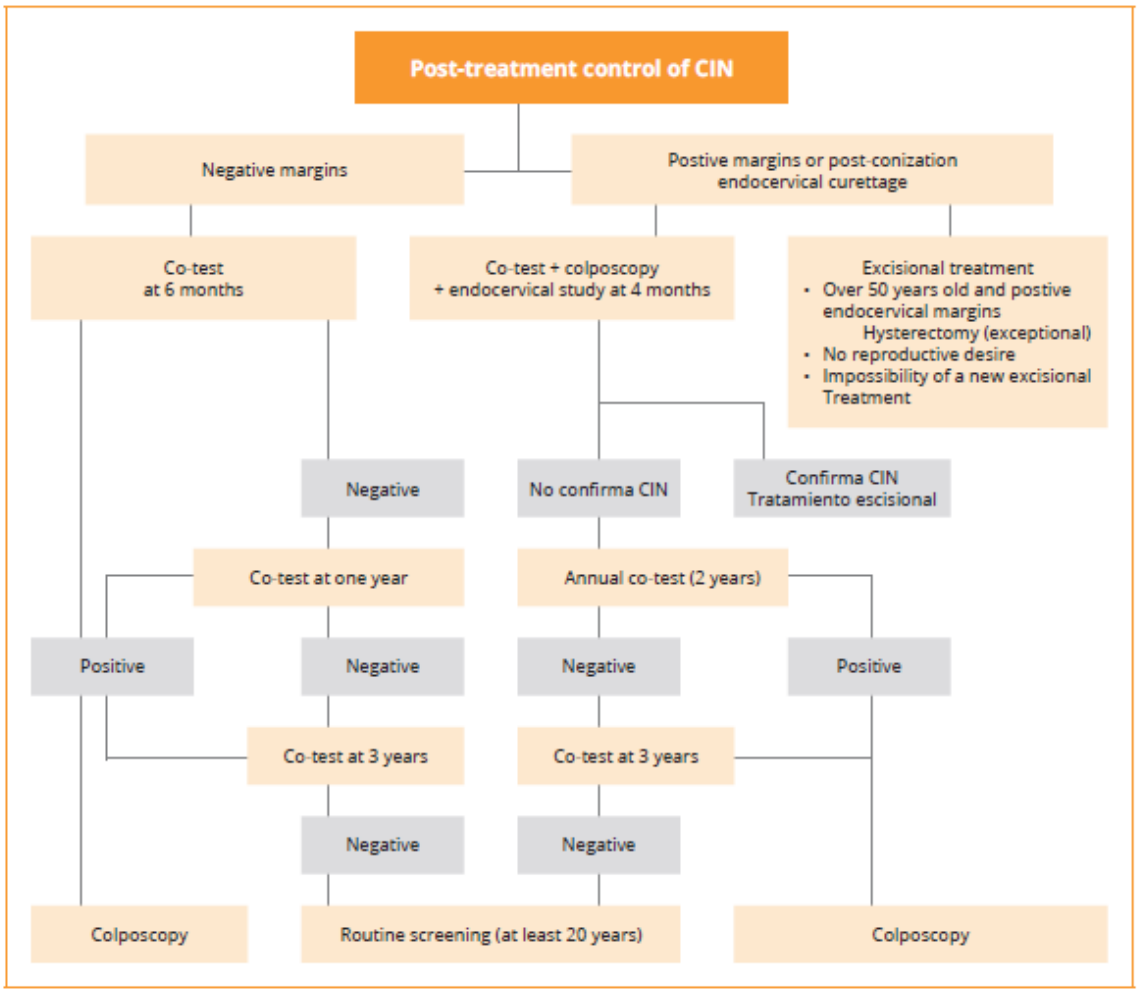

Figure 9: *Algorithm for post-treatment of CIN lesions, taken from European Guideline (1)*

3. JUSTIFICATION

Cervical intraepithelial neoplasia (CIN) is a precancerous lesion which can be treated effectively before it turns to an invasive cancer. More than 95% of this injuries are related to VHP.(1) The recommended screening and management explained before is achieving great results to detect and treat precancerous injuries. The techniques used, ablative methods such us laser ablation, cryotherapy and cold coagulation are effective for treating CIN. However, the most extended treatment is the conization using LEEP. As it was explained before, usually it is well tolerated, but it can be an invasive treatment. It has some risks such us bleeding, infection and reproductive complications. It is known that these risks increase with re-conization. Due to those risks and complications, it is important to do this procedure only if needed.

Once the conization is done, the histopathological results can be free- margins or affected margins. If the margins affected are endocervical the European Guidelines recommend excisional treatment. If the affected margins are exocervical two different options are recommended: To **repeat the conization amplifying the margins or to follow-up the patients**. Both options are accepted but there's no information due to the incidence of local recurrence in each option.

Nowadays, what's done with these patients is to treat them with conization when they have multiple risk factors. These risk factors are controverted (14). In the Jun-yu Chen study, **no significantly difference** was seen for local recurrence comparing the following risk factors: age, gravity, and parity (15). These results were supported by Alonso et al (16). Meanwhile, other studies showed that age, lesion grade, and margin involvement are **significant predictors** of HPV persistence and CIN recurrence after treatment. To conclude, although there are lots of studies made, the indications to repeat the conization are still not clear.

The studies published of this subject are retrospective and observational (17)(18). Moreover, some of the analysed specimens after re-conization, showed non-malignant cells. Seeing that, a randomized controlled clinical trial should be done. It should be pointed out which cases needs an invasive procedure or which ones need to be followed-up. In clinical medicine, finding a balance between therapeutic effectiveness and iatrogenic harm is often challenging, but this study could avoid an invasive procedure to some patients and the consequences that goes with the conization technique.

4. HYPOTESIS

Closely monitoring patients with affected margins after conization for exocervical lesions (both H-Sil or L-Sil) has the same rate of recurrence as re-conization.

5. OBJECTIVES

To compare the results between closely monitoring with re-conization in women with positive exocervical margins after conization for both H-Sil or L-Sil.

6. METHODOLOGY

6.1 STUDY DESING

This study will be a clinical trial with four arms.

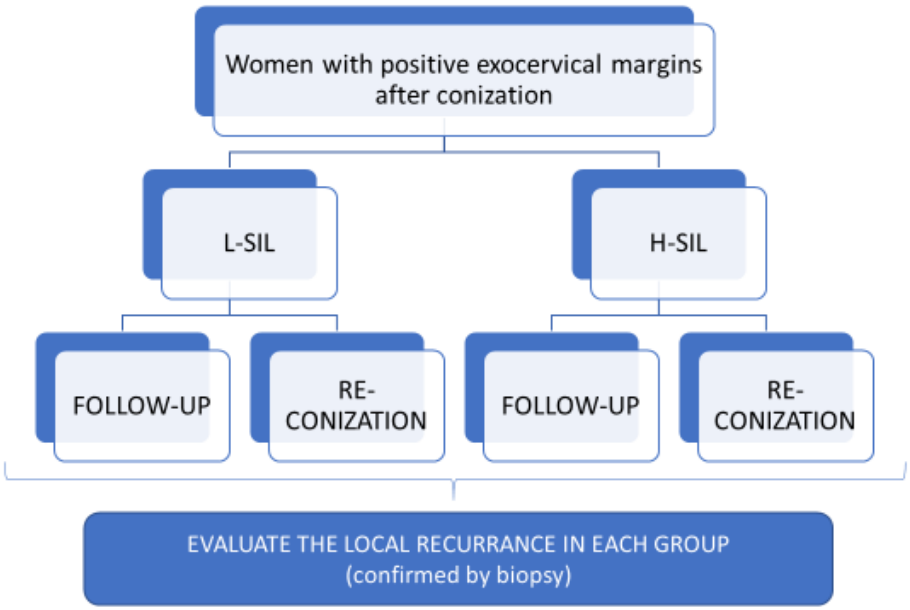

Figure 10: *Diagram of the arms of the study*

6.2 STUDY POPULATION

Inclusion criteria

Patients must meet all the following criteria to enter in this study

1. Women with precancerous injuries L-SIL (CIN1) and H-SIL (CIN2 and CIN3).
2. Conization procedure practised with exocervical margins affected.
3. Women who have read the Informative sheet for participants (Annex 1).
4. Women who read and signed the study informed consent (Annex 2).
5. Women who read and signed the surgery informed consent (Annex 3).

Excluding criteria

Patients cannot meet any of the following criteria to enter in this study

1. Positive endocervical margins affected
2. Gravidity
3. Immune-depressed patients including VIH affected
4. Unavailability to follow-up

6.3 SAMPLE SELECTION

The sampling system will be consecutive, so it won't be probabilistic. Every patient seen in the hospitals involved in this study (and which meet criteria of inclusion and not exclusion) will be enrolled in this clinical trial. The two groups will be assigned randomly to the patients included in the study avoiding, this way, the selection bias.

In a bilateral contrast with a level of signification (α) of 5%, with a potency (1-β) of 80, expecting a moderate effect and a 15% of losses for each arm, 36 women per arm are needed. The data from the reference hospitals of the Comarca de Girona will be collected for 6 months according to a multicentric essay.

The computations were carried out with the Prof. Marc Saez' software based on the library pwr of the free statistical environment R (version 3.5.1).

6.4 MASKING

Usually the patients involved in clinical trials don't know which procedure is made to them, using the masking to avoid the bias. Unfortunately, in this study the patients can't be blinded, so they'll know in which group they are. To reduce this bias, the professionals who evaluate the procedures will be blinded, not knowing whether the patient is in the following up group or in the re-conization one.

6.5 VARIABLES

Dependent variable: local recurrence confirmed histopathologically.

Independent Variable: closely following-up or re-conization.

The patients in this study will be randomized so, the frequency of the covariables should be distributed equally in both groups. Even though, to avoid the confusing bias the following covariables will be considered.

Co-variables:

- Age: in years. A continue numeric variable
- Number of pregnancies/ Gravidity: A continue numeric variable
- Tobacco: Yes, no and ex-smokers (considering the time that they quit smoking). A qualitative variable
- Alcohol: Low consume, medium consume, high consume, no-consume. A qualitative variable
- IMC: we will categorize our patients in 4 groups measured with kg/m^2 and considering the WHO classification according to the risk; IMC <25, 25-30, 30-35, >40. A qualitative variable
- HPV: positive or negative after conization. A qualitative binary variable
- HPV vaccination: yes (3 doses) or not. A qualitative binary variable
- STD: A qualitative binary variable
  - Chlamydia: positive or negative
  - Gonorrhoea: positive or negative
  - VIH: positive (viral load ≥ 100.000 copies/ml) or negative
- Number of sexual partners: A discrete variable

6.6 DATA COLLECTION

The patients who received an invasive technique (conization) due to a precancerous injury (HSIL or LSIL), will receive an appointment after a month to discuss the biopsy results. The one's who have positive exocervical margins are the candidates to participate in this study. The information of this study will be explained to them (annex 1). The ones who agreed to enter in this study should read and sing the consents (Annex 2).

Once the consents are signed, the groups will be assigned randomly, and the following procedures made are explained below.

6.7 INTERVENTIONS

FOLLOW-UP GROUP:

The follow-up group must come to the health centre every 4months. A cytology and colposcopy will be practised each time. In addition to these tests, once per year, an HPV test will be done. If no abnormalities are found the patients will be dismissed after two years.

If any atypical cells are found a conization will be done.

The techniques used were explained in the introduction.

RE-CONIZATION GROUP

As soon as this group is assigned, the patients will be introduced to the colposcopy waiting list (45 days). After the procedure is made, achieving negative margins, the patients will be followed up 6 months after the procedure. If the results are as expected, the next follow-up should be done 24 months after the last control.

7. STATISTICS

All the analysis will be carried out stratifying for H-SIL lesions and L-SIL.

Descriptive and simple inference:

The dependent variables and the covariables will be summed up stratifying for following-up group and the re-conization group.

The dependent variable and the qualitative covariables will be summarized using proportions and the quantitative variables using the mean, standard deviation, the median and interquartilic range (IQR) depending if they are continuous (mean, standard deviation) or discrete variables (median and IQR).

The difference of proportions, of the means and of, the median of the dependent variable and the covariables will be compared in the following-up group and re-conization group using the chi-square (or the Fisher test if the expected frequencies are lower than 5), t-student IU Mann-Whitney, respectively.

Multivariate analysis:

The effectiveness of the intervention will be assessed using a logistic regression for each of the two groups (LSIL and HSIL). The response variable will be the local recidive and the explanatory variable will be re-conization or following up, adjusting by the covariables. The quantitative covariables will be categorized (for example using quartiles) just in case the relationship between them is non-lineal and interpretation is needed

8. ETHICAL CONSIDERATION

The study for an ethics review to the **Clinical Research Ethics Committee** (CEIC) of the Hospital Universitari de Girona Dr. Josep Trueta. If the study fulfills the required criteria, it will assess its approval. In addition, all recommendations given by the committee will be considered.

The confidentiality of the database used will be respected during the procedure according to the **Spanish Organic Law 15/1999** (13 de diciembre, de Regulación del Tratamiento Automatizado de los Datos de Carácter Personal). All women's data will be managed anonymously in order to protect their privacy. Moreover, the right of accessing to any kind of information concerning the patient will be guaranteed as well as the right of modifying or erasing their personal data.
Study participants will be given the information sheet (annex I) and they will be asked to sign the informed consent (annex II) in order to be included in the study.

This study will also follow the **Law 14/2007** of 3rd July, of biomedical investigation that includes surgical interventions as "invasive procedures" and insists, amongst others, the necessity of prevailing health, interest and comfort of the human being that participates in a biomedical investigation over science and society interest.

The study will be carried out following the principles of the **WMA Declaration of Helsinki** and in accordance with the Medical Research Involving Human Subjects Act (last revised in 64th General Assembly, Fortaleza, Brazil, in October 2013).

9. LIMITATIONS

It is known that in clinical trials the most important bias to avoid is the selection bias. To reduce this mistake, the two groups of patients will be randomized according to the confusing variables that we have considered. The two groups (follow-up group and re-conization group) must be equivalent. There's the possibility that the patients with low-grade injuries have less risk factors comparing to the high-grade injuries. That's something that it has been already taken in account. The two groups will be analysed individually. Multiple confusing factors may influence association between dependent and independent variables. To avoid the confusing bias a multivariant analysis will be made.

Another bias that it's needed to avoid is the withdrawals to follow up. Some of the women participating in this study could stop coming to the health centre. That's why the patients that can't accomplish a regular follow-up were excluded of the study. Nevertheless, the validity of the statistical results may be affected depending on the losses. A 15% of losses were considered to analyse the data.

The impossibility of double-masking has already been explained, in the Masking part.

Compliance bias also must be controlled. That's the bias that occurs when women prefer to be in one group instead of the one that was assigned to them. For example, if the follow-up group is assigned to them, there's the possibility that they want to receive the re-conization procedure. To reduce this bias what we are going to do is to randomize the assignation of the groups. In the clinical trial paper that we are giving to the patients we will explain this randomized condition to assign the group and the patients will know that they can't choose the group to guarantee the feasibility of the study. Properly information will be given to them, explaining that there's no evidence of which treatment is the best and that this study can provide useful information for future patients.

In this study, all the procedures done (cytologies, HPV tests, conization, and colposcopy) are operator-dependent techniques. Skilled gynaecologists will be needed to perform the techniques before explained and an experienced pathologist to analyse the specimens.

10. CHRONOGRAM

STAGE 0- PREPARATION

- Activity 1: Two months. The protocol of the study will be designed
- Activity 2: One month. The protocol will be presented to the CEIC (Ethics Committee of Clinical Research).

STAGE 1 – DATA COLLECTION

- Activity 3: First meeting for coordination and giving the work plan information will be done. After that, the team meetings will be done every 4 months.
- Activity 4: Identify the women that can be invited to participate in this study. This activity will be carried out during two years until all the patients needed (144 women) are found. The study will be explained to them and the patients who sign the forms will be included in the study.
- Activity 5: Collect the data referred to the variables and covariables.
- Activity 6: The women will be distributed in two groups randomly. Then the corresponding procedures will be made depending on that groups.
- Activity 7: Follow-up the patients for two years since they enter into the study.

STAGE 2 – DATA ANALYSE

- Activity 8: Two months will be required to make the statistical analyse. Once all the patients have finished the following-up routine for two years.

STAGE 3 – INTERPRETATION RESULTS

- Activity 9: Conclusion extraction.

STAGE 4 – PUBLISHING RESULTS

This stage will include:

- Publishing the results on scientific journals
- Presenting them on a National Congress
- Presenting them on an International Congress

CHRONOGRAM										
	Year	2018	2019			2020/21	2021/22	2022		
	Months	December	January	February	March to December	January to December	January to December	2 months	2months	At the end
Stage 0	Protocol Writing									
	Ethical approval									
Stage 1	First Meeting									
	Patients Reclutment									
	Data Collection									
	Follow-up rutine									
Stage 2	Data analyse									
Stage 3	Interpretation results									
Stage 4	Presenting results									

Figure 11: *Chronogram of the study*

11. FEASIBILITY

11.1 MEDICAL TEAM

The medical team in this study will be composed for pathologists and gynaecologists. They are employed by Hospitals included in the study, so additional doctors won't be needed. The follow-up procedures and the conization technique will be done by the gynaecologists. And the biopsy analysis for the pathologists.

A Project Manager will be hired to coordinate and control data quality, due to the fact that this multicenter study comprises many hospitals and there must be an extra effort or reinforcement on these aspects to avoid rectifiable errors than can reduce easily the value of the study. We will hire a statistical analyzer as well to process the statistical analysis implicated. The multicentric study will be carried out in the following hospitals: Hospital de Figueres, Hospital de Palamós, Hospital Sant Jaume d'Olot, Hospital Universitari Doctor Josep Trueta de Girona, Hospital Santa Caterina**,** Hospital Comarcal Sant Jaume de Calella, Hospital de Campdevànol and Hospital Comarcal de Blanes. All of them will be well-trained and will work coordinately to fulfill the marked objectives.

11.2 RESOURCES

Necessary means such as operation rooms and follow-ups (cytology, colposcopy, and HPV test) will be provided by the hospitals respectively. The operation room's availability depends on the hospital's characteristics. No hospitalization is needed for those having the conization procedure. The material required for this trial is the standard material used in a colposcopy intervention, or in the follow-up in hospital.

The specimens and biopsies from all the procedures done in this study will be analysed in the pathology service of each hospital. In cases where it is not available, they will be sent to the Hospital Trueta to be analysed.

11.3 PATIENTS

The number of patients needed is 36 for each brunch, it sums up to a total of 144 patients with positive exocervical margins after a conization. To achieve this number of patients this study will be carried out until the sample needed is achieved. According to the number of patients seen each year, two years minimum will be needed.

12. BUDGET

Research team and personnel are employed by the Hospitals included in the study. That's why, it's no necessary to hide any worker for clinical functions. So, no additional cost for staff will be included in the budget. It's necessary a statistical expert for data analysis. 160h of work are needed, and 35€/h are payed so the total costs will be 5,600€.

An External supervisor is needed to coordinate and control the study between hospitals. This person will work 8h per week, earning 25€/hour for two years, it will cost a total of 19.200€

The procedures made in this study are done by routine in the daily medicine, so extra-money won't be needed. However, the costs of the procedures done in this study are explained in the following table.

Table 3 *Prices of the procedures done in this study*

PROCEDURE	MONEY
VHP test	25€
Cytology	5€
Colposcopy	50€
Conization procedure (including Operation Room)	1200 €

The cost of printing materials for information sheets and informed consent have been considered. A total cost of 50€, considering that 3 sheet copies for each patient (0'05€/copy) are needed.

Once the study is finished it will be disseminated to scientific community. All collected data will be reflected on a scientific paper for the purpose of publish it in scientific journals with open access. Publication costs are budgeted on 2,500€. The costs of attending to a national congress are considered. A cost of 1000€ is supposed for the admission fee in a national congress for two people, and a cost of 1500€ for an international congress. We expect an extra expend of 1000€ for travel transportation and accommodation (2 people). The total expenses for the publication and dissemination of our study will entail a cost of 6.000€.

***Table 4**: Budget needed for this study*

BUDGET	COST
Material costs	50€
-Printing	
Human costs	
-Statistical expert	4800€
- External supervisor (8h/2years)	19.200€
Dissemination	6000€
-Publishing cost	2500€
-National Congress	1000€
-International Congress	1500€
-Traveling	1000€
TOTAL	**36.050€**

13. PROJECT IMPACT ON THE NATIONAL HEALTH SYSTEM

Cervical cancer affects to many women all over the world. Since the screening is applied more precancerous injuries are found. As it was explained in the introduction, the number of injuries treated is increasing due to the further detection on early stages. The screening protocols and management of the precancerous injuries should try to find the perfect balance between therapeutic effectiveness and iatrogenic harm. This is often challenging. As it was explained in the introduction, the guidelines showed two options after positive exocervical margins. These two options are the ones compared in this study. If the results show no difference between the local recurrence in the Follow-up group compared to the re-conization group, this could avoid lot of conization. The complications, the money expended, and the possibility of not-taking off the complete injurie should be considered. Also, the possibility that the injuries regress spontaneously. This study could conclude that the follow-up procedures are enough in some women, avoiding the re-conization.

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15. ANNEXES

15.1 ANNEX 1

FULL D'INFORMACIÓ PER A LA PACIENT

Títol de l'estudi: ***Re-conització versus seguiment en pacients amb marges exocervicals positius després d'una conització per L-SIL o H-SIL***.

Vostè ha estat convidada a participar en un estudi d'investigació sobre el procediment més apropiat a seguir després d'una conitzacio amb marges exocervicals afectats en lesions d'alt o Baix grau. Abans de decidir si vol formar-ne part o no, és important que entengui perquè s'està realitzant la recerca i què inclou. Si us plau, prenguis el temps necessari per llegir aquest formulari que inclou un resum informatiu sobre l'estudi, no ha de decidir avui si vol participar-hi o no, prengui's el seu temps. L'equip que en forma part la convidem a preguntar-nos tot allò que no li hagi quedat clar o si te alguna pregunta a realitzar.

Per què es realitza aquest estudi?

El càncer cervical es la tercera neoplàsia en el mon. Al nostre país s'han estudiat moltes tècniques de detecció precoç i, per sort, la incidència d'aquest càncer està disminuint. Això també implica que hi ha moltes opcions a realitzar en quant a procediments i en alguns casos especials, no està clar quina tècnica és millor. La raó per la qual estem fent aquest estudi és per comparar dos procediments i veure quin dona millors resultats. Aquests dos procediments estan aprovats i son opcions acceptables. La primera opció és re-intervenir (re-conitzacio), i la segona fer un seguiment (colposcòpia, test del VPH, i citologia). Si els resultats no demostres menys recurrències amb la re-conització podrem estalviar a moltes pacients aquesta operació.

Quantes dones participaran en aquest estudi?

En aquest estudi participaran aproximadament 144 dones de la província de Girona que tenen marges exocervicals positius després d'una conització per lesions pre-canceroses (HSIL o LSIL). Aquesta investigació contemplarà dos grups. En un grup tornarem a realitzar una conització de la zona afectada; i l'altre grup farem un seguiment cada quatre mesos realitzant procediments de colposcòpia i citologia (i una detecció de VPH cada any). En tots dos grups, li demanarem que vagi a la clínica durant dos anys per fer el seguiment.

Què passarà si hi participo?

Si vostè accepta participar en l'estudi, se li assignarà un dels dos grups aleatòriament. Ha de saber que les dues opcions realitzades a cadascun dels dos grups son opcions habituals recollides a la guia de practica clínica de la *Asociación Española de Patología Cervical y Colposcopia (AEPCC)*. A part d'això, se li sol·licitarà que ens faciliti la informació sobre les seves dades personals que sigui rellevant per a l'estudi.

És obligatori participar-hi?

La participació en aquest estudi és totalment voluntària. Si decideix participar-hi, haurà de firmar el consentiment informat en el qual vostè declara haver entès tot el que fa referència a participar en l'estudi. Pel contrari, si decideix no participar-hi, la seva atenció mèdica no es veurà afectada en cap moment. Podeu canviar d'opinió més tard i deixar de participar encara que haguéssiu acceptat anteriorment.

Com es mantindrà la confidencialitat de la meva informació personal?

Per tal de garantir en tot moment el compliment de la *Llei Orgànica de Protecció de Dades de Caràcter Personal (5/2018)*, la informació recopilada durant aquest estudi es mantindrà confidencial i només serà utilitzada amb finalitat d'investigació. No s'utilitzarà el seu nom en cap informe de l'estudi sinó que la seva identificació personal estarà codificada a través d'una sèrie numèrica aleatoritzada. A més, tindrà dret a consultar tota la informació recopilada sobre vostè en aquest estudi i a rectificar qualsevol dada errònia.

Què se'n farà de la informació obtinguda a partir de l'estudi?

La publicació dels resultats sempre es durà a terme mantenint la confidencialitat de les seves dades personals. Una vegada finalitzat l'estudi, es preveu publicar els resultats en revistes d'interès científic de l'àrea de coneixement de la patologia cervical per tal que altres centres i pacients puguin beneficiar-se de les troballes del nostre estudi.

Qui ha revisat l'estudi?

L'estudi ha estat revisat pel Comitè d'Ètica i Investigació Clínica (CEIC) de l'Hospital Universitari de Girona Dr. Josep Trueta, el qual ha estat acceptat.

Si té qualsevol pregunta no dubti en dirigir-se a qualsevol persona de l'equip.

Moltes gràcies per la seva atenció.

15.2 ANNEX 2

CONSENTIMENT INFORMAT DE L'ESTUDI

TÍTOL DE L'ESTUDI: ***Re-conització versus seguiment en pacients amb marges exocervicals positius després d'una conització per L-SIL o H-SIL***

Jo, Sr/Sra. amb DNI

Afirmo que:

- He rebut i llegit el full d'informació sobre l'estudi que se m'ha entregat.
- He pogut fer totes les preguntes necessàries respecte a l'estudi i han sigut respostes de manera satisfactòria.
- He rebut suficient informació sobre les característiques i objectius de l'estudi, els possibles riscos i la importància de la meva contribució per l'avanç de la medicina.
- He estat informat per l'investigador.....de les implicacions i la finalitat de l'estudi
- Entenc que la meva participació és voluntària.
- Entenc que les dades facilitades per mi seran totalment confidencials i que seran eliminats del registre un cop finalitzat l'estudi.
- Entenc que puc revocar el meu consentiment informat de participació a l'estudi, sense haver de donar explicacions i sense que això afecti a la meva assistència sanitària. D'acord amb el que s'ha esmentat anteriorment, accepto voluntàriament la participació a l'estudi. Dono permís perquè la informació resultant d'aquest estudi sigui utilitzada en futures investigacions relacionades sobre aquesta patologia.

A _____ , a _____ de _____ 20___

Signatura del participant: Signatura de l'investigador:

15.3 ANNEX 3

CONSENTIMENT INFORMAT CIRUGIA

Descripció del Procediment

Es tracta d'una intervenció quirúrgica consistent en l'extirpació d'una part del coll de l'úter en forma de con, i la finalitat de la qual pot ser diagnòstica i/o terapèutica.

En el meu cas concret el motiu és _____

La conització pot efectuar-se amb bisturí, amb làser o amb nansa electroquirúrgica. En la meva situació s'efectuarà mitjançant _____

Procediments Alternatius: M'ha estat explicada l'existència d'altres possibles opcions terapèutiques com a amputació cervical, tractament destructiu local i histerectomia en determinades condicions.

Conseqüències Segures: M'han estat explicant les precaucions, i tractament en el seu cas, que he de seguir després de la intervenció i que em comprometo a observar.

Riscos Específics

Les complicacions específiques potencials de la intervenció són: hemorràgia (immediata o tardana), estenosi cervical (estretor), coll uterí incompetent, extirpació incompleta de la lesió (marges positius, lesió residual), cremades accidentals en cas d'utilitzar electrocirurgia, perforació vaginal amb entrada a la cavitat abdominal i excepcionalment, perforació uterina.

Si en el moment de l'acte quirúrgic sorgís algun imprevist, l'equip mèdic podrà modificar la tècnica quirúrgica habitual o programada.

Observacions i Contraindicacions

La intervenció necessita d'anestèsia, que serà valorada pel servei corresponent. El procediment es pot realitzar també amb anestèsia local.

En casos concrets, aquesta cirurgia pot realitzar-se en règim de CMA (Cirurgia Major Ambulatòria), essent possible que li donin d'alta el mateix dia de la cirurgia.

Si necessita una intervenció quirúrgica, pot presentar dolor a la zona de la ferida degudes a la cirurgia i al procés de cicatrització, el nostre servei, conjuntament amb el Servei d'Anestesiologia, si fes falta, la tractarà el mateix, fent-li saber que pot perllongar-se durant uns dies o fer-se continu.

Pot ser necessària una transfusió de sang, molt excepcionalment.

Anatomia Patològica: La peça o peces extirpades en la intervenció se sotmetran a estudi anatomopatològic posterior per obtenir el diagnòstic definitiu, essent la pacient i/o persona designada o representant legal en el seu cas, informats dels resultats de l'estudi.Així mateix he comprès que depenent dels resultats anatomopatològics i, per tant, del diagnòstic definitiu.
Tota intervenció quirúrgica, tant per la pròpia tècnica operatòria, com per la situació vital de cada pacient (diabetis, cardiopatia, hipertensió, edat avançada, anèmia, obesitat...) porta implícites una sèrie de complicacions comunes i potencialment serioses que podrien requerir tractaments complementaris, tant mèdics com quirúrgics, així com un mínim percentatge de mortalitat.
Comprenc que malgrat l'adequada elecció de la tècnica i de la seva correcta realització poden presentar-se efectes indesitjables, derivats de tota intervenció i que poden afectar tots els òrgans i sistemes.

Consentiment i confidencialitat

Es garanteix la confidencialitat i preservació en l'anonimat de totes les dades aquí consignades.
Es podrà utilitzar part dels teixits obtinguts amb caràcter científic, en cap cas comercial, excepte que jo manifesti el contrari. La realització del meu procediment pot ser filmat amb finalitats científiques o didàctiques, excepte que jo manifesti el contrari. Se m'ha informat de la possibilitat d'utilitzar el procediment en un projecte docent sense que comporti risc addicional sobre la meva salut.
Declaro, a més, no haver ocultat informació essencial sobre el meu cas, els meus hàbits o règim de vida, que poguessin ser rellevants, als metges que m'atenen.
Que conec i assumeixo els riscos i/o seqüeles que poguessin produir-se per l'acte quirúrgic pròpiament dit, per la localització de la lesió o per complicacions de la intervenció, a pesar de què els metges posin tots els mitjans al seu abast. Conec, per altra banda, el meu dret a revocar aquesta autorització en qualsevol moment. Aquest consentiment no suposa cap renuncia a possibles reclamacions futures en l'àmbit que cregui oportú.

Autorització

Declaro que he estat informat pel metge dels aspectes més importants de la intervenció quirúrgica que s'em va a realitzar, de la seva normal evolució, de les possibles complicacions i riscos de la mateixa, de les seves contraindicacions, de les conseqüències que es derivarien en el cas que no em sotmetés a l'esmentada intervenció i de les alternatives a aquesta tècnica quirúrgica. Estic satisfet/a de la informació rebuda. He pogut formular totes les preguntes que

he cregut convenients i m'han estat aclarits tots els dubtes plantejats. Declaro, a més, no haver ocultat informació essencial sobre el meu cas, els meus hàbits o règim de vida, que poguessin ser rellevants als metges que m'atenen. Sé, per altra banda, que m'intervindrà el facultatiu que, dins de les circumstàncies de l'equip mèdic en el dia de la intervenció, sigui el més adequat per al meu cas.

Per tot això, DONO EL MEU CONSENTIMENT PER A SER OPERAT, així com per què, durant la intervenció, el cirurgià prengui les mostres biològiques que consideri necessàries per a l'estudi del meu procés, o les imatges necessàries per a l'adequada documentació del cas. En el cas que, durant la intervenció, el cirurgià trobi aspectes de la meva malaltia que li exigeixin o li aconsellen modificar el procediment inicialment projectat, podrà fer-ho de la manera que millor convingui al meu salut, advertint a la meva família o, si no n'hi , prenent la decisió per ell mateix. També entenc que, tot i les nombroses i acurades mesures d'higiene de l'equip assistencial que m'atén, l'acte quirúrgic i l'estada a l'hospital són un factor de les anomenades infeccions hospitalàries, que són excepcionals, però possibles. Conec, d'altra banda, el meu dret a revocar aquesta autorització en qualsevol moment.

Aquest consentiment es formula d'acord amb el que estableix la Llei 21/2000 de 29 de desembre publicada al DOGC núm. 3303 de l'11 de gener del 2001.

Signatura Pacient: Data: