

# Outcomes of Two Years Follow-Up after Loop Electrosurgical Excision Procedure in a University Hospital

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**Introduction:** We aimed to determine our experience on Loop electrosurgical excision procedure (LEEP) in patients with cervical preinvasive lesions in an academic hospital in two years follow-up period.

**Materials and Methods:** Data from 64 patients with cervical preinvasive lesion who underwent LEEP were analyzed retrospectively. Human papillomavirus (HPV) status, cytological outcomes of patients before LEEP, and after 2 years follow-up period were documented.

**Results:** Prior to LEEP, 94.52% of patients were positive in terms of HPV status. HPV positivity rate was detected as 13.89% after LEEP. The most common detected HPV type in residual lesions was HPV 16. 67.19% of patients who underwent LEEP have negative cytology after two years follow-up period. The other cytological outcomes at this period were as follows; 21.88% of patients had ASCUS, 9.38% of the patients had LSIL and 1.56% of patients had HSIL cytology. Surgical margin status was positive in 6.25% of LEEP specimens. There were 3 patients who underwent re-LEEP in two years follow-up period for HSIL.

**Conclusion:** The LEEP procedure was applied to patients with HSIL and ASC-H with satisfactory recurrence rates in two years follow-up period.

**Keywords:** LEEP, HSIL, HPV, LSIL, cervical cancer, preinvasive lesion

## Introduction

The majority of cervical cancer cases are composed of women who have not been screened or not screened sufficiently for cervical cancer. Moreover 50% of patients diagnosed with cervical cancer have not previously had cervical cytology. Among the screening methods, Hpv and pap-smear tests are widely used (1).

Cervical cytological abnormalities and cervical cancer may develop in a small portion of high-risk Hpv positive cases. Hpv can cause temporary or persistent infection (2). Generally, temporary infections cause LSIL and persistent infections cause HSIL. Women with persistent infection may progress to HSIL or cervical cancer within 1 or 2 years (3). Cervical preinvasive

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lesions are classified histologically as benign, LSIL (CIN-I), HSIL (CIN-II and CIN-III). In addition, if CIN-II and CIN-III are not treated, it can progress to cervical cancer in 10-20 years (4). Therefore, histologically confirmed cases of CIN-II and CIN-III require treatment. For this purpose, there are 3 treatment options applied generally. These are cryotherapy, loop electro surgical excision procedure (LEEP) and cold conization. There is no consensus on which of these methods is superior. However, LEEP and cold conization procedures seems advantageous in terms of follow-up since pathological material is obtained (5). In addition, there are randomized controlled studies showing the risk of premature birth. In recent years, smear test and HPV test have been increasing in our outpatient clinic for cervical cancer screening both alone and as a co-test. The application of the LEEP procedure is also increasing due to increasing abnormal cervical pathology results. This study aims to reveal the 2-year follow-up outcomes of patients who underwent LEEP in our clinic.

### **Materials and Methods**

This retrospective study was approved by the local ethics committee for clinical research of Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey. Between January 2015 and January 2017, data from patients who underwent LEEP with the diagnosis of cervical preinvasive lesions were retrospectively analyzed.

Inclusion criteria were as follows: patients over the age of 18 with biopsy or endocervical curettage (ECC) proven ASC-H/HSIL/CIN2/3 with LEEP. The exclusion criteria of the study were as follows; the ones with prior LEEP history, diagnosed or underwent treatment of

any type of malignancy, suspicious adnexial mass, and cognitive limitations, and, incomplete records due to missing data or loss to follow-up. LEEP procedures in Mugla are done in operating room with sedation and anesthetics. Immediately prior to LEEP, Lugol's solution is used to identify the transformation zone and a LEEP electrode is selected to best fit the targeted tissue to be excised. An endocervical curettage (ECC) is subsequently performed. In follow up visits, targeted biopsies and ECC are used when clinically appropriate without use of anesthetic or sedation.

Cervical cytologies were prepared using liquid based tools and slides were examined using thin-prep procedure. Cervical cytology reports were determined according to 2001 Bethesda System; negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells-unspecified (ASC-US), low grade squamous intraepithelial lesion (LSIL), atypical squamous cells-high grade not excluded (ASC-H), high grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC). The results with ASCUS and above accepted as abnormal cytology. The Bethesda system was conducted by pathology experts while cytopathological examination of the cervicovaginal material collected from patient for Pap-test. Histological diagnoses were determined as benign, LSIL (CIN-I), HSIL (CIN-II and CIN-III), and SCC.

We used a commercial kit; digene HC2 HPV DNA Test (Qiagen Germantown, Inc., MD, USA) for HPV typing. This kit can detect 13 types of high-risk HPVs (16,18,31,33,35,39,45,51,52,56,58, 59,68) and 5 types of low-risk HPVs (6,11,42, 43,44). Patients characteristics such as age, gravida, parity, BMI (body mass index), history of smoking, diabetes mellitus and hypertension, indication for LEEP, HPV status before LEEP,

need for re-LEEP, surgical margin status of LEEP specimen and cytological outcomes after 2 year follow-up period were recorded. The necessary information was obtained from colposcopy forms, pathology and operative reports, and hospital database.

**Statistical Analysis**

Statistical analyses were performed using Statistical Package for the Social Sciences software, version 23 (SPSS, Inc., Chicago, IL). The data were expressed as the mean and range for continuous variables, and binary variables were reported as counts and %. Descriptive statistics were used to summarize baseline characteristics and follow up details.

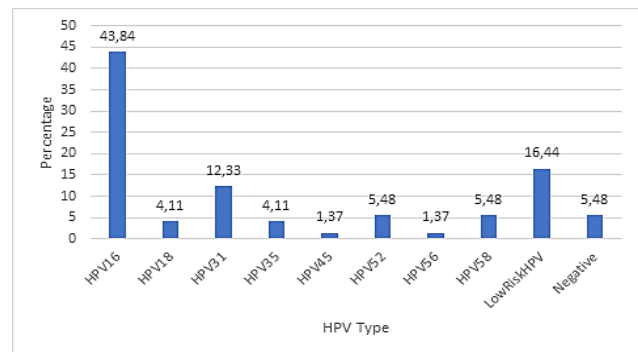
**Results**

During this period, 74 patients underwent LEEP by one surgeon with advanced experience on cervical preinvasive diseases. Among those patients, 2 had pathologic confirmation of microinvasive cervical cancer on LEEP pathology specimen. Medical records of eight patients could not be found and were lost to follow up. A total of 64 patients who underwent LEEP were included. The baseline descriptive statistics of the patients are listed in Table 1.

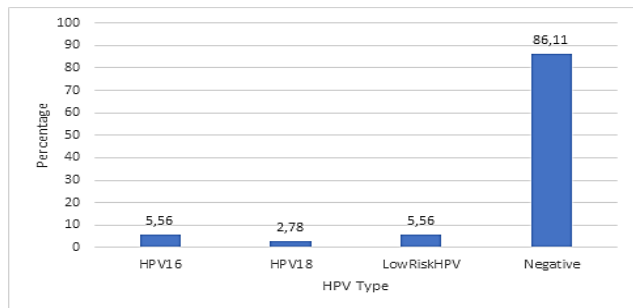
**Table 1.** Descriptive statistics of studied group

Variable	LEEP patients
Age	39.96±7.39 (26-59)
BMI	28.12±2.51 (23-34)
Gravidy	2.32±1.03
Parity	1.90±0.81
Smoking, n(%)	24 (37.5)
Diabetes, n(%)	6 (9.4)
Hypertension, n(%)	13 (20.3)
LEEP indication, n(%)	
▪ HSIL	61 (95.31)
▪ ASC-H	3 (4.69)
Re-LEEP n (%)	3 (4.69)
Margin positivity, n(%)	4 (6.25)

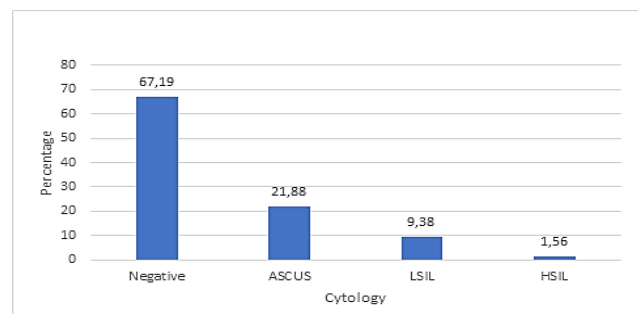
The average age of 64 patients who underwent LEEP was 39.96±7.39 years. The mean BMI of patients was 28.12±2.51. The mean gravidy and parity of those patients were 2.32±1.03 and 1.90±0.81, respectively. In 64 patients, 37.5% have smoking, 9.4% have diabetes mellitus and 20.3% have hypertension history. Indications for LEEP were HSIL in 61 patients and ASC-H in 3 patients.



**Figure 1.** Disrtibution of HPV types before LEEP



**Figure 2.** Distribution of HPV types of patients after two years follow-up for LEEP



**Figure 3.** Cytological outcomes after two years follow-up

Distribution of HPV types of patients before LEEP are shown in Figure 1. The most common detected HPV type was HPV 16 (43.84%) before

LEEP. HPV 31 was the second common high risk HPV type seen before LEEP. Of the 4 patients, there was no HPV type detected before LEEP. Distribution of HPV types of patients after two years follow-up for LEEP are shown in Figure 2. Of the 35 patients, 86.11 % of patients was negative for HPV after two years follow-up. The most common detected HPV types were HPV 16, low risk HPV types and HPV 18, respectively.

The cytological outcomes outcomes of the study group after two years follow-up were documented in Figure 3. 67.19% of patients who underwent LEEP have negative cytology after two years follow-up. 21.88% of patients have ASCUS, 9.38% of the patients have LSIL and 1.56 % of patients have HSIL cytology after two years follow-up. Four of 64 LEEP specimen (6.25%), surgical margin status were positive. There were 3 patients who underwent re-LEEP in two years period for HSIL. All of the patients who underwent re-LEEP were positive in terms of surgical margin status. One patient of the studied group underwent bilateral salpingo oophorectomy laparoscopic hysterectomy and for abnormal uterine bleeding in the sixth month of follow-up period.

## Discussion

In this research, we evaluated the two years follow-up outcomes of patients who underwent LEEP procedure for HSIL/ASC-H proven histopathologically. According to this report, it was revealed that LEEP procedure was an effective surgical option in the management of high grade cervical preinvasive diseases. Indeed, there were detected satisfactory outcomes and regression in cytopathological and HPV status of patients after two years follow-up period of LEEP.

In the present study, 1.56% of patients with pre-operative CIN 2/3 in colposcopic biopsy

showed persistence of the CIN 2/3 lesion. We observed resolution of the disease in 67.19% of patients with preoperative CIN 2/3. However, nearly 98% of the patients showed regression after LEEP. There was a dramatic regression after LEEP in two years follow-up period. Our study demonstrates a very high efficacy of LEEP for the treatment of CIN 2/3 with persistent disease in only 1.56% of patients and no recurrence in two year follow-up period. Previously published recurrence rates after LEEP procedure were 1.5, 2.2, 9.1 and 11.9% for CIN 2/3 (6–9). According to the results of these studies, there were much more margin positive cases than those in our study. We think that low margin positive cases may have a major role in lower recurrence rate of our study.

Papalia and his colleagues used laser ablation in combination with LEEP and reported lower recurrence rates as 3.2% (10). In our hospital, we did not have laser ablation technology. Although we did not use laser in this study, recurrence was not seen in any patient.

After LEEP operations, follow-up of HPV status of patients is very important. Kim et al reported 85% of patients after LEEP showed HPV clearance in the six month follow-up (11). Jing et al. reported HPV positivity of the patients as 95.6% before LEEP and 29.8% after LEEP in two years follow-up period (12). Bae et al. reported HPV status as 93% before and as 35.1% after LEEP and they concluded that detection of HPV status after conization may help to identify treatment failure or recurrence (13). In our study, we observed that the ratios of HPV negative patients increased from 5% to 86% after LEEP. Although the follow-up time was longer as two years, HPV clearance rate was similar to Kim et al.'s study. In this context, our study confirms that HPV clearance rate

increases gradually after LEEP. But the strict follow-up of HPV status of patients is necessary after operation for HPV persistence, especially for high risk genotypes. Some authors had reported that high-risk HPV status after LEEP is a better predictor of CIN recurrence than colposcopy or cytology results (11,14). However, some authors stated that high-risk HPV load prior to conization serves as a causative agent for recurrence(9).

In the study of Jing et al., 71% of patients who underwent LEEP were surgical margin positive (12). In our study, only 4 (6.25%) patients were positive in regard of surgical margin. Surgical margin status of LEEP patients is a major risk factor for recurrence or persistence of cervical intraepithelial neoplasia (15). Patients with positive surgical margin after LEEP have more likely experience recurrent CIN (16). In the literature, there are recurrence rates as high as 47% for patients with positive margin (17). In our study population, three of 4 patients with positive margin underwent LEEP again. Of these 3 patients, all of them were positive for HPV 16 subtype. Spontaneous regression was seen in one patient and HPV clearance was detected in her follow-up period. These findings of our study emphasizes the critical importance of persistence in high-risk HPV subtypes especially for HPV 16 at the follow up period of margin positive cases. Moreover, Bruno et al. reported that 40% of the relapsing cases in their study were seen in margin negative cases with persistent HPV 16 infection (18). We strongly agree with this opinion. If HPV 16 persistency is seen at the follow-up, a crucial attention must be given even the pathology report is margin negative.

The limitations of our study were having the retrospective design and small sampling

size with lack of a comparative group. The strength of our study was the completeness of cytological data and the low lost-to-follow-up rate. In future, researches may be planned as in prospective nature designed to evaluate adverse events, oncological findings and the quality of life of patients.

CIN recurrency may be encountered mostly within the subsequent two years follow-up period of LEEP. The rate of recurrence after LEEP is higher in HPV positive. Therefore, these patients necessitates careful monitorization. In identification of residual lesions or recurrences, Pap-smear and HPV testing have a central role at the follow-up strategies. However, recommendation favoring the use of more effective follow-up strategies for the margin positive patients should be supported with researches involving longer follow-up periods and larger patient series.

### **Ethical Statement**

This retrospective study was approved by the local ethics committee for clinical research of Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey.

### **Conflict of Interests**

The author declared no conflicts of interests.

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