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A B S T R A C T

Objectives: To identify predictive factors of the absence of high-grade intraepithelial lesion (HGSIL) in cervical excisional therapy specimen.
Methods: Data from 835 women who underwent excisional therapy for a cervical intra epithelial lesion at the department of Gynaecology from two university hospitals, between January 2015 and December 2020 were reviewed. Demographic data, referral cytology, colposcopic findings, results of cervical biopsy and endocervical curettage were retrieved. Primary outcome was the absence of HGSIL on cervical excisional specimen analysis defined by the identification of no intraepithelial lesion or of low-grade lesion only.
Results: The absence of HGSIL on specimen was observed in 137 (16.4%) cases. Three factors were identified to have a significant and independent impact on the probability of the absence of HGSIL on specimen: age higher than 40 years (aOR: 1.8; 95%CI: 1.1-3.0; p=0.024), a small abnormal transformation zone (TZ) (aOR: 2.3; 95%CI: 1.4-3.7; p=0.001) and the result of the cervical biopsy at the time of colposcopic assessment not showing HGSIL (aOR: 8.6; 95%CI: 4.7-15.5; $p < 0.001$). No significant impact of the referral cytology nor of the colposcopic impression were observed.
Conclusion: Although the result of cervical biopsy performed at the time of colposcopic assessment is the key risk factor for the absence of HGSIL on excisional specimen, age over 40 and a small abnormal TZ are the two other identified risk factors. Practitioners should consider these findings when deciding for excisional therapy.

Introduction

Cervical cancer is a strictly virus-induced cancer and must necessarily go through precancerous stages (HGSIL) before invasion [1]. Over the last decades, screening programmes have demonstrated to consistently reduce the incidence and mortality of cervical cancer [2–5]. Ablative and/or excisional treatments of HGSIL are highly effective for preventing progression to cancer [6]. Large loop excision of the transformation zone (LLETZ) is the most widely used treatment in routine practice [6]. Although highly efficient, this excisional procedure is associated with increased risk of subsequent premature delivery [7,8]. Additionally, healing process might result in cervical stenosis and endocervical extent of the squamocolumnar junction, jeopardizing long-term post-treatment follow-up [9–11].

With the tendency to delay the age of first pregnancy and the high number of patients diagnosed with HGSIL in childbearing age, limiting the consequences of excisional therapy is a genuine public health issue [12]. Although excisional therapy should be indicated in patients with proven HGSIL or at least with a maximal probability of HGSIL, colposcopic appreciation is sometimes difficult. Excisional therapy may be indicated despite a negative biopsy, or even in the lack of a biopsy if colposcopy did not show any abnormality with a type 3 transformation zone following high-grade referral cytology

Abbreviations: HPV, Human Papilloma Virus; HGSIL, High-grade lesion; LGSIL, Low-grade lesion; CIN, intra epithelial neoplasia; TZ, transformation zone; ECC, endocervical curettage; LLETZ, Large loop excision of the transformation zone; IFCPC, International Federation of Cervical Pathology and Colposcopy; AIC, Akaike information criterion; ADK, in-situ adenocarcinoma; AGC, Atypical Glandular Cells; ASCH, Atypical Squamous Cell cannot exclude High grade lesion; ASCUS, Atypical Squamous Cell of Undetermined Significance; HSIL, High grade Squamous Intraepithelial Lesion; LSIL, Low-grade squamous intraepithelial lesion

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Précis: Cervical biopsy showing no high-grade lesion (HGSIL), small abnormal transformation zone and age over 40 are risk factors for the absence of HGSIL.

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[13]. Despite proven HGSIL at preoperative cervical biopsy, specimen analysis does not always confirm this diagnosis, possibly ending in low-grade lesion (LGSIL) only and even sometimes in the lack of any lesion. The risk of having no HGSIL on the excision specimen despite HGSIL at cervical biopsy is estimated to be 25% [14,15]. Identified risk factors for such situation are a low-grade referral cytology, minor changes colposcopic impression, CIN2 at cervical biopsy, and non-16/18 high-risk HPV infection [14,16–19]. Considering the absence of any lesions, previous studies report a risk between 16% and 19% with risk factors being the same as those mentioned above, as well as a prior negative HPV testing, or a low HPV viral load [20–22]. Overall, few studies have evaluated this risk, with most of them suffering from methodological flaws such as retrospective nature and small size of the studied population. Additionally, these studies focused on one or two main risk factors only and didn't consider all pre-operative factors as a whole [23,24]. In most of these studies, although overall colposcopic impression was reported, precise details were lacking such as the type of the TZ, the size of the abnormal TZ and the numbers of cervical biopsies performed [14,16]. More studies are therefore needed to precisely identify risk factors of the absence of HGSIL in cervical excisional therapy specimen, helping clinicians to select patients in whom an excisional therapy is useless without risking missing an invasive lesion.

The aim of this study is to determine predictive factors of the absence of HGSIL when performing an excisional therapy and therefore to establish a profile of patients in whom it is preferable to opt for surveillance rather than surgical excisional therapy.

Materials and methods

Patients

Medical charts from all women who underwent excisional therapy at the department of Gynaecology from two university hospitals between January 2015 and December 2020 were retrieved and analyzed. All women who had an excisional therapy performed following a referral colposcopic examination eventually completed with one or multiple cervical biopsies were included. Patients with invasive carcinoma on cervical biopsy and with ungradable intra epithelial lesion on the excisional specimen were excluded. Patients for whom clinical data were missing, especially precise initial colposcopic examination report data were also excluded from our analysis.

Indications of colposcopy were abnormal screening cervical cytology, abnormal looking cervix and post-coital bleeding. Colposcopic examinations were performed by experienced colposcopists after systematic staining with 5% acetic acid followed by 3% iodine. Colposcopic findings were classified according to the 2011 IFCPC nomenclature [25]. Cervical biopsies were possibly performed according to colposcopists' decision, depending on colposcopic findings and impression. No see and treat management were performed. Some patients were also referred directly for large loop excision of transformation zone (LLETZ) after that a colposcopy had been performed elsewhere, with colposcopic and cervical biopsies' reports attached.

The study protocol received institutional approval from the Ethics Committee of the French college of Obstetricians and Gynaecologists (CEROG-2022-GYN-0302).

Excisional therapies

All excisional therapies were performed in theatre under either local or general analgesia. Except for one patient who had a cold knife conisation, all had a LLETZ performed. Excisional therapies were carried out under direct colposcopic guidance. No excisional therapy was performed during pregnancy.

Data

Medical data including patients' characteristics, indication of colposcopy, referral cytology, colposcopic impression, type of TZ, size of the abnormal TZ, results of possibly performed cervical biopsy and endocervical curettage were retrospectively retrieved from medical charts. Patients with a history of repeated abnormal screening cervical cytologies were defined by at least two subsequent abnormal results (either low grade, high grade or both). Abnormal TZ was considered as small if only one cervical quadrant of the cervix was affected. Collected data included demographic data such as age, height, weight, smoking status, history of immunosuppression, parity, menopausal status and possible pregnancy at the time of colposcopy. Final histological diagnosis was collected directly from the pathology report. The main outcome was the absence of HGSIL on cervical excisional specimen analysis defined by the identification of no intraepithelial lesion or of LGSIL only.

Statistical analysis

Continuous variables were expressed as mean (± standard deviation) and compared using t-tests. Categorical variables were expressed as counts (%) and compared using χ^2 or Fisher's exact tests. Binary logistic regressions were then used to identify factors associated with the he absence of high-grade intraepithelial lesion in cervical excisional therapy specimen. Backward stepwise procedure was performed to select statistically significant factors in the multivariate models, first selecting in the regression variables displaying univariate association with a significance threshold of p=0.20, then removing from the model non-significant variables (threshold of p=0.05). A forward stepwise procedure was also used to confirm the variable selection. The C-index (area under ROC curve) and the Akaike Information Criterion (AIC) were used to compare model fit. All statistical tests were two-sided using a threshold p-value of 0.05. Analyses were performed using SPSS Statistics 20.0 (IBM Inc., Armonk, NY, USA).

Results

Patients

During the study period, a total of 962 excisional therapies were performed in both participating centers. Forty patients were excluded because of an invasive carcinoma on the cervical biopsy and 12 because of an ungradable intraepithelial lesion on the surgical specimen. Data was missing for 75 procedures, and patients were therefore excluded. Finally, a total of 835 excisional procedures were included for analysis.

Patient's characteristics are summarized in Table 1. The mean age was 40.4 (±10.4) years with 153 (18.3%) menopausal women. Twenty-one (2,5%) women were diagnosed with an intra-epithelial lesion during pregnancy, with the decision of excisional therapy made after a new colposcopic examination following delivery. A type 3 transformation zone was observed in 185 (22.4%) cases. Normal colposcopic examination was observed in 13 (1.6%) cases, with minor and major changes observed in 202 (24.4%) and 521 (62.6%) cases, respectively. No biopsy had been performed during colposcopy in 59 (7.5%) patients: 16 had a endocervical curettage only showing HGSIL; 27 had a high-grade referral cervical cytology with colposcopy showing a type 3 TZ with no abnormality identified (of whom 12 had a history of treatment for HGSIL); 10 had a previous biopsy showing HGSIL several months earlier with a colposcopic control just before the excisional therapy showing persistent major changes; 3 had a persistent LGSIL; 3 had an endocervical lesion at colposcopy inaccessible to a biopsy. One and two or more biopsies were performed in 376 (47.9%) and 350 (44.6%) cases, respectively. Cervical biopsies

Table 1
Patients' characteristics (n= 835).

Age Mean (*years*) (±SD)	40.4 (± 10.4)
BMI Mean (±SD)	23.6 (± 5)
Smoking	425 (51.6)
Immunosuppression*	45 (5.4)
Nulliparous	231 (28)
Postmenopausal	153 (18.3)
History of previous treatment for HGL	104 (12.5)
Excisional therapy	96 (11.5)
Laser ablation	8 (1)
History of repeated abnormal screening cervical cytologies prior to excisional therapy**	29 (3.5)
Referral screening cytology	
ASCUS	149 (17.8)
HSIL	219 (26.2)
LSIL	159 (19)
AGC	17 (2)
ASCH	181 (21.7)
Other	102 (13.2)
Colposcopy performed during pregnancy	21 (2.5)
Type 3 TZ	185 (22.4)
Colposcopic impression	
Normal examination	13 (1.6)
Minor changes	202 (24.4)
Major changes	521 (62.6)
Suggestive of invasive cancer	29 (3.5)
Aspecific findings	66 (7.9)
Small abnormal TZ†	350 (46.5)
Number of cervical biopsies performed	
0	59 (7.5)
1	376 (47.9)
≥ 2	350 (44.6)
Cervical biopsy results	
Absence of any intraepithelial lesion	16 (2)
LGL	42 (5.4)
HGL	678 (86.8)
ADKIS	17 (2.2)
Ungradable intraepithelial lesion	28 (3.6)
ECC	57 (6.8)
ECC results	
Absence of lesion	16 (28.1)
Low grade lesion	4 (7)
HGL	28 (49.1)
In situ adenocarcinoma	2 (3.5)
Ungradable CIN	7 (12.3)

Values are expressed as n (%), otherwise specified.
ADK: in-situ adenocarcinoma; AGC: Atypical Glandular Cells; ASCH: Atypical Squamous Cell cannot exclude High grade lesion; ASCUS: Atypical Squamous Cell of Undetermined Significance; ECC: endocervical curettage; HGL: High-grade lesion; HSIL: High grade Squamous Intraepithelial Lesion; LGL: low-grade intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; TZ: transformation zone.
* HIV positive (n=15), auto-immune disorders under immunosuppressors therapies (n=18), immune deficiency (n=2) and transplanted patients under immunosuppressors (n=10).
** low-grade cytologies (n=20) and high-grade cytologies (n=9).
† Only one cervical quadrant affected.

showed the absence of HGSIL in 58 (7.4%) cases. All of these 58 patients were referred for a diagnosis cone biopsy despite a negative biopsy for various reasons: history of repeated abnormal cervical cytologies with a colposcopic examination finding a type 3 transformation zone twice, persistent low-grade lesion for more than two years, colposcopic signs suggesting invasion. Finally, of the 835 excisional therapies included, the absence of HGSIL was found in 137 (16.4%) specimen with 61 (44.5%) of them showing no intraepithelial lesion at all.

Identification of risk factors for the absence of HGSIL in excisional specimen

Patients with no HGSIL on excisional specimen were significantly older than others: 47.0 (± 11.5) years vs. 39.1 (± 9.6) years, respectively (p<0.001) (Table 2). They were significantly less likely to smoke: 56 (41.8%) vs. 369 (53.6%), respectively (p=0.013). Repeated abnormal screening cervical cytologies prior to excisional therapy was more often observed in these patients: 13 (9.5%) vs. 16 (2.3%), respectively (p<0.001). Patients with no HGSIL were significantly more likely to have a type 3 transformation zone at referral colposcopic examination: 67 (49.3%) vs. 118 (17.1%), respectively (p<0.001). The overall colposcopic impression was less severe in these patients as major changes or changes suggestive of invasive cancer were significantly less often reported: 60 (43.8%) vs. 461 (66.3%) and 4 (2.9%) vs. 25 (3.6%), respectively (p < 0.001). Patients with no HGSIL on excisional specimen were more likely to have a small abnormal TZ than others: 64 (67.4%) vs. 286 (43.5%), respectively (p<0.001). When performed, these patients were also likely to have a significantly lower mean number of cervical biopsies performed: 1.24 (±1.03) vs. 1.55 (±0.84), respectively (p<0.001). Finally, those patients were significantly more likely to have had an ECC performed: 21 (15.3%) vs. 36 (5.2%), respectively (p < 0.001).

An analysis of the impact of the time lapse between colposcopy and excisional therapy and between referral cytology and excisional therapy on the probability of the absence of HGSIL on specimen was also performed. No significant impact was found for those delays.

Multivariate analysis

In multivariate analysis, three factors were found to have a significant and independent impact on the probability to achieve the absence of HGSIL on the excisional specimen (Table 3). Age was one of those, with a cut-off of 40 years significantly increasing this probability: aOR 1.8 (95%CI: 1.1-3.0; p=0.024). The second independent risk factor was the identification of a small abnormal TZ: aOR 2.3 (95%CI: 1.4-3.7; p=0.001). The risk factor with the strongest effect was a cervical biopsy showing no HGSIL: aOR 8.6 (95% CI: 4.7-15.5; p<0.001). Adding age and the identification of a small abnormal TZ to the model with cervical biopsy alone improved the C-index from 0.662 to 0.747 and the AIC from 476.0 to 463.9 (likelihood ratio test p <0.001). Neither the severity of cytological abnormalities, nor of colposcopic impression were found to significantly impact the risk of the absence of HGSIL on excisional specimen.

Risk of no HGSIL in patients with a cervical biopsy showing HGSIL or ADKIS

Among the 695 patients with initially proven HGSIL or ADKIS following initial colposcopy and biopsy, 58 (9.7%) were finally found to have no HGSIL on excisional specimen analysis. The same two risk factors for the absence of HGSIL were identified in this population: age, with a cut-off of >40 years (p=0.028), and a small abnormal TZ at colposcopic examination (p=0.003) (Table 4).

Discussion

Our study shows the results of the cervical biopsy at the time of colposcopic examination along with the size of the abnormal TZ and the age of the patients to be the three independent risk factors for the absence of HGSIL on the excisional specimen in routine practice. Surprisingly and contradictory to previous literature, the referral cytology results and the colposcopic impression were not identified as risk factors [14,16,22]. With the inclusion of all excisional therapies that were performed following a referral colposcopic examination, whatsoever the practice of previous cervical biopsy and its result, our study aimed to assess the risk of the absence of HGSIL in routine clinical situation and not in very selected population. However, with such outcome observed in only 137 (16.4%) patients and the absence of intra epithelial lesion in 61 (7.3%) patients, the rates reported are lower than those commonly reported in literature [14,15,20–22]. This result somehow testifies for the strict selection of patients

Table 2
Comparison of patients' characteristics depending on the final histology of excisional specimen.

	Excisional specimen analysis		p
	No lesion or LGL	High grade lesion or more*	
Age Mean (*years*) (± SD)	47.0 (± 11.5)	39.1 (± 9.6)	<0.001
BMI Mean (± SD)	23.8 (± 4.9)	23.5 (±5.0)	0.543
Smoking	56 (41.8)	369 (53.6)	0.013
Immunosuppression	9 (6.6)	36 (5.2)	0.534
Nulliparous	29 (21.8)	202 (29.1)	0.092
Post-menopausal	49 (36)	104 (14.9)	<0.001
History of treatment for previous HGL	22 (16.1)	82 (11.7)	0.162
Excisional therapy	22 (16.1)	74 (10.6)	
Laser ablation	0 (0)	8 (1.1)	
History of repeated abnormal screening cervical cytologies prior to excisional therapy	13 (9.5)	16 (2.3)	<0.001
Referral screening cytology			
ASCUS	26 (19)	123 (17.6)	0.666
HSIL	31 (22.6)	188 (26.9)	
LSIL	22 (16.1)	137 (19.6)	
AGC	3 (2.2)	14 (2)	
ASCH	34 (24.8)	147 (21.1)	
Other	21 (15.3)	89 (12.8)	
Colposcopy performed during pregnancy	2 (1.5)	19 (2.7)	0.555
Type 3 TZ	67 (49.3)	118 (17.1)	<0.001
Colposcopic impression			
Normal examination	4 (2.9)	9 (1.3)	<0.001
Minor changes	31 (22.6)	172 (24.7)	
Major changes	60 (43.8)	461 (66.3)	
Suggestive of invasive cancer	4 (2.9)	25 (3.6)	
Aspecific findings	38 (27.7)	28 (4)	
Small abnormal TZ**	64 (67.4)	286 (43.5)	<0.001
Number of cervical biopsies performed			
0	29 (22.5)	30 (4.6)	<0.001
1	57 (44.2)	319 (48.6)	
≥ 2	43 (33.3)	307 (46.8)	
Cervical biopsy result			
Absence of lesion	11 (10.5)	5 (0.7)	<0.001
LGL	24 (22.9)	18 (2.7)	
HGL	57 (54.3)	621 (91.9)	
ADKIS	1 (1)	16 (2.4)	
Ungradable intraepithelial lesion	12 (11.4)	16 (2.4)	
ECC	21 (15.3)	36 (5.2)	<0.001
ECC result			
Absence of lesion	10 (47.6)	6 (16.7)	0.044
Low grade lesion	2 (9.5)	2 (5.6)	
HGL	6 (28.6)	22 (61.1)	
In situ adenocarcinoma	0 (0)	2 (5.6)	
Ungradable intraepithelial lesion	3 (14.3)	4 (11.1)	

Values are expressed in n (%), otherwise specified.
ADKIS: adenocarcinoma in-situ; AGC: Atypical Glandular Cells; ASCH: Atypical Squamous Cell cannot exclude High grade lesion; ASCUS: Atypical Squamous Cell of Undetermined Significance; ECC: endocervical curettage; HGL: High-grade lesion; HSIL: High grade Squamous Intraepithelial Lesion; LGL: low-grade intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; TZ: transformation zone.
* Patients with high-grade lesion, in situ adenocarcinoma or invasive lesion.
** Only one cervical quadrant affected.

undergoing excisional therapy in our institution; such selection possibly biasing our results. We therefore believe this situation to explain why referral cytology nor colposcopic impression were identified as risk factors for the absence of HGSIL. Thus, the previous selection of patients undergoing excisional therapy was likely to have been already guided by the results of the referral cytology along with colposcopic impression. Although it is possible our study could not be representative of all practices, we believe our study to be relevant for clinical practice in optimal settings.

Table 3
Multivariate analysis of risk factors predicting absence of high-grade lesion or more in excisional specimen.

Factor	aOR (95%CI)	p
Age > 40 years	1.8 (1.1-3.0)	0.024
Small abnormal TZ†	2.3 (1.4-3.7)	0.001
Cervical biopsy showing no lesion or LGL	8.6 (4.7-15.5)	< 0.001

LGL: low-grade lesion; TZ: transformation zone.
† Only one cervical quadrant affected.

The fact that age was found to have a significant impact on the absence of HGSIL is unexpected and contradictory with results from previous studies [14,16,21,22]. Additionally, one could expect the risk of the absence of HGSIL on excisional specimen to decrease with

Table 4
Impact of age and size of the abnormal TZ on the probability of the absence of HGL on excisional specimen among patients having had HGL on previous cervical biopsy (n=695).

		Excisional specimen		p
		Absence of HGL	HGL or more	
Age	<40 years	31 (53.4)	436 (68.4)	0.020
	>40 years	27 (46.6)	201 (31.6)	
Size of the abnormal TZ	1 quadrant	35 (63.6)	263 (42.7)	0.003
	≥ 2 quadrants	20 (36.4)	353 (57.3)	

Values are expressed in n (%), otherwise specified.
HGL: high-grade lesion.
*Include patients with absence of intra epithelial lesion, low grade intra epithelial lesion or ungradable intra epithelial lesion on cervical biopsy.

age, along with the increasing probability for cervical cancer [1]. Our finding could simply reflect a higher acceptance for excisional therapy in older women without any childbearing issue and therefore for the appliance of less selection criteria in older women. In our study, the size of the abnormal transformation zone was also significantly associated with the absence of HGSIL. Our study is the first to identify this risk factor [17,21]. However, the impact of the size of the TZ has been already demonstrated to influence the probability for underdiagnosis of HGSIL as more biopsies are commonly required with the increasing size of the abnormal TZ [26,27]. Additionally, the likeliness of HGSIL has been shown to increase with the size of the TZ [28]. One could consider our result to support the likeliness of a full removal of a possible HGSIL by the cervical biopsy performed at the time of initial colposcopic examination in case of a small abnormal TZ.

The result of the biopsy was the risk factor with the most important impact on the probability of the absence of HGSIL. This result is consistent with previous published data [16,17,20]. Previous studies also demonstrated a significant association of prior negative HPV testing and low HPV viral load [21,22]. We could not investigate the impact of HPV testing as our patients had no such test performed. This is explained by the introduction of HPV testing for primary screening in women over 30 in our country only in 2019, shortly before the end of our inclusion period.

Along with the age, our results emphasize the importance of colposcopic examination with biopsy prior to excisional therapy. Using these three risk factors as a scoring system, the absence of HGSIL varied from 3% in women with none of those three risk factors identified up to 68% in those over 40 having a small abnormal TZ and a cervical biopsy showing no HGSIL. Although imperfect and hardly exploitable in women with only one or two identified risk factors, such gradation in the final risk of the absence of HGSIL on excisional specimen could be applied in routine practice. Avoidance of excisional therapy in women combining all these three risk factors could be considered. In these selected women, clinicians could opt for surveillance rather than excisional therapy with closed surveillance by an experienced colposcopist. Prospective studies are needed to properly assess this hypothesis. Finally, although our study didn't find a significant association between the absence of HGSIL and the delay between colposcopic examination and excisional therapy, a slight trend can be noticed, with an increase of the delay in patients with absence of HGSIL, which should be explored in further studies.

Despite the large number of patients included, our study suffers from limitations inherent to its retrospective nature that should be considered when interpreting our results. However, we believe this bias to be limited by the use of exhaustive hospital databases, surgical and histological reports, and the very low rate of excluded cases due to missing data. Additionally, a selection bias cannot be ruled out as all included cases were treated in the two centers only, in which practices are well codified and might differ from other centers. We believe the large inclusion criteria to be a major strength of our study. Indeed, the inclusion of all women who underwent an excisional therapy whether a cervical biopsy had been performed or not, and no matter the result, is highly representative of what is done in routine clinical practice and makes our results exportable to most of clinical settings. Finally, in considering multiple details from the referral colposcopic examination, we did not restrain our analysis to the sole colposcopic impression and made a precise analysis of colposcopic criteria such as the type or the size of the TZ.

Conclusion

Although the result of cervical biopsy performed at the time of colposcopic assessment is the key risk factor for the absence of HGSIL on excisional specimen, age over 40 and a small abnormal TZ are the two other identified risk factors. Combining these three risk factors improved the prediction of the absence of HGSIL. Thus, excisional therapy could be avoided in women combining those three risk factors. Instead, these women could be offered close surveillance by an experienced colposcopist. Practitioners should consider these findings when deciding for excisional therapy.

Declaration of Competing Interest

All authors have no conflict of interest to declare.

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