Optimal cone size to predict positive surgical margins after cold knife conization (CKC) and the risk factors for residual disease

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Abstract

Objective: To determine the optimal cone size to achieve a reliable sensitivity and specificity for clear surgical margins after cold knife conization (CKC).

Material and Methods: The medical reports of patients who had high-grade cervical intraepithelial lesions, carcinoma in situ, or stage 1A1 microinvasive carcinoma in their CKC specimens between June 2008 and January 2015 were reviewed retrospectively.

Results: In total, 315 women fulfilled the inclusion criteria. The mean age of the patients was 40.7 years. The conization results were microinvasive carcinoma and high-grade squamous lesion (HSIL) for 8 and 307 patients, respectively. Ninety-nine patients had positive surgical margins. Eighty-one patients with positive cone margins underwent the repeat excisional procedure and 35 of them showed residual disease. In the univariate analyses, the patient age, menopausal status, and mean cone height parameters showed statistically significant differences between the patients with positive and negative margins. Also, residual disease was associated with the menopausal status and age of the patients.

Conclusion: There is no optimal cone depth that is applicable for all patients. The most important predictors for positive margins are the menopausal status of the patient and that more than two quadrants are involved. However, the menopausal status and age of the patients were still predictors for residual disease. (J Turk Ger Gynecol Assoc 2016; 17: 159-2)

Keywords: Cold knife conization, residual disease, surgical margin

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Introduction

Cervical cancer is the most preventable gynecological cancer; the treatment of high-grade cervical lesions leads to a decreased incidence of cervical cancer (1). The diagnosis and surgical treatment of high-grade cervical preinvasive lesions depends on the colposcopic findings (2). The main purpose of the treatment is to remove the cervical lesion with adequate surgical margins as well as the whole transformation zone (TZ) (3). Studies have shown that the most important predictor for residual disease or disease recurrence is positive cone margins (4, 5). Positive surgical margins after loop electrosurgical excision procedures (LEEPs) are seen more frequently and have been extensively studied compared with cold knife conization (CKC) (6). Margin-positive patients are more likely to have recurrent disease, and the recurrence is earlier than seen in margin-negative patients (7). When there is no visible lesion in the ectocervix or when the lesion is located in the endocervical canal, it can be challenging to achieve clear margins without compromising future obstetric outcomes. Also, a deeper cone height and repeat excisions after positive surgical margins are associated with adverse obstetric outcomes (8). There is no clear definition of the optimal cone size in the treatment of high-grade cervical intraepithelial lesions. The depth of the cone specimen is usually determined in the operating room according to the age, parity, fertility desire, and initial colposcopic findings of the patient. The objective of the present study was to determine the optimal cone size needed to achieve a reliable sensitivity and specificity for clear surgical margins.

Material and Methods

After approval of the Institutional Review Board, the medical records of patients who had undergone a CKC procedure in Zekai Tahir Burak Women's Health Training and Research Hospital between June 2008 and January 2015 were reviewed. We included only the patients with preceding colposcopic biopsy results showing high-grade cervical lesions [i.e., cervical intraepithelial neoplasia (CIN) 2/3 or high-grade squamous lesion (HSIL)]. The patients whose conization results showed lesser abnormalities [i.e., CIN-1, low-grade squamous in-

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traepithelial lesion (LSIL), or normal epithelium] and invasive carcinomas were excluded, so we collected only the follow-up data of the patients with conization results of CIN 2/3 and carcinoma *in situ* (CIS). Written informed consents were obtained from all subjects either before the colposcopic procedures or CKC procedures.

All of the excisional procedures were performed in the operating room using a scalpel under general or regional anesthesia. As the standard procedure, the hemostatic sutures were applied lateral margins of the cervix using no. 0 polyglactin (Vicryl; Ethicon, Cincinnati USA); endocervical curettage was applied and the base of the CKCs were cauterized using a high-voltage spray mode. In the presence of a visible lesion in the cervix, the conization margins were adjusted accordingly, otherwise a standard cone-shaped specimen was removed with the intent of including the entire TZ. A silk suture was placed at the 12 o'clock position of the cone specimen for orientation and the specimens were transported to the pathology depart ment in a formalin solution container. Specimens were divided into four quadrants and each quadrant was examined in at least three consecutive slices. The surgical margins were considered as positive if the lesion was cut-through or closer than 1 mm to the margin.

The cone volume was calculated using the radius (r) and height (H) reported in the pathology result after formalin fixation, by the formula ($\pi.r^2.H/3$). If the base of the cone was elliptical rather than circular, then the mean of the two perpendicular diameters was used to calculate the radius of the cone base. The patient characteristics, dimensions of the conization specimens, and surgical margin status (endocervical and ectocervical) were analyzed in a descriptive manner. The associations between the cone margin status and mean cone diameter, cone height, and cone volume were investigated.

The Statistical Package for the Social Sciences (SPSS) version 21 for Macintosh (SPSS Inc.; Chicago, IL, USA) was used for data interpretation. 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. A multivariate logistic regression model was used to calculate the odds ratios when the univariate analyses showed a significant difference of the variables. $P<0.05$ was considered statistically significant.

Results

Overall, 315 women fulfilled the inclusion criteria (CKC result CIN2/3 or microinvasive carcinoma) among 486 CKCs. All the patients had a prior high-grade cervical cytology result. The mean age of the patients was 40.7 years. Patients' ages ranged from 23 to 73 years. In total, 240 women were premenopausal, while the remaining 75 women were postmenopausal. Eight conizations showed microinvasive carcinoma, while the remaining 307 patients had HSIL in the conization specimens. In total, 216 women (68.6%) had clear margins, while the remaining 99 women (31.4%) had positive margins. Positive margins were ectocervical, endocervical, or both for 22 (7%), 75 (23.8%), and 2 (0.6%) patients, respectively. The study design is summarized in Figure 1.

In the univariate analyses, the patient age, menopausal status, and mean cone height parameters showed statistically significant differences between the patients with positive and negative margins: patients with positive margins had smaller cone heights than those with negative margins (13.7 mm vs. 15.1 mm, respectively; $p<0.05$). Also, patients with positive margins tended to be older and postmenopausal. Twenty-seven percent of the premenopausal patients had positive margins, whereas 46.7% of the postmenopausal patients had positive surgical margins in the CKC specimens ($p<0.01$). Age and menopausal status were included in the multivariate analysis; the age of the patients was not an independent risk factor associated with margin status, whereas menopausal status was still found to be an independent risk factor associated with positive margin status. The detailed demographic and clinical characteristics of the patients are shown in Table 1. However, the cone volume, cone diameter, and cone height were not associated with the margin status of the conization specimens. The only pathological factor that was associated with the margin status was the number of quadrants involved in the conization specimen. If three or more quadrants were involved with HSIL, the risk of positive surgical margins was 2.71 times higher than for the patients with two or more involved quadrants. A receiver operating curve (ROC) was created for the association between cone height and margin status, and it was found that a 21-mm cone height provided 93% sensitivity and 71% specificity to achieve clear surgical margins (Table 2). However, the area under the ROC was calculated as 0.567, which means it was not statistically significant (Figure 2). Eighty-one (82%) of the patients with positive cone margins underwent repeat excisions; 49 of them underwent hysterectomy, while the remaining 32 of them underwent reconization. A total of 35 patients had residual disease in their re-excision specimens. The clinicopathological characteristics of the patients according to the residual disease status are shown in Table 3.

In the univariate analyses, residual disease was associated with the menopausal status and age of the patients; 17 of 49

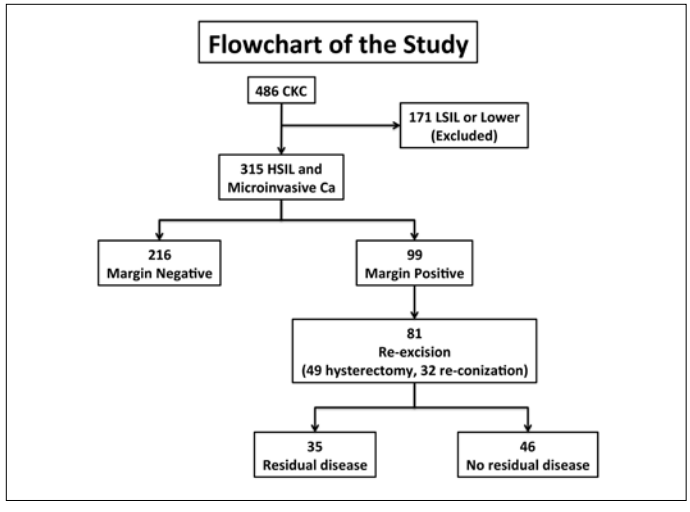

Figure 1. Flowchart of the study

CKC: cold knife conization; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; microinvasive ca: microinvasive carcinoma

Table 1. Detailed demographic and clinical features of the patients with negative and positive conization margins

	Margin Negative (N=216)	Margin Positive (N=99)	p	OR
Age (Mean±SD)	39.3±9.3	43.5±9.3	<0.01[a]	
Menopausal Status			<0.01[b]	1.8
Premenopausal N=240 (%)	176 (73%)	64 (27%)		
Postmenopausal N=75 (%)	40 (53.3%)	35 (46.7%)		
Preceding Cytology			>0.05[b]	
ASC-US	33 (15.3%)	5 (5%)		
LSIL	18 (8.3%)	9 (9%)		
HSIL	146 (67.6%)	74 (74.7%)		
ASC-H	12 (5.5%)	5 (5%)		
AGC	2 (1%)	0		

ASC-US: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells cannot exclude HSIL; AGC: atypical glandular cells; OR: odds ratio

[a]Student's t-test was used.

[b]Fisher's exact test was used.

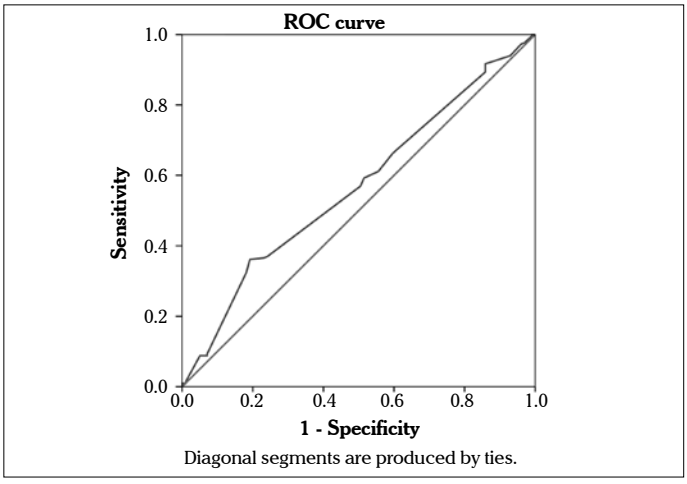

Figure 2. ROC curve

(35%) premenopausal women had residual disease, while 18 of 32 (56%) postmenopausal women had residual disease in their re-excision specimens (p<0.05). The mean age of the patients with and without residual disease was 47.4±9 and 42.6±9 years, respectively (p<0.05).

The number of positive quadrants was not associated with residual disease status. Also, the diameter, depth, and volume of the conization specimen were not a predictor for residual disease.

Discussion

Approximately one-third of the CKC specimens had positive surgical margins in the present study. The prevalence of positive margins reported in the previous studies was similar to our study, Costa et al. (9) and Sun et al. (10) reported the prevalence of positive cone margins in the CKC specimens in their study as 27%. In the former study, the authors reported that the cone size was not an independent risk factor for positive cone margins. In the latter study, Sun et al. (10) found that the conization depth and multiquadrant involvement were significant factors associated with positive margins in both univariate and multivariate analyses. Kliemann et al. (2) reported similar results in their study. They found the cone height and lesion size as independent prognostic factors for positive margins. Positive margins were associated

Table 2. Pathological characteristics of margin-positive and margin-negative patients

	Margin Negative (N=216)	Margin Positive (N=99)	p	OR
Mean Cone Diameter (mm)	28.3	29	>0.05[a]	
Mean Cone Volume (mm^3)	3559	3556	>0.05[a]	
Mean Cone Height (mm)	15.1	13.7		
<21 mm (N=288)	196 (68%)	92 (32%)	<0.05[a]	
≥21 mm (N=27)	20 (74%)	7 (26%)		
Positive quadrants	N (%)	N (%)		
1 quadrant	99 (45.8%)	1 (3%)		
2 quadrants	62 (28.7%)	28 (28.3%)		
3 quadrants	31 (14.4%)	36 (36.4%)		
4 quadrants	24 (11.1%)	32 (32.3%)	p<0.001[b]	
≥3 quadrants	55 (25.5%)	68 (68.7%)	p<0.001[c]	2.71

[a]Independent samples t-test was used.

[b]Fisher's exact test was used.

[c]Chi-square test was used.

OR: odds ratio

Table 3. Clinicopathological characteristics of the patients according to residual disease status

	Residual disease		
	Negative (N=46)	Positive (N=35)	p
Age (mean±SD)	42.5±9	47.3	<0.05[a]
Menopausal status			<0.05[b]
Postmenopausal (N=32)	14 (43.7%)	18 (56.3%)	
Premenopausal (N= 49)	32 (65.3%)	17 (34.7%)	
Positive quadrants			<0.05[b]
<3 (N=26)	16 (61.5%)	10 (38.5%)	
≥3 (N=55)	30 (54.5%)	25 (45.5%)	
Conization			>0.05[c]
Diameter (mean)	30.4 mm	28.3 mm	
Depth (mean)	13.9 mm	14.5 mm	
Volume (mean)	3757 mm^3	3943 mm^3	

[a]Independent samples t-test was used.

[b]Fisher's exact test was used.

[c]Chi-square test was used.

with a shallow cone height and the menopausal status of the patient. In the majority of cases, the operator cannot see a visible lesion in the cervix and performs the conization with the intent to remove the entire TZ and the lesion.

We found that a 21 mm cone height provided 93% sensitivity and 71% specificity to achieve clear surgical margins. The cervix has varying size and shape among women, and there are no objective criteria that help the surgeon to achieve clear surgical margins.

In a recent study that aimed to identify the predictors of residual disease after cervical conization, the authors concluded that positive ECC and a volume of disease 50% or greater were predictors of residual disease, whereas more than two involved quadrants was not associated with positive margin status (11). However, Tasci et al. (12) reported that more than two involved quadrants was one of the most important factors for residual disease after cervical conization. Nevertheless, we did not demonstrate a relationship between the number of quadrants involved and residual disease. In the present study, the patient's age and menopausal status were significantly related with residual disease.

There are several studies that investigate the optimal cone depth to achieve clear surgical margins. Papoutsis et al. (13) reported that the optimal cut-off value of cone depth to achieve clear surgical margins is 10 mm; however, Kliemann et al. (2) showed that the mean depth of cone specimens were 17.1 mm and 22.4 mm among the patients with positive and negative surgical margins, respectively. We found that cone depth was significantly different between margin-positive and margin-negative patients, but multivariate analysis showed that cone depth alone was not an independent predictor of margin status. Also, we did not find cone diameter and cone volume as a predictor of a positive surgical margin. The liberal excision of deep cone specimens should be avoided because greater cone heights are associated with a greater risk of stenosis (14), bleeding (15), and poor obstetric outcome (16). Therefore, cone depth should be individualized for each patient considering the age of the patient, size of the cervix, and TZ.

The main limitation of the present study is its retrospective design. In addition, the CKC procedures were performed by several different surgeons, including less experienced ones, which may lead to an increased positive margin status.

In conclusion, there is no optimal cone depth that is applicable for all patients. A significant proportion of patients with HSIL will have a positive surgical margin after CKC, and the most important predictors for positive margins are the menopausal status of the patient and more than two quadrants involved. However, the menopausal status and age of the patients are still predictors for residual disease.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Zekai Tahir Burak Women's Health Training and Research Hospital (Approval date and number: 31.07.2015/14).*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

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References

1. Petry KU. Management options for cervical intraepithelial neoplasia. Best Pract Res Clin Obstet Gynaecol 2011; 25: 641-51. [Crossref]
2. Kliemann LM, Silva M, Reinheimer M, Rivoire WA, Capp E, Dos Reis R. Minimal cold knife conization height for high-grade cervical squamous intraepithelial lesion treatment. Eur J Obstet Gynecol Reprod Biol 2012; 165: 342-6. [Crossref]
3. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol 2007; 197: 346-55. [Crossref]
4. Kietpeerakool C, Khunamornpong S, Srisomboon J, Siriaunkgul S, Suprasert P. Cervical intraepithelial neoplasia II-III with endocervical cone margin involvement after cervical loop conization: is there any predictor for residual disease? J Obstet Gynaecol Res 2007; 33: 660-4. [Crossref]
5. Woelber L, Choschzick M, Eulenburg C, Hager M, Jaenicke F, Gieseking F, et al. Prognostic value of pathological resection margin distance in squamous cell cancer of the vulva. Ann Surg Oncol 2011; 18: 3811-8. [Crossref]
6. Kietpeerakool C, Srisomboon J, Ratchusiri K. Clinicopathologic predictors of incomplete excision after loop electrosurgical excision for cervical preneoplasia. Asian Pac J Cancer Prev 2005; 6: 481-4.
7. Miyoshi Y, Miyatake T, Ueda Y, Morimoto A, Yokoyama T, Matsuzaki S, et al. Prediction, based on resection margins, of long-term outcome of cervical intraepithelial neoplasia 3 treated by Shimodaira-Taniguchi conization. Arch Gynecol Obstet 2012; 285: 1427-32. [Crossref]
8. Simoens C, Goffin F, Simon P, Barlow P, Antoine J, Foidart JM, et al. Adverse obstetrical outcomes after treatment of precancerous cervical lesions: a Belgian multicentre study. BJOG 2012; 119: 1247-55. [Crossref]
9. Costa S, De Nuzzo M, Terzano P, Santini D, De Simone P, Bovicelli A, et al. Factors associated with cone margin involvement in CIN patients undergoing conization-equivalent electrosurgical procedure. Acta Obstet Gynecol Scand 2000; 79: 586-92. [Crossref]
10. Sun XG, Ma SQ, Zhang JX, Wu M. Predictors and clinical significance of the positive cone margin in cervical intraepithelial neoplasia III patients. Chin Med J (Engl) 2009; 122: 367-72.
11. 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. [Crossref]
12. 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. [Crossref]
13. Papoutsis D, Rodolakis A, Mesogitis S, Sotiropoulou M, Antsaklis A. Appropriate cone dimensions to achieve negative excision margins after large loop excision of transformation zone in the uterine cervix for cervical intraepithelial neoplasia. Gynecol Obstet Invest 2013; 75: 163-8. [Crossref]
14. Baldauf JJ, Dreyfus M, Ritter J, Meyer P, Philippe E. Risk of cervical stenosis after large loop excision or laser conization. Obstet Gynecol 1996; 88: 933-8. [Crossref]
15. Girardi F, Heydarfadai M, Koroschetz F, Pickel H, Winter R. Cold-knife conization versus loop excision: histopathologic and clinical results of a randomized trial. Gynecol Oncol 1994; 55: 368-70. [Crossref]
16. Andia D, Mozo de Rosales F, Villasante A, Rivero B, Diez J, Perez C. Pregnancy outcome in patients treated with cervical conization for cervical intraepithelial neoplasia. Int J Gynaecol Obstet 2011; 112: 225-8. [Crossref]