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# Predictors of residual carcinoma or carcinoma-in-situ at hysterectomy following cervical conization with positive margins

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## HIGHLIGHTS

- We hypothesized that factors in the conization specimen predict residual disease at hysterectomy.
- In squamous histology, positive ECC, combined positive endocervical margin and ECC and disease volume ≥50% predicted residual disease at hysterectomy.
- In glandular histology, no conization characteristics studied were predictive of residual disease at hysterectomy.

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## ABSTRACT

*Objectives.* Identify predictors of residual carcinoma or carcinoma-in-situ (CIS) at hysterectomy following cervical conizations with CIS and positive margins or endocervical curettage (ECC) or microinvasive cervical cancer.

*Methods.* Patients with cervical conization with CIS and positive margins, ECC or microinvasive carcinoma who underwent hysterectomy within 6 months of conization were identified. Conization and hysterectomy specimens were re-reviewed to assess volume of disease, ECC and margin status and residual carcinoma. Standard statistical tests were used.

*Results.* 83 patients were included. 34 (41%) had residual carcinoma in the hysterectomy specimen: 23 CIS, 9 microinvasive and 2 invasive disease. In patients with squamous histology predictors of residual disease included a positive ECC ($p = 0.04$), combined endocervical margin and ECC (69% if both positive, 38% either positive, 11% if both negative, $p = 0.01$) and volume of disease ≥50% ($p = 0.01$). In patients with glandular histology no factor predicted residual disease. Type of conization, >2 involved quadrants, and the presence of microinvasion in the conization specimen did not predict residual disease. No patient with squamous histology had >Stage IA1 disease at hysterectomy, whereas 2 (2.4%) with adenocarcinoma had >Stage IA1 disease at hysterectomy.

*Conclusions.* Residual carcinoma or CIS is present in nearly half of hysterectomies after conization with CIS and positive ECC, margins or microinvasion. Patients with squamous histology may not require repeat conization prior to definitive therapy. No factors predict residual disease with adenocarcinoma. In women with AIS with negative margins and ECC and no microinvasion, it appears reasonable to proceed with simple hysterectomy.



## Introduction

The recommended management for carcinoma in-situ (CIS) of the cervix or suspected microinvasive (Stage 1A1) cervical cancer diagnosed by biopsy is cervical conization with post-conization endocervical curettage (ECC). This procedure is diagnostic and potentially therapeutic depending on the final pathology. Conization allows for removal of the affected portion of the cervix with curative intent, but also serves to evaluate for the presence of invasive disease (depth of invasion >3 mm or the presence of lymphvascular space invasion) that would require more extensive treatment. In cases where conization margins and ECC are negative and the patient desires definitive treatment, a simple hysterectomy is an appropriate next step [1,2]. However, management of the patient with carcinoma in-situ (CIS) involving a margin or the ECC or microinvasive cervical cancer with a positive margin who desires definitive treatment is less well established. Data regarding the risk and extent of residual disease in these settings are limited. Without

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strong data regarding this question, physicians are left with difficulty in counseling patients with this finding who desire definitive treatment about the most appropriate next step in their care. Whether it is safe to move directly to simple hysterectomy or whether a repeat conization is needed first to exclude any residual or occult invasive disease is not entirely clear.

In this study, we hypothesized that factors present in the conization specimen of women with CIS and positive margins or ECC or microinvasive carcinoma are predictive of residual disease in the hysterectomy specimen and can be used to guide recommendations for further therapy. Our objectives were to validate these predictive factors and to identify a group of women who could have definitive treatment with simple hysterectomy following conization for CIS with positive margins or ECC or microinvasive cervical cancer.

## Materials and methods

After IRB approval, pathology records from 1998 to 2012 were reviewed at Cedars-Sinai Medical Center and Olive View-UCLA Medical Center to identify patients who underwent cervical conization by LEEP or cold knife technique with final pathology from the conization that revealed CIS with positive margins, positive ECC or microinvasive disease and who then underwent hysterectomy within 6 months of conization. Patients with CIN I or II or CIS with negative margins and negative ECC or the presence of LVSI on conization were excluded from the analysis. Demographic and surgico-pathologic data were abstracted from the medical records. Pathology slides from conization and hysterectomy were re-reviewed by two gynecologic pathologists to confirm post-conization ECC and margin status, number of quadrants with CIS or microinvasive cancer, volume of CIS or microinvasive carcinoma, and residual disease in the hysterectomy specimen. A standardized protocol was used to accession the specimens in a circumferential fashion however the number of slides representing each specimen was dependent on the size and topography of the specimen. In order to standardize volume of disease across specimens with different numbers of slides, the proportion of specimen involved with carcinoma was calculated as a ratio from 0 to 1.0 by dividing the number of slides with CIS or microinvasive carcinoma over the total number of slides for that conization specimen × 100 as a surrogate marker for volume of disease. A hysterectomy specimen was considered to contain residual disease if CIS, microinvasive, or invasive disease was present.

When evaluating the predictive impact of a positive post-conization ECC, or positive margin on residual in-situ or invasive carcinoma in the hysterectomy specimen, patients with coexisting microinvasive cancer and high-grade dysplasia of the same histology (e.g.,: Stage IA1 SCCA and CIS) were analyzed based only on the most severe histology (in this example only as Stage IA1 SCCA). Patients with coexisting mixed histologies (both glandular and squamous abnormalities) were analyzed based on which histology was dominant in the specimen. In patients who underwent repeat conization prior to hysterectomy, only pathology results from the conization performed closest in time to the hysterectomy were included in the analysis.

Fisher's exact test was used to test for associations between categorical variables and the presence of residual disease in the hysterectomy specimen. All tests were two-sided and a p-value $<0.05$ was considered significant.

## Results

1200 pathology records were reviewed in order to identify 83 patients who met inclusion criteria for this study. The median age in our cohort was 47 with a range of 26–76 years of age. Twenty-one patients (25%) were smokers. Seven patients (8%) had undergone a prior LEEP or CKC. Review of conization pathology revealed 31 patients with CIS, 27 patients with Stage IA1 squamous cell carcinoma (SCCA), 18 patients with adenocarcinoma in-situ (AIS), and 7 patients with Stage IA1 adenocarcinoma. Nine (11%) of the patients had co-existing histologies present on their conization specimen; 6 patients had both squamous CIS and AIS, 1 patient had both Stage IA1 SCCA and AIS, and 2 patients had both Stage IA1 adenocarcinoma and squamous CIS. Details of the conization pathology and margin status of the cohort are shown in Table 1.

Cold knife conization was performed in 55 women (66%) and loop electrosurgical excision procedure (LEEP) was performed in 28 women (34%). Median time from cervical excisional procedure to hysterectomy was 2.4 months (range 1.5–6 months). The endocervical margin was interpretable in 82 cases (99%), the ectocervical margin was interpretable in 82 cases (99%), and the post-conization endocervical curettage (ECC) was performed in 67 cases (80%). At the time of conization, 38 women (45%) had a positive ECC, 58 (70%) had a positive endocervical margin, and 20 (24%) had a positive ectocervical margin. Of the 38 women with a positive ECC, 36 had CIS and 2 had microinvasive carcinoma in the ECC. Of the 58 women with a positive endocervical conization margin, 54 had CIS and 4 had microinvasive carcinoma at the endocervical margin. Of the 20 women with a positive ectocervical conization margin, 19 had CIS and 1 had microinvasive carcinoma at the ectocervical margin. Based on these conization findings, 74 patients underwent simple hysterectomy (18 vaginal hysterectomies and 56 abdominal hysterectomies), and 9 patients underwent a modified radical hysterectomy with staging. The indication for modified radical hysterectomy in the 9 patients that underwent this procedure was endocervical margin or ECC positive for carcinoma-in-situ in 7 patients and endocervical margin or ECC positive for carcinoma in 2 patients. On hysterectomy pathology in these 9 patients, there was no residual carcinoma in-situ or carcinoma in 8 patients and microscopic Stage IBI adenocarcinoma in one patient. None of the patients that underwent modified radical hysterectomy and staging had positive lymph nodes.

34 of 83 patients (41%) had residual disease in the hysterectomy specimen, of whom 23 were CIS, 9 were microinvasive, and 2 were invasive cancer. Table 2 shows the histopathologic findings of the hysterectomy specimen on the basis of the ECC alone, endocervical margin alone, ectocervical margin alone and ECC and endocervical margin combined in patients with squamous histology. Predictors of residual carcinoma (CIS or greater) at hysterectomy included a positive ECC ($p = 0.04$) or the combined status of endocervical margin and ECC (69% if both positive, 38% either positive, 11% if both negative, $p = 0.01$). The risk of residual invasion <3 mm was 21% if both the ECC and endocervical margin were positive, 10% if either ECC or endocervical margin were positive and 0% if both ECC and the endocervical margin were negative. Isolated margin status (endocervical or ectocervical) was not predictive of residual disease ($p = 0.08$ and $p = 0.35$, respectively). Three patients with squamous CIS on conization had Stage IA1 SCCA at hysterectomy, however no patients with squamous histology had greater than Stage IA1 disease at hysterectomy or the presence of lymphvascular space invasion.

The histopathologic findings of the hysterectomy specimen along with the status of the ECC alone, endocervical margin alone, ectocervical margin alone, and ECC and endocervical margin combined in patients with AIS or microinvasive adenocarcinoma are shown in Table 3. In patients with these histologies neither the status of the ECC ($p = 0.08$), endocervical margin ($p = 0.63$), ectocervical margin (0.06), nor the combination of ECC and endocervical margin ($p = 1.00$) were predictive of residual carcinoma in the hysterectomy specimen. Three patients

**Table 1**
Details of the conization pathology results and margin status.

| Conization result | Positive[a] ECC | Positive[a] endocervical margin | Positive[a] ectocervical margin |
|---|---|---|---|
| CIS (n = 31) | 19 (61%) | 21 (68%) | 6 (19%) |
| 1A1 SCCA (n = 27) | 8 (30%) | 18 (67%) | 8 (30%) |
| AIS (n = 18) | 7 (39%) | 15 (83%) | 6 (33%) |
| 1A1 adeno (n = 7) | 4 (57%) | 4 (57%) | 0 |

[a] Positive for carcinoma-in-situ or carcinoma.