Arch Gynecol Obstet (2012) 286:1549–1554
DOI 10.1007/s00404-012-2493-1

GYNECOLOGIC ONCOLOGY

Assessment of cervical intraepithelial neoplasia (CIN) with colposcopic biopsy and efficacy of loop electrosurgical excision procedure (LEEP)

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Received: 29 April 2012 / Accepted: 19 July 2012 / Published online: 3 August 2012

Abstract
Purpose Conization for suspected high grade cervical intraepithelial neoplasia (CIN) is often performed based on abnormal cytology only. Loop electrosurgical excision procedure (LEEP) is a very common technique in this context. The present study analyses the accuracy of preoperative assessment of CIN with cytology plus colposcopic biopsy and assesses the efficacy of LEEP for the treatment of CIN.
Methods Two-hundred and sixty-six consecutive patients treated with LEEP for suspected CIN at our center were retrospectively analyzed. Cytology, HPV-DNA testing, colposcopically directed cervical biopsy and/or endocervical curettage were performed to assess cervical lesions before and 3–6 months after surgery.
Results Median age of the patients was 34 years. Median follow-up was 50 months. Preoperative HPV testing was positive for high risk types in 77.9 %. All patients underwent LEEP without further ablative procedures. Complete excision of the lesion could be achieved in 84.3 %; in 13.5 % margins were not securely cleared and in 2.2 % the lesion was not excised entirely. Overall complication rate was 5.4 % (mainly postoperative bleeding and pain). Overall concordance of colposcopic biopsy and cone histology was 85.8 %. The concordance rate was higher for CIN 2/3 (95.1 %) compared with CIN 1 (63.2 %). Nine patients (3.4 %) had persistent disease after 3 months, 4 (1.5 %) developed disease recurrence and underwent reconization. HPV testing at 3–6 months after surgery was negative in 78.5 %; 2 of the patients developing disease recurrence had a persistent HPV infection after surgery.
Conclusions Assessment of cervical lesions with colposcopic biopsy is an accurate method (concordance with cone histology 85.8 %). Surgical treatment of high grade CIN with LEEP is a safe procedure with low recurrence rates, resulting in a clearance of cervical HPV infection in the majority of cases.

Keywords LEEP · Conization · CIN · Colposcopy · Cervical biopsy

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Introduction

Appropriate management of women with cervical intraepithelial neoplasia (CIN) is a critical component of cervical cancer prevention. Improper management can increase the risk for cervical cancer on the one hand and the risk for complications from overtreatment such as preterm delivery on the other [1, 2]. Annually, about 90,000 conizations for suspected high grade CIN are performed in Germany [3]. In contrary to current recommendations, most of the procedures are performed based on abnormal cytology results only [3]. Reported sensitivity of conventional cytology varies widely. Overall sensitivity is 50–75 % for low grade lesions (CIN 1) and 55–90 % for high grade lesions (CIN 2 and 3), while specificity varies from 80 % for low grade lesions to 96 % for high grade lesions [4, 5]. The positive predictive value for a mild to moderate dysplasia is 70 %, compared to 80 % for carcinoma in situ [6, 7]. To

minimize the negative effects from false positive cytology, colposcopically directed biopsy is recommended before surgery for suspected CIN 2 and 3 in Germany [8]. However, recent data from Stoler et al. [9] have questioned the value of colposcopic biopsy for evaluation of CIN, showing a concordance rate of only 42–57 % between colposcopic biopsy and cone histology dependent on the time point the biopsy was obtained. We therefore analyzed the accuracy of cytology, colposcopic biopsy and HPV testing in presurgical work-up of suspected high grade CIN in a large cohort of 266 women treated with loop electrosurgical excision procedure (LEEP).

LEEP is currently one of the most common techniques for conization; it was described to effectively eradicate CIN 2/3 [10, 11]. Due to the implementation of this method, morbidity of conization has decreased significantly compared to cold knife procedure [12, 13]. However, existing analyses show a great variation regarding the surgical extent and reported recurrence rates (5–30 %) [14–16]. In the present study, we therefore also investigated the efficacy and safety of LEEP for the treatment of CIN.

Patients and methods

Two-hundred and sixty-six consecutive patients with cytologically suspected cervical intraepithelial lesion attending our colposcopy clinic for diagnosis and surgery were included in this study. All patients were treated by the same gynaecologic oncologist (JS). Detailed patient characteristics are listed in Table 1. During the investigational period, the institutional approach in case of referral for cytologically suspected dysplasia consisted of a work-up with conventional cytology, colposcopy, Human Papillomavirus (HPV) testing and targeted biopsy and/or endocervical curettage in case of unsatisfactory colposcopy. LEEP was performed in case of an CIN 2/3 detection in targeted biopsy or as a diagnostic procedure in case of highly suspected CIN 2/3 in colposcopy and cytology despite insignificant biopsy or in case of an invisible transformation zone. In some patients LEEP was indicated without suspected high risk disease following the patients' wish for maximum safety after recurrent abnormal smears. In these cases LEEP was a diagnostic procedure after completed family planning. All patients underwent LEEP under colposcopic vision after iodine application. With the procedure all colposcopically abnormal findings were excised, aiming for a tissue depth of 6 mm. In cases with suspected endocervical disease separate loop excisions for the vaginal portion of the cervix and the intracervical portion were performed with different sling sizes ("top-hat" technique). No further ablative procedures were performed. Hemostasis was obtained with a ball electrode cautery. Patients were re-evaluated for persistent disease 3–6 months after surgery with cytology, HPV testing, colposcopy and if indicated cervical biopsy and/or endocervical curettage.

Informed consent had been obtained from all included patients to access their tissue and review their medical records when they first attended the clinic according to the Investigational Review Board and Ethics Committee guidelines (Ethics Committee of the Medical Board Hamburg reference number 190504). Clinicopathological factors were evaluated by reviewing medical charts and pathological reports. All pathological studies were performed by specialized gynaecopathologists. Tissue slides were reviewed for histological findings and free resection margins, and clinical outcome was followed from the date of primary surgery to June 2009.

HPV high risk DNA testing

Analysis of HPV high risk DNA status was performed with Hybrid Capture II tests (HC2; Digene, Gaithersburg, MD, USA) from cervical smears according to the manufacturer's instructions as described before [17].

Colposcopy criteria

For preoperative colposcopic evaluation International Federation for Cervical Pathology and Colposcopy (IFCPC) colposcopic criteria were used (Barcelona 2002) to identify potential high grade disease [18].

Cytology

For cytological analysis, we performed cervical smears with plastic spatula and endocervical cytobrush. All cytologies in this study were based on conventional slide samples.

The Munich classification II is traditionally used to classify cervical cytology results in Germany [19]. It is a five-step system with Pap I/II (normal cells/inflammation), Pap III (atypical cells of unknown significance) Pap IIId (low or intermediate grade dysplasia), Pap IVa (high grade dysplasia), Pap IVb (high grade dysplasia with suspected microinvasion) and Pap V (cancer). Results of this classification do not correspond directly with the Bethesda system [20, 21]. To enable comparison between both classification slides were reviewed and results from the Munich classification translated as follows: Pap I/II correspond to "negative for intraepithelial lesion or malignancy" (NILM), Pap IIID correspond to low grade or intermediate grade squamous intraepithelial lesion (LSIL), Pap IVa/b correspond to high grade squamous intraepithelial lesion (HSIL) and Pap V correspond to cancer [3, 22, 23].

Table 1 Patients' characteristics ($n = 266$)

Age (years)	Median: 34 range 17–71
In house cytology results	
Pap I–II (corr. NILM)	35 (13.15 %)
Pap IIId (corr. LSIL)	86 (32.33 %)
Pap IVa (corr. HSIL)	61 (23 %)
Pap V (cancer)	3 (1.12 %)
Not redone	81 (30.4 %)
Colposcopic biopsy results	
No dysplasia	4 (1.5 %)
CIN 1	32 (12 %)
CIN 2	46 (17.3 %)
CIN 3	108 (40.6 %)
Cancer	1 (0.4 %)
Not performed	75 (28.2 %)
Preoperative HPV testing	
Positive for high risk types	207 (77.8 %)
Negative for high risk types	59 (22.2 %)
Surgical results	
Complete excision of the lesion	224 (84.2 %)
Not entirely excised lesion	6 (2.3 %)
Ambiguous pathological findings	36 (13.5 %)
Cone histology	
CIN 1	45 (16.9 %)
CIN 2	41 (15.4 %)
CIN 3	136 (51.1 %)
Carcinoma	5 (1.9 %)
Metaplasia	19 (7.1 %)
Benign	20 (7.5 %)
Complications	
Bleeding	15 (5.4 %)
Pain	3 (1.1 %)
No complications	251 (94.6 %)
HPV testing 3–6 months after LEEP	
Positive	58 (21.8 %)
Negative	208 (78.2 %)
Median follow-up after surgery (months)	50 (range 3–102)
Persistent disease	9 (3.4 %)
No persistent disease	257 (96.6 %)
Disease recurrence	4 (1.5 %)
No disease recurrence	262 (98.5 %)

Corr. correspond to, *NILM* Negative for intraepithelial lesion or malignancy, *LSIL* Low grade squamous intraepithelial lesion, *HSIL* High grade squamous intraepithelial lesion

Statistical analysis

All statistical analyses were conducted using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA) and Stata 11.0 (2009 StataCorp LP, College Station, TX, USA). To compare cytological, colposcopic and histological findings, concordance rates between these examinations were calculated.

Results

A total of 266 patients with CIN were analyzed in this study. Detailed patient characteristics are listed in Table 1. Median age of the patients was 34 years. Preoperative HPV testing was positive for high risk types in 77.8 %. Complete excision of the lesion with LEEP could be achieved in 84.2 %, in 13.5 % margins were not securely cleared and in 2.3 % the lesion was clearly not excised entirely (of the later patients 3 received second surgery immediately, while the others underwent close observation). 5.4 % of the patients suffered from intensified postoperative bleeding and/or pain after LEEP. All bleedings could be treated by either cauterization ($n = 2$), suturing ($n = 6$) or application of ferric subsulfate paste ($n = 4$).

Postoperative histology showed CIN 2/3 in 66.5 % and CIN 1 in 16.9 % of the patients. The concordance rates of cytology with postoperative histology are shown in Table 2. Overall concordance was 51.9 % (including patients with recurrent Pap IIId and CIN 2 in cone histology). Of the patients with initial HSIL cytology 85.2 % showed a CIN 2/3 lesion in cone histology, whereas 13.1 % of these patients had no lesion or a CIN 1 in definitive histology. However, only 44.3 % of the patients with CIN 3 in cone histology had shown a HSIL cytology result preoperatively. Sixty percent of the patients with normal cytology had a high grade lesion in cone histology.

With colposcopic biopsy the overall concordance rate of preoperative and postoperative diagnosis for all lesions was 85.8 % (Table 3). The concordance rate was higher for CIN 2/3 (95.1 %) compared with low grade lesions (CIN 1) (63.2 %). Of the 144 patients with CIN 2/3 in cone histology, 137 had shown a high grade preoperative histology as well (95.1 % concordance). In 18 % of patients with low grade lesions in preoperative biopsy, cone histology came back CIN 2/3.

Of 38 patients with postoperative CIN 1 who received colposcopic biopsy preoperatively, 63.2 % had already shown low grade lesion as result of presurgical work-up. In these, surgery was performed as a diagnostic procedure after completed family planning following the patients' wish for maximum security after persistent abnormal smears or invisible transformation zone. In the remaining patients a high grade dysplasia had been histologically verified with targeted biopsy preoperatively.

Median follow-up was 50 months, 9 patients (3.4 %) had persistent disease (CIN 3) after 3 months (in two of these cases the lesions had not been excised entirely), while 4 patients (1.5 %) developed disease recurrence defined as

Table 2 Concordance between cytology and postoperative histology

		Cone histology					All
		No dysplasia	CIN 1	CIN 2	CIN 3	Cancer	
Preoperative cytology	Pap I/II (corr. NILM)	4 (2.2 %)	10 (5.4 %)	7 (3.7 %)	14 (7.6 %)	0 (0 %)	35 (18.9 %)
	Pap IIId (corr. pers. LSIL)	9 (4.9 %)	20 (10.8 %)	18 (9.7 %)	39 (21.1 %)	0 (0 %)	86 (46.5 %)
	Pap IVa/b (corr. HSIL)	1 (0.5 %)	7 (3.8 %)	9 (4.9 %)	43 (23.2 %)	1 (0.5 %)	61 (33.0 %)
	Pap V (corr. cancer)	0 (0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.5 %)	2 (1.1 %)	3 (1.6 %)
All		14 (7.6 %)	37 (20.0 %)	34 (18.3 %)	97 (52.4 %)	3 (1.6 %)	185 (100 %)

Corr. correspond to, *NILM* Negative for intraepithelial lesion or malignancy, *LSIL* Low grade squamous intraepithelial lesion, *HSIL* High grade squamous intraepithelial lesion

Table 3 Concordance between preoperative colposcopic biopsy and cone histology ($n = 191$)

		Cone histology					All
		No dysplasia	CIN 1	CIN 2	CIN 3	Carcinoma	
Colposcopic biopsy	No dysplasia	2 (1.1 %)	1 (0.5 %)	0 (0 %)	1 (0.5 %)	0 (0.0 %)	4 (2.1 %)
	CIN 1	2 (1.1 %)	24 (12.6 %)	3 (1.6 %)	3 (1.6 %)	0 (0.0 %)	32 (16.7 %)
	CIN 2	2 (1.1 %)	13 (6.8 %)	23 (12.0 %)	13 (6.8 %)	2 (1.1 %)	154 (80.7 %)
	CIN 3	1 (0.5 %)	3 (1.6 %)	9 (4.7 %)	92 (48.0 %)	2 (1.1 %)	107 (56 %)
	Carcinoma	0 (0.0 %)	0 (0.0 %)	0 (0 %)	0 (0 %)	1 (0.5 %)	1 (0.5 %)
All		6 (3.1 %)	38 (19.9 %)	35 (18.3 %)	109 (57 %)	3 (1.6 %)	191 (100 %)

newly diagnosed CIN 2/3 after at least one normal smear and colposcopic examination after first surgery; all 4 underwent re-conization. The HPV-screening 3–6 months after surgery was negative in 78.5 % of the patients. Two of the patients developing disease recurrence had a persistent HPV infection after LEEP. None of the patients with presurgical CIN 2/3 in targeted biopsy and negative definitive sample or CIN 1 developed recurrent disease.

Discussion

We present an analysis of 266 women undergoing LEEP for suspected CIN demonstrating a high concordance of colposcopic biopsy with cone histology (85.8 % overall concordance rate) as well as a satisfying efficacy and safety of the procedure itself.

In our study, the concordance rate of cytology and cone histology was 51.9 % for all lesions. Fourteen percent of the patients with a HSIL had no lesion or CIN I in definitive histology and only 44.3 % of the patients with CIN 3 in cone histology showed HSIL cytology preoperatively. These results are in line with previously published concordance rates that vary widely from 11 to 95 % with an overall sensitivity of 50–75 % for low grade lesions (CIN 1) and 55–90 % for high grade lesions (CIN 2/3) [4, 5]. In contrast to other publications reporting much lower rates, however, the concordance of colposcopically directed biopsy and cone histology was 85.8 % for all and 95.1 % for high grade lesions in our study [9, 24]. The accuracy of the biopsy results was better for high (CIN 2/3) than for low grade lesions (CIN 1) (63.2 %). Opposite to other analyses, our data therefore support the value of colposcopic examination with target biopsy for the assessment of CIN [9, 24]. A study of Boonlikit et al. assessing the accuracy and correlation between colposcopically directed biopsy and LEEP histology showed an overall concordance rate of 66.2 %. The diagnostic efficacy was also better for high grade lesions (CIN 2/3) (78.5 % concordance with postoperative histology) than for low grade lesions (CIN 1) (33.3 % concordance with postoperative histology) in their study. Better concordance rates for high grade lesions are most likely explained by a greater variability in pathological diagnosis of low grade lesions [25].

Possible explanations for the accuracy of colposcopic biopsy demonstrated in our study could be the monocentric design corresponding with highly educated colposcopists and the number of biopsies taken per patient. In previously published analyses better education of the examiner did, however, not always result in a higher colposcopic CIN 2/3 detection (35–43 % independent from the examiners education), while the number of biopsies taken in each patient significantly influenced the detection rate [26]. In the present study, we did not gather information about the

number of biopsies taken per patient; this should be subject to further research. Another explanation for the high concordance between colposcopic biopsy and cone histology could be to some extent a selection bias, as patients in this study were selected based on LEEP. This bias also explains 60 % of patients with normal cytology having a high grade lesion in cone histology.

In our study 10 % of patients with preoperative CIN 2/3 in colposcopic biopsy showed CIN 1/no disease in the definitive sample. Possibly, the high grade dysplasia was completely removed with the preoperative biopsy in these patients or a spontaneous regression of the lesion was induced by the biopsy. It is also possible that the previously diagnosed CIN 2/3 was not excised with the LEEP; however, none of these patients developed disease recurrence and 88.9 % were HPV high risk negative after surgery, rendering this explanation rather unlikely.

Our study demonstrates a very high efficacy of LEEP for the treatment of CIN with persistent disease in only 3.4 % and a recurrence rate of 1.5 %. Previously published recurrence rates vary between 2 and 9 % for CIN [27, 28]. Results are, however, difficult to compare as the surgical extent of LEEP varies widely. In this study, the depth of resection aimed for was 6 mm in cases with ectocervical disease on the basis of pathological studies of cervical anatomy [29]. Well-known risk factors for persistence/recurrence of CIN after LEEP are positive margins and persistent HPV infection. All patients in our analyses therefore underwent HPV testing 3–6 months postoperatively. Most of the patients cleared the infection, while in 21.5 % high risk HPV types were still detectable. Other authors describe a similar elimination rate of high risk HPV (80–86 %) and a persistence rate of 10–20 % after LEEP [30, 31]. Kim et al. [31] could demonstrate that the chance of HPV clearance increased gradually over time after conization with a higher risk for disease recurrence with longer persistence of HPV high risk infection. In our study, HPV retesting after conization was already performed 3–6 months after surgery. Nevertheless, the clearance rate observed in our study is similar to that reported by Kim et al. (HPV clearance at 3 months 54.4 and 85.7 % at 6 months). After surgery, 5.4 % of our patients suffered from easily controllable complications such as bleedings or abdominal pain. Previous reports are in line with these results: Postoperative bleeding and/or pain were described in 2.6–5.4 % [32, 33].

In conclusion, our study supports the accuracy of cervical assessment with colposcopy and targeted biopsy opposite to recent studies [9, 24]. Furthermore, the surgical treatment of cervical high grade lesions with LEEP is an effective method with low recurrence rate, resulting in HPV clearance in the majority of cases.

Acknowledgments This study was funded by internal departmental sources.

Conflict of interest All authors declare that there is no conflict of interest involved with the presented data. The study was funded by internal departmental sources.

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