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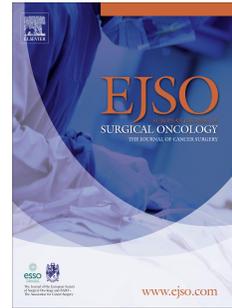
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Predictors of recurrence in high grade cervical lesions and a plan of management

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Running foot: Residual and Recurrence Rate of Treated High-Grade Cervical Lesions

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Précis: Positive endocervical margins are an important predictor of recurrence in high-grade cervical lesions, and though they do not always warrant retreatment, closer surveillance is recommended.

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Abstract

Objective: To identify predictors of recurrence and persistence of high-grade cervical dysplasia and to determine appropriate follow-up.

Design: prospective pilot study.

Setting: Gynaecological surgical center.

Population: Three hundred fifty-two patients were treated between 1999 and 2002 for high-grade lesions.

Methods: According to the accessibility of the transformation zone and the degree of dysplasia, patients were treated either by conization or by loop electrosurgical excision procedure (LEEP). Follow-up comprised colposcopy and Pap-smear screening 4 to 6 months after treatment as well as high-risk human papillomavirus (HR-HPV) testing before and after treatment.

Main outcome measures: underscore predictors of recurrence and propose a treatment flowchart for both management and follow-up.

Results: Of the 352 patients, 37 (10.5%) had true recurrence 6 months after initial surgical treatment and 6 patients (1.7%) had persistent lesions. Overall, 43 patients (12.2%) were considered as having recurrent disease. Patients were followed up for 5 years with a mean of 73 months. The most important predictor of recurrence was a positive HR-HPV test at 6 months postoperatively (odds ratio 38.8, 95% confidence interval 14.09, 107.05). The second significant predictor was positive endocervical margins and the third was positive pre-treatment HPV typing. A positive post-treatment HPV test had a more significant influence on risk than a positive test before treatment.

Conclusion: In agreement with recent findings, our study supports the usefulness of the HR-HPV test in the follow-up of treated high-grade lesions, especially when excision margins were positive.

Keywords: CIN II, CIN III, dysplasia, HPV test, recurrence, persistence, follow-up

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Introduction

Recurrence of high-grade cervical lesions is a frequent problem in clinical practice. Depending on the series, 5 to 15% of high-grade lesions recur within 2 years after surgical treatment (1,2). The incidence of high-grade squamous intraepithelial lesions (HSIL) has considerably increased in young women, and as the age of first pregnancy is rising in industrialized countries, cervical resection has become « sparing » in order to preserve the obstetric future of these patients. There are three possible treatment modalities: cryotherapy, loop electrosurgical excision procedure (LEEP) and conization. Mitchell (2) compared these modalities and found no significant difference in terms of complications, persistence or recurrence of lesions. With regard to obstetric prognosis, LEEP or conization increased the risk of preterm delivery and low birth weight but did not increase perinatal mortality. Sparing of cervical tissue leads to a variable number of incomplete resections, ranging from 7.8 to 31.8% according to the series (3,4). In most series, one of four treated patients had positive margins. The approach consisting of systematic surgical retreatment is currently debated (3, 8) and we still have to determine clinical and also histologic criteria which should prompt retreatment.

True residual disease occurs in only about 15% of cases (5,6). The risk of developing invasive carcinoma after treatment for HSIL is five times higher than in the general population (35). This fully justifies closer colposcopic and cytologic surveillance. Monitoring of patients treated for HSIL currently relies on the combination of Pap-smear and colposcopy (33). However, sensitivity of this association does not seem better than Pap-smear alone to detect residual and recurrent lesions. Cervical cytology has a sensitivity of no more than 70% according to most authors (7). As a consequence, false negatives (FN) are rather high with this method, which may delay the diagnosis of persistent or recurrent lesions.

Study objectives

The principal objective was to determine clinical and histologic predictors of recurrence or persistence (treatment failure following CIN II/III) of cervical HSIL. In addition, the prevalence of lesions with a positive HPV test was recorded at the time of the diagnosis and 6 months post-treatment.

We propose a flowchart to define the cases requiring surgical retreatment and to identify those for which cytologic and/or colposcopic follow-up is sufficient after initial treatment,.

Materials and Methods

This monocentric retrospective study included 352 patients with high-grade cervical dysplasia treated with standard surgical treatment between 1999 and 2002.

Surgical treatment

According to the accessibility of the transformation zone and the degree of dysplasia, these patients underwent either conization or LEEP (Table 1). All patients had a PAP-smear screening followed by colposcopy and biopsies. When the lesion was CIN II and the squamocolumnar junction was entirely visible, LEEP with a diathermic loop was performed. When the transformation area was not visible, conization was generally performed. In CIN III lesions, conization was carried out either with a scalpel or with Fischer's loop depending on their extent.

Patient follow-up

Colposcopic follow-up was routinely performed 4 to 6 months after initial treatment along with a Pap-smear. If these investigations were negative, another Pap-smear was taken at 6 months and then yearly. High-risk human papillomavirus typing (HR-HPV test) was routinely done at initial diagnosis and repeated with the follow-up smear at 6 months using the same technique. Testing for human papillomavirus was done by PCR-EIA using human papillomavirus general primer-mediated PCR with the primers GP5/6 (9,10). We used one assay to test for all 14 high-risk types of human papillomavirus (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). The histopathologic results of the exocervical and endocervical excision margins were systematically reviewed.

Criteria for residual or recurrent disease and treatment of recurrences

Criteria for residual or recurrent disease were based on positive histology of colposcopy-directed biopsy or endocervical curettage. Patients with two consecutive negative Pap smears and normal colposcopy (satisfactory colposcopy with no abnormality) were considered negative for residual or recurrent lesions whatever the PCR result. Histologic evidence of CIN of any grade (I, II, or III) was considered as residual or recurrent disease.

Patients with either an abnormal Pap-smear (lesions suggesting dysplasia) or abnormal colposcopy (CIN diagnosed on biopsies) at 4 months follow-up after treatment were considered as having residual disease. Patients with a normal PAP-smear and colposcopy at 4 months but with an abnormal PAP-smear or colposcopy at the next follow-up (between 8 and 24 months) were considered as having recurrent disease. Patients with residual or recurrent disease were referred for a second treatment.

Statistical analysis

Statistical analysis was done using XL Stat (Addinsoft©) and JMP 6.0 (SAS©) software.

Sample size and number of events were sufficient to allow comparison of qualitative and quantitative variables. Discontinuous variables were compared using the Mann-Whitney test (quantitative variables) and Fisher's exact test (qualitative variables). Multivariable analysis of predictors of recurrence was performed using the Cox model.

Results

Characteristics of the patients

Three hundred fifty-two patients were treated between 1999 and 2002 for high-grade cervical dysplasia. The diagnosis was suggested by cytology and routinely confirmed by colposcopy-guided biopsy. All patients had histologically proven high-grade lesions. Mean age of the patients was 36 years with a median of 34 years. The records of 422 patients were initially studied but 70 patients (16%) did not have complete follow-up or were lost to follow-up.

After surgical treatment, the lesion was graded CIN III in 244 cases (69%) and CIN II in 108 cases (31%) (Table 1).

Rate of recurrence or persistence (treatment failure) of cervical HSIL

Thirty-seven of the 352 patients (10%) had true recurrence 6 months after the initial surgical treatment and 6 patients (2%) had persistent lesions. Overall, 43 patients (12%) were considered as having recurrent disease. Follow-up was continued for 5 years with a mean of 73 months.

Treatment failure following CIN III was either more or less severe than the initial dysplasia. Of the 30 treatment failure following CIN III, 13 recurred as the same grade (43%) and 17 (57%) as CIN II or CIN I ($P = .35$). None presented as invasive carcinoma. Among the 13 cases of treatment failure following of CIN II, 3 recurred in a more aggressive mode as CIN III (21%), 3 as the same grade, and 7 as CIN I. In 85% of cases recurrence was diagnosed from the PAP-smear and in 15% of cases by colposcopy whereas the smear was normal or subnormal. The mean time to recurrence was 29 months (median 24 months). Severe dysplasia recurred on average later (30 months) than moderate dysplasia (15 months, $p = 0.03$).

Clinical and histologic predictors of disease recurrence (treatment failure)

Clinical and histological characteristics of the study group are shown in Table 1. These predictive factors were studied by univariate analysis. Positive endocervical margins ($p < 0.0001$, OR=4.48, CI=2.19, 9.16), positive pre-treatment HPV test ($p=0.01$, OR=8.3, CI=1.59, 43.5) and positive follow-up HPV test at 6 months ($p < 0.0001$, OR=38.8, CI=3.8, 10) were correlated with higher risk of treatment failure. Using multivariable analysis, these 3 factors were considered significant (Table 2). The most important predictor of treatment failure following CIN II and III was a **positive HR-HPV test at 6-month postoperative** follow-up (OR = 22.1, 95% CI = 7.5,25.5). The second significant predictor was **positive endocervical margins** (OR=8.9, 95% CI=6.4, 35.3) and the third was **positive pretreatment HPV typing** (OR=3.2, CI 95%= 2.1, 15.2). A positive initial HPV test significantly influenced the risk of recurrence, but its effect was less significant than a positive post-treatment test. We observed that age ($p=0.1$), positive exocervical margins ($p=0.7$), and treatment by LEEP rather than conization in the same indication ($p=0.09$) did not appear to be risk factors for recurrence.

Prevalence of lesions with a positive HPV test

The HR-HPV test was positive in 300 patients before treatment (85%) and at 6 months in 101 patients (29%).

Sensitivity of the HPV test at 6 months was 91% and its negative predictive value (NPV) was 98%. The probability of treatment failure with a positive HPV test at 6 months was 80%. On the other hand, when the HPV test was positive at the time of initial management, the probability of recurrence was only 14% (Table 3).

In order to quantify the value of the HPV test compared with simple analysis of surgical margins, we studied the positivity of the HPV test and the prevalence of recurrence in the subgroups of patients with positive and negative endocervical margins (Table 4). In 58% of patients with recurrence, both these criteria (endocervical margins and HPV test) were

positive, whereas in 7% of patients with recurrence (3 cases) both these criteria were negative. In the subgroup of patients with positive endocervical margins, the positive predictive value (PPV) of the HPV test was 100% and its negative predictive value (NPV) was 97%. In the subgroup of patients with negative endocervical margins, the PPV of the HPV test for recurrence was 28.7% and its NPV was 98.6%.

Discussion

Rates of recurrence and persistent lesions

The recurrence rates or treatment failure range in the literature from 2.5% to 48% (3-8, 11-20, 25, 26). Our findings are consistent with them (12%). The variability of the results of the literature probably depends on the technique used (LEEP or conization), on the varying incidence in each series of positive surgical margins and more generally on the precision of histopathologic examination. In several of these studies, no distinction was made between endocervical and exocervical margins among positive surgical margins. In addition, some series only concern residual lesions whereas others take both residual and recurrent lesions into account.

Since the study by Murdoch (3), the question of systematic retreatment of positive surgical margins has been raised. The difference of prognosis between endocervical and exocervical positive margins after excision needs to be emphasized.

Predictors of recurrence

The predictive factors of a residual or recurrent lesion have been systematically reviewed in specific studies (3-7,11-20). Positive margins are invariably found, but few studies have compared HPV typing before and after treatment (4,12). In our study, the predictive factors are positive endocervical margins, positive pre-treatment HPV test and the most important predictor of recurrence of CIN II and III are HR-HPV test at 6 month postoperative follow-up.

Although the status of the surgical margins is recognized as a predictor of treatment failure (15,21-26), this is nonetheless considered inappropriate as a method of surveillance, because

of the significant number of patients with clear margins who developed recurrent disease and patients with involved margins who were spontaneously cured.

1) HPV test before treatment:

Arbyn and al. showed in the meta-analysis that overall, HPV test after treatment predicted residual or recurrent CIN with high sensitivity. Furthermore, when lesions were treated by excision, HPV test predicted treatment outcome with higher sensitivity and specificity than histological assessment of the section margins (31).

Moreover, the rate of HSIL with a positive HPV test was 85.2%, slightly lower than the previously reported rates which were closer to 90% (4,27). Reported clearance rate of the HR-HPV test was 50 to 70% (28). In our series, clearance rate was 56.7% at 6 months.

2) HPV test after treatment

Elfgren and al. showed that HR-HPV test may be useful as a rapid intermediate end point for monitoring the efficacy of treatments. In this study, 81% of 109 patients with CIN I-III treated with cryosurgery or conisation were HPV test positive, only 9% remained positive at three months (32).

Several series assessed the role of post-treatment HPV test in association with cervical cytological test for recurrent cervical intraepithelial neoplasia (31,33-34). A systematic review of Chan and al. concluded HPV test at 3-6 months could identify approximately 91% of patients with residual or recurrent cervical intraepithelial neoplasia grade ≥ 2 but approximately 30% of them would undergo colposcopy in follow-up evaluation (34).

Nobenhuis (4) stressed the negative predictive value of the HR-HPV test (by hybrid capture or by PCR) after treatment. In this prospective study, only 2% of patients (2/103) with histologically proven CIN III had a false negative HR-HPV test. This very low rate of false negatives is largely compensated by the high sensitivity of the test, much greater than that of follow-up smear (4).

No series has yet assessed the role of post-treatment HPV test when the endocervical margins are positive. Our results could help with the decision for retreatment. Indeed, In our study, in the subgroup with negative endocervical margins patients, the PPV was 28.7% and the NPV was 98.6%, whereas in the subgroup with positive endocervical margins, the PPV was 100% and the NPV was 97%. Sensibility and specificity were respectively 93% and 100%. The rate of false negative was < 3%.

Follow-up of treated dysplasia

Patients treated for CIN must be followed regularly. Treatment failure rate varies in the literature from 2.5% to 48%, with an average around 10% (3-8, 11-20, 25, 26). The risk increases in patients older than 50 years, which is consistent with the observation that viral persistence increases with age (34).

Since 2006, the guideline of the American Society for Colposcopy and Cervical Pathology (ASCCP) includes HPV test for the management of atypical glandular cytology and for the follow-up after treatment for cervical intraepithelial neoplasia. Furthermore, ASCCP included HPV test in combination with cytologic screening in women aged 30 years and older (33).

In our series, as in a recent study (12), the preoperative specificity of the HR-HPV test is not sufficient and is lower than that of the smear, but it reaches a satisfactory level (nearly 80%) post-treatment. This inadequate preoperative specificity is due to the fact that the majority of lesions are positive. On the other hand, postoperative clearance of HPV markedly reduces the positivity rate of the test, increasing its specificity and its diagnostic value in terms of residual or recurrent lesions. In combination with cytologic smear, the specificity of this investigation becomes good and its excellent negative predictive value (98.4%) makes it very useful for monitoring treated dysplasia.

There is no consensus regarding the duration of post-treatment surveillance but we know patients treated for CIN have an increased risk for cervical cancer as compared to the general population within at least 10 years after treatment. An indicator that predicts successful outcome thus allowing to minimize the follow-up period would be particularly helpful. Several authors suggest follow-up after treatment should combine the HR-HPV test with the smear as it identifies patients with high risk of recurrence (4, 12, 29).

We suggest HPV test after treatment would be useful when surgical margins are positive because even if the PNV is not much improved (respectively 90.8% and 97%), PPV is improved by 70% (respectively 31.2% and 100%). Moreover, when surgical margins are positive, sensibility and specificity of HPV test after treatment are respectively 93 and 100%. Therefore, we would select more efficiently patients for the retreatment.

The question arises of increased costs due to post-treatment use of the HPV test. We suggest with the management described in our study to select patient with a benefit for the redo surgery and thus to avoid overtreatments. The cost/benefit ratio is certainly in favour of an extra HPV test (10 euros each) rather than a needless redo surgery.

We propose a treatment flowchart (Figure 1) for the management and follow-up of high-grade lesions. This flowchart is in line with recent publications (11,24,30) which encourage inclusion of the HR-HPV test in the follow-up of positive margins in order to reduce the number of overtreatments.

Conclusion

Recurrence or persistence of HSIL is relatively frequent (12%) and requires appropriate management. The oncogenic risk is now better defined, as we are able to identify persistence of viral replication, especially for certain serotypes. Inclusion of the HR-HPV test identifies more closely the indications for surgical retreatment, and also avoids overtreatment of certain patients. Clinical factors of recurrence, which have long been debated, have gradually become better known thanks to advances in molecular biology. The presence of positive endocervical margins, however, still remains an important factor of recurrence, and while this does not always warrant surgical retreatment, it implies at the very least a closer surveillance.

Disclosure of interest

No relevant financial, personal, political, intellectual or religious interest needs to be disclosed.

Contribution to Authorship

All authors contributed in the clinical part of the study. P.L. has contributed in the conception of the protocol and writing the manuscript. A.D. has contributed in the conception of the protocol and statistical analysis.

Details of ethics approval

No ethical approval was requested as this type of procedure is well recognised in clinical practice.

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Table 1. Clinical and Histopathologic Characteristics of Patients Treated for HSIL: Number of Patients (Percentage)

Clinical and histologic characteristics	Conization n=201, (%)	LEEP n=151, (%)	Total n=352, (%)
Average age (years)	38.1	33.3	36
CIN II	41 (11.6)	67 (19.1)	108 (30.7)
CIN III	160 (45.4)	84 (23.9)	244 (69.3)
Positive exocervical margins	15 (4.3)	9 (2.5)	24 (6.8)
Negative exocervical margins	186 (52.8)	142 (40.3)	328 (93.2)
Positive endocervical margins	28 (7.9)	21 (5.9)	49 (13.9)
Negative endocervical margins	173 (49.1)	130 (36.9)	303 (86.1)
Positive preoperative HPV test	207(58.8)	93 (26.4)	300 (85.2)
Positive HPV test at 6 months	70 (19.8)	31 (8.8)	101 (28.7)

CIN = cervical intraepithelial dysplasia; LEEP = loop electrosurgical excision procedure

Table 2. Predictors of Recurrence of HSIL

	No recurrence	Recurrence	<i>P</i>	Odds Ratio	95% CI
Average age ^a	36.4	33.6	0.109		
CIN III ^b	214	30	1	0.976	0.49, 1.93
CIN II	95	13	1	1.024	0.52, 2.03
Conization	171	30	0.09	1.862	0.945, 3.67
LEEP	138	13	0.09	1.862	0.945, 3.67
Conization CIN III	137	23	0.22	1.847	0.775, 4.39
Conization CIN II	34	7	0.234	2.093	0.67, 6.48
LEEP CIN III	77	7	0.22	0.542	0.23, 1.29
LEEP CIN II	61	6	0.234	0.478	0.15, 1.48
Positive exocervical margins	20	3	0.756	1.084	0.33, 3.52
Positive endocervical margins	33	15	< 0.0001	4.481	2.19, 9.16
Positive preoperative HPV test (PCR)	258	42	0.01	8.300	1.59, 43.5
Positive HPV test at 6 months	62	39	<0.0001	38.800	14.09, 107.05

^a: Mann Whitney test

^b: Fisher exact test and the Cox model for multivariable analysis

CIN = cervical intraepithelial dysplasia; LEEP = loop electrosurgical excision procedure;

PCR = polymerase chain reaction

Table 3. Sensitivity and Negative Predictive Value of the HPV Test Before Treatment and Six Months after Treatment of HSIL

	No		Total	Sensitivity	Specificity	PPV	NPV
	Relapse	relapse					
PO HPV +	42	258	300	97.7%	16.5%	14.0	98.1%
PO HPV -	1	51	52			%	
HPV ^a + at 6 months	39	62	101	90.7%	79.9%	38.6	98.4%
HPV ^a - at 6 months	4	247	251			%	

PO HPV = pre-operative HPV test; ^a HPV test 6 months after LEEP or conization; PPV = positive predictive value; NPV = negative predictive value

Table 4. Number of recurrence according to the positivity of margins and HPV test

	Recurrence	No Recurrence
Endocervical margins + HPV+	14 (32.5%)	0(0%)
Endocervical margins - HPV +	25 (58.2%)	62(20%)
Endocervical margins + HPV -	1(2.3%)	33(10.7%)
Endocervical margins – HPV -	3(7%)	214(69.3%)

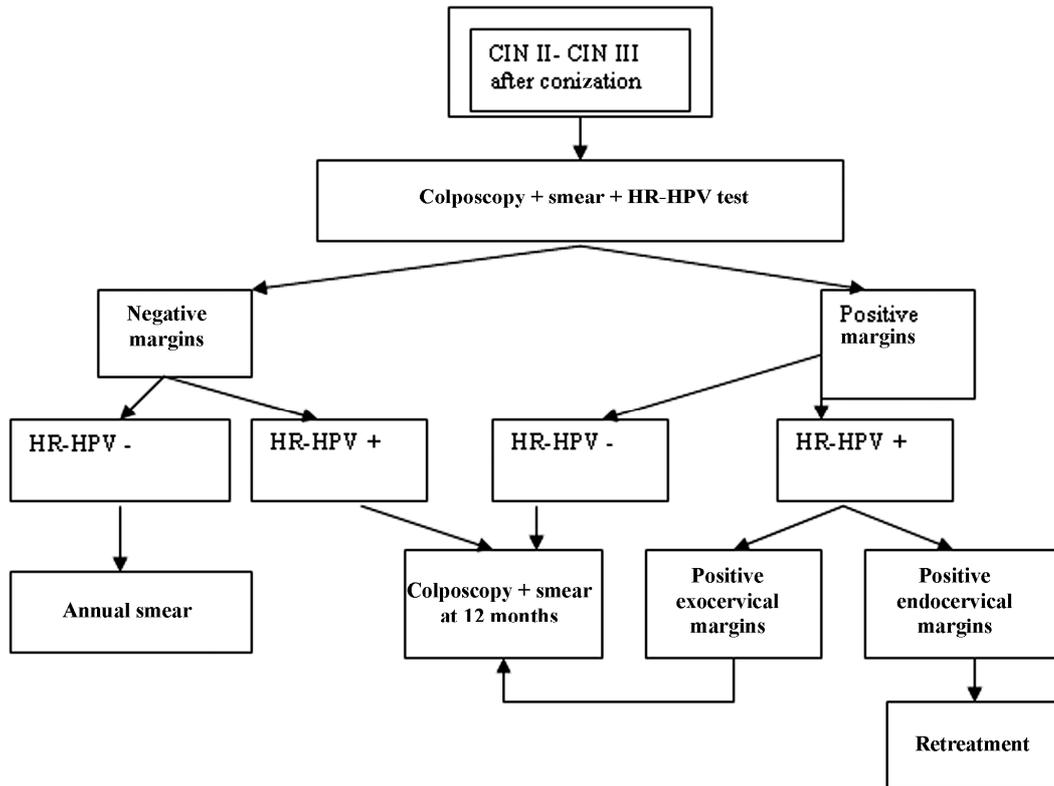


Figure 1. Follow-up of High-Grade Lesions Treated by Conization or LEEP According to Excision Margins and HR-HPV Test Results