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Predictors of high-grade residual disease after repeat conization in patients with positive surgical margins

Yagmur Minareci[1], Naziye Ak[2], Ozgur Aydın Tosun[3], Hamdullah Sozen[4], Rian Disci[5], Samet Topuz[4], Mehmet Yavuz Salihoglu[4]

[1]Eskisehir City Hospital, Department of Gynecologic Oncology, Eskisehir, Turkey

[2]Istanbul University, Institute of Oncology, Department of Medical Oncology, Istanbul, Turkey

[3]Istanbul Medeniyet University, Goztepe Research and Training Hospital, Department of Gynecology and Obstetrics, Division of Gynecologic Oncology, Istanbul, Turkey

[4]Istanbul University, Faculty of Medicine, Department of Gynecology and Obstetrics, Division of Gynecologic Oncology, Istanbul, Turkey

[5]Beykent University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Istanbul, Turkey

ABSTRACT

Objectives: No consensus exists on the subsequent management strategy of patients who exhibit positive surgical margin (PSM) after re-excision of high-grade cervical intraepithelial neoplasia (CIN). The aim of the study is to examine the predictors related to the persistence of high-grade CIN lesions after re-excision, where PSM was left behind.

Material and methods: The present retrospective study included patients with PSM who underwent repeated conization due to residual high-grade CIN lesions between January 2005 and December 2019. The SPSS software v20.0 was used for data interpretation and statistical analysis. P values less than 0.05 were accepted as statistically significant.

Results: Repeat conization was performed in 91 patients, 43 (47.3%) presented with PSM with high-grade CIN, 6 (6.5%) presented with micro-invasive carcinoma, and 42 (46.2%) presented with clear surgical margin or CIN 1 at the surgical margin. At the time of conization, patients who presented with lesions > 5 mm in repeat cone specimens, exhibited a significantly higher rate of residual disease ($p < 0.001$). Besides, the involvement of the endocervical margin with high-grade CIN was the predictor of residual disease in repeat cone specimens ($p = 0.006$).

Conclusions: In the cone specimen, the presence of lesion size greater than 5 mm and involvement of the endocervical margin were the predictors of high-grade residual disease after re-excision. Whether it is the first or second procedure, great care must be given to excise the lesion entirely at the time of the conization, preferably in one piece.

Key words: cancer of the cervix; cytology and GYN pathology; HPV infection and CIN

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INTRODUCTION

The treatment for pre-invasive neoplastic lesions aims to prevent invasive cervical cancer development. Conization is accepted as the first-line treatment modality of patients with high-grade cervical intraepithelial neoplasia (CIN) and may be performed by cold-knife excision or loop electrosurgical excision procedure (LEEP) [1]. However, in some cases, high-grade CIN lesions cannot be completely excised at the time of conization, exposing the patient to an increased risk of developing cervical cancer [2]. Researchers reported that 5% to 25% of cases after conization may exhibit surgical margin positivity, which is characterized by high-grade CIN lesions [3]. Thus, in a meta-analysis that including 35,109 cases, patients with clear surgical margins exhibited a prevalence of high-grade CIN lesions of 3% vs 18% compared to patients with positive or uncertain surgical margins, after the conization procedure [4]. The subsequent treatment strategy of patients with positive surgical margins (PSM) is still controversial. According to the 2019 guideline of the American Society for Colposcopy and Cervical Pathology (ASCCP), re-excision to achieve clear surgical margin should be the preferred next step [5]. However, re-excision

Corresponding author:
Yagmur Minareci
Eskisehir Şehir Hastanesi, B blok, 1. Kat, Jinekolojik Onkoloji Polikliniği, 71. Evler mah, 26080 Odunpazarı, Eskişehir, Turkey
e-mail: dryagmurminareci@gmail.com
tel.: +90 505 357 4361

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procedure reduces the amount of cervical stroma and may cause obstetric complications in further pregnancies [6].

Moreover, no consensus exists on the subsequent management strategy of patients who present with PSM after re-excision of high-grade CIN [7]. In the present study, we aimed to examine the predictors related to the persistence of high-grade CIN lesions after re-excision, where PSM was left behind.

MATERIAL AND METHODS

The patients who underwent repeated conization due to residual high-grade CIN lesions between January 2005 and December 2019 at the Istanbul University, Faculty of Medicine, Department of Gynecological Oncology were retrospectively evaluated. The inclusion criterion was the presence of a pathological diagnosis of positive surgical margin containing CIN ≥ 2 in re-excision specimen. Exclusion criteria were (a) presence of a pathological diagnosis of clear surgical margin in re-excision specimen, (b) presence of a pathological diagnosis of surgical margin containing CIN 1 lesion or invasive cancer in re-excision specimen, and (c) presence of missing data in hospital records while meeting the inclusion criterion. High-grade CIN lesions were considered CIN 2 and CIN 3. Re-excision procedure was performed by a gynecologic oncologist using either LEEP or cold knife.

The primary endpoint of the present study was to evaluate the correlations between the margin positivity after repeat conization with the following variables: age, parity, cytology result, menopausal status, conization technique (LEEP vs cold knife), endocervical curettage (ECC) result, cone volume, cone depth, largest lesion diameter, number of passes, and final pathological reports of first and repeat cone specimens. Iodine solution was used to mark the limits of the lesion before the conization. ECC was performed to evaluate the endocervical canal. LEEP was performed by a 15–20 mm loop electrode in a single pass when possible, and in the presence of large lesions, multiple passes were performed. PSM, either ectocervical or endocervical, was defined as the presence of high-grade CIN at the edge of the cone specimen in the final pathological evaluation. Following the diagnosis of PSM, in order to avoid treatment delay and to reduce the patient anxiety, patients underwent repeat conization within six weeks after the first conization. Cone volume was calculated with the formula = depth × width × length × π/3 × 1/4. The diameters of the cone specimens were obtained from the pathological report. Written informed consent was obtained from all the patients before surgery. The institutional review board and ethics committee approved our study protocol (ethics number: 1403, date: 2019), and they waived the requirement to obtain informed consent for study due to retrospective nature.

The SPSS software v20.0 was used for data interpretation and statistical analysis. Continuous variables have been shown in median with range, and they have been categorized based on median value to run appropriate statistical analyses. Categorical variables were compared with Fisher's exact test or chi-square test. A logistic regression model was used to measure association of variables for multivariate analysis. P values less than 0.05 were accepted as statistically significant.

RESULTS

We identified 114 patients who exhibited surgical margin positivity with high-grade CIN after first conization from the hospital records. Of the 114 patients, 23 (20.2%) underwent reflex extrafascial hysterectomy, and 91 (79.8%) exhibited repeat conization. At the time of repeat conization, among the 91 patients, 43 (47.3%) exhibited high-grade CIN lesion at the surgical margin, 42 exhibited (46.2%) clear surgical margin or CIN 1 lesion at the surgical margin, and 6 (6.5%) exhibited micro-invasive cancer. The clinicopathological features of 43 patients with PSM are detailed in Table 1. Among the 43 patients, 26 (60.5%) were smokers, 33 (76.7%) were at least primiparous, 10 (23.3%) were nulliparous. Median age was 35 years (range 29–55), median follow-up period was 31.1 months (range 7–156), median depth of cone specimen was 12 mm (range 10–20), and median diameter of lesion was 5 mm (range 1–13 mm). Leep and cold knife conization were performed in 39 (90.7%) and 4 (9.3%) women, respectively. Of the 39 patients with PSM who underwent LEEP conization, 18 exhibited CIN 3, and 21 exhibited CIN 2; of the four patients who had cold knife conization, 1 exhibited CIN 3, and 3 exhibited CIN 2 lesion. On the other hand, of the 42 patients with CIN ≤ 1, LEEP and cold knife conization were performed in 37 and 5, respectively. Of the 37 patients who underwent LEEP conization, 17 exhibited CIN 1; of the 5 patients who had cold knife conization, 4 exhibited CIN 1 lesion. Among the patients who exhibited leep conization, 37 (86%) required a single pass, and 6 (14%) required double passes. In addition, the clinical and demographic parameters of the patients (n = 43) with CIN ≥ 2 lesions at the surgical margin after repeat conization and those (n = 42) with CIN ≤ 1 were shown in Table 2. The most striking results to emerge from our data are stated under 2 main items: (a) the patients who presented with lesions > 5 mm in repeat cone specimens exhibited a significantly higher rate of residual disease ($p < 0.001$), and (b) in repeat cone specimens, the involvement of the endocervical margin with high-grade CIN was significantly higher in patients who presented with residual disease ($p = 0.006$). Severity of disease (CIN 2 vs CIN 3), ECC result, largest cone diameter, cone volume, and cone depth did not predict residual disease after repeat conization. In multivariate analysis, the risk of residual disease was

Table 1. Clinicopathological parameters of 43 patients with positive surgical margin after repeat conization

Characteristic	Values
Age, years, median (range)	35 (29–55)
Parity, n (%)	
Nullipara	10 (23.3)
Primipara	15 (34.9)
Multipara	18 (41.8)
Smoking status, n (%)	
Yes	17 (39.5)
No	26 (60.5)
Menopausal status, n (%)	
Premenapousal	39 (90.6)
Postmenapousal	4 (9.4)
Referral cytology result, n (%)	
ASC–US	7 (16.3)
LSIL	15 (34.9)
ASC–H	6 (13.9)
HSIL	15 (34.9)
Colposopic biyopsy result, n (%)	
CIN 2	6 (14.0)
CIN 3	37 (86.0)
First conization result, n (%)	
CIN 2	11 (25.6)
CIN 3	32 (74.4)
ECC, n (%)	
Positive	15 (34.9)
Negative	28 (65.1)
Endocervical margin involvement	
Positive	25 (58.1)
Negative	18 (41.9)
Number of passes, n (%)	
1	37 (86.0)
> 1	6 (14.0)
Conization technique, n (%)	
LEEP	39 (90.7)
Cold knife	4 (9.3)
Cone volume, cm^3, median (range)	13.5 (10.3–52.9)
Cone depth, mm, median (range)	12 (10–20)
Lenght of lesion, mm, median (range)	5 (1–13)
Follow–up period, months, median (range)	31.1 (7–156)

PSM — positive surgical margin; LEEP — loop electrosurgical excision procedure; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepitehial lesion; ASC-H — atypical squamous cells — cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepitehial lesion; CIN — cervical intraepithelial neoplasia; ECC — endocervical curettage

increased in patients who presented with lesion > 5 mm ($p < 0.001$) and even higher in patients with endocervical margin involvement ($p < 0.001$). No other variables were significantly associated with residual disease. Table 3 shows the relationship of the pathological reports between the first and repeat conization procedure.

In the subgroup analysis, of the 23 patients who underwent reflex extrafascial hysterectomy due to PSM after the first conization, 2 (8.7%) presented with invasive cervical cancer (stage 1B1) and underwent radical parametrectomy, upper vaginectomy, and lymph node dissection. The decision of reflex hysterectomy was mainly due to the gynecologic co-morbidity, including the presence of ovarian cystic lesion, uterine fibroid, endometrial hyperplasia, intractable menorrhagia, etc. Conversely, of the 91 patients who presented with repeat conization, 6 (6.5%) were diagnosed with micro-invasive cancer (stage 1A1) and underwent extrafascial hysterectomy. Interestingly, 1 of them received the final pathological diagnosis of invasive cancer (stage 1B1). Accordingly, this patient also underwent radical parametrectomy, upper vaginectomy, and lymph node dissection. The remaining 5 who presented with no residual disease in the hysterectomy specimen were followed up closely. Among the 43 patients with PMS after repeat conization, 12 (27.9%) underwent extrafascial hysterectomy directly, 4 (9.3%) underwent the third conization, and 1 out of 4 patients underwent the fourth conization using a cold knife one year after the third conization due to the presence of CIN 3 in biopsy specimen. Unfortunately, it was complicated by posterior fornix perforation and resulted in entry to the pelvic cavity. Therefore, diagnostic laparoscopy was performed. None of them received the final pathologic diagnosis of invasive cancer. Finally, for 27 of 43 patients (62.8%), no further intervention was performed, and they followed up with cytology and colposcopic evaluation (Fig. 1). In principle, repeat (third) conization was recommended to all 43 patients. However, the treatment choice was given primarily considering the fertility desire and age. Hysterectomy was preferred in patients who were in perimenopause and rejected the third conization procedure. On the other hand, young patients with fertility desire were followed up closely without intervention to preserve cervical stroma.

DISCUSSION

In the present study, we found that the presence of lesions greater than 5 mm and involvement of endocervical margins were the predictors of high-grade residual lesions in cone specimens after repeat conization. To our knowledge, this is the first study to investigate the predictors of residual disease in patients who received the re-excision procedure due to persistent surgical margin positivity. Our results may provide a prognostic tool for predicting which women with residual disease after repeat conization could be managed with a conservative strategy and which might require an aggressive treatment strategy.

Previous studies revealed that CIN 3 lesions tend to be confluent and are more likely to be solitary rather than multifocal in distribution, also they have shown that the larger CIN 3 lesions may exhibit a higher risk of progression to cancer [8]. In addition, previous reports revealed that the large CIN lesions were associated with a higher rate of post conization

Table 2. Comparison of the patient parameters with cervical intraepithelial neoplasia (CIN) ≥ 2 lesions at the surgical margin after repeat conization and those with CIN ≤ 1

Parameter		With margin positivity n = 43	Without margin positivity n = 42	p value
Age [years]	< 35 ≥ 35	16 (37.2%) 27 (62.8%)	12 (28.6%) 30 (71.4%)	0.39
Smoking status	Yes No	17 (39.5%) 26 (60.5%)	21 (50.0%) 21 (50.0%)	0.33
Parity	<1 ≥1	10 (23.3%) 33 (76.7%)	7 (16.7%) 35 (81.3%)	0.17
Menopausal status	Premenopause Postmenopause	4 (9.3%) 39 (90.7%)	3 (7.1%) 39 (92.9%)	0.72
Referral cytology result	ASC-US & LSIL ASC-H & HSIL	22 (51.2%) 21 (48.8%)	18 (42.9%) 24 (57.1%)	0.59
Colposcopic biopsy result	CIN 2 CIN 3	6 (14.0%) 37 (86.0%)	8 (19.0%) 34 (81.0%)	0.53
First conization result	CIN 2 CIN 3	11 (25.6%) 32 (74.4%)	14 (33.3%) 28 (66.7%)	0.55
Re-excision method	LEEP Cold Knife	39 (90.7%) 4 (9.3%)	37 (88.1%) 5 (11.9%)	0.72
Endocervical margin involvement	Positive Negative	25 (58.1%) 18 (41.9%)	12 (28.6%) 30 (71.4%)	0.006
ECC	Positive Negative	15 (34.9%) 28 (65.1%)	16 (38.1%) 26 (61.9%)	0.76
Lenght of lesion [mm]	< 5 ≥ 5	18 (41.9%) 25 (58.1%)	39 (92.9%) 3 (7.1%)	< 0.001
Cone volume [cm^3]	< 13.5 ≥ 13.5	18 (41.9%) 25 (58.1%)	15 (35.7%) 27 (64.3%)	0.56
Cone depth [mm]	< 12 ≥ 12	17 (39.5%) 26 (60.5%)	14 (33.3%) 28 (66.7%)	0.42

LEEP — loop electrosurgical excision procedure; ASC-US — atypical squamous cells of undetermined significance; LSIL — Low-grade squamous intraepitehial lesion; ASC-H — atypical squamous cells — cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepitehial lesion; CIN — cervical intraepithelial neoplasia; ECC — endocervical curettage

Table 3. The relationship of the pathological reports between the first and repeat conization procedure (n = 91)

First conization pathology	Repeat conization pathology					
	≤ CIN 1	CIN 2	CIN 3	Micro-invasive	Invasive	Total
CIN 2	14	9	2	0	0	25
CIN 3	28	15	17	6[†]	0	66
Total	42	24	19	6[†]	0	91

[†]One patient was diagnosed with invasive cancer after pathological evaluation of hysterectomy specimen; CIN — cervical intraepithelial neoplasia

residual disease. Chen et al. [9] published a retrospective analysis of 1,113 patients who underwent conization due to CIN 3 and examined the predictors of residual disease in 141 patients with PSM. They finally concluded that lesions greater than two-thirds of the cervix at visual inspection presented with a higher rate of surgical margin positivity (relative risk 1.3; 95% CI, 1.1–2.3). Similarly, Shaco-Levy et al. [10] retrospectively analyzed 376 women who presented with conization due to high-grade CIN to identify the predictors associated with PSM. The authors concluded that patients with extensive lesions demonstrated an increased risk of persistent/recurrent disease compared to patients with focal lesions in cone specimens (hazard ratio = 27.6; 95% CI, 8.9–85.5). Recently, Diaz et al. [11] evaluated the predictors of residual lesions comprised of carcinoma or high-grade CIN at hysterectomy specimens following conization procedure due to PSM or positive ECC or micro-invasive carcinoma. They reported that the presence of the disease in ≥ 50% of the total cone volume at the pathological evaluation was a predictor of residual disease (26% for < 50% vs 44%

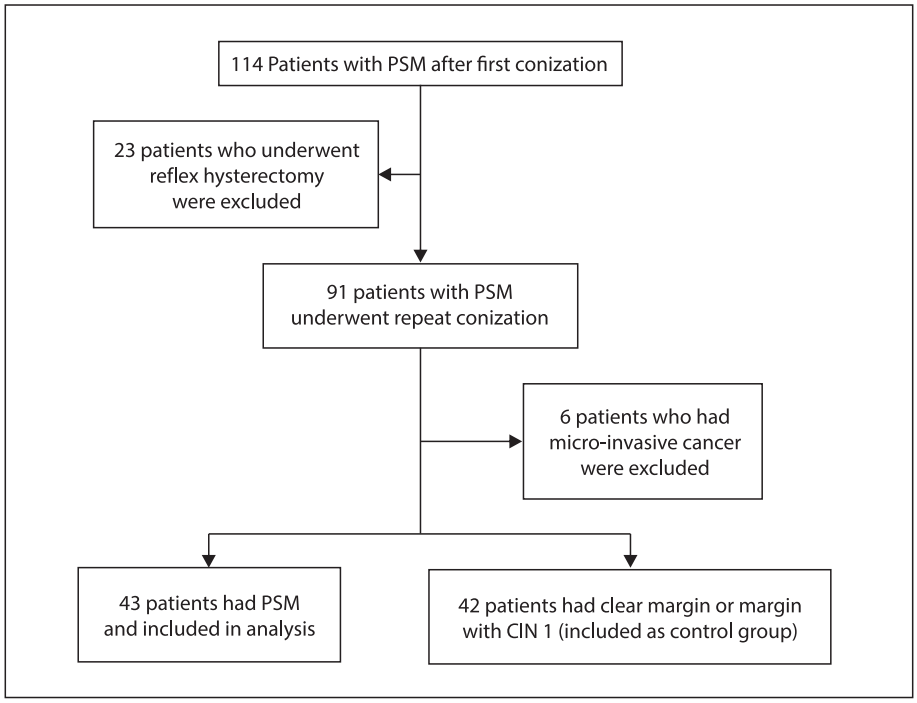

Figure 1. Flow Diagram of the study; PSM — positive surgical margin; CIN — cervical intraepithelial neoplasia

for ≥ 50%, $p < 0.01$). However, the results of all these studies were limited to patients who underwent the first conization procedure and did not address the risk of residual disease in patients who had repeat conization. In the present study, our results revealed that lesions > 5 mm in the cone specimen after repeat conization were significantly associated with persistent residual disease.

Conversely, the results of the present study were similar to those of other studies that stated that the involvement of endocervical margin was the predictor of residual disease. Roman et al. [12] stated that endocervical margin positivity was a significant predictor of post conization residual disease (22% with positive margin vs 3% without positive margin, $p < 0.03$). More recently, Park et al. [13] found that the presence of positive endocervical margin after conization was an independent predictor of residual disease. However, the studies mentioned above made these conclusions on the data obtained after the first conization. Finally, these authors highlighted that in the presence of positive endocervical margin after the conization procedure, repeat conization should be performed before definitive treatment. In our limited cohort, 2 patients with residual CIN ≥ 2 lesion after the first conization and 1 patient with micro-invasive carcinoma after the repeat conization presented with the diagnosis of invasive carcinoma in hysterectomy specimens. However, in these circumstances, repeat conization might be preventive for malpractice and exceptional surgical interventions including radical parametrectomy and upper vaginectomy [14]. Like the recommendations made by these authors, we strongly suggest repeat conization before hysterectomy in patients with PSM, particularly with endocervical margin involvement. However, our recommendation for repeat conization is a step that should be administered only in patients who are scheduled for hysterectomy. Patients who demonstrate fertility desire with PSM after initial conization should be managed according to the recommendations of ASCCP [5].

Interestingly, although only six patients demonstrated double passes during the repeat conization procedure, high-grade residual disease was found at the surgical margins in five specimens on pathological evaluation. Besides, all the lesions were reported as CIN 3 in cone specimens. Recent publications on the subject emphasized that multiple passes were significantly associated with the residual disease during the first conization procedure [15–17]. However, a small number of patients was found who demonstrated multiple passes in our study. Therefore, drawing a definitive conclusion was insufficient.

The present study exhibits some limitations. First, due to its retrospective nature, undetected bias might occur. Second, the limited number of patients in the study cohort is another disadvantage. Third, our clinical tendency to use LEEP more than cold knife for repeat conization to avoid complications of cold-knife excision might be a limitation of this study. Finally, the relationship between human papillomavirus types and residual disease after repeat conization

has not been evaluated. Conversely, a key strength of the present study is its design, in which we principally investigate the patients with persistent high-grade disease after repeat conization.

CONCLUSIONS

In conclusion, the present study revealed two predictors that were statistically associated with PSM after re-excision procedure. Accordingly, in re-excision specimens, the presence of lesions greater than 5 mm and the involvement of endocervical margin were the predictors of high-grade residual disease. We concluded that repeat conization should be preferred instead of reflex hysterectomy in patients with PSM after the first conization. Finally, whether it is first or repeat, great care must be given to excise the lesion entirely at the time of the conization procedure, preferably in one piece.

Disclosure

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Author contributions

Conceptualization, Methodology: Y. Minareci, H. Sozen, M.Y. Salihoglu, S. Topuz.

Software, Validation, Data Curation, Formal Analysis: Y. Minareci, N. Ak, O.A. Tosun.

Writing — original draft: Y. Minareci, H. Sozen, N. Ak, O.A. Tosun.

Writing — review & editing: Y. Minareci, H. Sozen, N. Ak, O.A. Tosun, M.Y. Salihoglu, S. Topuz.

Visualization, Supervision, Project Administration, Investigation, Resources: Y. Minareci, H. Sozen, N. Ak, O.A. Tosun, M.Y. Salihoglu, S. Topuz.

Statistical analysis: R. Disci

Conflict of interest

All authors declare no conflict of interest.

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