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Original Article

A randomized trial comparing limited-excision conisation to Large Loop Excision of the Transformation Zone (LLETZ) in cervical dysplasia patients

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ABSTRACT

Objective: To show noninferiority of a limited-excision (resection of the dysplastic lesion only) vs. classical Large Loop Excision of the Transformation Zone (LLETZ).
Methods: In this prospective, randomized, multicenter trial, women with human papillomavirus (HPV) positive cervical intraepithelial neoplasia grade 3 were randomized into two groups (1:1). Primary outcome was the rate of negative HPV tests after 6 months, secondary outcomes included cone size, complete resection rates as well as cytological and histological results after 6 and 12 months. A sample size of 1,000 was calculated to show noninferiority of the limited-excision compared to the LLETZ group using a noninferiority margin of 5%. Enrollment was stopped after 100 patients due to slow accrual.
Results: Patients in the limited-excision group did not show a lower number of negative HPV tests (78% [LLETZ]–80% [limited-excision]=–2%; 90% confidence interval=–15%, 12%). The limited-excision resulted in a substantially lower cone size (LLETZ: 1.97 mL vs. limited-excision: 1.02 mL; p<0.001) but higher numbers of involved margins (LLETZ: 8% vs. limited-excision: 20%). Although postoperative cytological results slightly differed, histological results were similar in both groups. One limited-excision patient received immediate re-conisation, whereas one patient in each group was scheduled for re-conisation after 6 months.
Conclusion: The limited-excision could represent a promising option to reduce the surgical extent of conisations while maintaining oncological safety. The trial was not sufficiently powered to reach statistical significance due to early termination. Nevertheless, the study provides important insights in the feasibility of a limited-excision and could serve as a pilot study for future trials.

Trial Registration: German Clinical Trials Register Identifier: DRKS00006169

Keywords: Cervical Intraepithelial Neoplasia; Conisation; Premature Birth

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Conflict of Interest
The authors declare no financial support of this study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Sven Mahner is involved in research support, advisory board, honoraria and travel expenses from AstraZeneca, Colvis, Medac, MSD, PharmaMar, Roche, Sensor Kinesis, Tesaro and Teva.

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INTRODUCTION

Cervical cancer is the second most common malignancy in women. In 2012, 527,600 patients were diagnosed worldwide and 265,700 women died from this disease [1]. Cervical intraepithelial neoplasia (CIN) is the direct precursor lesion of squamous epithelial cervical cancer and is classified in high-grade (CIN 2–3) and low-grade (CIN 1) dysplastic lesions. Every year, over 1 million women receive the diagnosis of CIN 1 and half a million are diagnosed with high-grade dysplasia [2]. While the median age of patients with cervical cancer is 49, patients with CIN are typically 10–15 years younger and of childbearing age [3,4]. According to international guidelines, non-pregnant women with the diagnosis of CIN 3 receive surgical treatment in terms of conisation [5]. In accordance with the definition of the Large Loop Excision of the Transformation Zone (LLETZ) operation, the transformation zone should be removed in addition to the dysplasia itself [6]. It is well known that the size of the removed cone directly correlates with the risk for preterm delivery [7-10]. Therefore, a reduction in cone size could potentially be of benefit for patients who still wish to conceive. In addition, a limited-excision could also be of advantage for other patient groups, e.g., women using therapeutic anticoagulation who would profit from a limited surgical wound. Nowadays, many surgeons already tend to reduce the size of the removed cone. However, it is unknown if a reduction in radicality results in oncologically equally safe outcomes. Strander et al. [11] for example observed that the risk for the development of cervical cancer in patients who were treated for cervical dysplasia increased progressively between 1958 and 2008. According to the authors this might be attributed to a reduction of the surgical extent over time.

In awareness of the need to remove as little tissue as possible to minimize surgery-associated risks but at the same time to maintain comparable oncological safety, we designed this trial to analyze whether a limited-excision approach is non-inferior in terms of postoperative negative human papillomavirus (HPV) rates compared to a classical LLETZ operation.

MATERIALS AND METHODS

The Evaluation of Clinical Outcome after Reduction of Conisation Size (ECO-ROCS) trial was a multicenter, prospective, noninferiority, randomized controlled trial. This study investigated whether the removal of the colposcopically visible lesion only is noninferior in terms of oncological safety compared to the classical LLETZ operation, in which the lesion including the transformation zone is removed. Sample size was calculated using the POWER procedure for noninferiority test in SAS 9.3 software (SAS Institute, Cary, NC, USA) with the parameters α=0.05, power=80% for a one-sided test and a noninferiority margin of 5% for the HPV negativity rate difference (LLETZ–limited-excision). A rate of 90% negative HPV tests was assumed as the expected postoperative HPV rate for LLETZ conisations 6 months postoperatively [12]. A 10% drop-out rate was added to the calculated sample size of 892 patients, whereby a total patient number of 1,000 patients was determined for the study.

Trial protocol and informed consent documents have been approved by the University of Munich Institutional Review Board (project number 275-14, 10.07.2014) as well as the local ethics committees and/or state chambers of physicians of all other participating study centers.

Overall, 14 German study centers, all of which run a specialized dysplasia clinic, agreed to include patients for this trial. The participating study centers and investigators are listed in

the German Clinical Trials Register (DRKS00006169). All participants completed written informed consent forms prior to participation in the trial.

Inclusion and exclusion criteria are depicted in **Table 1**. Patients were randomized 1:1 using a web-based randomization technique called "Randoulette," designed by the Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Germany [13]. Only the randomizing surgeons and the web-administrator were eligible to access the system. Randomization was performed using an unblended, stratified block randomization.

After randomization, the respective surgical method was carried out under colposcopic control using a thin, low-voltage, electrified wire loop known as a loop electrosurgical excision procedure electrode. In the LLETZ group, the lesion was removed in addition to the transformation zone. To define the extent of the transformation zone, an area of at least 4 mm surrounding the squamocolumnar junction was used. If the extent of the lesion was larger or colposcopic findings suggested a greater transformation zone, the resected area was adapted respectively. In case of limited-excision, only the colposcopically visible CIN-lesion was removed with a resection margin of 2 mm. An endocervical extent of 6–8 mm was aimed for regardless of the allocated surgical method. No additional endocervical cone was removed. **Fig. 1** shows a graphic illustration of both techniques. For further information and examples on both methods please refer to the published study protocol [14]. Cone volume was determined immediately after the operation in both groups using the principle of Archimedes [15]. The removed specimen was placed in a 15 mL tube filled with a pre-specified amount of sterile sodium chloride. An increase of saline volume measured in mL was interpreted as the volume of conisation specimen [15]. Post-operative histological analyses were performed at the local institutes of pathology by blinded pathologists and specimens were evaluated according to national guidelines. In addition to the grade and extent of dysplasia, surgical margins were assessed for the detection of dysplastic cells.

Primary endpoint of the study was the rate of negative HPV tests 6 months postoperatively since a negative postoperative HPV test is considered to be the test of cure [16]. Only HPV test kits that fulfilled the published criteria of Meijer et al. [17] were allowed for use in this study. Secondary endpoints were cone size, complete resection rate, cytological and histological results after 6 and 12 months as well as an additional HPV test 12 months after the operation. At follow-up visits, colposcopy, HPV tests, and Pap smears were collected. Biopsies were taken only in case of suspicious colposcopic findings and only the suspicious lesion itself was biopsied, i.e., 4-quadrant biopsy or endocervical curettage was not mandatory. HPV, cytological and histological analyses were carried out locally in each participating department by blinded cytologists and histopathologists.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Biopsy proven CIN 3	Pregnancy at time of inclusion and up to 6 months after the surgery
Positive HPV high risk test	Immunosuppressive medication including glucocorticoids
Colposcopically visible lesion	Prior HPV vaccination
Age ≥18 years	Known malignancy
Premenopausal	Known HIV infection
Written informed consent	Prior treatment for CIN 3
	Prior cervical surgeries

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

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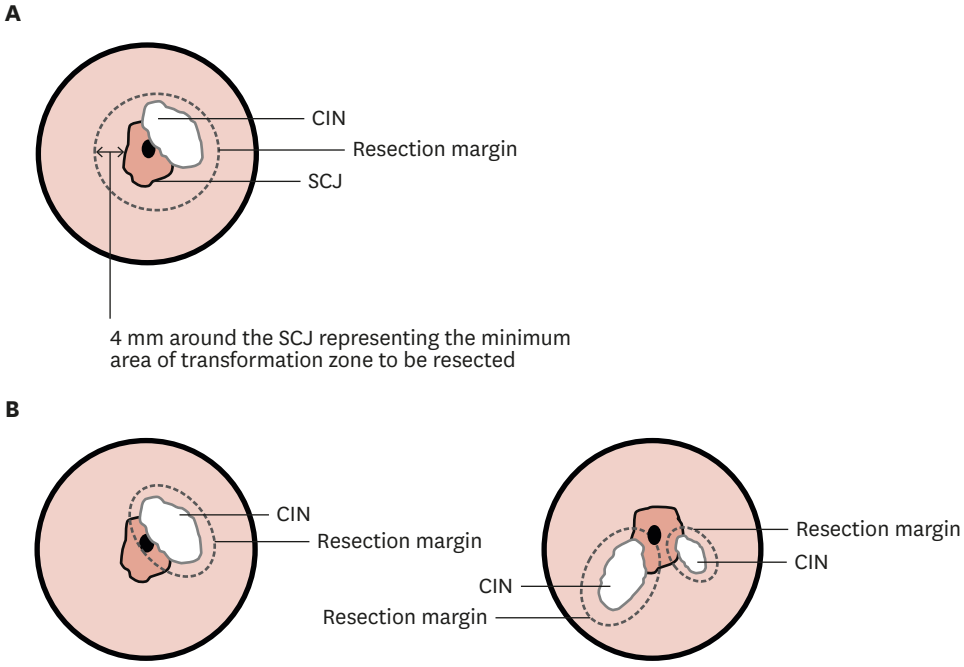

Fig. 1. (A) Graphic example of a LLETZ conisation using a minimum of 4 mm around the SCJ. (B) Graphic example of a limited-excision conisation using a distance of 2 mm around the lesion(s). Adapted from Schwarz et al. [14]. CIN, cervical intraepithelial neoplasia; LLETZ, Large Loop Excision of the Transformation Zone; SCJ, squamocolumnar junction.

1. Statistical analysis

To assess if the HPV rate of the limited-excision group was noninferior to the LLETZ group after 6 months, the difference (LLETZ–limited-excision) of the observed HPV negative rates as well as a corresponding 90% confidence interval (CI) using Newcombe (hybrid) Score were calculated. Noninferiority was established if the upper limit of the 90% CI of the rate difference was below the pre-specified noninferiority margin of 5%. Effects of secondary nominal endpoints were described using rates and rate differences with corresponding 90% CI using Newcombe (hybrid) Score method. The difference in cone size was described using mean and was analyzed using the nonparametric Wilcoxon-Mann-Whitney U test. The error level for both tests was set at α=0.05. All analyses were carried out using the SAS 9.4 (SAS Institute).

RESULTS

1. Peri-operative

In total 100 patients (n=50 per group) recruited in four study centers were included between September 2014 and December 2016. After this period, the trial was terminated due to slow recruitment.

Median age of patients in the LLETZ group was 31.6 years (range, 23.8–47.3) and 31.0 (range, 23.9–43.4) in the limited-excision group.

Mean cone size in patients with LLETZ was almost double the volume of the size in patients, who received the limited-excision method (limited-excision: 1.02 mL [median: 0.6 mL] vs. LLETZ: 1.97 mL [median: 2.0 mL]; p<0.001).

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Table 2. Peri-operative patient characteristics

Characteristics	LLETZ (n=50)	Limited-excision (n=50)
Median age (yr)	31.6	31.0
HPV high risk		
Negative	0 (0)	0 (0)
Positive	50 (100)	50 (100)
HPV 16+	22 (44)	14 (28)
HPV 18+	1 (2)	2 (4)
Pap smear		
Negative*	0 (0)	1 (2)
Suspicious	50 (100)	49 (98)
Histology		
Clear margins	46 (92)	40 (80)
Involved margins	4 (8)	10 (20)
Mean cone size (mL; n=49)	1.97	1.02†
No. of re-conisations	0	1

Values are presented as number (%).
HPV, human papillomavirus; LLETZ, Large Loop Excision of the Transformation Zone; NILM, negative for intraepithelial lesion or malignancy.
*Only NILM Pap smears are categorized as negative; †p<0.001.

LLETZ operation yielded 92% clear margins (46/50) compared to 80% of patients (40/50) in the limited-excision group (difference=12%; 90% CI=0%–24%). The patients of 3 (LLETZ) vs. 9 (limited-excision) showed high-grade dysplasia (CIN 2 or CIN 3) either at the endo- or ectocervical border. The option of immediate re-conisation was discussed with all patients and one woman in the limited-excision group decided to undergo surgery. Peri-operative results are summarized in **Table 2**.

2. Post-operative (6 months)

Patients were scheduled for follow-up visits 6 and 12 months after the operation. All follow-up results after 6 months are summarized in **Table 3**. Detailed cytological and histological results can be found in **Supplementary Tables 1** and **2**.

Eighty percent (40/50 patients) in the limited-excision group compared to 78% (39/50) in the LLETZ group were HPV high risk negative 6 months postoperatively (difference=−2%; 90% CI=−15%, 12%).

Table 3. Post-operative (6 months) patient characteristics

Characteristics	LLETZ (n=50)	Limited-excision (n=50)	Difference (90% CI)
HPV high risk		(n=49)	−2% (−15%, 12%)
Negative	39 (78)	39 (80)	
Positive	11 (22)	10 (20)	
HPV 16+	6 (12)	4 (8)	
HPV 18+	1 (2)	0 (0)	
Pap smear			8% (−7%, 23%)
Negative*	35 (70)	31 (62)	
Suspicious	15 (30)	19 (38)	
Histology			−2% (−13%, 9%)
Normal	43 (86)	44 (88)	
Dysplastic†	7 (14)	6 (12)	
No. of re-conisations	1	1	-

Values are presented as number (%).
CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; LLETZ, Large Loop Excision of the Transformation Zone; NILM, negative for intraepithelial lesion or malignancy.
*Only NILM Pap smears are categorized as negative; †Dysplastic histology includes CIN 1–3 lesions. Patients on whom no biopsies had been performed due to unsuspicious colposcopy as well as patients with benign pathologic reports are summarized under the histological category "normal."

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Table 4. Post-operative (12 months) patient characteristics

Characteristics	LLETZ (n=42)	Limited-excision (n=38)	Difference (90% CI)
HPV high risk			−4% (−15%, 8%)
Negative	37 (88)	35 (92)	
Positive	5 (12)	3 (8)	
HPV 16+	4 (11)	4 (11)	
HPV 18+	0 (0)	1 (3)	
Pap smear	(n=41)		−16% (−30%, −2%)
Negative*	30 (73)	34 (89)	
Suspicious	11 (27)	4 (11)	
Histology			N/A
Normal	39 (93)	38 (100)	
Dysplastic†	3 (7)	0 (0)	
No. of re-conisations	0	0	-

Values are presented as number (%).
CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; LLETZ, Large Loop Excision of the Transformation Zone; N/A, non-applicable; NILM, negative for intraepithelial lesion or malignancy.
*Only NILM Pap smears are categorized as negative; †Dysplastic histology includes CIN 1–3 lesions. Patients on whom no biopsies had been performed due to unsuspicious colposcopy as well as patients with benign pathologic reports are summarized under the histological category "normal."

Four patients in the limited-excision group and 6 patients in the LLETZ group were persistently HPV 16 positive, whereas no patient in the limited-excision group and only 1 patient in the LLETZ group was persistently HPV 18 positive. With regards to secondary endpoints, cytological results differed slightly in both groups. Seventy percent (35/50 LLETZ patients) vs. 62% (31/50 limited-excision patients) showed a negative for intraepithelial lesion or malignancy (NILM) smear, 30% (15/50 LLETZ patients) vs. 38% (19/50 limited-excision patients) were diagnosed with a suspicious smear (difference=8%; 90% CI=−7%, 23%).

The higher number of suspicious Pap smear results did not translate into a higher amount of biopsy-proven high grade dysplastic lesions: Histological results after 6 months were similar in both groups (88% limited-excision vs. 86% LLETZ patients showed no dysplastic lesions; difference=−2%; 90% CI=−13%, 9%). One patient in each group was diagnosed with CIN 3 and scheduled for re-conisation.

3. Post-operative (12 months)

Twelve months postoperatively 88% (37/42, LLETZ) compared to 92% (35/38, limited-excision) of patients showed negative HPV high risk test results (difference=−4%; 90% CI=−15%, 8%). Seventy-three percent (30/41, LLETZ) vs. 89% (34/38, limited-excision) had a Pap smear result without evidence of dysplasia (difference=−16%; 90% CI=−30%, −17%). Two CIN 1 and one CIN 2 were diagnosed in the LLETZ group, whereas there was no dysplasia histologically detected in the limited-excision conisation group. No patient was scheduled for re-conisation. All follow-up results after twelve months are summarized in **Table 4**.

DISCUSSION

This is the first prospective, randomized trial comparing a limited-excision approach with classical LLETZ in terms of oncological safety.

Primary goal of the study was to investigate if the upper limit of the 90% CI (difference of negative HPV tests LLETZ−limited-excision after 6 months) was below the pre-specified 5% noninferiority margin. HPV status was taken as a surrogate parameter to assess oncological

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safety, since a negative HPV test is generally accepted as test of cure [16]. This is due to the fact, that the negative predictive value for a negative HPV test after conisation is between 92% and 100% [18-22]. However, no long-term follow-up was assessed which would be necessary to ultimately rule out increased cervical cancer rates after years.

Surprisingly in this study, the limited-excision group tended to perform better compared to the LLETZ group in terms of HPV negativity 6 months after the operation (difference negative HPV tests LLETZ–limited-excision=–2%; 90% CI=–15%–12%). This trend even increased after 12 months (difference=–4%; 90% CI=–15%, 8%). Noninferiority margin was pre-defined to be 5% after 6 months according to clinical considerations. Therefore, noninferiority was not established (upper CI limit: 12%) which is likely due to early termination and resulting limited sample size. Nevertheless, despite the fact that only 10% of the initially planned patient number was included, the results indicate that patients in the limited-excision group show only at maximum 12% (after 6 months), respectively 8% (after 12 months) lower HPV negative rates compared to the LLETZ group. Depending on the individual patient, this risk might be acceptable, e.g., for patients of childbearing age or with certain comorbidities that require a surgical wound as small as possible. HPV types 16 and 18 are known to cause 70% of cervical cancers [23]. We therefore analyzed these HPV types in both patient groups. While patients in the LLETZ group showed a higher pre-operative percentage of HPV 16 positivity (LLETZ: 44% vs. limited-excision: 28%) the ratio of patients who turned negative in the first post-operative control after 6 months was similar (LLETZ: 3.7 vs. limited-excision: 3.5). Numbers of HPV 18 positive patients (pre-operative: LLETZ 2% vs. limited-excision 4%, post-operative LLETZ: 2% vs. limited-excision: 0%) are very limited but neither point to an increased risk of HPV 18 persistence in the limited-excision group. However, these results could have been influenced by post-operative HPV vaccination which has not been monitored.

Secondary endpoints in this study were cone sizes and complete resection rates as well as cytological and histological follow-up results after 6 and 12 months.

Mean cone size in the limited-excision group was almost half of the volume compared to the LLETZ group (LLETZ: 1.97 mL vs. limited-excision: 1.02 mL; $p<0.001$). The reduction in cone size is particularly important with regards to obstetrical complications since it has been shown that larger cone sizes correlate with an increased risk of pre-term delivery [7-10]. Nevertheless, it needs to be mentioned as a limitation that the amount of fulguration which has not been monitored in this study, could also contribute to the extent of damaged cervical tissue.

The number of involved margins was 2.5 times higher in the limited-excision vs. the LLETZ group (4/50 vs. 10/50) which reflects the difficulty of a limited-excision approach. Given that in this study all surgeries were performed by surgeons experienced in the field of colposcopy-guided conisations, general implementation of the limited-excision approach could have an impact particularly on cone sizes and complete resection rates.

Interestingly, the finding of increased involved margins in the limited-excision group did not translate into higher numbers of histologically confirmed high-grade dysplasias during follow-up (6 months, LLETZ: 14% vs. limited-excision: 12%; 12 months, LLETZ: 7% vs. limited-excision: 0%). Only cytological results at the 6 months-visit showed higher numbers of suspicious smears in the limited-excision group (LLETZ: 30% vs. limited-excision: 38%). However, the discrepancy between cytological and histological findings is in line with published literature that also shows a tendency for cytological overcall of results [24].

In conclusion, our results point into the direction that a limited-excision approach could represent a safe alternative for patients with high-grade dysplasia. However, due to early termination the trial was not sufficiently powered to establish statistical significance. Additionally, it needs to be mentioned that the limited-excision approach goes along with certain limitations. To enable a targeted excision of the lesion, the whole lesion needs to be colposcopically accessible. Especially with older patients who are more likely to have a T3 type transformation zone, these criteria could be difficult to apply. Although there was no age limitation in our study, the number of patients older than 40 was still limited (n=5) and therefore did not allow for evaluation of outcome specifically in this patient population. Therefore, despite promising initial results, further studies with higher patient numbers are needed to confirm oncological safety of a limited-excision approach and should also investigate the impact on various risks like post-operative bleeding, scarring or obstetrical outcome.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Pap smear results 6 and 12 months after the operation

Click here to view

Supplementary Table 2

Histology results 6 and 12 months after the operation

Click here to view

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