**Cukurova Medical Journal**
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2018;43(Suppl 1):24-29
DOI: 10.17826/cumj.394448

**ARAŞTIRMA / RESEARCH**

# Effect of endocervical glandular involvement on residual and recurrent disease in patients with high grade cervical dysplasia

## Yüksek dereceli servikal displazi hastalarında endoservikal glandüler tutulumun rezidüel ve tekrarlayan hastalık üzerine etkisi

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*Cukurova Medical Journal 2018;44(Suppl 1):24-29*

**Abstract**

**Purpose:** The aim of this study was to evaluate the effect of endocervical glandular involvement on residual and recurrent disease in high-grade cervical dysplasia.

**Material and Methods:** Patients underwent Loop Electrosurgical Excision Procedure (LEEP) or Cold Knife Conization (CKC) between January 2015 and June 2016 were identified. Patients that had low grade lesions in conization specimens were excluded. The data were collected for age, menopausal status, cytology, colposcopic findings, conization procedure, HPV positivity and subtype, diameters of specimen, number of pieces, pathologic data including status of margins, endocervical glandular involvement (EGI) and recurrence. Prognostic effect of EGI on residual and recurrent disease were evaluated

**Results:** Of 282 patients, 204 were eligible. Median age was 41 years in both groups. Age, menopausal status, cytology, diameters of specimen, number of pieces, colposcopy findings and conization procedure did not differ between groups.. Surgical margin positivity was higher in EGI positive group. HPV type 16 positivity was significantly higher in EGI positive patients. EGI was found to be the only prognostic factor for residual disease and was not a prognostic factor for recurrent disease.

**Conclusion:** Our findings showed that EGI appears as a poor prognostic factor for residual disease but not for recurrence in patients with high-grade cervical dysplasia.

**Key words:** Endocervical glandular involvement, cervical dysplasia, surgical margin

**Öz**

**Amaç:** Bu çalışmanın amacı yüksek dereceli servikal displazide endoservikal gland tutulumunun rezidü ve recurrent hastalık üzerine etkisini araştırmaktır.

**Gereç ve Yöntem:** Ocak 2015-Haziran 2016 tarihleri arasında loop electrosurgical excision procedure (LEEP) ya da soğuk konizasyon yapılan hastalar belirlendi. Konizasyon spesimeninde düşük dereceli displazisi bulunan olgular dışlandı. Yaş, menaposal durum, servikal sitoloji, kolposkopik bulgular, konizasyon işlemi, HPV pozitifliğ ve alt tipi, spesimen boyutları, endoservikal gland tutulumu, cerrahi sınırların durumu, ve rekürrens verileri hasta kayıtlarından elde edildi. Endoservikal gland tutulumunun rezidüel ve rekürren hastalık üzerindeki prognostic etkileri derğerlendirildi.

**Bulgular:** 208 yüksek dereceli servikal displazisi bulunan olgudan 204'ü çalışmaya dahil edildi. Yaş, menaposal durum sitoloji, spesimen boyutları, çıkarılan parka sayısı, koloposkopik bulgular, ve konizasyon işlemi açısından gruplar arasında fark yoktu Cerrahi sınır pozitifliği gland tutulumu olan grupta daha fazlaydı. HPV 16 pozitifliği gland tutulumu olan grupta daha yüksek idi. Endoservikal gland tutulumu rezidü hastalık için prognostik faktör iken rekürrens için prognostic etksinin olmadğı bulundu.

**Sonuç:** Çalışmamız endoservikal gland tutulumunun yüksek dereceli servikal displazide kötü prognostik faktör olduğu rekürrens için prognostik etkisinin olmadığı sonucuna varmıştır.

**Anahtar kelimeler**: Endoservikal glandüler tutulum, servikal displazi, cerrahi sınır

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Geliş tarihi/Received: 13.2.2018 Kabul tarihi/Accepted: 11.4.2018 Published online: 8.9.2018

## INTRODUCTION

Cervical conization is a well-known treatment approach for high-grade cervical intraepithelial neoplasia (CIN). Accomplishing negative surgical margin is of high importance for residual and recurrent disease, while a positive surgical margin requires further intervention[1]. In previous studies, researchers frequently addressed the importance of patient age, parity, extent of disease, number of sweeps and the volume of cone for predicting residual disease[2,3]. These factors were considered as the most important risk factors for residual disease in patients underwent cervical conization for high grade CIN.

Endocervical glands are located in cervical stroma under basement membrane of normal squamous epithelium and may be involved by neoplastic lesions. The involvement of such glands by high-grade CIN can mimic invasive disease and might be misdiagnosed as invasive cervical carcinoma, which requires meticulous evaluation[4]. Besides, the prognostic significance of endocervical gland involvement (EGI) is unclear in the current literature. Lu et al. and Kim et al.[5,6] advocated no significant prognostic value for EGI, whereas Demopulos et al. suggested EGI as a valuable prognostic factor for residual and recurrent disease[7].

Since low-grade cervical dysplasia requires expectant management, its expansion into endocervical glands has been considered of low importance. EGI has been reported to be associated mostly with high-grade CIN[8]. Furthermore, EGI may increase the severity of the disease, which may result in surgical margin positivity after cervical conization. Therefore, in this study we aimed to evaluate the effect of EGI on surgical margin positivity in patients who underwent cervical conization for high-grade cervical neoplasia.

## MATERIALS AND METHODS

### Study design

This retrospective study was conducted at a referral center for national cervical screening program after approval of the institutional review board. Helsinki Declaration principals were followed. The data were collected from hospital records of patients underwent Loop Electrosurgical Excision Procedure (LEEP) or Cold Knife Conization (CKC) between January 2015 and June 2016. Patients diagnosed with CIN 2-3 and had at least 1 year follow up information were included. Patients with normal pathology or CIN 1, and insufficient follow up data were excluded. For all patients age, menopausal status, cervical cytology, HPV testing results, colposcopic biopsy findings, type of conization, diameters of conization specimen, number of excised tissue pieces were recorded. Included patients were divided into two groups according to presence of EGI and the groups were compared for clinical and pathological characteristics. Follow up records for one year after cervical conization were also reviewed. Biopsy confirmed CIN II-III lesions were considered as recurrent disease.

### Cervical conization procedures

In both groups, cervical conization procedure was performed via LEEP or CKC by experienced gynecologic oncology specialists. LEEP conization was performed under general anesthesia, while spinal anesthesia was administered for CKC procedure. All surgically excised specimens were labelled at 12 o'clock position. In addition, endocervical curettage (ECC) was performed after each cervical conization procedure. Hemostasis was established by electrocoagulation with ball cautery and/or suturing when required.

### Histological examination

All surgical specimens were formalin fixed and paraffin embedded for histological sectioning and examination. The specimen diameters were measured in three dimensions as anteroposterior, transverse and vertical lengths. A black ink was used for surgical margin orientation. Tissue blocks were sectioned, stained by hematoxylin and eosin, and examined by experienced gynecological pathologists under optical microscope. Histological sections were evaluated for EGI.

### Statistical analysis

Normality of data was evaluated with Kolmogorow-Smirnov test or Shapiro Wilk test. Continuous variables were compared using independent sample t test or Mann Whitney U tests. Categorical data were compared using Chi-Square test. Fishers' exact test was used when an expected value problem existed. Logistic regression analysis was used to determine risk factors for surgical

margin positivity. A p value <0.05 was considered as statistically significant.

## RESULTS

Of 282 identified patients with high-grade cervical intraepithelial neoplasia, 204 subjects were included in the present study. Median age was 41years in both EGI positive and negative groups. Menopausal status, specimen diameters, percentages of utilized conization procedures, number of excised pieces were also similar between two groups. Characteristics and comparison of the patients according to EGI positivity were shown in Table 1.

**Table 1. Clinical and pathological characteristics of patients with and without endocervical gland involvement**

| Parameters | EGI Negative (n=105) | EGI Positive (n=99) | P-value |
|---|---|---|---|
| Age (years) | 41 (25-59) | 41 (25-79) | 0.873 |
| Menopausal status (Yes) | 22 (21) | 26 (26.3) | 0.372 |
| Cervical Cytology | | | |
| Normal | 12 (11.4) | 9 (9.1) | 0.618 |
| ASC-US | 21 (20) | 25 (25.3) | 0.370 |
| ASC-H | 22 (21) | 18 (18.2) | 0.583 |
| AGUS | 0 (0) | 2 (2) | 0.143 |
| LGSIL | 31 (29.5) | 17 (17.2) | 0.038 |
| HGSIL | 19 (18.1) | 28 (28.3) | 0.084 |
| Colposcopic Biopsy | | | 0.017 |
| CIN 2 | 77 (74.8) | 54 (55.7) | |
| CIN 3 | 17 (16.5) | 27 (27.8) | |
| Not Available | 9 (8.7) | 16 (16.5) | |
| Procedure | | | 0.716 |
| Cold Knife Conization | 10 (9.5) | 8 (8.1) | |
| LEEP | 95 (90.5) | 91 (91.9) | |
| Specimen Diameters | | | |
| Anterior-posterior | 2.30 (1-5) | 2.5 (1-5.5) | 0.057 |
| Transverse | 1.60 (0.3-3) | 2 (0.4-4) | 0.118 |
| Vertical | 1 (0.2-2.5) | 1 (0.2-3.5) | 0.248 |
| Surgical Margin | | | <0.001 |
| Negative | 80 (76.2) | 37 (37.4) | |
| Positive | 25 (23.8) | 62 (62.6) | |
| Endocervical Margin Positivity | 9 (8.6) | 45 (45.5) | <0.001 |
| Ectocervical Margin Positivity | 19 (18.1) | 36 (36.4) | <0.001 |
| Endo+Ectocervical Margin Positivity | 3 (2.8) | 21 (21.1) | <0.001 |
| HPV (+) | 94 (91.3) | 94 (96.9) | 0.093 |
| HPV Subtype | | | 0.047 |
| 16 | 66 (69.5) | 78 (83) | 0.013 |
| 18 | 2 (2.1) | 3 (3.2) | 0.603 |
| Other | 27 (28.4) | 13 (13.8) | 0.024 |
| Number of Excised Pieces | | | 0.572 |
| One | 76 (73.1) | 75 (76.5) | |
| Two | 28 (26.9) | 23 (23.5) | |
| Disease Recurrence | 2 (1.9) | 10 (10.1) | 0.016 |

Data are given as median (range) or number (%). P<0.05 was considered significant

In both groups, LEEP was the most common conization procedure (90,5% vs. 91,9%, EGI negative vs. positive, respectively). Cervical cytological abnormality was observed in 90,9% and 89,6% of the patients with and without EGI groups, respectively. In patients with negative EGI LSIL

was found to be more common (p=0.038). HPV positivity was comparable between two groups.

**Table 2. Prognostic factors for residual disease in patients with high-grade cervical intraepithelial neoplasia.**

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| Age | 1.0 | 0.96-1..06 | 0.590 |
| Menopausal Status | | | |
| Premenopausal | Reference | | |
| Postmenopausal | 1.71 | 0.55-5.27 | 0.348 |
| EGI | | | |
| No | Reference | | |
| Yes | 5.9 | 3.13-11.28 | <0.001 |
| Specimen Diameters | | | |
| Anterior-posterior | 0.9 | 0.6-1.4 | 0.836 |
| Transverse | 1.6 | 0.7-3.4 | 0.180 |
| Vertical | 0.5 | 0.2-1.2 | 0.147 |
| Type of Procedure | | | |
| CKC | Reference | | |
| LEEP | 1.8 | 0.6-5.3 | 0.286 |
| Number of Pieces | | | |
| One | Reference | | |
| Two | 0.6 | 0.3-1.4 | 0.304 |

EGI, endocervical gland involvement; CI, confidence interval; CKC: cold knife conization; LEEP, loop electrosurgical excision procedure. P<0.05 was considered significant.

**Table 3. Evaluation of prognostic factors for recurrent disease in patients with high-grade cervical intraepithelial neoplasia.**

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| Age | 1,0 | 0.90-1.12 | 0,879 |
| Menopausal Status | | | |
| Premenopausal | Reference | | |
| Postmenopausal | 2.86 | 0.22-35.7 | 0.414 |
| EGI | | | |
| No | Reference | | |
| Yes | 1.6 | 0.29-9.62 | 0.565 |
| Specimen Diameters | | | |
| Anterior-posterior | 1.3 | 0.5-3.1 | 0.457 |
| Transverse | 0.7 | 1.3-3.7 | 0.703 |
| Vertical | 1.2 | 0.1-10.8 | 0.838 |
| Type of Procedure | | | |
| CKC | Reference | | |
| LEEP | 1,6 | 0.2-13.3 | 0.642 |
| Number of Pieces | | | |
| One | Reference | | |
| Two | 7.7 | 0.6-9.7 | 0.113 |
| Endocervical SM | | | |
| No | Reference | | |
| Yes | 30.4 | 4.8-19.2 | <0.001 |
| Ectocervical SM | | | |
| No | Reference | | |
| Yes | 0.9 | 0.2-3.7 | 0.991 |

EGI, endocervical gland involvement; SM, surgical margin; OR, odds ratio; CI, confidence interval; CKC, cold knife conization; LEEP, loop electrosurgical excision procedure. P<0.05 was considered significant.

However, HPV type 16 positivity was significantly higher in patients with EGI (p=0.013). Both endocervical and ectocervical margin positivity were higher in patients with EGI compared to EGI negative group. Multiple logistic regression analysis revealed that only the presence of EGI was a significant independent factor for surgical margin positivity (OR:5.9, 95%CI:3.1-11.1; p<0,001). Multiple regression analysis results are represented in Table 2.

Although, disease recurrence was significantly higher in EGI positive patients, EGI was not a significant prognostic factor for disease recurrence (OR: 1,6 95%CI 0,2-1,6 p=0,565). We found only endocervical margin positivity as a prognostic factor for recurrence (OR:30,4 95%CI 4,8-19,2 p<0,001). Evaluation of risk factors for recurrence in patients with CIN 2-3 was given in Table 3.

## DISCUSSION

In previous studies, EGI was reported to be present in nearly % 40 of the cases with high grade cervical dysplasia and was regarded as a poor prognostic factor for residual and recurrent disease[7,8]. Our results showed similar findings in support of those reports. Although EGI mostly observed in high-grade cervical dysplasia[8] it may also be observed in low grade lesions. However, EGI with low-grade dysplasia has not shown of clinical significance. On the other hand, EGI was shown to be associated with recurrent and residual disease independent of surgical margins[9]. HPV type 16 and 18 are the most common carcinogenic subtypes that are responsible for 70 % of all cases[10]. HPV type 16 positivity was reported to be 59 % in patients with high-grade cervical neoplasia[11]. Similarly, in the current study, HPV type 16 positivity was about 70%, and higher rate was observed in EGI positive patients. This presence of carcinogenic type HPV might a reason for and explain the expansion the neoplastic lesion into endocervical glands. However, further studies are needed to uncover the underlying process and the association between high risk HPV positivity and EGI.

Involvement of endocervical glands with dysplastic cervical lesion might be considered as a sign of expansive nature of the disease that shows higher tendency for involvement of surrounding tissue. According to this point of view, the risk of having margin positivity appears as more likely for EGI positive patients. Recently, Güdücü et. al reported that margin positivity was related with the extent of the disease[12]. In the current study, higher surgical margin positivity in EGI positive patients may be attributable to the expansion of the disease into stromal glands. Several prognostic factors for surgical margin positivity were found such as age, parity[13], ECC positivity[14], multiple sweeps and involvement of >50% volume of cervix[2]. In our study, however, factors including age and multiple sweeps were not significant prognostic values. Contrary to other studies, we found that the only prognostic factor for surgical margin positivity was EGI positivity[6,13,15].

Endocervical margin positivity was reported to be associated with recurrent/persistent disease[16]. In our study, we also showed that endocervical margin positivity was a prognostic factor for persistent disease. However, EGI was not found to be as prognostic factor for persistent disease. Therefore, it becomes more evident that providing negative surgical margins is the most effective approach in case of extensive disease caused by glandular involvement.

The main limitation of our study is related to its retrospective design. Nevertheless, it has also strengths in including balanced numbers of patients in both groups with similar baseline characteristics such as age, menopausal status, and type of conization procedure. Homogeneous features in study and control groups enabled to reduce potential confounding factors in the determination of prognostic factors for surgical margin positivity. Besides, one year follow up data was another strength of the present study.

In conclusion, we investigated the relation between EGI and surgical margin positivity, and our study showed that EGI was a significant predictive factor for surgical margin positivity in patients with high-grade CIN. Based on our results, we suggest EGI as prognostic finding in the treatment of patients with high-grade cervical dysplasia.

## REFERENCES

1. Arbyn M, Redman CW, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem Maghami S et al. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. Lancet Oncol. 2017;18:1665-79.

2. Ayhan A, Tuncer HA, Reyhan NH, Kuscu E, Dursun P. Risk factors for residual disease after cervical conization in patients with cervical intraepithelial neoplasia grades 2 and 3 and positive surgical margins. Eur J Obstet Gynecol Reprod Biol. 2016;201:1-6.
3. Park JY, Lee KH, Dong SM, Kang S, Park SY, Seo SS. The association of pre-conization high-risk HPV load and the persistence of HPV infection and persistence/recurrence of cervical intraepithelial neoplasia after conization. Gynecol Oncol. 2008;108:549-54.
4. Robbie M. Blaustein's Pathology of the female genital tract. Pathology. 2003;35:457.
5. Moore BC, Higgins RV, Laurent SL, Marroum M-C, Bellitt P. Predictive factors from cold knife conization for residual cervical intraepithelial neoplasia in subsequent hysterectomy. Am J Obstet Gynecol. 1995;173:361-8.
6. Kim H-J, Kim K-R, Mok JE, Nam JH, Kim YT, Kim YM et al. Pathologic risk factors for predicting residual disease in subsequent hysterectomy following LEEP conization. Gynecol Oncol. 2007;105:434-8.
7. Milojkovic M. Residual and recurrent lesions after conization for cervical intraepithelial neoplasia grade 3. Int J Gynaecol Obstet. 2002;76:49-53.
8. Nagi CS, Schlosshauer PW. Endocervical glandular involvement is associated with high-grade SIL. Gynecol Oncol. 2006;102:240-3.
9. Savage EW, Matlock DL, Salem FA, Charles EH. The effect of endocervical gland involvement on the cure rates of patients with cervical intraepithelial neoplasia undergoing cryosurgery. Gynecol Oncol. 1982;14:194-8.
10. Harper DM, Williams KB. Prophylactic HPV vaccines: current knowledge of impact on gynecologic premalignancies. Discov Med. 2010;10:7-17.
11. Anderson LA, O'rorke MA, Wilson R, Jamison J, Gavin AT. HPV prevalence and type-distribution in cervical cancer and premalignant lesions of the cervix: A population-based study from Northern Ireland. J Med Virol. 2016;88:1262-70.
12. Güdücü N, Sidar G, Başsüllü N, Türkmen İ, Dünder İ. Endocervical glandular involvement, multicentricity, and extent of the disease are features of high-grade cervical intraepithelial neoplasia. Ann Diagn Pathol . 2013;17:345-6.
13. Lu C-H, Liu F-S, Tseng J-J, Ho ES-C. Predictive factors for residual disease in subsequent hysterectomy following conization for CIN III. Gynecol Oncol. 2000;79:284-8.
14. Diaz ES, Aoyama C, Baquing MA, Beavis A, Silva E, Holschneider C et al. Predictors of residual carcinoma or carcinoma-in-situ at hysterectomy following cervical conization with positive margins. Gynecol Oncol. 2014;132:76-80.
15. Tasci T, Turan T, Ureyen I, Karalok A, Kalyoncu R, Boran N, et al. Is there any predictor for residual disease after cervical conization with positive surgical margins for HSIL or microinvasive cervical cancer? J Low Genit Tract Dis. 2015;19:115-8.
16. Cui Y, Sangi-Haghpeykar H, Patsner B, Bump JM, Williams-Brown MY, Binder GL et al. Prognostic value of endocervical sampling following loop excision of high grade intraepithelial neoplasia. Gynecol Oncol. 2017;144:547-52.