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Research

Does the "Risk-based Management Model" for Residual Disease in Patients with High-grade Cervical Intraepithelial Lesions Cause Overtreatment?

Yüksek Dereceli Servikal İntraepitelyal Lezyonları Olan Hastalarda Rezidüel Hastalık için "Risk Bazlı Yönetim Modeli" Aşırı Tedaviye Neden Olur mu?

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ABSTRACT

Objective: This study aimed to determine the residual disease status of high-grade cervical intraepithelial lesion-positive (HSIL) patients with margin positive at first cervical excision.

Methods: This study included patients with HSIL-positive surgical margins following cervical excision procedures between March 2015 and August 2020. The patients with normal histopathology results, cervical intraepithelial neoplasia (CIN)1, CIN2-3 with negative surgical margins, and confirmed cervical malignancy were excluded. HSIL in the second cervical excision pathology was accepted as a residual disease. Demographic and clinical characteristics, pathology results and human papilloma virus genotypes of the patients were assessed.

Results: Surgical margin was positive in 354 (21.3%) of 1,656 patients who underwent cervical excision procedures with the indication of HSIL. Computer-based medical records of 330 patients who underwent the second cervical excision procedure from these patients were reviewed and analyzed. Residual disease was diagnosed in 31.3% (31/99) patients whose first cervical biopsy was CIN2 and in 48.4% (112/231) patients with CIN3. Additionally, 3 of the patients with CIN3 had microinvasive cervical cancer in final pathology. In patients with residual disease (≥ CIN2), the rate of CIN3 at first excision, the rate of smokers, and the rate of glandular involvement in the excision specimen was higher (respectively; p=0.04, p=0.01, p=0.03).

Conclusion: Residual disease high in patients with the first cervical excision histopathology of CIN3, endocervical glandular involvement, and previously or currently smoked. In the disease management of women with CIN3 and positive margins, re-excision rather than follow-up may be a better option.

Keywords: Cervical intraepithelial neoplasia, residuel disease, human papilloma virus

ÖZ

Amaç: Bu çalışmanın amacı, ilk servikal eksizyonda cerrahi sınır pozitif olan yüksek dereceli servikal intraepitelyal lezyon pozitif (HSIL) hastaların rezidüel hastalık durumunu belirlemektir.

Gereç ve Yöntem: Bu çalışmaya Mart 2015 ile Ağustos 2020 tarihleri arasında servikal eksizyon işlemleri sonrası HSIL cerrahi sınırı pozitif olan hastalar dahil edildi. Histopatoloji sonuçları normal, servikal intraepitelyal neoplazi (CIN)1, cerrahi sınırı negatif olan CIN2-3 ve doğrulanmış servikal malignitesi olan hastalar çalışma dışı bırakıldı. İkinci servikal eksizyon patolojisinde HSIL rezidüel hastalık olarak kabul edildi. Hastaların demografik ve klinik özellikleri, patoloji sonuçları ve insan papillom virüsü genotipleri incelendi.

Bulgular: HSIL endikasyonu ile servikal eksizyon işlemi uygulanan 1.656 hastanın 354'ünde (%21,3) cerrahi sınır pozitifti. Bu hastalardan ikinci servikal eksizyon prosedürü uygulanan 330 hastanın bilgisayar tabanlı tıbbi kayıtları incelendi ve analiz edildi. İlk servikal biyopsisi CIN2 olan hastaların %31,3'ünde (31/99), CIN3'ü olan hastaların %48,4'ünde (112/231) rezidüel hastalık tanısı konuldu. Ayrıca CIN3'lü hastaların 3'ünde son patolojide mikroinvaziv serviks kanser vardı. Rezidüel hastalığı olan hastalarda (≥ CIN2), ilk eksizyonda CIN3 oranı, sigara içenlerin oranı ve eksizyon örneğinde glandüler tutulum oranı daha yüksekti (sırasıyla; p=0,04, p=0,01, p=0,03).

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Sonuç: İlk servikal eksizyon histopatolojisi CIN3 olan, endoservikal glandüler tutulumu olan ve daha önce veya halen sigara içen hastalarda rezidüel hastalık oranı yüksektir. CIN3 ve pozitif sınırlara sahip kadınların hastalık yönetiminde takip yerine yeniden eksizyon daha iyi bir seçenek olabilir.

Anahtar Kelimeler: Servikal intraepitelyal lezyon, rezidüel hastalık, insan papillom virüsü

INTRODUCTION

The adoption of risk-based cervical cancer screening programs has significantly reduced the incidence of cervical cancer (1). However, cervical cancer; it is still an important health problem in women without appropriate follow-up and treatment, and women with recurrent or residual disease (2,3). The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends treatment for patients with histologically diagnosed high-grade cervical intraepithelial lesions (HSIL, includes CIN2-3) (1). The most commonly used treatment method is loop electrosurgical excision procedure (LEEP) of the transformation zone or cold knife conization (CKC) (4,5). However, these procedures may not remove the lesions and may result in positive surgical margins (5).

In a large population-based study, it was shown that 23% of women had positive surgical margins after cervical excision (6). Even in patients whose lesion is removed, the risk of recurrence of high-grade lesions is higher than in the general population (6). Therefore, the positivity of surgical margins, which is predisposing to residual disease, is a legitimate cause for anxiety for the patient. However, as it is difficult to find a balance between iatrogenic harm and therapeutic efficacy, there has not yet been reached consensus on the further management of these patients (1). Therefore, the management strategy ranges from follow-up cytology to second conization and even hysterectomy (1). While performing cytological follow-up may miss a more severe underlying disease, repeated excisions may cause surgical complications and increased morbidity.

The main question for patients with positive surgical margins is their residual disease status in patients after excision. In this study, we immediately performed a second surgical procedure on patients with positive surgical margins after the first cervical excision. Thus, it determines the baseline residual disease risk in patients with positive surgical margins.

METHODS

Study Design and Patient Selection

Pathology records of the patients who underwent LEEP or CKC between March 2015-August 2020 were retrospectively screened. CIN2 and 3 cases with performed the second excision procedures due to positive margins were included in the study. Patients with normal histopathology results, CIN1, CIN2-3 with negative surgical margins, and confirmed cervical malignancy were excluded. The study protocol was approved by our institutional review board (University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Non-Interventional Research Ethics Committee-decision no: 2021/08-10, date: 16.08.2021). Informed consent could not be obtained from the patients because of the retrospective design of the study.

The surgical margin was positive in 354 (21.3%) of 1,656 patients who underwent cervical excision procedure for HSIL during the study period. Of these patients, the data of 330 patients who underwent a second surgical procedure in our institution and met the inclusion criteria were analyzed.

Interventions

Initial LEEP and CKC

Preoperative evaluation, including cervical cytology, colposcopy and colposcopy-directed cervical biopsy was underwent in all patients. Schiller test was performed to determine the borders of the excision area before conization. LEEP was performed under local anesthesia and CKC was performed under general anesthesia by residents in the operating room under expert supervision. These procedures were conducted in a standard manner as previously described (7). Conization specimens were marked with a suture at 12 o'lock to locate the lesions. After all, conization, endocervical curettage was performed using a uterine curette (size 0) and the samples were sent separately for histopathological examination. Hemostasis was obtained by electrocoagulation.

Human Papilloma Virus (HPV) Test

To identify HPV genotypes, we analyzed cervical samples preoperatively using Hybrid Capture 2 for HPV types 16, 18, and 12 other high-risk HPV (hrHPV) (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). HPV genotyping was divided into two categories: HPV type 16/18 and non-HPV-16/18 oncogenic types.

Further Surgical Procedures

The type of the second surgical procedure to be performed for patients with positive margins was based on the clinical and pathological characteristics of each patient. All patients

underwent a second surgery within 30 days of the first excision. Second surgical procedures included CKC, LEEP, or hysterectomy, depending on the suitability of the cervix.

Pathological Examination

Positive surgical margins were defined as the presence of CIN2 or CIN3 at the ectocervix. The specimens were examined for cone depth, histological grade (CIN2 or CIN3), surgical margin state and the presence or absence of CIN2 and CIN3 in endocervical curettage (ECC) sampling were recorded. According to the pathology reports of the second operation, the patients were divided into two groups as ≤ CIN1 and ≥ CIN2. CIN1 lesions included CIN1 and normal biopsy results, whereas CIN2 lesions included CIN2, CIN3, and microinvasive cervical cancer.

Statistical Analysis

All statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows (SPSS, Inc., Chicago, IL). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov/Shapiro-Wilk's test. Differences in the means of the continuous variables were assessed using the Mann-Whitney U test or independent samples t-test; the difference in the categorical variables was assessed using the chi-square test. $P<0.05$ was considered statistically significant.

RESULTS

Surgical margins were positive in 354 (21.3%) of 1656 patients who underwent cervical excision for HSIL during the study period. Computer-based medical records of 330 patients who underwent the second cervical excision procedure were reviewed and analyzed. Re-excision procedure was not performed in 24 patients with positive margins. The first lesions of all these patients were CIN2, and CIN persisted in 7 patients in their follow-up 1 year later. The median age of the patients was 44 (25^{th}-75^{th} percentile, 36-49) and 67.9% were premenopausal patients. Other demographic characteristics are shown in Table 1. LEEP (88.7%, 293 patients) or CNK (11.3%, 37 patients) was used as the initial cervical excision procedure. HPV genotyping was performed on all patients before the procedure and the most detected genotype was HPV 16 (74.5%, 246 patients). The mean depth of the first cervical excision pathology specimen of margin-positive patients was 11.1±4.7 mm. In the histopathological results after the first cervical excision, 30% of the patients (99 patients) reported CIN2 and 70% of had CIN3. Additionally, 73.3% of patients had a glandular involvement at the first cervical excision (Table 2).

In the analysis of the final pathology results after the second cervical excision, residual disease was detected in 31.3% (31/99) of the patients whose first cervical histopathology was CIN2. However, 48.4% (112/231) of the patients whose first cervical excision histopathological result was CIN3 had residual disease. Additionally, microinvasive cervix ca be detected in the final pathology in 3 of the patients with CIN 3 (Table 3).

Table 1. Baseline demographic characteristics of margin positive patients

Characteristic	Values
Number of patients	330
Age (years)	
Median (min-max)	44 (24-78)
25^{th}-75^{th} percentiles	36-49
Gravida	
Median (min-max)	3 (0-12)
25^{th}-75^{th} percentiles	2-3
Parity	
Median (min-max)	2 (0-8)
25^{th}-75^{th} percentiles	2-3
Smoking status of patients	
Never smoked	171 (51.8%)
Currently or previously smoked	90 (27.2%)
Not known	69 (21%)
Menopausal status of patients	
Premenopausal	224 (67.9%)
Postmenopausal	106 (32.1%)

Min-max: Minimum-maximum, the data is presented as median (25^{th} percentile; 75^{th} percentile) or ratio

Margin-positive patients were divided into two groups according to the final pathology result after the second excision, as those with residual disease (≥ CIN2) and those without (≤ CIN1). Both groups were compared according to their demographic and pathological results. In the group with residual disease, the rate of CIN3 at the first excision, the rate of smokers, and the rate of glandular involvement in the excision specimen was higher. (respectively; $p=0.04$, $p=0.01$, $p=0.03$). There was no statistical difference between the groups in terms of age, parity, gravida, menopausal status, endocervical canal pathology and depth of the first cervical excision specimen (Table 4).

DISCUSSION

The positivity of the surgical margin in the histopathology of patients who underwent cervical excision procedure with the indication of HSIL is the most important determinant of

Table 2. Pathology results and HPV genotypes of margin positive patients

Characteristic	Values
Surgical technique (initial procedure)	
LEEP	293 (88.7%)
CKC	37 (11.3%)
HPV 16 +	246 (74.5%)
HPV 18 +	225 (68.1%)
Non HPV 16/18 +	84 (25.4%)
Depth of initial leep specimen (mean ± SD, mm)	11.1±4.7
Presence of glandular involvement in the initial procedure	242 (73.3%)
Initial cervical excision (LEEP/CKC) pathology	
CIN2	99 (30%)
CIN3	231 (70%)
ECC	
≤ CIN1	195 (59%)
≥ CIN2	135 (41%)
Second cervical pathology	
≤ CIN1	187 (56.6%)
≥ CIN2	143 (43.4%)

HPV: Human papilloma virus, SD: Standard deviation, LEEP: Loop electrosurgical excision procedure, CKC: Cold knife conization, CIN: Cervical intraepithelial neoplasia

CIN recurrence. Guidelines could not reach a consensus on whether these patients should undergo a second surgical procedure. In this study, we immediately performed a second surgical procedure on margin-positive patients and provided an understanding of the residual disease status. Our study showed residual disease in 31.3% of patients with initial histopathology of CIN2 and 48.4% of patients with CIN3. Microinvasive cervix ca be present in 3 patients with CIN 3. Additionally, the rate of glandular involvement in the first excision sample was higher in the group with residual disease.

Based on the risk-based management model, ASCCP; states that it may be preferable to follow margin-positive patients with cytology and ECC at 4-6 month intervals, at the same time re-excision is acceptable and hysterectomy can be performed if re-excision is impossible (1). However, the International Federation of Gynecology and Obstetrics recommends reoperation in CIN3 patients with positive surgical margins (8). In fact, the main reason for all these discussions is that the "wait and see strategy" carries a high risk of HSIL margin-positive patients. Periodic follow-up may increase the recurrence rate and patient anxiety and may miss a more severe underlying disease. However, repetitive surgery can cause complications and morbidity. Additionally, the goal of reaching the negative surgical margin may require larger excisions, but this may also increase the risk of obstetric harm.

Previous studies have shown that margin-positive HSIL patients have a residual disease rate of 44-67% on histopathology after the second cervical excision (9,10). In our study, the residual disease rate was 43.3% (143/330). In patients with initial cervical excision pathology CIN3, the residual disease rate was 48.4%. Moreover, 3 of these patients were diagnosed with microinvasive cervix ca at the second excision. In our study, we did not detect residual disease in 68.7% of patients with positive margins for CIN2 and in 51.6% of patients with positive margins for CIN3. Some authors suggest that vaginal acidity and thermal destruction will promote epithelial regeneration of the cervix (11). Especially in CIN2 margin positive patients, the regression rates of the lesions seen after the second excision were remarkable. However, ≥ CIN3 was detected in 34.1% (79/231) of the patients whose initial pathology was CIN3. Considering that the risk of progression to invasive carcinoma depends on the severity and size of the CIN lesion, and that approximately one-third of women with untreated CIN3 will eventually develop invasive cervical cancer, our findings suggest that secondary surgical intervention should be performed in patients with margin-positive CIN3 lesions.

Table 3. Classification of second cervical excision pathologies of HSIL margin positive patients

Initial cervical excision pathology	Second cervical pathology					
	Normal	CIN1	CIN2	CIN3	Microinvasive ca	Total
CIN2	44 (44.4%)	24 (24.3%)	26 (26.3%)	5 (5%)	0	99 (100%)
CIN3	53 (23%)	66 (28.5%)	33 (14.2%)	76 (33%)	3 (1.3%)	231 (100%)
Total	97	90	59	81	3	330

CIN: Cervical intraepithelial neoplasia, HSIL: High-grade cervical intraepithelial lesion

Table 4. Comparison of clinical and pathological results of magin positive patients with and without residual disease

Characteristic	Patients with residual disease (n=143)	Patients without residual disease (n=187)	p-value
Age (years)	43 (25-78)	44 (24-76)	0.12
Gravida	3 (1-12)	3 (0-11)	0.21
Parity	2 (0-7)	2 (0-8)	0.33
Currently or previously smoked	49 (34.2%)	41 (21.9%)	0.01
Menopausal status of patients			
Premenopausal	92 (64.3%)	132 (70.5%)	0.22
Postmenopausal	51 (35.7%)	55 (29.4%)	
Surgical technique (initial procedure)			
LEEP	136 (95.1%)	157 (83.9%)	0.02
CKC	7 (4.9%)	30 (16.1%)	
Initial cervical pathology			
CIN2	31 (21.6%)	68 (36.3%)	0.04
CIN3	112 (78.4%)	119 (63.7%)	
ECC			
≤ CIN1	92 (64.3%)	103 (55%)	0.09
≥ CIN2	51 (35.7%)	84 (45%)	
Presence of glandular involvement in the initial pathology	117 (81.8%)	125 (66.8%)	0.03
Depth of initial cervical excision Specimen (mean ± SD, mm)	11±4.6	11.5±4.9	0.5
HPV 16 +	111 (77.6%)	135 (72.1%)	0.3
HPV 18 +	99 (69.2%)	119 (63.6%)	0.3
Non HPV 16/18 +	38 (26.5%)	46 (24.5%)	0.6

HPV: Human papilloma virus, SD: Standard deviation, LEEP: Loop electrosurgical excision procedure, CKC: Cold knife conization, CIN: Cervical intraepithelial neoplasia, ECC: Endocervical Curettage

Another histopathological finding that was significantly higher in residual disease in our study was the presence of cervical glandular involvement. Levine et al. (12) reported that endocervical glandular involvement in cervical excision specimens was associated with a higher incidence of positive margins and poor response to treatment. In our study, the rate of glandular involvement was higher in margin-positive patients with residual disease. Endocervical glands are located in the cervical stroma below the basement membrane of normal squamous epithelium and may be involved by neoplastic lesions. The involvement of such glands with high-grade CIN may mimic invasive disease and be misdiagnosed as invasive cervical carcinoma. Lu et al. (4) and Kim et al. (13) argued that the glandular involvement is not a significant prognostic value, while Demopoulos et al. (14) reported that glandular involvement is a valuable prognostic factor for residual and recurrent disease and is mostly associated with high-grade CIN. The involvement of the endocervical glands can be considered a sign of the diffuse nature of the disease with a higher propensity for involvement of surrounding tissues. Considering this situation, the risk of residual disease seems to be higher in the presence of glandular involvement in patients with positive surgical margins, as in our study.

Age and menopausal status are another factor emphasized in relation to residual disease risk. Zhu et al. (15) reported in their study that increasing age is a high-risk factor for persistent HSIL after LEEP. Similarly, Chen et al. (16) reported that being older than 50 years is a risk factor for residual lesions. As the authors explain the relationship between increasing age and menopausal status with residual disease; they claimed that the decrease in estrogen levels in menopause causes upward migration of the cervical transformation zone and HSIL lesions settle higher and form higher permanent lesions (15,16). However, in our study, we

did not find an association between residual disease and age, and menopausal status.

Recently, a systematic review compared the efficacy and safety of various excisional treatments for residual disease for treating cervical dysplasia (17). They observed that CKC reduced the risk of residual disease compared to LEEP. Women undergoing LEEP had an approximately 2-fold increase in positive margin rate compared with CKC. In contrast, LEEP is faster, inexpensive and requires less expertise than cold conization (18). LEEP is mostly performed as the first cervical excision procedure in our institution. Therefore, although our data is not homogeneous in terms of the first surgical excision procedure; residual disease after CKC is 18% (7/37) compared with 46% (136/293) after LEEP. Although CKC appears advantageous in terms of residual disease, meta-analyses have determined that the depth of excision is associated with the risk of preterm delivery and that CKC carries a particularly high risk (19,20). There several studies have investigated the optimal excision depth to achieve clear surgical margins Papoutsis et al. (21) reported that the depth of conization should be at least 10 mm to provide negative surgical margins. In our study, patients with and without residual disease were 11 and 11.5 mm, respectively, and did not predict residual disease.

Our findings showed that the rate of residual disease is high in patients with the first cervical excision histopathology of CIN 3, endocervical glandular involvement, and previously or currently smoked. Almost all the patients were hrHPV positive. Previous studies have already shown that the presence of HPV is important for patient follow-up rather than pre-procedure. A comprehensive systematic review conducted in 2017 reported the failure of treatment with the indication of HSIL (margin positivity); it was reported that post-treatment hrHPV was predicted more accurately than surgical margin positivity (22).

Strengths of our study include a consistent approach used to treat HSIL and the availability of expert pathological review. Moreover, all patients underwent reoperation within 30 days for more accurate identification of residual disease and little chance of new disease or regression. The limitations were because the study was retrospective, over a long time, and limited to a single institution. However, a prospective study design is difficult given the relative rarity of margin positivity.

CONCLUSION

In conclusion, our findings suggest that it is appropriate to recommend repeat excision rather than a follow-up for women with CIN 3 and positive margins.

ETHICS

Ethics Committee Approval: The study protocol was approved by our institutional review board (University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Non-Interventional Research Ethics Committee-decision no: 2021/08-10, date: 16.08.2021).

Informed Consent: Informed consent could not be obtained from the patients because of the retrospective design of the study.

Authorship Contributions

Concept: M.A., M.S., Design: M.A., M.S., Data Collection or Processing: S.Y.K., S.E., Literature Search: S.Y.K., Writing: M.A., S.Y.K.

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

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