



**POST-CONIZATION FOLLOW-UP OF PATIENTS WITH HIGH GRADE
SQUAMOUS INTRAEPITHELIAL LESION TREATED BY LEEP PROCEDURE:
A LITERATURE REVIEW**

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ABSTRACT

An appropriate follow-up in post-conization patients for cervical precancerous lesions is crucial in cervical cancer screening program. Conization is used on patients who have been diagnosing with high grade cervical intraepithelial diseases (i.e. CIN2/3, adenocarcinoma in situ)[1, 2]. HPV-DNA test is recently combined with cytology as an adjunct test in the follow-up of cervical intra-epithelial neoplasm patients after the loop electrosurgical excision procedure (LEEP)[3, 4]. The addition of this test to the cytology follow-up after the conization makes the differentiation possible of women with low risk (in both tests negative) being able to benefit from a routine follow-up, from those with high risk having at least one positive test, whose surveillance must be reinforced with triage by colposcopy prolonged in time and extended beyond the cervix. As the primary detection and diagnosis test of cervical lesions, the follow-up of patients after conization must profit from the addition to HPV-DNA test [5].

Keywords: cervical intra-epithelial neoplasia, electrosurgical conization, HPV, follow-up.

INTRODUCTION

Cervical cancer is one of the most common malignant diseases which affect young women [6, 7]. It has been reported that each year about 528,000 women develop cervical cancer while 266,000 deaths occur worldwide from cervical cancer[8, 9]. High grade cervical intraepithelial neoplasia lesions are the primary cause of invasive cervical cancer which can be prevented or detected. The standard treatment of women with earlier disease detection is the cervical excision[10] or conization conducted by loop electrosurgical excision[8, 11]. However, all women are followed up after conization as they have a high risk to develop CIN2+ than the general woman population. An adequate follow-up is needed to identify the persistent high-risk human papillomavirus (Hr-HPV) infection, which is observed to be the primary causal factor of invasive cancer. Hr-HPV test combined with cytology may prevent the potential recurrent disease in post-conization follow up routine[12]

1. Situations and risk factors of recurrence after CIN2+ treatment.

1.1 High risk HPV infection:

Most of the cervical cancers are caused by specific types of human papillomavirus (HPV) infection[13], and HPV 16,18,31,33,52,58 has been identified as high-risk responsible for 75% of cervical intra-epithelial neoplasm and most of the genital cancers [9, 14]. The prevention of cervical cancer is based on the detection and management of premalignant lesions induced by high-risk human papillomavirus (hr-HPV). Hr-HPV testing between 3 and 6 months after conization is important for predicting the risk of disease persistence or recurrence. Such testing can assist in designing patient management , Hr-HPV positive patients after procedure should undergo frequent and meticulous post-therapy surveillance, while Hr-HPV negative patients do not require such high-level surveillance and could undergo routine surveillance [15]. The decrease in HPV post-conization is as a result of the excision of the transformation zone, associated with the induced immune response.

1.2. Risk factor:

The persistent high-risk human papillomavirus Hr-HPV infection and the residual disease arise with incomplete removal at the first conization, are the risk factors for have recurrent disease CIN2+[16-18]. One retrospective study confirmed that a positive Hr-HPV test between 3 and 6 months post-conization is a significant risk factor for CIN[15]. To characterize the risk factors for high grade cervical intraepithelial neoplasm lesions, many pieces of ongoing researches, and some studies suggest that margin status, lesion size and severity, smoking, age and, persistent infection are the risk factors of the recurrent or residual disease after conization for high grade lesions. However, in a recent review[19], the rate of residual disease after conization is high when positive endocervical margins were found in LEEP specimens.

1.3 Predictive value:

A negative HPV test results in the general female population has a long-term negative predictive value to develop high-grade cervical lesions. Excision of CIN precursor lesion can prevent high risk human

papillomavirus to progress into cervical cancer[20]. The relative risk of a high-grade lesion on post-conization overgrown margins is 6.09 (IC 95% = 3.87-9.60) corresponding to an absolute risk of 18% versus 3% in the case of negative margins. The risk of recurrence is high if positive margin status is found in the HPV testing [21]. A recent retrospective published paper, reported that a short cone length, cytology result of squamous cell carcinoma before the treatment, and the number of quadrant disease (≥ 2 quadrants) are the risk factors of margins status[3, 22]. The Danish 2012 guidelines recommended 3 years routine screening for women with negative margins and tested negative for both HPV and cytology at 6 months. A regular control over re-conization for patients with positive margins and follow-up must continued more than 10 years [23]. Long-term prospective follow up study in Sweden, showed that after 3 years of follow up, a negative predictive value in both tests, is considered as reliable cure test for 100%(95%CI 99.8-100%) [8]

2. Recurrence after treatment of CIN2+

After conization, recurrent disease may occur in small percentage of patients, and adequate follow-up remains an essential part of patient management [24]. The different therapeutic methods have the same rate of recurrence vary between 5-18%[25]. However, the excision techniques are recommended because the cone-shaped section of precancerous tissue in the cervix provides a biopsy sample for histology analysis. In one research article[26], multiple pieces of LEEP specimen would increase the incidence of incomplete excision. In a series 502 of patients with cervical conization, mean age 38.5 years (21-71years), mean follow up 33 months (1-94 months), recurrence is found in 50 patients(10%). 40% of patients with positive surgical margin had CIN recurrence compare to 9.5% found with negative surgical margin. The CIN recurrence is significantly higher in HPV positive group than the negative one (27.2% vs 1.8%, $p < 0.001$) [27].

3. Persistence HPV infection

High-grade lesions CIN2+ have a risk of persistence and progression into cervical cancer after treatment (3%-20%) [14, 16]. Hr-HPV types seem to be important as a persistent risk factor, as expected HPV 16/18/31/33/45 is readily found in recurrence specimens. O.K Vintermyr et al. study found 47/49 (95.9%) women with CIN2+ recurrence had the hr-HPV persistent infection in which 75% were HPV 16/18.[12, 28]. In a recent review[29] women over 45 year old are predictive of HPV persistence. Age is considered to be a prognostic factor of high risk HPV infection [30]. For Codde, E, et al. [18] found the risk in adenocarcinoma in situ lesions more than 8 mm with endocervical margins.

4. Clinical management in post-therapeutic surveillance

4.1. HPV-DNA test:

HPV-DNA test in follow up of post-conization patients was therefore evaluated and compared with cytology. HPV-DNA test is more sensitive, less specific than cytology test in the detection of CIN2+. Its

sensitivity allowed detecting recurrent cervical lesions but also the vaginal lesions escaping in cervical cytology test[31]. The persistent hr-HPV infection [32] can easily be diagnosed by HPV-DNA test, which has a high significance in the detection of persistent or recurrent disease in patient with cervical intraepithelial neoplasm after conization. The introduction of the HPV-DNA test in the follow up protocol is necessary supported by literature: CAMILLA F[33] reported that at 4 to 6 months after the treatment; HPV-DNA test is more sensitive than cytology to detect women at risk for recurrent cancer within 2 years (Table1).

	Sensitivity(%) %(95% CI)	Specificity(%) %(95% CI)	PPV (%) %(95%	NPV (%) %(95% CI)
Cytology	81.0(58.1-94.6)	85.2(82.0-88.0)	16.8(58.1-94.6)	99.2(97.9-99.8)
High risk HPV	95.2(76.2-99.9)	82.4(79.0-85.4)	16.7(10.5-24.6)	99.8(98.8-100)
Combined testing	95.0(76.2-99.9)	73.2(69.3-76.8)	11.6(7.3-17.4)	99.8(98.7-100)

Table 1 test performance at first follow up (4-6 months) for prediction of CIN2+ up to 2 years later for 588 women

4.2 Cervical cytology:

Cytology is the most commonly used tool because of its low cost and easy to perform [1, 34]. Cytology test has a substantial effect in reducing cervical cancer in the screening programs but its average sensitivity is compensated by its repeat control. In the process of post-conization follow-up, the sensitivity and specificity of cytology test are still low in the screening programs observation[32]. The number of false negative is high in cytology test[16]; the reason could be the implication of different pathologist to give an interpretation to the test. For that we need more studies of patients followed for more than 2 years after treatment of high-grade CIN, based on abnormal cytology only. Therefore, the decrease in cytology could be compensated if the test is repeated, but there is lack of compliance of patients with Pap smear and cytology follow up.

4.3 HPV combined with cytology test:

The usual method for follow up after conization has been repeated cervical cytology and colposcopy. Since the high-risk human papillomavirus infection is being found in the pathogenesis of cervical cancer, HPV testing combined with cytology is integrated into the follow-up programs. HPV testing has been recently associated to the cytology test as an adjunct test in the follow up of patients after conization for cervical lesions[4]. Routine post-therapeutic HPV-DNA test combined with cervical cytology can provide a better prediction for relapsed disease. The false negatives of HPV test are corrected by cytology, and the both tests together have the highest test sensitivity without loss of specificity. The risk for CIN2+ is low for women with HPV and cytology negative at 3 months follow-up than those with HPV negative alone. HPV test has a high negative predictive value, once associated with cytology allowing for space surveillance in low-risk patients.

4.4 Colposcopy:

Colposcopy with directed cervical cone biopsy and endocervical curettages under LEEP conization is a diagnostic procedure and also an appropriate treatment by the excision of the transformation zone for cervical intraepithelial neoplasia[11]. Post conization follow up by colposcopy is not easy to realize because of the healing process that produce images be like with HPV infection (parakeratosis) or atypical changes in grade2 HPV- induced (metaplasia). Postmenopausal patients with cervical stenosis after conization, or when homeostatic points have been applied on the side of the cervix are the factors that make the visualization difficult of the junction area [35]. Evaluation is surgical-depend with inter-examiner variation. And diagnosis by colposcopy or by curettage specimen is not reliable especially in the differentiation of a micro invasion disease. Colposcopy does not offer superior performance as cytology and is not recommended in the first intention in post conization follow up routine. But colposcopy[20] improved the sensitivity of the cytology when they are associated or provides additional information to the cytology and it is recommended in at three to six months after conization. Compare to cytology examination, colposcopy does not bring much information, but it is essential in the screening population (for abnormal Pap smear test or a positive HPV DNA test). It could be an excellent triage review in post conization follow up procedure.

5. Follow-up treatment

The risk of cervical cancer is high in patients who underwent cervical conization due to inadequate compliance with follow-up[17]. In many studies recurrence occur mostly 2 years after the treatment. Persistent high-risk HPV infection is a relative risk of invasive cancer after treatment[36]. Thus, patients treated for CIN2+ had a slight tendency to a higher risk in the long run, they should attend the screening program after their treatment, extend the surveillance beyond the age limit for standard screening for cervical lesions, and other potential targets of HPV infection. The first control is indicated between three and six months after treatment with Pap smear combining HPV test. The predictive value if is negative in both of the two tests a control will be allowed at 18 months after conization and if it maintained negative in both tests a similar follow up as for the general female population will be extended for more than 25 years. In case of positivity in one of the couple tests or both, colposcopy is necessary. Once colposcopy seems to be normal, patients will be followed 6 months later by both cytology and HPV test [37]. But if the colposcopy is not interpretable: and only the HPV test is positive, it is necessary to wait for clearance of the HPV infection and followed by HPV and cytology test. Or when it is only the cytology which seems abnormal, the following options are indicated:

- Cytology shows ASC-H or HSIL: patient need a repeat cervical conization[19, 38].
- Cytology shows ASCUS or LSIL: it seems to follow the patient at 6 months for an appropriate treatment[13, 39]. Gosvig et al. reported[40] the risk of recurrent CIN2+ in HPV negative in long term follow-up (table 2).

No.	Before conization		Conization		After conization		
	Cytology	Biopsy	Cone	Margins	Cytology at FU1	Relapse	Time from FU1 to diagnose of CIN2+
1	HSIL	CIN3	CIN3	Positive	Normal	CIN2	3 months
2	HSIL	CIN3	CIN3	Negative	Normal	CIN3	2 years and 8 months
3	HSIL	CIN2	CIN2	Negative	LSIL	CIN2	3 years and 6 months
4	HSIL	CIN3	CIN3	Negative	Normal	CIN3	4 years and 8 months
5	LSIL	CIN3	CIN1	Uncertain	Normal	CIN2	5 years and 5 months
6	LSIL	CIN2	CIN3	Positive	Normal	CIN3	5 years and 8 months
7	normal	CIN3	CIN3	Positive	Normal	CIN3	6 years and 5 months
8	HSIL	CIN3	CIN3	Negative	Normal	CIN2	7 years
9	ASCUS	CIN3	CIN2	Negative	Normal	CIN2	7 years and 10 months
10	HSIL	CIN3	CIN3	Positive	Normal	CIN3	8 years and 3 months
11	HSIL	CIN3	CIN1	Negative	Normal	CIN3	9 years and 5 months
12	HSIL	CIN3	CIN3	Uncertain	Normal	CIN3	10 years and 1 month

Table 2 detail of women testing HPV negative at first visit after conization that developed CIN2+ during follow up

CONCLUSION

A follow-up protocol by cytology and HPV testing to monitor for residual and recurrent disease is therefore recommended. Women treated for CIN have a five-time risk of developing cervical than the general population. The risk will increase with incomplete follow up. HPV testing at 6 months post-conization screening is sensitive to identify women at high-risk CIN2+ recurrence than cytology test.

Abbreviations:

LEEP: LOOP ELECTROSURGICAL EXCISION PROCEDURE

HPV: HUMAN PAPILLOMAVIRUS

CIN: CERVICAL INTRAEPITHELIAL NEOPLASIA

ASC-H: ATYPICAL SQUAMOUS CELLS CANNOT EXCLUDE HSIL

HSIL: HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION

ASCUS: ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE

LSIL: LOW GRADE SQUAMOUS INTRAEPITHELIAL LESION

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