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Evaluation of the results of loop electrosurgical excision procedure surgical margin positivity and recurrence

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ABSTRACT

Objectives: Loop electrosurgical excision procedure (LEEP), which is effectively used in the diagnosis and treatment of cervical intraepithelial neoplasia (CIN), can be performed under general and local anesthesia. The aim of this study is to retrospectively examine whether the chosen anesthesia method affects the surgical margin and the factors affecting the surgical margin.

Materials and Methods: Data of 122 patients who met the inclusion criteria and underwent LEEP between 2016 and 2021 were retrospectively analyzed. Demographic data (age, body mass index, alcohol and smoking); gynecological anamnesis: Gravida, parity, number of living children, number of abortions, menopausal status, type of contraceptive method and presence of additional metabolic diseases (hypertension, diabetes, coronary artery disease) were recorded from the patients' files and epicrisis. LEEP indications and pre-LEEP HPV information were recorded. LEEP procedure data: Anesthesia method used; general or local anesthesia, positive surgical margin rate (for example, the presence of CIN II/III at the ectocervical and/or endocervical resection margins was considered positive), size of the removed piece (anteroposterior length, transverse length and height, volume), pathology results were recorded and factors affecting margin positivity were examined.

Results: It was determined that the type of anesthesia administered (general or local), patient age older than 40 years, patient being in menopause, and the size and volume of the sample taken during LEEP had no effect on margin positivity, whereas high-grade cervical cytology before LEEP, the presence of endocervical gland involvement, and the number of multiple passes in the excision were shown to increase the risk for margin positivity.

Conclusion: We found that high-grade cervical cytology before LEEP, the presence of endocervical gland involvement, and multiple passes in excision were risk factors predicting a positive surgical margin; however, the type of anesthesia did not affect the surgical margin.

Keywords: HPV; LEEP; cervical intraepithelial neoplasia

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INTRODUCTION

Cervical cancer is among the preventable cancers with screening methods. Cervical cancer precursor lesions are defined as cervical intraepithelial neoplasia (CIN). CINs can be detected by smear and colposcopic biopsy and can be treated with conization methods [cold conization, loop electrosurgical excision procedure (LEEP)] without the need for advanced surgical operations.

Conization is the surgical removal of the lesioned part of the cervix in the shape of a cone. The application of this procedure using a scalpel is called cold conization, and the application of this procedure using a "U" shaped cautery tip is called the LEEP procedure. The presence of a lesion on the surgical margins of the piece taken as a result of post-procedure pathology is considered a positive surgical margin/positive margin, and in this case, the patient may require reconization or further surgery (trachelectomy) or hysterectomy. LEEP can be performed under local anesthesia (LA) or general anesthesia (GA), depending on patient preference, surgeon experience, and clinical parameters such as cervical anatomy, prolapse of the vaginal side walls, and pain during colposcopy.[1] The advantages of LEEP performed under LA include avoiding the risks associated with GA, eliminating the need for an operating theater, and, consequently, being more available and lower in cost. However, LEEP under LA can be more difficult to perform and can potentially lead to a smaller sample size and higher recurrence rates.[2] Data on positive surgical margin rates, the risk of recurrence of the cervical lesion, and the need for reconization are sparse and in consistent in the literature. Some studies suggest that a positive margin after LEEP is an important factor in recurrence and an indicator of the quality of clinical practice.[3] A meta-analysis has shown that positive surgical margins have an increased risk of residual or recurrence compared to negative surgical margins.[4] Previous studies have also found a fivefold increase in the risk of treatment failure with positive margins. However, it is not yet clear which factors influence positive margins after LEEP surgery. Studies evaluating LEEP procedures performed under GA and LA have found that patient satisfaction, pain, and procedure related complications rates are comparable between the two approaches. However, data on the rate of positive surgical margin detection after LEEP procedures performed under GA and LA and the need for reconization procedures are insufficient in the current literature.

In this retrospective study, we compared the rate of positive surgical margins, the need for reconization and post LEEP findings in patients who underwent LEEP under GA and LA.

MATERIALS AND METHODS

This retrospective study was carried out by retrospectively analyzing the cases treated with LEEP procedures and followed up between January 1, 2016 and December 31, 2021 in the Gynecological Oncology Clinic of Muğla Sıtkı Koçman University Training and Research Hospital. The study was approved by the Clinical Research Ethics Committee of Muğla Sıtkı Koçman University (E-72855364-050.01.04-608052).

Demographic data [age, body mass index (BMI), smoking]; gynecological anamnesis: Gravida, parity, number of living children, number of abortions, menopausal status, type of contraceptive method, and presence of additional metabolic diseases (hypertension, diabetes, coronary artery disease) were recorded from the patients' files and epicrisis. LEEP indications and pre-LEEP HPV information were recorded. LEEP procedure data: Method of anesthesia used; general or LA; positive surgical margin rate (for example, the presence of CIN II/III at the ectocervical and/or endocervical resection margins was considered positive); size of the removed piece (anteroposterior length, transverse length, and height); pathology results were recorded.

The LEEP procedure was performed by a single gynecology oncology specialist with knowledge and experience in the field.

Digene HC2 HPV DNA test (Qiagen Germantown, Inc., MD, USA) was used for HPV typing in our hospital. This kit can detect 13 types of high-risk HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and 5 types of low-risk HPV (6, 11, 42, 43, 44).

SurePath liquid-based cytology preperats available in our hospital were used as smear method.

In the LEEP procedure performed under LA, patients were prepared in the dorsal lithotomy position in the local procedure room in the outpatient clinic. A sterile speculum was inserted into the vagina, and 8 cc prilocaine was applied to the four quadrants of the cervix at 2, 4, 7, and 11 o'clock. After waiting for 60 seconds to ensure adequate anesthesia, cervical excision was performed using a LEEP tip suitable for the size of the cervix. The hemorrhages occurring in the cervix were coagulated with a 50W knob-tipped cautery.

In the patient group who underwent GA, standard monitoring was performed according to ASA recommendations after the patients were taken to the operating room. All patients received 1.5 mg/kg propofol, 1 mcg/kg fentanyl, and a laryngeal mask suitable for the patient' body weight under standard anesthetic management. For maintenance of anesthesia, 1 MAC desflurane and a 0.4/0.6 oxygen/air mixture were administered. After the anesthesiologist gave approval to start the procedure, a sterile

speculum was inserted into the vagina, and cervical excision was performed using a LEEP tip in accordance with the size of the cervix. The hemorrhages occurring in the cervix were coagulated with a 50W knob-tipped cautery.

In both procedures, the samples were taken to the pathology laboratory in a formaldehyde solution.

Age, smoking status, presence of chronic diseases, BMI, number of pregnancies and births, presence of menopause, whether they used a hormonal contraceptive method, smear result, HPV positivity status, cervical biopsy result (if any), under which anesthesia method the LEEP procedure was performed (general or local), size of the piece taken after the LEEP procedure, pathology result reports, presence of a positive surgical margin, and presence of endocervical gland involvement were recorded as data.

Population and Sample of the Study

Criteria for inclusion in the study: Patients who were found to be HPV 16-18 positive, had intraepithelial lesions as a result of smear, and underwent LEEP due to HGSIL (CIN II-III) as a result of colposcopic biopsy at the Gynecological Oncology Clinic of Muğla Sıtkı Koçman University Training and Research Hospital were included in the study.

Exclusion criteria for the study: Patients who did not attend routine check-ups and were lost to follow-up within the first year after the procedure were not included in the study.

Statistical Analysis

Statistical analyses were performed in the Statistical Package for Social Sciences (SPSS) version 18.0 package program. The descriptive statistics of the data were given in tables. The suitability of the numerically measured data for a normal distribution was analyzed by the Shapiro-Wilk test. Parametric tests were used for normally distributed variables, and non-parametric tests were used for non-normally distributed variables. Student's independent, Mann-Whitney U, and chi-square (Pearson chi-square, Monte Carlo chi-square) tests were used to compare independent groups with each other. A probability value of $p<0.05$ was considered significant.

RESULTS

A total of 122 patients who were found to be HPV 16-18 positive in screening, who had intraepithelial lesions on smear, who underwent LEEP after colposcopic biopsy revealed HGSIL (CIN II-III), and including 61 patients who were margin-positive and 61 patients who were margin-negative according to pathology results were included in our study. When the groups were evaluated in terms of demographic data, it was observed that they were homogenous (Table 1).

There was no statistically significant difference between margin positive and negative patients in terms of age older than 40 years ($p=0.415$). The mean age of margin-positive patients was 34.8±8.81 years, and the mean age of margin-negative patients was 37.8±11.39 years. It was found that body mass index and intrauterine device use did not make a statistically significant difference in margin positivity ($p=0.887$, $p=1.000$). It was observed that 29.50% (n=18) of the margin-positive women had alcohol consumption, and alcohol consumption did not make a difference in margin positivity or negativity when compared with non-users ($p=0.840$). Similarly, for smoking, 41.00% (n=25) of the patients with margin positivity were found to be smokers, and smoking did not make a difference ($p=1.000$).

According to margin positivity and the presence of menopause, margin groups were divided as positive and negative. The menopause classification was grouped by the presence or absence of menopause. In the statistical analysis, margin-positive patients who were in menopause at the same time constituted

Table 1. The effect of demographic characteristics on margin positivity

Variables	Group 1 Margin positive (n=61)	Group 2 Margin negative (n=61)	*p*-value
Age>40[a]	14 (23.00)	19 (31.10)	0.415
Body mass index (kg/m² [b])	25.80±4.17	26.09±4.22	0.887
Menopause[a]	8 (13.10)	18 (29.50)	0.045
Vaginal delivery[a] 1	11 (36.70)	14 (42.40)	0.797
≥2	19 (63.30)	19 (57.60)	
Alcohol consumption[a]	18 (29.50)	16 (26.20)	0.840
Smoking[a]	25 (41.00)	25 (41.00)	1.000
Use of intrauterine device[a]	7 (11.5)	7 (11.5)	1.000

[a]: Frequency values (percentage rates); [b]: Mean values ± standard deviation

13.10% (n=8), while those who were not in menopause constituted 86.90% (n=53) of the group. Margin-negative patients who were in menopause at the same time constituted 29.50% (n=18) of the group, while those who were not in menopause constituted 70.50% (n=43). There was a significant difference between the margin groups and the presence or absence of menopause (p=0.045), and this difference was caused by the non-menopausal group.

Similarly, in the comparison of vaginal deliveries (1 or ≥2) according to margin positivity and negativity, margin positivity was observed in 36.7% (n=11) and negativity in 42.40% (n=14) of vaginal deliveries. In those who had two or more vaginal deliveries, margin positivity was 63.30% (n=19) and negativity was 57.60% (n=19). In the analysis between the margin groups and vaginal delivery groups, it was observed that there was no difference between these groups (p=0.797) (Table 1).

Table 2. Effect of pathology material on margin positivity

	Group 1 Margin positive (n=61)	Group 2 Margin negative (n=61)	*p*-value
LEEP material[a]			
Length (mm)	23.88±5.89	24.6±5.87	0.873
Width (mm)	11.01±2.36	10.83±2.48	0.885
Height (mm)	17.6±3.67	17.8±3.56	0.820
Volume (cm³)	1.62±0.84	1.67±0.89	0.709
Pathology result[b]			
CIN II	23 (37.70)	43 (70.50)	0.001
CIN III	38 (62.30)	18 (29.50)	0.001
Endocervical[b]			
Positivity	15 (24.60)	3 (4.90)	0.004
Negativity	46 (75.40)	58 (95.10)	0.004

[a]: Mean values ± standard deviation; [b]: Frequency values (percentage rates)

Those with endocervical positivity were margin-positive with 24.60% (n=15) and margin-negative with 4.90% (n=3). Those with endocervical negativity were margin-positive with 75.40% (n=46) and margin-negative with 95.10% (n=58). In the analysis performed according to the margin positivity and negativity of endocervical positive and negative patients, a significant difference was found, and this difference was observed in both endocervical negative and margin negative groups (p=0.004) (Table 2).

In the analysis performed between the groups with CIN II and CIN III in LEEP pathology results and those with positive and negative margin, it was observed that the margin-negative groups of those with CIN II (70.50%) (n=43) in LEEP pathology results made a significant difference, whereas in those with CIN III (62.30%) (n=38), this difference was due to the margin-positive group (p=0.001) (Table 2).

In the LEEP materials taken, the mean length of the sample of those with positive margins was 23.88±5.89 mm, the mean height was 17.67±3.67 mm, the mean width was 11.01±2.36 mm, and the mean volume was 1.62±0.84 cm³; negative ones were found to be 24.63±5.87 mm, 17.67±3.67 mm, 11.01±2.36 mm, 1.67±0.89 cm³, respectively. The analysis of length, width, height and volume values on margin positivity and negativity showed no significant differences (p=0.873, p=0.820, p=0.885, p=0.709, respectively) (Table 2).

In the multivariate analysis of variance, it was seen that the margin positivity rate of patients with CIN III detected in the LEEP pathology result made a significant difference (p=0.001). Similarly, there was a significant difference in the number of multiple passes in the way the LEEP material was obtained with the margin positivity rate (p=0.045). Endocervical positivity was found to make a significant difference in margin positivity (p=0.011) (Table 3).

Table 3. Evaluation of age, anesthesia type, endocervical positivity, menopausal status, transformation zone type and pathology results on margin positivity according to single and multiple analysis of variance

Variables	Univariate analysis			Multivariate analysis		
	Hazard rate	95% CI	*p*-value	Hazard rate	95% CI	*p*-value
Age (≤40y or >40y)	1.51	0.67-3.39	0.310	1.12	0.27-4.58	0.870
Anesthesia type (general or local)	1.46	0.67-3.14	0.330	1.29	0.53-3.16	0.560
Endocervical positivity (present or not)	0.15	0.04-0.58	0.005	0.168	0.04-0.67	0.011
Menopausal status (present or not)	1.97	0.76-5.11	0.160	1.12	0.21-5.99	0.890
Number of transitions	0.35	0.15-0.77	0.009	0.41	0.17-0.98	0.040
Transformation zone type	1.31	0.68-2.52	0.410	1.14	0.51-2.53	0.730
Pathology	0.23	0.11-0.50	0.0002	0.24	0.10-0.59	0.001

CI: Confidence interval

The type of anesthesia (general or local) had no effect on margin positivity (p=0.560) (Table 3).

DISCUSSION

Cervical cancer is an important disease in terms of public health today, and this situation is expected to continue in the near future. The slow course of cervical cancer pathogenesis compared to other malignancies distinguishes it from other malignant diseases. Therefore, the importance of screening, identification, and treatment of preinvasive lesions is increasing. As a result, it is aimed at improving the treatments used in current management, increasing patient satisfaction and comfort, and reducing disease progression.[5]

LEEP surgery is frequently used in the treatment of cervical preinvasive lesions compared to all other methods and is offered as the primary option in developed countries. Another reason for preference is that it provides diagnosis and treatment at the same time in the indicated patient population. In addition, perioperative and postoperative complication rates are lower compared to other treatment modalities.[6]

A positive surgical margin is one of the most important predictors of recurrence.[4] Therefore, gynecologists should know how to avoid a positive surgical margin when performing LEEP and should make every effort to prevent inadequate excision.[7]

LEEP is a method that can be performed under GA or LA. Our Ministry of Health and national associations have made no additional recommendations for the selection of anesthesia. Likewise, while international associations and organizations such as World Health Organization, ASCCP and ACOG do not make a standard recommendation on the selection of anesthesia for excision procedures, the United Kingdom National Health Service Guide recommends that excision procedures for cervical preinvasive lesions be performed under LA.[8-11]

There are a limited number of studies in the literature comparing anesthetic methods for LEEP. Tzur et al.[2] examined the effect of general and LA on recurrence in 146 patients undergoing LEEP. Under GA compared with LA, the proportion of positive sample margins was similar for both the endocervical margin [16/71 (22.5%) and 16/75 (21.3%), respectively; p=0.861] and the ectocervical margin [14/71 (19.7%) and 11/75 (14.7%], respectively; p=0.418. The type of anesthesia was not shown to make a difference for margin positivity.[12] Güngördük et al.[13] evaluated a total of 244 patients who underwent LEEP (123 under LA and 121 under GA) and found margin positivity in 14 (11.3%) patients in the LA group and 11 (9.9%) patients in the GA group and found that the type of anesthesia did not make a statistically significant difference on margin positivity. Our study demonstrated that the type of anesthesia preferred during LEEP had no effect on margin positivity, supporting the existing literature. It is obvious that margin positivity is a risk factor for recurrent disease.[14] Considering that the type of anesthesia to be chosen has no effect on margin positivity, LA seems to be more practical and applicable in terms of being simpler, shorter hospital stay, and less costly compared to GA.

In their retrospective study including 1.359 patients, in which they evaluated the involvement of margin, disease recurrence and incidence of complications, Xiang et al.[15] found that the rate of premenopausal patients with positive margins in the LEEP materials was 6.9%, while the rate of postmenopausal patients was 16.9%. Xiang et al.[15] showed that menopause is a risk factor for positive surgical margins (95% confidence interval: 1.6-5.9, p<0.01). In our study, it was found that menopause was not a risk factor for margin positivity. A higher rate of margin positivity was found in the premenopausal patient group. In the menopausal period, the size of the cervix atrophies compared to the premenopausal period.[16] There as on why we obtained different results from the existing literature may be due to the higher rate of specimen removal with multiple passes during the LEEP procedure and the higher number of premenopausal patients.

Kanjanasirirut et al.[17] analyzed 547 patients who underwent LEEP in a study on the factors affecting margin positivity and showed that 74.1% (n=405) of these patients were multiparous, 25.9% (n=142) were nulliparous, 39.0% (n=158) of multiparous patients, and 6.3% (n=9) of nulliparous patients were margin positive. The Kanjanasirirut et al.[17] study revealed that multiparity was an important factor for a positive surgical margin after LEEP. Durmuş et al.[18] found margin positivity in 30.6% (n=82) and margin negativity in 69.4% (n=186) of 268 patients who underwent conization. Margin positivity was found in 9.5% (n=2) of 7.8% (n=21) nulliparous patients in the study. Durmuş et al.[18] reported a significantly lower surgical margin positivity rate in nulliparous patients.[18] In our study, unlike the current literature, no significant difference was found between the number of vaginal deliveries and margin positivity. While the margin positivity rate of patients who delivered vaginally was compared in our study, no distinction was made in terms of mode of delivery in the other studies analyzed. Larger-scale studies should be conducted to reach a meaningful and clear conclusion in the study design in which similar subgroups will be compared in terms of mode of delivery.

Kanjanasirirut et al.[17] found that 54.5% (n=145) of 266 patients with endocervical gland involvement were margin-positive. In our study, we found that the risk of margin positivity increased

in the presence of endocervical gland involvement, supporting the current literature.

Papoutsis et al.[19] reported that a conization height of more than 10 mm resulted in significantly less residual disease. In the subgroups with conization depth <10 mm and >10 mm, the number of lesions not completely removed was 64/222 (28.0%) and 28/139 (20.0%), respectively (p=0.013). Beyer et al. reported 100% negative margin cones with a cone height of 20 mm. Resection height values between 10 and 19.9 mm resulted in 73% negative margin cones.[20] Öz et al.[21] found that cone volume, cone length, and cone height of conization samples were not related to the margin status of conization samples, but the mean cone height was significantly different between margin-positive and margin-negative patients. The cone heights of patients with positive margins were smaller than those of patients with negative margins (13.7 mm and 15.1 mm, respectively $p \leq 0.05$).[21] In our study, we found that length, width, height, and volume values did not produce significant differences in the analysis of margin positivity and negativity. Thereas on why we did not find statistically similar results with the existing studies may be that the mean height of the LEEP materials taken in our study was higher than the risk limit specified in the studies examined.

In the study of Fan et al.[22] 94.7% (n=54) of the margin-positive cases were HSIL. In a study of 135 patients, 57.8% (n=78) were margin negative and 42.2% (n=57) were margin positive. Univariate analysis in the study by Sun et al.[23] showed that parity, cytological grade, multiple quadrants of CIN III by punch biopsy, gland involvement, as well as depth of conization, were significant factors associated with a positive margin (p=0.05). Multivariate analysis revealed that the cytological grade of CIN III (odds ratio=1.92) was the significant determinant increasing the risk of positive margin.[23] In our study, we determined that the risk of a positive margin increased as the grade of HSIL increased, supporting the literature.

Study Limitations

The fact that our study design was retrospective, there was no randomization, and the low number of patients can be considered weaknesses. However, the strength of our study is that LEEP procedures were performed by the same surgeon in a single center, and a more homogeneous group was formed by including only patients with HPV 16-18 positivity by excluding patients with invasive cancer and carcinoma *in situ* on cervicalcytology before conization and similarly excluding patients with invasive cancer and carcinoma *in situ* on final pathology.

CONCLUSION

High-grade cervical pathology before LEEP, the presence of endocervical gland involvement, and multiple passes in excision are risk factors predicting a positive surgical margin. The type of anesthesia applied does not affect the surgical margin.

ETHICS

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Muğla Sıtkı Koçman University (E-72855364-050.01.04-608052).

Informed Consent: Retrospective study.

Contributions

Surgical and Medical Practices: H.E.T., K.G.; Concept: H.E.T.; Design: H.E.T.; Data Collection or Processing: H.E.T., K.G.; Analysis or Interpretation: H.E.T., B.S.; Literature Search: B.S.; Writing: H.E.T.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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