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ORIGINAL RESEARCH

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Comparing loop electrosurgical procedure pathology results in the inpatient and outpatient setting

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Abstract

Loop electrosurgical excision procedures (LEEPs) provide diagnostic information and may be therapeutic. There is limited evidence comparing LEEP outcomes as they relate to treatment setting. We sought to evaluate specimen outcomes of inpatient versus outpatient LEEPs. All patients who underwent LEEP over eight years at a single institution were identified retrospectively. Chart review was conducted to extract data. We analyzed 868 LEEP specimens; 86.4% from the outpatient and 13.6% from the inpatient setting. There was no significant difference in the rates of positive margins or thermal artifact. Fragmentation of the specimen was noted in 39% of inpatient LEEPs compared to 26.1% of outpatient LEEPs ($p = 0.14$). The median depth of specimen was 8 millimeters in both groups. These results suggest that outpatient LEEP may be equally effective in the management of cervical intraepithelial neoplasia with potential cost and patient safety implications.

Keywords

Cervical cancer; Cervical intraepithelial neoplasia; Colposcopy; LEEP; Loop electrosurgical excision procedure

1. Introduction

The management of cervical intraepithelial neoplasia (CIN) hinges on factors such as patient age, degree of cellular atypia, parity and patient preference for treatment versus observation. The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends observation with repeat testing for low grade squamous intra-epithelial lesions (LSIL) and treatment over observation for high-grade squamous intraepithelial lesions (HSIL), previously CIN2 and CIN3 [1]. Similarly, the Europe Against Cancer Programme recommends that LSIL warrants repeat cytology or colposcopy and treatment for HSIL [2]. Treatment options include excision *via* loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC), or ablation using cryotherapy or a carbon dioxide (CO_2) laser. Ablative procedures leave no specimen for pathologic analysis and should only be used in patients whose dysplasia has been thoroughly characterized and when the risk of invasive cancer is thought to be extremely low [3]. Excisional procedures are thus recommended over ablative techniques by the ASCCP for management of HSIL [3].

LEEP entails the use of a diathermy wire loop to excise the transformation zone and areas of known cervical dysplasia as visualized on prior colposcopy. LEEP has been shown to be efficacious in the management of cervical dysplasia [4]. In the past, society guidelines have recommended the use of CKC over LEEP due to fear that thermal artifact from the latter may impact the pathologist's ability to determine margin status. However, a recent meta-analysis demonstrated no significant difference in rates of residual disease or disease recurrence between the two methods [5].

The majority of LEEPs are performed in the outpatient office setting. While no cost analysis has been done to compare the costs of inpatient LEEPs to outpatient office LEEPs, it can be assumed that an outpatient office LEEP is more cost effective. Despite the ability to perform a LEEP in the office, there are many reasons why patients or providers may choose to undergo LEEP in the operating room.

While outpatient office LEEPs are more common than inpatient LEEPs, there is limited data on whether the setting in which a LEEP is performed affects specimen quality and interpretation. Only one previous study examined whether LEEP setting influenced specimen quality or patient outcomes, finding that regardless of the setting in which the LEEP was performed, outcomes were similar [6]. However, this study did not explore reason for treatment setting and the potential impact on outcomes. Thus, the present study sought to assess whether the setting in which a LEEP is performed is associated with specimen quality and to evaluate decision making for inpatient versus outpatient LEEP.

2. Materials and methods

After Institutional Review Board approval was obtained, all patients who underwent a LEEP at our academic institution between November 2013 and August 2021 were identified

via electronic medical record (EMR) query retrospectively. Eligible patients were nonpregnant women >18 years old. The outpatient setting is defined as an office or clinic-based procedure where only local anesthesia was used. At our institution intracervical blocks are administered using lidocaine with or without epinephrine. No other medications or analgesics are provided to the patient. The inpatient setting is defined as an outpatient or inpatient surgical center where regional or general anesthesia was administered prior to the procedure. Given the retrospective nature of this study, decision for inpatient versus outpatient LEEP was a joint decision by the provider and patient, no randomization occurred. Women who underwent two or more LEEPs during the study period were included as separate encounters for each LEEP. Women who underwent a cold knife conization were excluded from this study.

Patient demographics, parity, clinical risk factors, insurance type, provider type and LEEP setting were abstracted from the medical record. In addition, human papilloma virus (HPV) testing, colposcopy pathology and LEEP pathology were collected specifically looking at thermal artifact, margin status, specimen depth and specimen fragmentation. The rationale for the treatment setting of LEEP was collected through the medical record by reviewing clinical notes written by providers. The general gynecology offices at our institution have access to LEEP equipment in the outpatient setting; however, the gynecologic oncology offices do not. Both round and triangle LEEP loop electrodes are used at our institution. In this study a range of different sized loops were found to be used by providers.

All LEEP specimens at our institution are processed using routine prosecting techniques, which entail serial sectioning of the specimen and microscopic examination of the entire specimen. Immunohistochemistry for p16 is not routinely performed. However, if severe thermal damage is noted along the edge of the epithelium of the specimen, p16 staining is performed to evaluate for dysplasia. p16 staining is also used to further characterize morphologically atypical changes in which the presence of high-grade dysplasia is uncertain, or scenarios in which a high-grade squamous intraepithelial lesion was seen on a prior biopsy, but high-grade pathology is not seen on the LEEP specimen [7].

Statistical analysis was performed using SPSS (https://www.ibm.com/products/spss-statistics). Median values with interquartile ranges (IQR) were used to describe continuous data, and categorical variables were displayed as frequencies and percents. Mann-Whitney U tests were used to compare continuous variables. Chi-square tests were used to compare categorical variables. Multinomial logistic regression was used to evaluate categorical clinical outcomes adjusted for significant demographic differences. The statistical significance level was set at a p-value of < 0.05.

3. Results

From November 2013 to August 2021, 868 LEEPs were performed at our institution. Of these procedures, 86.4% (750/868) were performed in the outpatient setting and 13.6% (118/868) in the inpatient setting. Table 1 describes patient demographics and provider type.

Pathology results of both the colposcopy and LEEP specimens, in addition to HPV testing results, are shown in Table 2. A significant difference in both colposcopy and LEEP pathology results was noted overall when comparing inpatient to outpatient procedures. When excluding patients with ACIS or SCC on colposcopy pathology, there was no significant difference in LSIL or HSIL results between the inpatient and outpatient setting, $p = 0.71$. To explore potentially clinically relevant differences, colposcopy and LEEP pathology results were categorized into three groups: (1) benign and LSIL pathology (CIN1), (2) HSIL pathology (CIN2 and CIN3), and (3) adenocarcinoma *in situ* (ACIS) or squamous cell carcinoma (SCC) pathology. Multinomial logistic regression demonstrated that compared to inpatient procedures, patients in the outpatient setting were less likely to have ACIS or SCC on colposcopy (odds ratio (OR) = 0.08, 95% confidence interval (CI) 0.04–0.19) and LEEP pathology (OR = 0.37, 95% CI 0.17–0.80).

The LEEP specimens were further analyzed looking at margin status, presence of thermal artifact, specimen depth and specimen fragmentation, as shown in Table 3. The only significant difference was the rate of fragmentation of the LEEP specimens. Fig. 1 demonstrates the median and quartile ranges of depth of the specimens. When comparing the LEEP specimens by provider type (gynecologic oncologists *vs.* general obstetrician-gynecologists), no differences were noted in depth of the LEEP specimen (median 8 mm for both provider types, $p = 0.95$), presence of artifact (4.4% *vs.* 4.7%, $p = 0.93$), fragmented specimens (23.8% *vs.* 27.9%, $p = 0.89$), or positive margins (38.1% *vs.* 21.3%, $p = 0.66$).

Of the 118 patients who underwent an inpatient LEEP, 115 (97.5%) had a reason for an inpatient procedure documented in the EMR, demonstrated in Fig. 2. The most common reason for an inpatient LEEP was patient preference (31.3%) followed by difficult anatomy (25.2%). A patient's preference was generally cited as anxiety or poor tolerance of in-office colposcopy examination. Difficult anatomy was described as a cervix flush with the vagina, large body habitus, redundant vaginal tissue, or the inability to visualize the cervix completely. The comorbidities requiring an inpatient procedure included patients with an increased bleeding risk (including hemophilia, use of anticoagulation medication, liver disease), multiple sclerosis with neurologic impairment and mental delays. Concurrent cases with LEEP included a scheduled ear-nose-throat surgery, hysteroscopy or dilation and curettage, laser ablation for vaginal dysplasia, mid-urethral sling placement, or repair of gynecologic fistula.

Further sub-analysis was conducted in the inpatient LEEP group only, under the assumption that the most technically challenging LEEPs would be for patients with difficulty anatomy or large areas of dysplasia. When considering the inpatient group only, there was no significant difference in rates of fragmentation (45.5% *vs.* 34% $p = 0.26$), positive margin status (27.2% *vs.* 23%, $p = 0.64$), thermal artifact (3.0% *vs.* 4.9%, $p = 0.66$), or median specimen depth (7 mm *vs.* 8 mm, $p = 0.37$) in patients with difficulty anatomy or large areas of dysplasia versus other indications.

TABLE 1. Demographics, provider type and insurance status of patients undergoing LEEP.

	Inpatient LEEP	Outpatient LEEP	*p*-value
Age (Median ± IQR)	39 ± 21	34 ± 12	<0.001
BMI (Median ± IQR)	26.6 ± 8.0 kg/m^2	24.0 ± 6.1 kg/m^2	<0.001
Parity (Median)	2	1	<0.001
Race Ethnicity (N, %)			
Non-Hispanic White	51 (43.2%)	387 (51.6%)	
Hispanic	45 (38.1%)	174 (23.2%)	
American Indian or Alaskan Native	0	3 (0.4%)	0.030
Native Hawaiian or Pacific Islander	1 (0.8%)	3 (0.4%)	
Mixed, not otherwise specified	5 (4.2%)	52 (6.9%)	
Provider Type (N, %)			
Generalist	99 (83.9%)	747 (99.6%)	
Oncologist	19 (16.1%)	2 (0.3%)	<0.001
Family Medicine	0	1 (0.1%)	
Insurance Status			
Public	69 (58.5%)	247 (32.9%)	<0.001
Private	46 (39%)	489 (65.2%)	

LEEP: loop electrosurgical excision procedures; IQR: interquartile ranges; BMI: body mass index.

TABLE 2. HPV, colposcopy and LEEP pathology results.

	Inpatient LEEP	Outpatient LEEP	*p*-value
HPV Testing (N, %)			
16 positive	18 (20.5%)*	153 (25.8%)**	
18 positive	8 (9.1%)*	37 (6.2%)**	0.390
Non 16/18, not otherwise specified	63 (71.6%)	411 (69.2%)	
Colposcopy Results (N, %)			
Benign	8 (6.8%)	37 (4.9%)	
LSIL/CIN1	6 (5.1%)	50 (6.7%)	
HSIL/CIN2	28 (23.7%)	309 (41.2%)	
HSIL/CIN3	51 (43.2%)	319 (42.5%)	<0.001
ACIS	11 (9.3%)	10 (1.3%)	
SCC	4 (3.4%)	0	
Not performed/inadequate	10 (8.5%)	25 (3.4%)	
LEEP Results (N, %)			
Benign	33 (28%)	133 (17.7%)	
LSIL/CIN1	6 (5.1%)	51 (6.8%)	
HSIL/CIN2	12 (10.2%)	214 (28.5%)	<0.001
HSIL/CIN3	57 (48.3%)	323 (43.1%)	
ACIS	7 (5.9%)	17 (2.3%)	
SCC	3 (2.5%)	12 (1.6%)	

**One patient was positive for both HPV 16 and 18, included in each category separately.*
***Seven patients were positive for both HPV 16 and 18, included in each category separately.*
LEEP: loop electrosurgical excision procedures; HPV: human papilloma virus; LSIL: low grade squamous intra-epithelial lesions; CIN: cervical intraepithelial neoplasia; HSIL: high-grade squamous intraepithelial lesions; ACIS: adenocarcinoma in situ; SCC: squamous cell carcinoma.

TABLE 3. Characteristics of LEEP specimens.

	Inpatient LEEP	Outpatient LEEP	*p*-value
Fragmented specimen (N, %)	46 (39.0%)	196 (26.1%)	0.01
Thermal artifact present (N, %)	6 (5.1%)	32 (4.2%)	0.69
Depth of specimen (Median ± IQR)	0.80 ± 0.60 cm	0.80 ± 0.70 cm	0.76
Positive margin (N, %)	30 (25.4%)	158 (21.1%)	0.29

LEEP: loop electrosurgical excision procedures; IQR: interquartile ranges.

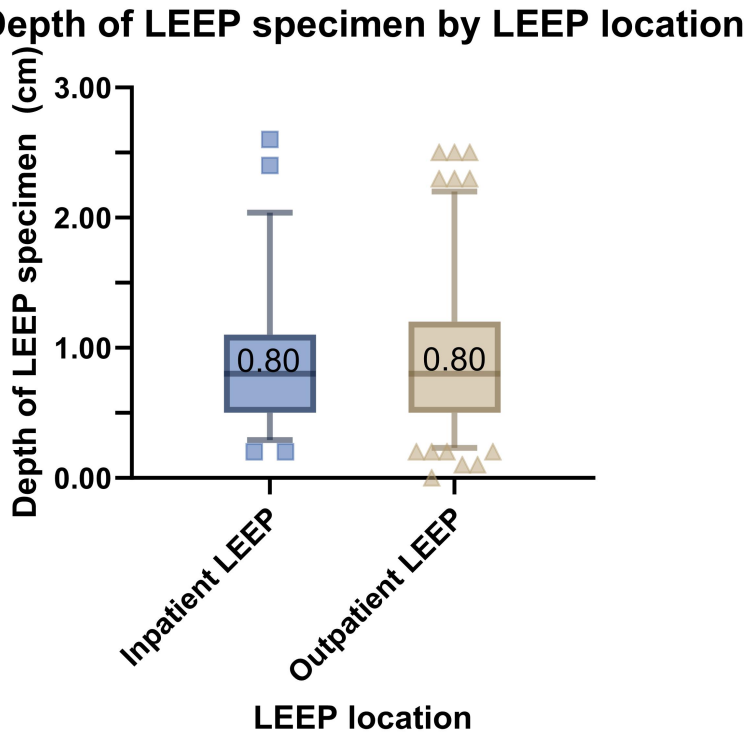

FIGURE 1. Comparison of LEEP specimen depth. Whiskers 1–99 percentile with outliers plotted.

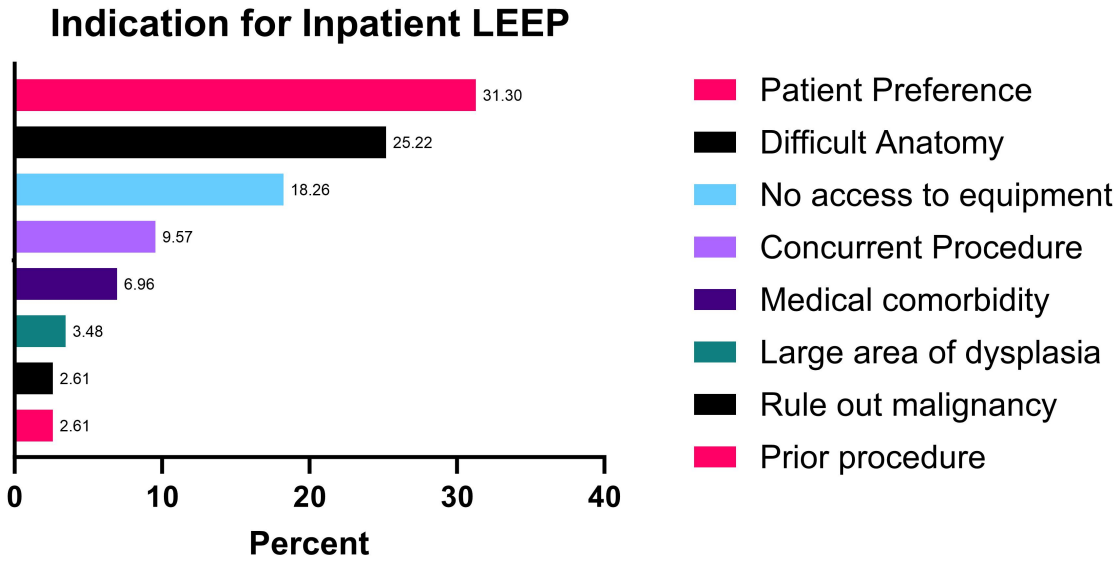

FIGURE 2. Indication for inpatient LEEP.

4. Discussion

In this single institution, retrospective study, we were able to analyze 868 LEEPs over a period of 8 years, the majority of which were performed in the outpatient setting. Patients who received an inpatient LEEP tended to be older, have a higher body mass index (BMI) and higher parity compared to the outpatient group. Patients with an inpatient LEEP tended to have higher-grade lesions compared to the outpatient group. However, when ACIS and SCC colposcopy results were excluded from analysis, there was no significant difference in colposcopy results. Additionally, no significant difference was seen between inpatient and outpatient LEEPs with respect to thermal artifact and margin status. This may be a result of more ubiquitous use of p16 immunohistochemical staining to evaluate specimen margins at our institution, specifically when margins are affected by thermal damage. The median specimen depth was 8 mm for both groups despite a range in loop electrodes used by our providers. The only significant difference between groups was the rate of fragmentation, which was higher in the inpatient setting.

Our study did demonstrate some similarities to the prior retrospective study analyzing LEEPs in the inpatient versus outpatient setting [6]. The prior study showed no significant difference between incomplete excision or thermal artifact, similar to our results. Our study demonstrated a median depth of 8 mm compared to a mean of 9.35 mm in inpatient setting compared to 8.4 mm in the outpatient setting in the aforementioned retrospective study, $p = 0.71$. However, this prior research did not comment on fragmentation or reason for inpatient LEEP.

A prospective study of 100 LEEPs compared effects of local, locoregional and general anesthesia on pathology specimens [8]. They found that while there was no difference in specimen depth when fresh, there was a significant difference in specimen depth when fixed with formaldehyde; 8.8 millimeters in the local anesthesia group compared to 11.2 mm in the general anesthesia group. Local anesthesia can cause local edema which could explain the similar depth prior to fixation. It could be inferred that the depth of resection is larger in women undergoing LEEP with general or locoregional anesthesia. However, our study did not show a difference in specimen depth when fixed by pathology among women undergoing an inpatient LEEP, which is done under general anesthesia at our institution.

Excisional procedures optimally remove an intact specimen to facilitate accurate interpretation of margin status. The European Society of Gynaecological Oncology (ESGO) recommends that care should be taken to provide an intact (unfragmented) specimen with minimal artifact [9]. A retrospective study recently demonstrated that fragmented specimens tend to have higher rates of both indeterminate and positive margins in addition to higher rates of high-grade lesion recurrence [10]. However, this was not the case when controlling for unfragmented LEEP specimens plus a top-hat for better sampling of the endocervical canal. Our study demonstrated a significant difference in the rates of specimen fragmentation between the inpatient and outpatient groups, 39% compared to 26.1%. When looking at the inpatient LEEPs only, we compared results of patients with areas of large dysplasia or difficult patient anatomy to the remainder of patients and saw similar rates in fragmentation. It can be inferred that inpatient LEEPs have higher rates of fragmentation that are not alone due to larger areas of dysplasia or difficult anatomy.

Excisional procedures for women with cervical dysplasia can increase risks of future obstetric complications. Multiple studies and systematic reviews have demonstrated that LEEPs increase the risk of preterm delivery and premature rupture of membranes [11–13]. A Cochrane review of 69 studies including 65,000 women who underwent a LEEP demonstrated an increased risk of preterm birth, but the relationship to specimen depth was overall low-quality data [14]. A retrospective study of all deliveries in Denmark over a 9-year period did show that increasing cone depth was associated with an increased risk of preterm delivery with an estimated 6% increased risk of preterm birth for every additional millimeter excised. This rate significantly increased with specimens greater than 10 millimeters. A median depth of specimen for both our study groups was 8 millimeters. Thus, our results suggest that recommendation for an inpatient versus outpatient LEEP specifically should not be based on future fertility desires.

Compared to prior data, the present study utilizes a larger study population and therefore may provide more generalizability to patients undergoing LEEPs. Limitations include those inherent to retrospective chart reviews, which may not fully account for patient differences in selection for inpatient versus outpatient treatment setting. We were not able to examine complication rates between the two groups, given their uncommon frequency and unreliable follow up information. In addition, we did not follow up on Pap or colposcopy results after LEEPs to determine the adequacy of the excision in achieving a cure between the inpatient and outpatient groups.

5. Conclusions

These results suggest that outpatient LEEP may be equally effective in the management of CIN, with potential cost implications. In addition, LEEPs under general anesthesia put the patient at risk for anesthesia-related complications which could be avoided. There are many ways that our institution could facilitate more office-based LEEPs. Twenty-one (18%) of the inpatient LEEPs were performed in the operating room due to no access to LEEP equipment, this could be remedied by purchasing the equipment required. Thirty-six (30.5%) patients had an inpatient LEEP due to poor tolerance of colposcopy or anxiety. At our institution, dilation and curettage is performed in the same office where women receive oral versed and intramuscular ketorolac prior to their procedure. Preprocedure medications to reduce anxiety and discomfort could allow for office-based LEEPs where patients feel comfortable with their procedure.

AVAILABILITY OF DATA AND MATERIALS

Raw data were generated at the University of California San Diego. Data are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

ALB—study conception, literature review, data collection, data analysis and interpretation, statistical analysis, writing of the manuscript; HM—data collection, writing of the manuscript; NP—data collection, writing of the manuscript; MBJ—data analysis and interpretation, statistical analysis; OF—data collection, manuscript reviewing and editing; RNE—data analysis and interpretation, manuscript reviewing and editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted *via* retrospective chart review. This study was approved by the IRB committee of the University of California San Diego (approval ID 210452). The IRB of the University of California San Diego approved a waiver of consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Dr. Eskander reports the following disclosures. Consultant to/received honoraria from: Agenus Inc., Aravive Inc., AstraZeneva, Clovis Oncology Inc., Eisai Inc., Elevar Therapeutics, Genmab/Seattle Genetics, GlaxoSmithKline, GOG Foundation, ImmunoGen, Merck, Mersana Therapeutics, Myriad Genetic Laboratories Inc., Novocure Inc.

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