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Risk of residual disease and invasive carcinoma in women treated for adenocarcinoma in situ of the cervix☆

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HIGHLIGHTS

- LEEP is associated with a higher rate of positive margins compared with CKC in patients with AIS.
- There is a high rate of residual disease at hysterectomy following cone biopsy for AIS.
- Patients undergoing conservative management for AIS should be counseled regarding the potential risks of residual and recurrent disease.

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ABSTRACT

Objective. Cervical adenocarcinoma in situ (AIS) is increasing in incidence among reproductive-age women. Cervical conization is an alternative to hysterectomy that allows future fertility, however reports regarding the risk of residual AIS and underlying adenocarcinoma are conflicting. The purpose of this study was to determine the outcomes of a large cohort of women treated for AIS.

Methods. The medical records of 180 women with cervical AIS evaluated at the University of Texas MD Anderson Cancer Center and its outlying clinics between 1983 and 2011 were reviewed for demographic information, treatment history, pathologic findings and outcomes.

Results. The mean age at diagnosis was 33.8 years (range 17.6–76.1 years). 172 of the 180 women had at least one cone biopsy performed, with 110 (64.0%) undergoing a cold knife cone (CKC), and 62 (36.0%) undergoing a loop electrosurgical excision procedure (LEEP) as their initial method of treatment. Positive margins were noted in 35.0% of patients undergoing CKC compared with 55.6% undergoing LEEP ($p = 0.017$). 71 patients ultimately underwent hysterectomy with residual disease noted in 10 patients (14.1%), 8 patients (11.3%) with residual AIS and 2 patients (2.8%) with invasive carcinoma. Of the 101 patients who did not undergo hysterectomy, 2 patients (2.0%) developed recurrent AIS at a median of 27.5 months (range 18–37 months) from the last cone, and none developed invasive carcinoma.

Conclusion. Patients undergoing conservative management for AIS with cervical conization alone should be monitored closely and counseled regarding the potential risks of residual and recurrent disease, even when negative cone margins are obtained.

Introduction

Cervical adenocarcinoma in situ (AIS) was initially described in 1952 by Hepler et al. [1], and is recognized as a precursor to invasive cervical adenocarcinoma. Similar to squamous cervical intraepithelial neoplasia (CIN), infection with human papillomavirus (HPV) is necessary, yet insufficient, for the development of AIS [2,3]. As the mean age at diagnosis of AIS is in the mid to late 30s, many patients have not completed childbearing and a more conservative approach is preferred [4–8]. Although hysterectomy is the definitive therapy for AIS, cervical conization is considered an acceptable alternative in women who desire fertility preservation. There have been conflicting reports regarding rates of recurrence and residual disease in women undergoing cervical conization for AIS [2,4,5,7,9–14]. Therefore, the ideal management of women with AIS remains controversial.

In this study, we report the outcomes of a large cohort of patients with AIS, treated by either conservative means with cervical cone alone or with hysterectomy. The purpose of the study was to determine the rate of residual disease in patients undergoing hysterectomy, as well

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Table 1
Demographic and clinical characteristics.

Characteristic	
Age (years) (N = 180)	
Mean (standard deviation)	33.8 (8.8)
Median (range)	32.7 (17.6–76.1)
Body mass index (kg/m^2) (N = 133)	
Mean (standard deviation)	25.9 (6.3)
Median (range)	24.0 (12.0–45.9)
Race (N = 179)	
African-American	8 (4.5%)
Asian	9 (5.0%)
Hispanic	22 (12.3%)
White	140 (78.2%)
Smoking status (N = 150)	
Current	25 (16.7%)
Previous	21 (14.0%)
Never	104 (69.3%)

as to estimate the recurrence rate of AIS and progression to invasive adenocarcinoma in women managed conservatively.

Materials and methods

We performed a retrospective cohort study at The University of Texas MD Anderson Cancer Center and its outlying clinics. Institutional Review Board approval was obtained with a waiver of informed consent. All patients diagnosed with cervical AIS between 1983 and 2011 were identified using computerized databases from the Departments of Gynecologic Oncology and Pathology. Pathology reports were reviewed and patients with AIS on Papanicolaou (Pap) test, cervical biopsy, cone specimen, or hysterectomy specimen were included. Patients with invasive disease were excluded. All pathology slides were read by a gynecologic pathologist with expertise in cervical cancer and pre-invasive disease.

One hundred eighty patients were identified. Medical records were reviewed for demographic data, treatment history, pathologic findings, and outcomes. A positive margin was defined as AIS within 1 mm of the surgical margin. Residual disease was defined as AIS found in the pathology specimen of the subsequent procedure if performed within 3 months of the prior procedure. If the subsequent procedure was performed after 3 months, this was considered recurrent disease. The follow-up period was defined as the time between initial AIS diagnosis and the date of last contact.

Demographic and clinical characteristics were summarized using descriptive statistics. Fisher's exact test was used to compare groups of interest for various outcomes. All p-values are 2-sided, and were considered significant if <0.05. All analyses were performed using SAS 9.1 for Windows (Copyright© 2002–2003 by SAS Institute Inc., Cary, NC) and StatXact-7© for Windows (Copyright© 2005, 1989–2005, Cytel Software Corporation, Cambridge, Massachusetts).

Table 2
Margin status in patients undergoing cold knife cone (CKC) vs. loop electrocautery excision procedure (LEEP).

Margin status*	CKC (N = 100)	LEEP (N = 54)
Positive	35 (35.0%)	30 (55.6%)
Negative	65 (65.0%)	24 (44.4%)

* p = 0.017; margin status unknown in 17 patients.

Results

One hundred eighty patients were evaluated with cervical AIS between 1983 and 2011. Demographic information is shown in Table 1. The mean age at diagnosis was 33.8 years (range 17.6 to 76.1 years). Of the 150 patients with smoking history available, 31% were current or former smokers. The majority of patients (87%) were asymptomatic at the time of diagnosis. A co-existing squamous lesion was present in 99 of the 180 patients (55%).

Primary management included cold knife cone (CKC) (n = 110, 61.1%), loop electrosurgical excision procedure (LEEP) (n = 62, 34.4%), hysterectomy (n = 6, 3.3%), and was unknown in 2 patients (1.1%) (Fig. 1). Of the 110 patients who underwent a CKC as their initial management, 100 had margin status available with 35 patients (35.0%) having positive cone margins, and 65 patients (65.0%) having negative cone margins (Table 2). Of the 62 patients who underwent an LEEP as their initial management, 54 had margin status available with 30 patients (55.6%) having positive cone margins and 24 patients (44.4%) had negative cone margins. LEEP was associated with a significantly higher rate of positive margins compared with CKC (p = 0.017).

An ECC was performed at first conization in 82 patients (48.0%), and was positive in 11 patients (13.4%). Of the 11 patients with a positive ECC, 10 underwent subsequent conization with 6 patients (60.0%) having residual AIS in the specimen. Of the 126 patients in whom focality was available, AIS was noted to be multifocal in 67 patients (53.2%). Patients with multifocal disease were noted to have higher rates of positive cone margins (n = 38, 56.7%) compared with patients without multifocal disease (n = 16, 27.1%) (p = <0.001).

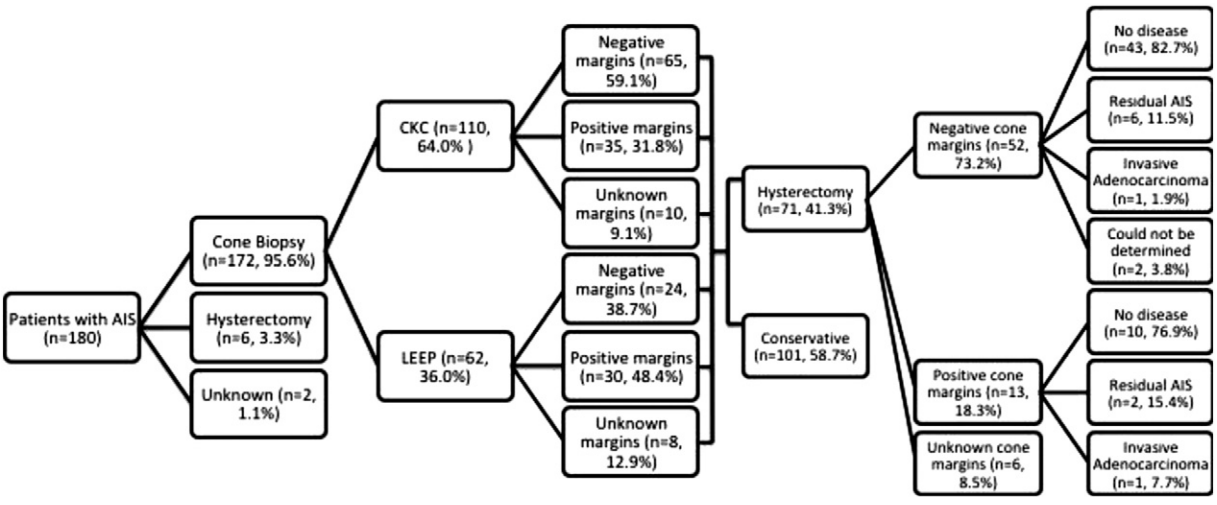

Fig. 1. Patient treatment algorithm.