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Cytologic Follow-up in Patients with CIN Treated by LLETZ, Cold Knife Conization and Semm's Cold Coagulation

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A B S T R A C T

Management of cervical premalignant lesions starts with abnormal Pap smear. Regular screening of asymptomatic women (the Pap smear) allows us to diagnose and treat preinvasive lesions before they progress to cervical cancer. There is a wide variety of ablative and destructive methods used in treatment of cervical premalignant lesions. In this study we have compared follow-up cytology results in patient groups treated by LLETZ (Large Loop Excision of the Transformation Zone), Cold Knife Conization (CKC) and Semm's cold coagulation (Electrocoagulation, ECG) according to CIN on target biopsy specimen, and definite therapeutic approach according to patient age, parity and lesion grading. The aim was to evaluate therapeutic success in all three patient groups on the basis of control cytology findings. Normal cytology findings after treatment were recorded in 43 women in LLETZ group (88%), 22 women in CKC group (73%) and in 22 women from the Semm's cold coagulation group (73%). The importance of the use of diagnostic and therapeutic guidelines and regular follow up is emphasized, bearing in mind primarily the young female population with severe preinvasive lesions of uterine cervix. Treating cervical preinvasive lesions offers an excellent opportunity to prevent the occurrence of cervical cancer in the large majority of women with abnormal cervical smears.

***Key words**: cervical intraepithelial neoplasia, large loop excision of the transformation zone, cold knife conization, Semm's cold coagulation*

Introduction

Cervical cancer has a slow progress, from preinvasive cervical intraepithelial neoplasia (CIN) to invasive phases, which means that the disease can be diagnosed while in the phase of pre-invasive lesion, and treated successfully thanks to the regular screening of asymptomatic women (the Pap smear). In new cytological classification[1] cervical lesions have been divided into two groups: High grade Squamos intraepithelial lesion (HSIL) and Low grade Squamos intraepithelial lesion (LSIL). CIN I lesions belong to LSIL group and CIN II and CIN III belong to HSIL group. After the detection of CIN in Pap smear it is advisable to perform colposcopy. Due to colposcopic finding and previous cytologic abnormality decision must be made to perform target biopsy and endocervical curettage. If the control Pap smear reveals HSIL definite treatment is mandatory. There is a wide variety of ablative and destructive methods used in treatment of cervical premalignant lesions. For decades, local ablative techniques have been used to treat cervical premalignant lesions[2]. The shared disadvantage of all ablative techniques is the absence of large resection specimens for histopathological analysis. These techniques proved to be effective to treat cervical preinvasive lesions[2] but have now largely been replaced by low-morbidity excisional techniques, the most frequent of which are Cold Knife Conization (CKC) or LLETZ (Large Loop Excision of the Transformation Zone). The excisional techniques offer the advantage of obtaining a large specimen for pathological assessment to define the disease as well as the completeness of treatment. Cold-knife conization has been the traditional procedure for diagnosis and treatment of cervical dysplasia and early cervical carcinoma not more

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than IA2. It is typically performed in a hospital setting with general or local anesthesia. The concept of the large loop brought a huge change in the approach of clinicians to cervical preinvasive lesions. This was described in 1989 by Prendiville et al.[3] who published their results of treatment using a wide, large, thin wire loop. The results showed a low complication rate and morbidity coupled with a 98% success rate of treatment. In comparative studies, LLETZ was found to be as effective or better treatment for cervical preinvasive lesions than laser[4] or cryotherapy[5].

In many clinics, LLETZ has now become the standard of care for cervical preinvasive lesions.

TABLE 1
CYTOLOGY PRIOR TO LLETZ ACCORDING TO AGE GROUPS

Age	ASCUS	CIN I	CIN II	CIN III	Total
21–40	2	3	14	24	43
>40	0	1	4	2	7
Total	2	4	18	26	50

LLETZ – Large Loop Excision of the Transformation Zone; CIN – Cervical Intraepithelial Neoplasia; ASCUS – Atypical Squamos Cell of Undetermined Significance

TABLE 2
BIOPSY SPECIMENT HISTOLOGY PRIOR TO LLETZ

Age	Chronic endocervicitis	CIN I	CIN II	CIN III	Total
21–40	0	3	15	25	43
>40	1	0	3	3	7
Total	1	3	18	28	50

LLETZ – Large Loop Excision of the Transformation Zone; CIN – Cervical Intraepithelial Neoplasia

As it maintains cervical reproductive function, it is suitable for patients who wish to retain their fertility.

In this study we have compared follow-up cytology results in patient groups treated by LLETZ, CKC and Semm's cold coagulation (Electrocoagulation, ECG) according to CIN on target biopsy specimen, and definite therapeutic approach according to patient age and lesion grading. To aim was to evaluate therapeutic success in all three patient groups on the basis of control cytology findings.

Patients and Methods

The study included patients allocated to particular therapy group according to diagnostic and therapeutic guidelines for preinvasive lesions of the uterine cervix[6,7] during the period from January 1, 1999 till December 31, 2000.

LLETZ was performed in 157, CKC in 42 and Semm's cold coagulation in 30 women. The patient mean age was 33.7 years in the LLETZ group, 36.5 years in CKC group and 30.0 years in the Semm's cold coagulation group. LLETZ prevailed in young nulliparous women and CKC in parous women. Cytology control was available only in 50 out of 157 (32%) women with LLETZ, 30 out of 42 (71%) women with CKC and in all 30 women with Semm's cold coagulation.

Results

The distribution of cytology findings according to the age of the patients prior to LLETZ is shown in Table 1. HSIL is predominant in age group 21–40 years.

The distribution of biopsy specimen histology according to the age of the patients prior to LLETZ is shown in Table 2. HSIL prevails in 46 out of 50 patients (92%). The distribution of histology findings according to the

TABLE 3
HYSTOLGY OF LLETZ SPECIMEN ACCORDING TO AGE GROUPS

Age	Chronic endocervicitis	CIN I	CIN II	CIN III	Normal	Total
21–40	3	2	9	28	1	43
>40	0	1	2	4	0	7
Total	3	3	11	32	1	50

LLETZ – Large Loop Excision of the Transformation Zone; CIN – Cervical Intraepithelial Neoplasia

TABLE 4
CONTROL CYTOLOGY AFTER LLETZ ACCORDING TO AGE GROUPS

Age	ASCUS	CIN I	CIN II	CIN III	Normal	Total
21–40	1	0	1	1	40	43
>40	2	1	1	0	3	7
Total	3	1	2	1	43	50

LLETZ – Large Loop Excision of the Transformation Zone; CIN – Cervical Intraepithelial Neoplasia; ASCUS – atypical squamos cell of undetermined significance

age of the patients after LLETZ is shown in Table 3. The highest prevalence of HSIL can be noticed in age group 21–40. 37 out of 43 women (86%) with HSIL are from this group.

The distribution of control cytology findings according to the age of the patients after LLETZ is shown in Table 4. The high percentage of normal cytology findings is satisfactory; however there are three cases of HSIL after LLETZ.

The distribution of cytology findings according to the age of the patients prior to CKC is shown in Table 5.

TABLE 5
CYTOLOGY PRIOR TO CKC ACCORDING TO AGE GROUPS

Age	ASCUS	CIN I	CIN II	CIN III	Total
21–40	0	0	1	19	20
>40	0	2	4	4	10
Total	0	2	5	23	30

CKC – Cold Knife Conization; CIN – Cervical Intraepithelial Neoplasia; ASCUS – atypical squamos cell of undetermined significance

TABLE 6
BIOPSY SPECIMEN HISTOLOGY IN WOMEN SCHEDULED FOR CKC

Age	Chronic endocervicitis	CIN I	CIN II	CIN III	Total
21–40	3	0	2	15	20
>40	0	2	2	6	10
Total	3	2	4	21	30

CKC – Cold Knife Conization; CIN – Cervical Intraepithelial Neoplasia

The distribution of biopsy specimen histology according to the age of the patients prior to CKC is shown in Table 6. CIN III prevails in age groups 21–40 years. 15 out of 21 patients with CIN III are in this group (72%).

The distribution of histology findings according to the age of the patients after CKC is shown in Table 7. CIN III prevails in age group 21–40 years. Out of 25 patients with HSIL, 22 of them had CIN III (88%). 4 cases of chronic endocervicits in age group >40 years suggests that between biopsy and CKC we should repeat control cytology and colposcopy and accordingly to those findings decide on further treatment. Although CKC was preformed in one patient in group >40 years, revealing CIN I on definitive histology, it was done due to major colposcopic changes.

The distribution of control cytology findings according to the age of the patients after CKC is shown in Table 8.

ECG was performed after cytology screening and colposcopy. Following colposcopic criteria had to be met:

– Squamocollumnar junction is fully visible
– Lesion is clearly marked from surrounding tissue.

ECG was preformed only on those patients who had biopsy specimen histology no greater than CIN II.

The distribution of control cytology findings according to the age of the patients after ECG is shown in Table 9.

In the LLETZ group, 32 out of 50 (64%) histology specimens revealed CIN III, whereas in the CKC group it was found in 22 out of 30 (72%) women. Normal cytology findings after treatment were recorded in 43 women in LLETZ group (88%), 22 women in CKC group (73%) and in 22 women from the Semm's cold coagulation group (73%).

TABLE 7
CKC SPECIMEN HYSTOLGY ACCORDING TO AGE GROUPS

Age	Chronic endocervicitis	CIN I	CIN II	CIN III	Normal	Total
21–40	0	0	3	17	0	20
>40	4	1	0	5	0	10
Total	4	1	3	22	0	30

CKC – Cold Knife Conization; CIN – Cervical Intraepithelial Neoplasia

TABLE 8
CONTROL CYTOLOGY AFTER CKC ACCORDING TO AGE GROUPS

Age	ASCUS	CIN I	CIN II	CIN III	Normal	Total
21–40	3	1	1	1	14	20
>40	2	0	0	0	8	10
Total	5	1	1	1	22	30

CKC – Cold Knife Conization; CIN – Cervical Intraepithelial Neoplasia; ASCUS – Atypical Squamos Cell of Undetermined Significance

TABLE 9
CONTROL CYTOLOGY AFTER ECG IN 30 PATIENTS WITH PREVIOUS HISTOLOGY FINDING OF CIN II

Cytology finding	ASCUS	CIN I	CIN II	CIN III	Normal
Total	3	3	1	1	22

ECG – Electrocoagulation; CIN – Cervical Intraepithelial Neoplasia; ASCUS – Atypical Squamos Cell of Undetermined Significance

Discussion

LLETZ has been demonstrated to be a very effective way of treating CIN[4,8–10]. Effectiveness is often regarded as achieving normal cytology after treatment. Follow-up schedules vary from 3- to 6-monthly cytology/colposcopy follow-up assessments, after which the intervals increase to 6–12 monthly for 5–10 years. The majority of studies reported abnormal cytology findings in less than 15% of cases[8–11]. Factors associated with an increased risk of recurrence have been identified as involved margins at LLETZ, grade of disease, age of the patient, HPV status. Excisional margins may be positive in as many as 48% of cases[12]. More concern is caused by involved endocervical margins as this represents invisible disease. Marginal ectocervical lesions, in many cases, may have been destroyed with the use of the ball cautery[10]. Clear margins have not been found to guarantee normal cytology follow-up, and only some of the patients with involved margins had abnormal cytology at follow-up[8–10].

The histological assessment of completeness of LLETZ excision cannot be used as a strong predictor of persistent or recurrent disease.

The grading of CIN as found in the biopsy has some correlation with risk of recurrence[13]. Patients with CIN 3 have a much higher risk of residual or recurrent cervical preinvasive lesions and this may develop over prolonged follow-up[13]. Increasing age is identified as an independent risk factor for persistent or recurrent cervical preneoplasia[9]. Patients aged 50 years or more with involved endocervical margins constituted the highest risk group for recurrent disease[9]. This should be kept in mind when arranging follow-up schedules.

Patients with clear margins at CKC have a very low risk of subsequent abnormal smears of less than 1%[14]. Reich et al.[15] performed a study of 390 patients with involved margins after CKC, followed for a mean of 19 years clinically and with cytology and colposcopy, and found that 306 (78%) had no residual or recurrent disease, 78 (20%) had persistent cervical preinvasive lesions, and six (2%) had invasive cervical carcinoma. The risk of recurrence was higher in cases of involvement of both endo- and ectocervical margins than when only one margin was involved. Orbo et al.[16] found recurrent disease in 42 of 371 patients after CKC, but could not detect a significant correlation between relapse and margins on univariate analysis. Chao et al.[17] found that 279 of 765 (36%) patients treated with CKC had involved endo- or ectocervical margins. After 3 years of follow-up, the recurrence rate for CIN was 10.3%. Both HPV positivity at follow-up and involved margins had a significant association with recurrent disease and abnormal follow-up cytology. They proposed that HPV positivity at follow-up may predict those patients that will undergo recurrence.

Conclusion

The importance of the use of diagnostic and therapeutic guidelines and regular follow up is emphasized, bearing in mind primarily the young female population with severe preinvasive lesions of uterine cervix. Treating cervical preinvasive lesions offers an excellent opportunity to prevent the occurrence of cervical cancer in the large majority of women with abnormal cervical smears.

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CITOLOŠKO PRAĆENJE BOLESNICA S CIN-OM LIJEČENIH DIJATERMIJSKOM EKSCIZIJOM (LETZ), KLASIČNOM KONIZACIJOM I HLADNOM KONIZACIJOM PO SEMMU

S A Ž E T A K

Liječenje premalignih lezija vrata maternice započinje sa patološkim nalazom Papa testa. Regularni probir asimptomatskih žena pomoću Papa testa i drugih dijagnostičkih postupaka omogućuje nam da dijagnosticiramo i liječimo preinvazivne lezije prije nego što progrediraju u rak vrata maternice. Postoji širok izbor ablativnih I destrukcijskih metoda koje se koriste u liječenju premalignih lezija vrata maternice. U ovoj studiji uspoređivali smo kontrolne nalaza cervikalnih obrisaka (Papa test) kod pacijentica liječenih dijatermijskom ekscizijom (LLETZ- Large Loop Excision of the Transformation Zone), klasičnom konizacijom i hladnom koagulacijom po Semmu po osnovnom kriteriju: na ciljanoj biopsiji CIN (Cervikalna intraepitelna neoplazija), a primjena definitivnog zahvata s obzirom na dob, paritet i stupanj lezije. Terapijski uspjeh u sve tri grupe pacijentica smo odredili na osnovu citoloških nalaza. Normalne citološke nalaze poslije liječenja su imale 43 žene u LLETZ grupi (88%), 22 žene u CKC grupi (73%) i 22 žene u grupi liječenoj hladnom koagulacijom po Semmu (73%). Ističemo važnost primjene dijagnostički-terapijskog postupnika te redovitih kontrola nakon zahvata, prije svega, imajući na umu mlade nerotkinje koje trebaju sačuvati reprodukcijski potencijal. Liječenje premalignih promjena na vratu maternice pruža nam izuzetnu mogućnost da spriječimo pojavnost raka vrata maternice u većine žena sa patološkim obriscima vrata maternice (Papa test).