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## **Value of large loop excision of the transformation zone (LLETZ) without histological proof of high-grade cervical intraepithelial lesion: Results of a two-year continuous retrospective study**

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**Title:** Value of large loop excision of the transformation zone (LLETZ) without histological proof of high-grade cervical intraepithelial lesion: results of a two-year continuous retrospective study.

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## Abstract

*Objective:* Large loop excision of the transformation zone (LLETZ) conization has been associated with adverse obstetrical outcomes. In an approach to reduce the number of performed LLETZ procedures, we conducted this study to evaluate whether “diagnostic” LLETZ should still be performed, by analyzing their yield in terms of detection (and treatment) of real high-grade squamous intraepithelial lesion (HSIL).

*Methods:* During a two-year study period, all patients who underwent a LLETZ procedure in our institution were retrospectively included. Study participants were divided into two groups according to LLETZ indication: a biopsy-proven HSIL group, and a non-biopsy-proven HSIL group. The results of the final histological examination were recorded, as well as excision margin status and specimen dimensions.

*Results:* During the two-year study period, 396 LLETZs were performed, 283 (71%) of which were indicated by biopsy-proven HSIL. In the non-biopsy-proven group, final histological showed 50 cases of HSIL (44%) and 4 cases of carcinoma (3.6%), versus respectively, in the biopsy-proven group, 221 (78%) HSIL and 28 (9.9%) carcinoma ( $p < 0.001$ ). Regarding margin status and specimen dimensions, no intergroup difference was observed between the two groups.

*Conclusion:* So called “diagnostic” LLETZ allowed the detection of severe cervical lesions in almost half of cases, without increasing specimen dimensions in comparison with classical conization indications. Moreover, they also allowed an efficient treatment as showed by similar margins status. Our results therefore strengthen the idea that “diagnostic” LLETZ, when specific indications are respected, should not be overlooked as a major part of our therapeutic arsenal.

**Keywords:** Pap smear; LLETZ; biopsy; colposcopy; follow-up.

## Introduction

Pap smear screening and management of intraepithelial lesions have led to a decreased incidence of cervical cancer over the last decade, and conization has emerged as the flagship treatment of high-grade/pre-invasive lesions of the cervix. However, despite the proven efficacy of large loop excision of the transformation zone (LLETZ) conization — the most widely used surgical technique—pregnancy outcomes and other medical aspects must also be considered when deciding on the treatment of cervical lesions. Conizations must therefore be fully justified in order to avoid unnecessary surgical interventions and adverse outcomes.

An obvious approach to reduce the number of performed LLETZ procedures is to target “diagnostic” conizations. These procedures are performed in the presence of a clinical suspicion of high-grade squamous intraepithelial lesion (HSIL) without formal histological proof. To address this issue, we conducted this study to evaluate whether “diagnostic” LLETZ should still be performed, by analyzing the yield of this procedure in terms of detection (and treatment) of real HSIL.

## Materials and methods

This retrospective single-center observational study was performed at Amiens-Picardie University hospital, France, based on data collected from patients treated in our institution from January 2016 to December 2017.

All patients who underwent a LLETZ procedure in our institution were included. Study participants were divided into two groups according to LLETZ indication: a biopsy-proven HSIL group, and a non-biopsy proven HSIL group. The latter comprised persistently abnormal Pap smears (> 18 months) or eloquent colposcopic images, with no or less severe than HSIL biopsy results. The following data were recorded for patients in the two groups: age, parity, body mass index (BMI), active tobacco intoxication, hormonal treatment (either contraception or postmenopausal hormone

replacement therapy), and history of LLETZ. The initial Pap smear cytology leading to the surgical procedure was also recorded. This either consisted of the only cytological result indicating the colposcopy and later leading to LLETZ, or the first Pap smear in a series of surveillance cytologies in case of persistent abnormal results leading to surgery. Other recorded preoperative variables were adequate visualization of the squamocolumnar junction on colposcopy and detection of oncogenic HPV, when this information was available.

All colposcopies and LLETZ were performed in our institution by a specialist colposcopist. Each patient underwent colposcopic examination immediately prior to surgery, which was usually performed by the same gynecologist who performed the colposcopy. LLETZ was performed under local, regional or general anesthesia using a semicircular loop electrode (four possible diameters: 10, 15, 20, 25 mm). Conization followed colposcopic lesions limits when such lesions were present. In case of diagnosis colposcopies, procedures were performed in order to excise the entire transformation zone and 2-3 mm beyond the iodine-non-staining area, as well as to allow a complete excision of glandular crypts, at least 7 mm in depth. The following characteristics were recorded during the procedure: need for further resection, use of destructive therapy (using ball diathermy or laser vaporization), performance of electrocauterization, and total dimensions of the excised specimen (depth and volume) before formaldehyde fixation. The results of the final histological examination were recorded; only the most severe diagnosis was recorded when several lesions coexisted. Lastly, the status of the ectocervical and endocervical excision margins was documented; margins were described as negative when both were free of any sign of dysplasia.

Data are expressed as the mean  $\pm$  standard deviation (SD) for continuous variables and as number (percentage) for qualitative variables. Continuous variables were compared using the Mann-Whitney test or the Student t test (as appropriate), while categorical variables were compared using a  $\chi^2$  test, Kruskal-Wallis test or Fisher's exact test. Statistical analyses were performed with p-value® freeware (<https://www.pvalue.io>, Paris, France). The threshold for statistical significance was  $p < 0.05$  (two-sided).

Data were obtained from our institution's centralized electronic patient records. The study was approved by the local institutional review board (10<sup>th</sup> of September, 2018, Amiens, France).

## Results

During the two-year study period, 396 LLETZs were performed, 283 (71%) of which were indicated by biopsy-proven HSIL. Non-biopsy-proven HSIL indications comprised: 56 cases of colposcopic suspicion of high-grade dysplasia without biopsy, 49 cases of colposcopic suspicion of high-grade dysplasia with biopsy showing at most low-grade dysplasia, and eight cases of abnormal Pap smear persisting for more than 18 months (figure1). Absence of biopsy in colposcopic high-grade suspicion situations, though not in line with current guidelines, was a strategy chosen by the practitioner based on his/her experience in colposcopic images and/or patient reluctance towards biopsy.

Patients in whom LLETZ was performed for an indication other than a biopsy-proven HSIL were significantly older, and significantly less frequently used hormonal therapy. The two groups also differed in terms of the initial cytology leading to LLETZ, presence of oncogenic HPV, and complete visualization of the squamocolumnar junction. In the non-biopsy-proven HSIL indications, initial cytology for the 56 cases of colposcopic suspicion of high-grade dysplasia without biopsy was: 19 ASCUS, 16 LSIL, 11 HSIL, six ASCH, one AGC and three unknown. For the 49 cases of colposcopic suspicion of high-grade dysplasia with biopsy showing at most low-grade dysplasia, initial cytology was: 16 ASCUS, 20 LSIL, four HSIL, five ASCH, three AGC and one unknown. For the eight cases of abnormal Pap smear persisting for more than 18 months, initial cytology was: four ASCUS, one LSIL, one HSIL and two ASCH. No intergroup difference was observed in terms of either LLETZ procedure characteristics or dimensions of the excised specimen (Table 1).

In the non-biopsy-proven HSIL indications, final histological results for the 56 cases of colposcopic suspicion of high-grade dysplasia without biopsy were: 31 high-grades, 24 normal or low-grades, one cancer. For the 49 cases of colposcopic suspicion of high-

grade dysplasia with biopsy showing at most low-grade dysplasia, they were: 18 high-grades, 28 normal or low-grades, three cancers. For the eight cases of abnormal Pap smear persisting for more than 18 months, they were: one high-grade and seven normal or low-grades. Statistically significant differences in terms of the final histological results were observed between the two groups with higher proportions of HSIL and carcinoma in the biopsy-proven HSIL group, and a higher proportion of low-grade and normal results in the non-biopsy proven HSIL group. Finally, margin status was not significantly different between the two groups (Table 2).

## Discussion

The therapeutic efficacy of conization can be explained by the natural history of cervical intraepithelial lesions, as, although 47 to 91% of low-grade squamous intraepithelial lesions regress, about 21% progress to HSIL and almost 1% invade the basement membrane [1-3]. Only 35% of HSILs resolve spontaneously, whereas 1% of cases progress towards invasion every 24 months [3]. The overall likelihood of progression of a high-grade lesion towards invasion during the patient's lifetime is greater than 12%, thereby clearly justifying conization in the presence of biopsy-proven cervical HSIL [4]. Nevertheless, excisional treatments should be limited to specific medical indications, especially in this population, in which the obstetric prognosis is often an essential issue. Studies conducted over the course of nearly the past 30 years distinctly showed that surgical removal techniques such as LLETZ were associated with adverse pregnancy outcomes [5, 6]. In a recent meta-analysis comprising 53 studies and 4,599,416 participants, Kyrgiou et al. reported that excisional treatments increased overall prematurity by a relative risk of 1.87 (95% CI [1.64-2.12]) [7]. In these circumstances, preterm births as well as premature labor and premature rupture of membranes are the direct consequences of a cervical amputation resulting in cervical incompetence during pregnancy, which is worsened by increasing dimensions of the excision specimen [7, 8].

In order to avoid these potential obstetric complications, it is therefore essential to identify situations in which conization is unnecessary. The role of conization has been clearly established in the presence of biopsy-proven HSIL. However, we observed 12.1% of low-grade (or lower) dysplasia on the final histological examination of cases of LLETZ indicated by high-grade biopsies. This mismatch between biopsy and final histological examination is a well-known phenomenon, and some authors have reported even lower correlations. In their retrospective study, Witt et al. observed that, in a cohort of 306 patients with biopsy-proven HSIL, only 73% of cases presented high-grade dysplasia on final histological examination [9]. In another study based on 170 HSIL biopsies, the correlation between biopsy and final histological results was only 51.2% [10]. Several possible explanations have been proposed for these discordant results. The first explanation is that elective cervical biopsy has partly or even completely removed the lesion, and that the residual high-grade lesion is destroyed by the inflammatory tissue response secondary to the biopsy. Other possible explanations include inaccurate LLETZ that “misses” the high-grade lesion, biopsy overdiagnosis and histological underdiagnosis [11]. Finally, the time interval between the initial biopsy and the surgical procedure could also play an important role in view of the natural history of cervical lesions and the possibility of spontaneous regression. However, this explanation remains controversial, as Barker et al. reported that surgery performed 12 weeks after the initial biopsy did not negatively affect the correlation between biopsy and final histological examination, which was 84% for all types of biopsies in their study [10].

In contrast with biopsy-proven HSIL, the other indications for LLETZ remain a subject of debate, as partial cervical amputation without histological proof may be an excessively invasive procedure and, at first glance, not very cost-effective in terms of oncologic benefit. Nevertheless, in these situations observed in our study, histological examination of excision specimens showed that almost one-half (48%) of patients actually presented a high-grade lesion or even a cancer (in four cases). A recent study based on nearly 15,000 conizations reported similar findings, with 52.1% of lesions identified preoperatively as low-grade diagnosed postoperatively as HSIL or more advanced lesions [12]. These findings imply that only about one-half of true high-grade cervical lesions can be formally demonstrated by biopsy prior to surgery, and that the clinical setting must be taken into account in order to identify all precancerous lesions,

including less obvious lesions. Consequently, in a suggestive clinical setting, a cervical biopsy should always be performed, and in case of discordance between its results and the colposcopic impression, “diagnostic” LLETZ could be an acceptable option.

“Diagnostic” LLETZ performed in an equivocal clinical setting may also be justified by the fact that, compared to LLETZ performed for biopsy-proven HSIL, specimen dimensions are not increased and excision margins are not more often positive. Although it could be suspected that, in order to be sure of obtaining a histological diagnosis, surgeons may tend to perform deeper resection, thereby resulting in larger specimen dimensions, this was not the case in our study, as no significant difference in cone volume was observed between LLETZ performed for biopsy-proven HSIL and LLETZ for non-biopsy-proven HSIL (mean volumes of 2.65 cm<sup>3</sup> versus 2.48 cm<sup>3</sup>, respectively,  $p=0.25$ ). The same applied to total specimen depth (11.7 mm versus 11.1 mm,  $p=0.25$ ). These observations are essential as these two parameters are directly linked to rates of adverse obstetrical outcomes, as shown recently by a large English case-control study, in which authors observed an increasing risk of adverse obstetrical outcomes with increasing excisional depth and volume, particularly greater than 15 mm or 2.66 cm<sup>3</sup> respectively, situations that were associated with a doubling of the risk of both preterm and very preterm births [8]. Below 10 mm or 1.77 cm<sup>3</sup>, risk of preterm birth was not significantly affected par LLETZ.

Regarding postoperative margins, it could be argued that a true HSIL that could not be proven by biopsy is a lesion buried deeper inside the endocervical canal, and therefore a lesion whose extremities are caused to be less likely, if not ever, visualized. When tumor margins cannot be defined on colposcopy, this could result in higher positive margin rates ratio conization, making LLETZ a less effective treatment option in these indications. However, we did not observe any intergroup difference in terms of positive margin rates in our study. This parameter must also be taken into account when considering “diagnostic” LLETZ, as its therapeutic impact is probably identical to that of “therapeutic” LLETZ for biopsy-proven HSIL, as, although controversial, some authors have reported that positive margin status could be a predictive risk factor of recurrence. For instance, according to the results of a large meta-analysis conducted by Ghaem-Maghani et al., the risk of post-treatment recurrence was approximately 5.5-fold higher among women with positive margins compared to women with negative margins

(RR=5.47 [95% CI =4.37-6.83]) [13]. It also seems that margins mostly responsible for recurrence are endocervical margins rather than ectocervical margins, which have been shown by several authors as having but a negligible impact on this risk [14, 15].

This study presents a number of limitations. Firstly, the retrospective design of this study may have impacted the results via a selection bias commonly associated with this type of study. However, this potential bias was markedly reduced by the fact that all LLETZ procedures performed during the study period were included in the analysis. Secondly, the surveillance period between the first abnormal Pap smear and the LLETZ procedure when surgery was performed due to a persistent abnormal cytology, although always longer than 18 months, was not systematically specified in the medical charts. This information could have supported our conclusions as, if surveillance periods were distinctly over 18 months, spontaneous regressions would have probably occurred during that time laps, leading to higher rates of negative LLETZ specimen on histological examination: this could therefore signify that the actual rate of HSIL in situations of persistent abnormal Pap smears is in fact higher than what we observed at 18 months. In any case, these limitations do not contradict the fact that our results strengthen the idea that “diagnostic” LLETZ, when specific indications are respected, should not be overlooked as a major part of our therapeutic arsenal.

The authors declare no conflict of interest concerning this article.

Table 1: Patients' characteristics according to the indication for large loop excision of the transformation zone (LLETZ) indication.

	Biopsy-proven HSIL group	Non-biopsy-proven HSIL group	p-value
n	283 (71%)	113 (29%)	
Age, mean (y) ( $\pm$ SD)	37.8 ( $\pm$ 8.96)	46.6 ( $\pm$ 11.6)	<b>&lt;0.001</b>
Parity ( $\pm$ SD)	1.68 ( $\pm$ 1.33)	1.88 ( $\pm$ 1.50)	0.21
Body mass index (kg/m <sup>2</sup> )	24.5 ( $\pm$ 5.06)	24.1 ( $\pm$ 5.80)	0.52
Active smoker, n (%)	132 (53%)	41 (47%)	0.39
Hormonal therapy, n (%)			<b>0.047</b>
- none			
- estrogen	96 (34%)	52 (46%)	
- progestogens only	60 (21%)	14 (12%)	
- pregnant	88 (31%)	34 (30%)	
- unknown	4 (1.4%) 35 (42%)	0 13 (12%)	
History of LLETZ, n (%)	19 (6.7%)	10 (8.8%)	0.46
Initial cytology, n (%)			<b>&lt;0.01</b>
- normal	13 (4.6%)	0	
- ASCUS	87 (31%)	39 (35%)	
- LSIL	73 (26%)	37 (33%)	
- HSIL	61 (22%)	16 (14%)	
- ASCH	37 (13%)	13 (12%)	
- AGC	1 (0.35%)	4 (3.5%)	
- unknown	11 (3.9%)	4 (3.5%)	
Positive oncogenic HPV DNA, n (%)	221 (78%)	77 (68%)	<b>0.038</b>
Complete visualization of the transformation zone, n (%)	160 (57%)	34 (30%)	<b>&lt;0.001</b>
Local anesthesia, n (%)	73 (26%)	30 (27%)	0.87
Loop diameter, mean (mm) ( $\pm$ SD)	17.6 ( $\pm$ 4.77)	17.2 ( $\pm$ 13.9)	0.75
Further resection, n (%)	53 (19%)	18 (16%)	0.51
Adjuvant therapies (destructive therapy/electrocauterization), n (%)	264 (93%)	105 (93%)	0.90
Total specimen depth, mean (mm) ( $\pm$ SD)	11.7 ( $\pm$ 5.58)	11.1 ( $\pm$ 3.85)	0.25
Total specimen volume, mean (cm <sup>3</sup> ) ( $\pm$ SD)	2.65 ( $\pm$ 1.47)	2.48 ( $\pm$ 1.34)	0.25

SD = standard deviation

Table 2: Final histological results according to the indication for large loop excision of the transformation zone (LLETZ)

	Biopsy-proven HSIL group	Non-biopsy-proven HSIL group	p-value
High-grade, n (%)	221 (78%)	50 (44%)	<b>&lt;0.001</b>
Low-grade, n (%)	18 (6.4%)	27 (24%)	
Normal, n (%)	16 (5.7%)	32 (28%)	
Cancer (type), n (%):			
- infiltrative adenocarcinoma	1 (0.35%)	0	
- in situ adenocarcinoma	12 (4.2%)	2 (1.8%)	
- invasive squamous cell carcinoma	15 (5.3%)	2 (1.8%)	
Negative margins, n (%)	246 (87%)	91 (81%)	0.11

Figure 1: Flow chart

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