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GYNECOLOGIC ONCOLOGY

A multicentric randomized study comparing two techniques of magnification assisted loop excision of high-grade cervical intraepithelial neoplasia: video exoscopy and colposcopy

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Abstract
Purpose To compare loop excisions of cervical intraepithelial neoplasia grade 2 or worse (CIN 2+) under video exoscopy, or colposcopic guidance, with respect to safety and effectiveness.
Methods Prospective multicentric randomized trial of 300 patients, undergoing loop excision for CIN 2+ either under video exoscopy (group A) or colposcope (group B) guidance. Intra- and post-operative complications, resection margins, and removed cervical volume in both groups were evaluated.
Results 19.3 % of patients in video exoscopy group and 15.5 % in colposcopy group ($p = 0.67$) had transformation zone (TZ) 3. 45/151 (29.8 %) of group A patients and 48/149 (32.2 %) of group B patients underwent top-hat procedure, i.e., one superficial excision followed by one deeper removal of the endocervical tissue ($p = 0.74$). There was no difference in intra- and post-operative complications in the two groups. Positive endocervical resection margins (R0) were 9.9 % in video exoscopy group and 8.7 % in colposcopy group, respectively. Unclear endocervical resection margins (Rx) were 2.0 % in both groups. Mean total excised cervical volume was 1.20 cubic centimeter (cc^3) in group A, and 1.24 cc^3 in group B, respectively. Recurrent disease occurred in 2.3 % of patients at 6 months follow-up.
Conclusion Magnification assisted loop excision of CIN 2+ is equally effective and safe under colposcopic and video exoscopy guidance. The latter technique could potentially offer an alternative treatment of CIN 2+ lesions for doctors unfamiliar with colposcope

Keywords Colposcopy · Exoscopy · LEEP · Volume removed · Safety

All authors have contributed to the manuscript.

We dedicate this article to Anneliese Jähn 1932–2012 who dedicated her professional career to the prevention of cervical cancer at Charité University Medicine, Berlin, Germany.

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Introduction

Introduced in the late 80' loop excision under colposcopic guidance rapidly became the most popular therapy of cervical intraepithelial lesion grade 2 or worse (CIN 2+), due to its simplicity, cheapness, high success rate, and not life threatening nature of CIN 2+ [1–4].

Office-based see and treat strategies became popular: results were excellent, both for patients and health care givers, the main goal being the removal of CIN 2+ [5].

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The increasing age at childbearing in western societies, and the growing evidence of iatrogenic obstetric morbidity following loop excisions highlight the recent need to combine successful removal of CIN 2+ with minimal excision of healthy tissue [6–9]. Whereas visual inspection with acetic acid (VIA) is an effective method to handle CIN 2+ in low-resource areas, its use should be discouraged in more developed regions [10, 11]. In Germany, birthplace of colposcopy, despite European guidelines, cold knife conisation without magnification still accounts for 29 % of all treatment for CIN 2+, resulting in higher rates of margin positivity and excessive removal of healthy tissue; likewise, relative large series of cold knife conisation have been recently reported [12–15]. Recently introduced video exoscopic systems, can be considered as an alternative to colposcopy for doctors still performing bare eye excisions of CIN 2+ [16].

Aim of this prospective multicentric randomized study is to verify the effectiveness and safety of loop excision of CIN 2+ using a video assisted exoscopy system as a possible alternative to colposcope guidance.

Materials and methods

Between August 2011 and September 2012, women referred to the colposcopy and lower genital tract disease centre of the Charité University, Berlin, Campus Benjamin Franklin, Campus Charité Mitte, and the Colposcopy Clinic Wagner Stibbe, Bad Muender, Germany, were screened for participation in the study. All women aged 18–80 years old, referred to the three colposcopic centres with either histologically confirmed CIN 2+, or CIN 1 persistent >1 year, endocervical curettage (ECC) specimen positive for CIN, or a 2-grade discrepancy between Papanicolaou smear and cervical biopsy specimen, regardless of history of previous surgery of the cervix or pregnancy, were considered candidates for the trial. Exclusion criteria were previous or current neoplasia, radiotherapy of the pelvis, severe internistic concomitant diseases, psychiatric diseases, HIV-infection, drug consumption, active cervical inflammation or infection. Before eligible patients were randomized they were informed about the experimental study design and gave written consent at the time of the first visit. The three centres implemented a common prospective study protocol, which was approved by the Institutional Review Board of Charité University. The NIH registration number of this study is: NCT01601769. Before surgery all patients underwent biopsy. Follow-up visits, including PAP test and colposcopy, were scheduled quarterly; HPV typing was routinely done during the first visit, 3 months after surgery.

Post-operative haemorrhage was defined as the need for medical treatment after discharge, and cervical stenosis as the inability to insert a cotton Q-tip into the cervical os.

Each centre prospectively recruited 100 patients who were randomized to receive loop excision of CIN 2+, either under video exoscopy guidance (group A) or colposcopic assistance (group B). The computer-generated, simple randomization code was held in sealed grey envelope opened by the theatre nurse prior to surgery, in order to prepare either the exoscope or the colposcope.

Magnification was provided during all procedures either by colposcope or video exoscopy. We used a Carl Zeiss colposcope with a focal length of 25 cm, with a magnification power from 4× to 22×, and green filter, and a video exoscope based system, which has shown to be accurate for the diagnosis of CIN 2+ for video exocolposcopy [16, 17]. It consists of the VITOM® scope, xenon light source, HD camera system, AIDA HD documentation system, one monitor, and a mechanical support arm (Karl Storz, Germany). The 3-chip HD camera head provides a resolution of 1,920 × 1,080 pixels (full HD, progressive scan) with a frame rate of 50 frames oz. The output of the camera system is displayed on a 26-inch HD monitor. Luminance of the monitor is 400 cd/m^2. The optic is held by a mechanical holding arm. Documentation was made with the AIDA HD documentation system.

A Graves speculum with suction tube attached was inserted to expose vagina and cervix and was used for all operations. The cervix was evaluated natively, after application of 5 % acetic acid, and after 3 % iodine solution. The working distance of the colposcope is about 30 cm from the surgical site, while the operating range of the video exoscope varies from 30 to 60 cm. Colposcopic and video colposcopic findings and transformation zone (TZ) type were reported according to the criteria of the Committee on Nomenclature of the IFCPC [18].

In the majority of patients a paracervical block and cervical infiltration using 10 to 20 ml Lidocainhydrochlorid 1 % H_2O was performed by 10 physicians trained in colposcopic guided loop excisions, and mixed ability in laparoscopic surgery. General anaesthesia was used in patients when additional procedure was contemplated, i.e., laparoscopy, or if the patients were too anxious, or explicitly declined to be awake during the procedure.

An electrosurgical generator (Erbe, Tuttlingen, Germany) with the cut frequency set a max 180 W., effect 2–4, and the spray coagulation frequency set at 80 W., effect 2, was used. Cutting loops ranged from 5 to 25 mm in diameter. In a TZ1 only a superficial excision was performed. In TZ3 and sometimes in TZ2 a top-hat procedure, consisting of a conventional superficial loop excision, and a subsequent second deeper removal of the endocervical tissue using a smaller, i.e., 5 mm, diameter loop was

Table 1 Demographic characteristics of patients

	VITOM ($n = 151$)	Colposcopy ($n = 149$)	p value
Age	33 (r:22–83)	31 (r:22–74)	0.13
Menopause	16 (10.5 %)	10 (6.7 %)	0.32
Pregnant	7 (4.6 %)	5 (3.4 %)	0.07
Previous loop excision	3 (1.9 %)	6 (4 %)	0.48
TZ			0.67
TZ 1	41 (27.1 %)	44 (29.5 %)	–
TZ2	81 (53.6 %)	82 (55 %)	–
TZ3	29 (19.3 %)	23 (15.5 %)	–
Previous pregnancy	58 (38.4 %)	62 (41.6 %)	0.65
HPV test	130	128	–
High risk HPV	119/130 (91.5 %)	118/128 (92.1 %)	0.80
One pass	106 (70.2 %)	101 (67.8 %)	0.74
Top-hat procedure	45 (29.8 %)	48 (32.2 %)	–
Histology (adeno/squamous)	7/144 (4.8 %)	5/144 (3.4 %)	0.78
Seeking parenthood	67/135 (49.6 %)	75/139 (53.9 %)	0.55
Pregnancy after loop excision	7/67 (10.4 %)	5/75 (6.6 %)	0.61

performed followed by ECC [19, 20]. A ball electrode using pure coagulation frequency was used at the end of the procedure to superficially coagulate the bleeding areas or oozing of the external margins, avoiding as much as possible the 2–3 mm zone around the new os [21]. The measurement of the removed cervical volume was done by the surgeon, in the operating theatre, using the Archimedes principle. All cervical specimens were placed immediately after the loop excision in measuring cylinders, containing sterile saline solution, of different volume ranging from 10 ml to 5 ml, and to 2 ml, with graduation interval from 1 ml to 0.1 ml, according to the volume and shape of the excided cervical tissue. The rise of the saline solution column, after placing the specimen on the bottom of the cylinder, was considered to be equivalent to the volume of the excised cervical tissue, expressed in cubic centimetres (cc^3) [22]. Thereafter the specimens were marked by 12 h, on a cork tray, put in formalin and sent to the pathologists.

Statistics

The categorical variables were analyzed using the Chi-squared test. The numerical variables were analyzed using Student's t test and Mann–Whitney U test. Spearman correlation and regression models were done to examine the association between total removed volume, technique of magnification and clinical variables. All statistical analyses were conducted using Medcalc (MedCalc Software, Mariakerke, Belgium), and p values of <0.05 were considered statistically significant. At present there is no reliable data for calculating the sample size of the proposed trial. This study is powered to detect a 0.25 cc^3 of volume difference between the groups. We based our sample size calculations to test hypothesis 1. A sample size of 126 patients in each group is required to achieve 80 % power at an alpha level of 0.05 for student t test. We assumed that the distribution of data may not be normal; Mann–Whitney U test may be used to compare groups and reduce the influence of outliers. Therefore the sample size (126) was divided by the asymptotic relative efficiency value of 0.864 to overcome any type of distribution and a final sample size of 145 patients per group was calculated.

Table 2 Endocervical resection margins

	VITOM	Colposcopy	p value
R1 resection	15/151 (9.9 %)	13/149 (8.7 %)	0.93
R1 in one pass	8/106 (7.5 %)	9/101 (8.9 %)	0.80
R1 in top-hat procedure	7/45 (15.5 %)	4/48 (8.3 %)	0.43
Rx resection	3 (2 %)	3 (2 %)	0.93
Complication	3 post-operative hemorrhage	1 intraoperative and 6 post-operative hemorrhage	0.15

Results

300 patients were included in the study and were randomized to either video exoscopy assisted loop excision, (group A, 151 patients), or traditional colposcopic guided loop excision (group B, 149 patients). Mean age, demographic characteristics, kind of loop excision, TZ, histology, HPV status, are shown in Table 1.

Menopause and TZ3 were slightly more frequent in video exoscopy group (Table 1). TZ3 was more common in women >35 years old (27 vs. 10 %) ($p = 0.0001$).

The complication rate was similar in both groups ($p = 0.15$). Intraoperatively overall 1 out of 300 patients, in the colposcopy group, had a conspicuous bleeding (50 ml). Postoperatively three patients in video exoscopy group and six patients in colposcopy group, respectively, had a hemorrhage. No patient required neither hospitalization, nor transfusion (Table 2). At 3 and 6 month follow-up no patient developed dysmenorrhea, or cervical stenosis or had hematometra.

28 out of 300 patients (9.3 %) had positive endocervical resection margins (R1), 15 (9.9 %) in video exoscopy group and 13 (8.7 %) in colposcopy group ($p = 0.93$). R1

positivity after 1 pass was 8.7 % (17/207), 7.5 % in video exoscopy group (8/106) and 8.9 % in colposcopy group (9/101), respectively ($p = 0.80$). R1 positivity after top-hat procedure was 11.9 % (11/93), 15.5 % in video exoscopy group (7/45) and 8.3 % in colposcopy group (4/48), respectively, ($p = 0.50$) (Table 2). 8/11 patients with top-hat procedure, 5 in video exoscopy group and 3 in colposcopy group, had CIN 2+ in both loop fractions, i.e., external and internal excised cervical tissue. 3/11 patients, 2 patients in group A and 1 in group B, had CIN 2+ only in the internal loop excision, i.e., the second pass of the top-hat procedure.

Three patients (2 %) per group, ($p = 0.93$) had Rx resection, i.e., thermal alterations, which hampered the pathological evaluation of the endocervical margins ($p = 0.93$) (Table 2).

Pathological results of ECC were similar in both groups: ECC had no relation to magnification method and volume removed.

In the multivariate regression analysis, comprising magnification method, TZ, histological diagnosis, HPV risk, TZ3 was the only statistical significant factor, for both groups, to predict R1 ($p = 0.01$): odds ratio (OR) was 2.2 (CI 1.1–4.3).

First pass mean removed cervical volume was 1.08 cc^3 (95 % CI 0.96–1.20) in video exoscopy group, and 1.12 cc^3 (95 % CI 0.99–1.26) in colposcopy group ($p = 0.60$), respectively; second pass mean removed volume was 0.41 cc^3 (95 % CI 0.31–0.50) in video exoscopy group and 0.35 cc^3 (95 % CI 0.28–0.41) in colposcopy group ($p = 0.30$), respectively. The total removed cervical volume was similar in both groups (Table 3) (Fig. 1). All patients with TZ3 had top-hat procedure, consequently the total removed cervical volume correlated with TZ3 and increased in women >35 years old (1.5 cc^3) compared to women <25 (0.8 cc^3) and 25–35 years old (1 cc^3) ($p < 0.001$). Histological type of lesion and presence of high risk HPV did not correlate with the removed volume in both groups ($p = 0.78$ and $p = 0.80$).

10 out of 300 patients (3.3 %) were lost at 6 month post-operative follow-up. 19/290 patients underwent magnification guided biopsy or loop excision: three patients had CIN 2+/AIS, and five normal results in video exoscopy group; two patients had CIN 1, four CIN 2+ and five normal results in the colposcopy group, respectively ($p = 0.39$) (Table 4).

Table 3 Removed cervical volume

	VITOM (cc^3)	Colposcopy (cc^3)	p value
Volume (first pass)	1.08 95 % CI 0.96–1.20	1.12 95 % CI 0.99–1.26	0.60
Volume (second pass)	0.41 95 % CI 0.31–0.50	0.35 95 % CI 0.28–0.41	0.30
Mean removed total volume	1.20 95 % CI 1. 07–1.33	1.24 95 % CI 1.10–1.37	0.69

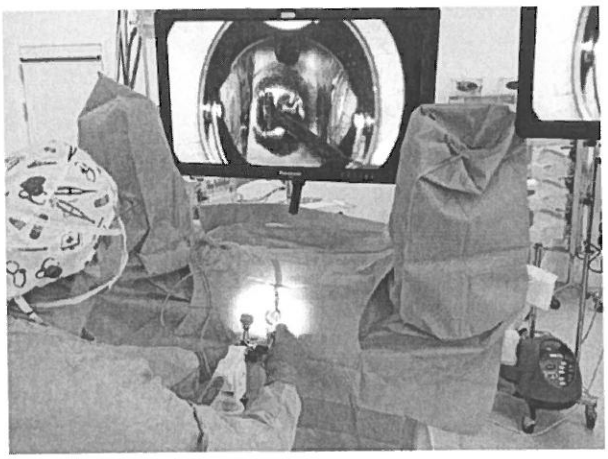

Fig. 1 VITOM guided loop excision in progress. The surgeon controls action on a video monitor. The VITOM exoscope with HD camera is mounted on a mobile support

Discussion

The findings in this study suggest that treatment of CIN 2+ can be equally safe and effective achieved by video exoscopy directed and colposcopic assisted loop excision of the TZ with respect to intra and post-operative complications, positive endocervical resection margins and excised cervical volume.

The two groups were homogeneous in terms of baseline characteristics (Table 1); likewise we had previously described the diagnostic comparability of colposcopy and video exoscopy system [16, 17]. No difference was observed in the two groups as for intraoperative and post-operative hemorrhage, (Table 2): globally 3.3 % of the patients experienced bleeding, consistent with other series [23, 24].

Though the study population is limited, no patient developed other post-operative problems, such as cervical stenosis, dysmenorrhoe and hematometra, possibly due to the cautious use of coagulation of the crater, around the new os, at the end of the operation and to the limited excised volume [21, 25].

Recurrence of disease is more common in R1 endocervical resections, and positive exocervical margins can be

Table 4 Histologic results of biopsy before loop, of loop excision, and patients' follow-up data

	VITOM				Colposcopy				p value
	Normal	CIN-1	CIN2-3/AIS	Carcinoma	Normal	CIN-1	CIN2-3/AIS	Carcinoma	
Biopsy before loop ($n = 298$)	2 %	16.6 %	81.45 %	–	2.7 %	13.5 %	83.8 %	–	0.49
Loop ($n = 300$)	1.3 %	3.3 %	94.1 %	1.3 %	6 %	2.6 %	88.1 %	3.3 %	0.16
Biopsy after loop ($n = 19$)	5/8	–	3/8	–	5/11	2/11	4/11	–	0.39

easily colposcopically evaluated at follow-up, hence we consider only patients with positive endocervical resection margins, as well patients with unclear endocervical resection margins (Rx), to be R1 [26, 27]. Patients with R0 resection and positive ECC were considered to have multifocal disease.

R1 rate was similar in both groups ($p = 0.93$). 34/300 (11.3 %) of patients had not in R0 resection, of whom 28 had R1 and 6 Rx status, respectively, matching with the quality standards of the European Federation of Colposcopy [28]. 3/93 patients (3.2 %) with top-hat procedure had exclusively R1 of the volume removed in the second pass, which would have gone undetected and classified as R0 with just one pass, at the expenses of a mean 0.4 cc^3 additional removed cervical volume. Mossa et al. [29] reported similar figures and puzzled the role of top-hat; yet we believe that in TZ3 the use of top-hat resection with a 5 mm loop, can limit the volume of the excised tissue with a single larger loop. Clearly patients with TZ3 do not profit from colposcopic assistance and TZ3 was the only factor to predict R1. However at 6 month follow-up recurrent disease (CIN 2+) was observed in just seven patients (2.3 %), thus much lower that the initial R1 rate [27, 30].

Treatment's recommendation of CIN 2+ differ greatly among pathologists and gynecologists: the former suggest an average 4–5 mm depth of excision to eliminate 99.7 % of CIN 2+, i.e., a very superficial, whereas the latter consider an average lower limit of 9 mm in depth of excised volume to be adequate [31–34]. However none of the gross dimensions of excised volume correlates with the microscopic measurement of stromal depth [35]. In addition obstetrics, due to the increasing number of patients with CIN 2+ and delayed motherhood advocate the need to guarantee optimal CIN2+ treatment along with maximal containment of iatrogenic post-loop obstetrical morbidity [6–9, 33]. In this respect VIA should be discouraged outside developing countries [11].

In the literature volumes of excised tissue are extremely seldom measured, imprecisely defined, whereas up to 4 cc^3 are considered to be a small tissue removal [22, 36, 37], and usually a linear dimension describes a cubic structure [38].

We tailor the peripheral resection of the ectocervical margin of CIN 2+ and our mean excised cervical volume was 1.2 cc^3 in group A, and 1.24 cc^3 in group B, respectively ($p = 0.69$), thus very limited (Table 2) and similar to [33, 39].

This study has a number of flaws: first it adds no new piece of information for gynecologists used to colposcopic assisted loop excision of CIN 2+, the colposcope being an excellent tool in experienced hands. We have too few reports of subsequent pregnancies, which on purpose we omit citing, hence invalid obstetric follow-up, to support and not just assume that this kind of surgery is patient-friendly, combining good treatment of CIN 2+ with scanty obstetric morbidity. Eventually, video exoscopic systems are not yet as widely accessible as colposcope.

Strengths of this study are its prospective nature, and the randomization of the patients. In addition, the precise evaluation of the excised volume, can help estimate the PTD risk in future pregnancies. Finally laparoscopic systems and trained laparoscopic surgeons are generally easily available in the most developed countries.

The video exoscopy system is clearly not superior to the gold standard colposcopic guided loop excision; additionally it just gives a 2D image on a screen, whereas stereoscopic colposcopy allows a 3D impression of depth for easier performance of loop excisions, hence video exoscopy may not only be regarded as a redundant piece of equipment in the operating room, but doubts may arise about the sense to use it.

Indeed we do not suggest any change to the state of the art: gynecologists used to colposcope-guided loop excisional of CIN 2+ should stand to their habits and not abandon their expertise. However video exoscopy could offer an alternative treatment for gynecologists not so familiar with this kind of surgery and still performing bare eye excisions of CIN 2+. The majority of gynaecologists performs laparoscopic surgery, and is used to translating 2D data into 3D anatomical structures. Video exoscopy has a very short learning curve, its ergonomy is superior to classical colposcopy, resulting in increased working comfort, and the final subjective impression of the surgeon is eventually comparable to stereoscopic colposcopy.

Conflict of interest Achim Schneider acts as advisor for Karl Storz, GSK and Sanofi Pasteur. He received honoraria for lectures.

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