Cervical intraepithelial neoplasia outcomes after treatment with cervical excisional procedures

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Abstract

Objective. *The aim of this study is the exploration of persistence/recurrence rate of cervical intraepithelial neoplasia (CIN) after treatment by cervical excisional procedures and to further investigate factors associated with disease.* ***Methods.*** *Medical and pathologic records of a number of 509 women during the period from January 2001 to March 2011, who underwent loop electrosurgical excision procedure or cold-knife conization, were taken into study. Multivariate logistic regression was performed to identify independent risk factors associated with persistent/recurrent CIN.* ***Results.*** *From 49 of the patients (9.6%) who had histological recurrent/persistent disease, CIN 1, CIN 2, and CIN 3/CIS were detected in 44.8%, 12% and 42% of the patients. A multivariable analysis showed that high-grade lesion (CIN 2 or CIN 3) and positive margin status at initial diagnosis were significant independent factors for recurrent/residual disease.* ***Conclusion.*** *Patients who had incompletely excised high-grade lesion on initial conization specimen, had high risk of recurrent/persistent disease. Thus, re-treatment of this group should be considered. The patients with low-risk of recurrence/persistence constituted the majority (92%), and cytological surveillance of these women seems to be appropriate.*

Keywords: *cervical intraepithelial neoplasia, conization, persistence, recurrence*

Introduction

In the past, local ablative techniques have been used to treat cervical intraepithelial neoplasia (CIN). But cervical excisional procedures like loop electrosurgical excision procedure (LEEP) or cold-knife conization (CKC) are currently the preferred methods of treating CIN[(1)]. Beside the treatment, these procedures yield a cervical specimen for histopathologic diagnosis. Especially since the 1990s, LEEP has been the treatment of choice for local treatment of CIN due to its various advantages over other methods[(2,3,4)]. Despite its effectiveness, recurrent or persistent CIN after LEEP may vary between 5% and 64%[(5)]. Also, the women who have been treated for CIN have an increased risk of invasive cancer of the cervix[(6)]. Furthermore, concerning that inadequate follow-up for women at high risk and excessive surveillance for women at low risk of recurrence has been raised. So, it is important for the clinician to determine which patients have higher risk of post-treatment CIN on the subsequent follow-up.

The aim of this retrospective study was to determine the persistence/recurrence rate of CIN after the treatment with LEEP or CKC. In addition, factors associated with persistent/recurrent disease were also investigated.

Methods

Study Population

We retrospectively reviewed the medical and pathologic records of women who underwent loop electrosurgical excision procedure (LEEP) or cold-knife cauterization (CKC) between January 2001 and March 2011 at the Kanuni Sultan Suleyman Research and Teaching Hospital. All patients had abnormal cervical smear and underwent colposcopic examination before the operation. Endocervical curettage (ECC) was performed in most of the patients to assess the endocervical canal, and punch biopsies from the suspicious areas were taken together with the colposcopic examination. If the result of punch biopsy was cervical intraepithelial neoplasia (CIN)1, cytological follow-up was recommended but if the result was CIN 2 or CIN 3, cervical excisional procedures were performed. We also performed a see and treat approach in some patients whose cytologic result was low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASCUS), high grade squamous intraepithelial lesion (HSIL) and atypical squamous cells cannot exclude HSIL (ASC-H). The other indications for conization included unsatisfactory colposcopy (defined as inability to visualize entire lesion or transformation zone on colposcopy), positive ECC, discrepancies between Pap smear and colposcopic biopsies, suspicion of microinvasive disease. If CIN 1 persists for at least 2 years, either continued follow-up or diagnostic excisional procedure was recommended. In low attendance, perimenopausal women who had CIN 1 lesion, initial treatment with LEEP was also performed after detailed information was given and consent was taken. CKC was preferred over LEEP in certain circumstances: 1. Cytology report indicating adenocarcinoma *in situ* 2. Cytology results of invasive cervical cancer where no lesion was visualized. 3. Postmenopausal patients with abnormal cytology where the cervix was too small to perform LEEP.

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On the medical records, age, parity, menopausal status, contraceptive method, smoking, and human immunodeficiency virus (HIV) status were obtained. Preoperative cytology, histology of ECC, satisfaction of colposcopy, indications for conization, histology of conization material, completeness of excision were obtained on the pathology reports.

Excisional procedures (LEEP/CKC)

All of cervical excisional procedures were performed by the same gynecologic-oncologists with the same surgical procedure in the study period. All procedures were performed under general anesthesia. Lugol solution (Schiller test) or acetic acid was not used in most of the cases, and ECC was not performed immediately after the procedures. Application of Monsel solution was also needed in certain cases. All cervical specimens were marked for correct orientation.

In LEEP, variable-sized loop electrodes were preferred according to the size of the cervix. Nearly, all of the LEEP specimens were taken with a single pass. After LEEP, surgical bed was routinely electrocauterized. CKC was performed using scalpels and hemostasis was achieved by interrupted vertical sutures.

Pathologic examination

All pathologic-cytologic specimens were reviewed by the same gyneco-pathologists in our center. In the study period, conventional Pap smear was taken for cytology, and was described using the Bethesda System 2001[7]. At least 10 sections from each LEEP specimen were reviewed for microscopic analysis. Pathology reports included the severity of the disease (as CIN 1/2/3, microinvasive or invasive cancer), cervical margin (positive/negative for dysplasia or cancer, or indeterminate for diagnosis) and ECC finding (positive/negative for dysplasia/cancer). Status of cervical margin was not classified as endocervical or ectocervical. Follow-up specimens were also reviewed with the same criteria mentioned above.

Patient follow-up

Patients who had low grade lesions (CIN 1) or less on histology of the conization specimens were routinely followed by cervical cytology performed every 3-4 months after the procedure in the first year, every 6 months in the second year, and annually thereafter. Patients who had CIN 2/3 and surgical margin negative were routinely followed by cervical cytology every 3-4 months after the conization in the first two years, and every 6 months for the following 3 years. Patients who had CIN 3 and positive surgical margin on the conization specimen were either treated by re-conization/hysterectomy within 3 months or followed by cytology according to the patient's desire for fertility preservation. Patients with abnormal cytology on follow-up were referred for colposcopy and ECC, if necessary. Invasive cancers were appropriately treated after the clinical staging was performed. Testing for human papillomavirus (HPV) was not carried out on the follow-up.

Criteria for persistent/recurrent disease

Persistent/recurrent disease was defined as histology of CIN 1 or higher at any time after the conization.

Statistical analysis

Statistical analyses were performed using SPSS 16.0 version (SPSS, Chicago, IL, USA).

Clinicopathologic parameters were analyzed by Fisher exact and chi-square tests. Multivariate logistic regression was performed to identify independent risk factors associated with persistent/recurrent CIN. If cervical margin was classified as indeterminate for diagnosis, it was included for analysis in margin positive group. $p<0.05$ was defined as statistically significant.

Kaplan Meier testing with log ranking was used for survival without recurrence/persistence. When calculating the survival without CIN, women were censored at the time of a histology indicating CIN.

Results

From total patients who underwent LEEP or CKC, only 509 patients were eligible for the study. Mean age of the patients was 41.2±8.2 years. 416 patients (81.7%) were premenopausal. LEEP and CKC were performed in 398 (78.2%) and 111 (21.8%) patients, respectively. After the procedures, high-grade CIN (CIN 2 or CIN 3), low-grade CIN (CIN 1), and no lesion were detected on 146 (28.6%), 206 (40.5%), 157 (30.8%) of the conization specimens. Complete excision of the lesion was achieved in 431 patients (84.7%). Because of diathermy artefact, surgical margin status could not be determined in 40 patients (7.9%). Anti-HIV test was negative in all of the patients. Table 1 summarized demographic and pathologic features of the patients with follow up.

The mean follow up time was 20.4±14.8 months (12-120 months). When patients with or without follow up were compared according to age and menopausal status, there were no statistically significant differences between two groups. However, patients who underwent LEEP had higher incidence of lost to follow up compared with the CKC (p=0.001). Also, CIN 2 or worse lesions were found with a higher incidence in patients with follow up compared with patients who were lost to follow up (p=0.02) (it was not shown in the table).

A total of 53 patients had abnormal follow-up cytologic results (10.4%). Cytologic abnormalities included LSIL (n=32), ASCUS (n=16), HSIL (n=4), ASC-H (n=1). Only 4 patients had normal colposcopy and biopsy results, and no lesion was detected during follow-up period. About 49 patients (9.6%) had histologically recurrent/persistent disease. CIN 1, CIN 2, and CIN 3/CIS were detected in 44.8% (n=22), 12% (n=6), and 42.8% (n=21) of the patients. A number of 24 patients were treated as immediate hysterectomy after excisional procedure. Another 24 patients with recurrent/persistent disease were treated on the follow-up period; of them 15 underwent LEEP, 5 CKC, and 4 patients hysterectomy, respectively. And one patient with CIN 1 lesion was followed by cytology.

Most of the patients with recurrent/persistent lesion were diagnosed during first 36 months after initial diagnosis (95.9%, n=47). 41 of them were diagnosed within first 12 months (85.7%) and 33 (67.3%) of the patients were recurred/persisted between 0-6 months. Only two patients recurred after 36 months; from which only one patient with initial CIN 3 lesion, another one with initial CIN 1 lesion, on conization recurred at 55 months and 108 months respectively.

Table 1 Demographics and pathologic features of the patients with follow-up

	N	%
Age (years)		
<50	421	82.7
≥50	88	17.3
Menopausalstatus		
Premenopause	416	81.7
Postmenopause	93	18.3
Parity		
<5	463	91
≥5	46	9
Contraceptive method		
IUD	101	19.8
OCs	29	5.7
Condom	21	4.1
Tubal ligation	15	2.9
None	343	67.4
Preoperative smear		
ASC-US	197	38.7
LSIL	210	41.3
HSIL	83	16.3
ASC-H	13	2.6
AGUS-NOS	6	1.2
Colposcopic findings		
Normal	91	17.9
Abnormal	418	82.1
Satisfactory colposcopy		
Yes	246	48.3
No	263	51.7
Biopsy results		
Normal	65	12.8
CIN 1	264	51.9
CIN 2	51	10
CIN 3	113	22.2
No biopsy	16	3.1
ECC results		
Normal	282	55.4
CIN 1	31	6.1
CIN 2	8	1.6
CIN 3	22	4.3
No biopsy	166	32.6
Method of excision		
LEEP	398	78.2
CKC	111	21.8
Histology of conization specimen		
No dysplasia	157	30.8
CIN 1	206	40.5
CIN 2	46	9
CIN 3/CIS	100	19.6
Margin involved with dysplasia		
No	431	84.7
Yes	78	15.3
Recurrent/persistent disease		
No	460	90.4
Yes	49	9.6

**Fisher exact test was used.*

IUD: Intrauterin device, OC: Oral contraceptive, CIN: Cervical intraepithelial neoplasia, CIS: Carcinoma in-situ, CKC: Cold-knife conization, LEEP: Loop electrosurgical excision procedure

Table 2 Comparison of demographic and pathologic parameters in patients with or without recurrent/ persistent disease

	No recurrence n=460 (%)	Recurrence n=49 (%)	p
Age			0.83
<50	381(82.8)	40(81.6)	
≥50	79(17.2)	9(18.4)	
Menopause			0.99
Yes	84(18.3)	9(18.4)	
No	376(81.7)	40(81.6)	
Parity			0.41*
<5	420(91.3)	43(87.8)	
≥5	40(8.7)	6(12.2)	
Preoperative colposcopic findings			0.49
Normal	84(18.3)	7(14.3)	
Abnormal	376(81.7)	42(85.7)	
Preoperative positive ECC			0.06
Yes	51(11.1)	10(20.4)	
No	409(88.9)	39(79.6)	
Excision result			<0.0001
≤CIN 1	348(75.7)	15(30.6)	
CIN 2+	112(24.3)	34(69.4)	
Margin status			<0.0001
Negative	410(89.2)	21(42.9)	
Positive	40(10.8)	28(57.1)	

**Fisher exact test was used .*
ECC: Endocervical curettage, CIN: Cervical intraepithelial neoplasia.

Table 3 A multivariate logistic regression test for recurrence/persistence

Variable	OR	95% CI	p*
Excision result			
≤CIN 1	ref.		
CIN 2+	0.17	0.09-0.35	<0.0001
Margin status			
Negative	ref.		
Positive	0.11	0.05-0.22	<0.0001

CIN: Cervical intraepithelial neoplasia.

Table 4 Disease-free survival rates according to risk factors

	Risk Factors*		
	None (n=323)	Any 1 (n=148)	All (n=38)
At 12 months	97.2%	93.9%	42.1%
At 24 months	95.9%	89.4%	42.1%
At 36 months	95.9%	89.4%	0%
At 48 months	95.9%	89.4%	0%
At 60 months	95.9%	82.6%	0%

**Risk factors: CIN 2/CIN 3 lesions and/or positive resection margin*

Comparison of demographic parameters of the patients with or without recurrent/residual disease can be seen at Table 2. Lesion grade of the excision material and positive excision margin were significantly related with recurrence/persistence of disease. A multivariable analysis showed that high-grade lesion (CIN 2 or CIN 3) and positive margin status at initial diagnosis were significant independent factors for recurrent/residual disease (OR:0.17, 95%CI: 0.09-0.35, p<0.0001 and OR:0.11, 95%CI: 0.05-0.22, p<0.0001, respectively)(Table 3).

Kaplan Meier survival analysis confirmed that patients with ≤CIN 1 lesions and negative margin status at initial diagnosis had a longer mean of estimated disease-free time compared with the patients who had CIN 2 or CIN 3 lesions and/or positive margin status at initial diagnosis (102.77 months vs. 78.82 months for ≤CIN 1 and ≥CIN 2; log rank <0.0001 and 100.29 months vs. 26.07 months for margin negative and positive groups; log rank <0.0001). When the patients were classified according to risk factors based on the results of regression analysis, 3 groups were determined: 1. Low-risk group: CIN 1 and clear margin 2. Intermediate-risk group: CIN 1 and surgical margin positive or CIN 2/3 and clear margin 3. High-risk group: CIN2/3 and surgical margin positive. Only 323 (63%), 148 (29%), 38 (7%) of the patients constituted low-risk, intermediate-risk, and high-risk groups. Around 11 patients in low-risk group (3.4%); 14 patients in intermediate-risk group (9.5%), and 24 patients in high-risk group (63.2%) had recurrent/residual disease. Disease-free survival rates according to classification of risk factors were summarized at Table 4. The mean of disease free time was significantly higher in patients without any risk factors (104.06 months) compared with only one risk factor (93.89 months) and patients who had both of risk factors (15.89 months) (log rank=0.01 and log rank <0.0001) (Figure 1).

Discussion

Current screening programs have reduced the incidence of invasive cervical cancer with an increase in the detection of premalignant lesions[8]. Cervical excisional procedures mainly LEEP has been a popular choice in the treatment of CIN with its high effectiveness and low morbidity[2,3]. However, still there is a risk of post-treatment CIN for some proportion of women. The cumulative rate of invasion 8 years after the treatment of CIN is 5.8 per 1000 which is five times higher than in the general population. Moreover, the risk remains constant throughout the 8 years of follow-up[9]. So, surveillance after the treatment of CIN is needed.

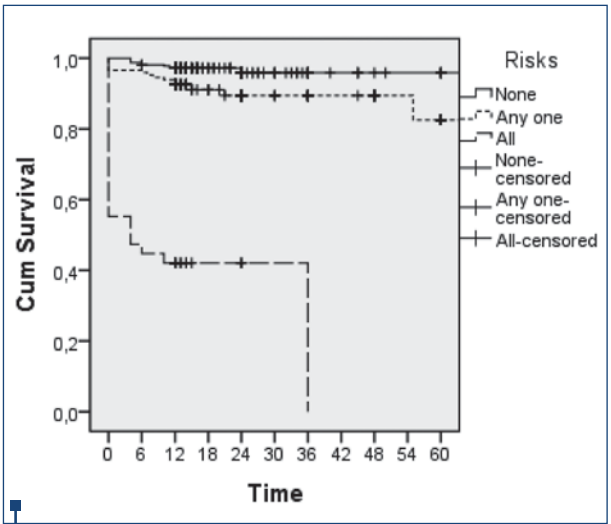

Figure 1. Time to recurrence/persistence of disease according to risk classification

There is controversy regarding the factors that are predictive of persistent/recurrent disease after the treatment of CIN[10,11]. Malapati et al. showed that HIV seropositivity, endocervical disease, and high-grade pathology or positive margin on LEEP specimen were associated with persistence/recurrence of CIN[12]. Ramchandani et al. found that only endocervical margin status and severity of neoplasia predicted the occurrence of persistent/recurrent disease[13]. In the present study, two independent risk factors for recurrence/persistence were identified, the presence of CIN at the margins of excision and high grade lesion on initial conization specimen. Using these factors, we divided the patients into three risk groups: 323 patients (63%) who had none of the risk factors, 148 patients (29%) who had at least one risk factor, and 38 patients (7%) who had both of the risk factors constituted low-risk, intermediate-risk, and high-risk groups, respectively. Most of the recurrences/persistences were detected in the high-risk group (63.2%, 24/38) whereas it was only 3.4% (11/323) and 9.5% (14/148) in the low-risk and the intermediate-risk groups, respectively (p<0.05). Similarly, Chen et al. found that the overall rate of recurrent/persistent disease in women with CIN 3 and positive margins (33.3%) was much higher than that in women with clear margins (2.2%)[14]. Although most of the studies in the literature indicated the importance of positive resection margin on the recurrence rate, there are no guidelines for specific post-treatment follow-up of the patients having incomplete excision[12,13,15]. Dobbs et al. suggested long term colposcopic and cytological follow-up in women with incomplete excision of CIN at initial LEEP[16], while Flannely et al. and Maghami et al. suggested a second operation for some of women who had incomplete excision of CIN[15,17]. However, it is a fact that most women with involved margins remain disease free on follow-up and recurrent disease may also occur in resection margin negative group[18]. Similar with the previous reports, we found the overall cure rate after complete conization to be 95%, whereas it was only 58% in the incomplete excision group which was lower than previous studies[18,19]. On the other hand, we also found that high-grade lesion on initial conization specimen was correlated with the risk of recurrence/persistence, and this was consistent with the literature[12,13,20].

In the present study, 49 patients (9.6%) had histologically recurrent/persistent disease whereas no cervical cancer was detected on the follow-up. On the contrary, in the study of Melnikow et al., which was one of the largest series in the literature, the data of 37142 women with CIN were reviewed and the cancer rate was found to be 37 per

100 000 woman-years at the end of the 18-year follow-up period while this rate was per 100 000 woman-years in control group[21]. The authors also analyzed the rates of subsequent CIN 2/3 up to 15 years after treatment, and showed that the rate fell rapidly over the first 4 years[21]. In our study, only two patients recurred after 36 months. One of them had CIN 3 lesion and the other one had CIN 1 lesion on initial conization specimen. Optimum time for active surveillance is not clear. Bornstein et al. suggested a follow-up protocol for women with CIN 2/3 that were treated with LEEP which consists of a Pap smear combined with colposcopy performed every 6 months for a period of 3 years, if margins are clear. If the margins are positive, the follow-up continues for 8 years[22]. However, Wright et al. suggested routine screening for at least 20 years after treatment of CIN[6].

Since HPV testing was not done in the study period, women treated for CIN were followed by cytology, and 49 of the 53 abnormal smears were confirmed by histology (92%). In a recent review, it was showed that sensitivities of cytology, high-risk HPV testing, and co-testing for predicting post-treatment disease in women treated for high-grade cervical disease were 79%, 92%, 95%, respectively[23]. They suggested that high-risk HPV or co-testing should be incorporated in post-treatment surveillance.

As we analyzed non-attendance group in our study, low grade lesions and performing LEEP were appeared as high-risk factors for lost to follow up. Similarly, Towler et al. showed that patients with lower grade cervical lesions may be more likely to be non-compliant with recommended follow-up than patients with higher grade lesions[24]. As CKCs were mostly performed in the group of higher risk of cervical cancer and the probability of progression to invasion was higher in the high-grade cervical lesions, the fear of having cancer made the patients more compliant.

Our study has some limitations. The mean follow up time was 20 months and most of the patients did not complete the whole surveillance programme, which might have resulted in a lower rate of recurrence/persistence of CIN. Testing for HPV was not performed during the study period. The involvement of surgical margin status was not classified as endocervical or ectocervical in the pathology reports, so it could not be analyzed separately in the outcomes of post-treatment CIN. However, the power of our study came from relatively large number of the patients and the definition of recurrence/persistence based on histological confirmation.

Conclusions

Patients who had incompletely excised high-grade lesion on initial conization had high risk of recurrent/persistent disease. Thus, re-treatment of this group should be considered. The patients with low-risk of recurrence/persistence constituted the majority (92%), and cytological surveillance of these women seems to be appropriate. ■

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