ONCOLOGY

Cervical conization of adenocarcinoma in situ: a predicting model of residual disease

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OBJECTIVE: To determine factors associated with the presence of residual disease in women who have undergone cervical conization for adenocarcinoma in situ (ACIS) of the cervix.

STUDY DESIGN: We identified women who underwent a cervical conization for a diagnosis of ACIS followed by repeat conization or hysterectomy between Jan. 1, 1995, and April 30, 2010. Data were summarized using standard descriptive statistics.

RESULTS: Seventy-eight patients met study criteria. The presence of ACIS at the internal conization margin or in the postconization endocervical curettage (ECC) correlated with residual ACIS ($P < .001$). A margin positive for ACIS was associated with residual glandular neoplasia in 68% of cases. An endocervical curettage positive for ACIS was associated with residual ACIS in 95% of cases. If both the margins and the endocervical curettage were positive for the presence of ACIS, 8% did not have residual disease, 77% had residual ACIS, and 15% had invasive adenocarcinoma. If both the internal conization margin and the postconization ECC were negative for the presence of ACIS, 14% of the final specimens had residual ACIS and none had invasive cancer.

CONCLUSION: The addition of postconization ECC to cone biopsy for ACIS of the cervix provides valuable prognostic information regarding the risk of residual ACIS. Women with ACIS who have both a negative postconization ECC and a negative conization margin have a 14% risk for residual ACIS and can be treated conservatively if desiring fertility. A positive postconization ECC or internal margin incurs significant risk of residual disease and 12-17% will have cancer.

Key words: adenocarcinoma in situ, cervical dysplasia, conservative management, endocervical curettage

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In 1952, Hepler et al[1] examined invasive adenocarcinoma of the cervix and noted the coexistence of adenocarcinoma in situ (ACIS). Soon thereafter, Friedell and McKay[2] published 2 case reports on patients with ACIS. They were the first published descriptions of this lesion. ACIS is described by pathologists as replacement of endocervical glandular cells by tall columnar cells with nuclear stratification, hyperchromatism, irregularity, and elevated mitotic activity.[3] In addition to the histologic findings, a defining characteristic of ACIS is that it precedes the development of invasive adenocarcinoma.[2] It is not uncommon for ACIS to occur in younger women, many of whom request a fertility sparing approach. Past data has been conflicting regarding whether conization histopathologic features can reliably predict the presence of residual disease, and most importantly, the presence of invasive disease in the residual cervix.[4-19,20,22-25]

The primary objective of this study was to determine factors associated with the presence of residual disease in women who have undergone cervical conization for ACIS of the cervix.

Materials and Methods

Institutional review board approval was obtained for this study. All women who underwent a cervical conization for a diagnosis of ACIS followed by either repeat conization or hysterectomy (or both) between Jan. 1, 1995, and April 30, 2010, at Los Angeles County/University of Southern California Medical Center and Norris Cancer Center were identified using the CoPath pathology archive database and the surgical database maintained by the Division of Gynecologic Oncology. The corresponding patient files were retrieved from the archives. Information regarding patient demographics, Papanicolaou smear results, colposcopic findings, colposcopic biopsy results, method of conization as well as conization and hysterectomy histopathology results was abstracted. We included patients with a concurrent diagnosis of cervical intraepithelial neoplasia. We excluded those with any degree of invasive adenocarcinoma on either the initial cervical biopsy or on the initial cone procedure.

Eighty-eight patients were initially identified. After excluding patients who did not have a second procedure after their initial conization, 78 patients remained and constituted our study group. All conization procedures were performed by resident physicians under

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TABLE 1
Conization characteristics

Variable	n (%)
Conization technique	
CKC	26 (33)
LEEP	52 (67)
Internal margin status	
Negative	44 (56)
Positive	34 (44)
Postconization ECC status	
Negative	51 (65)
Positive	18 (23)
Missing	9 (12)
Presence of squamous dysplasia	
Negative	49 (63)
Positive	29 (37)
Results of subsequent procedures	
Negative	45 (58)
ACIS	28 (36)
Cancer	5 (6)

ACIS, adenocarcinoma in situ; *CKC*, cold knife cone; *ECC*, endocervical curettage; *LEEP*, loop electrosurgical conization.

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direct supervision of a staff member in gynecologic oncology. The techniques used for cold knife cone (CKC) and loop electrosurgical conization (LEEP) have been described previously.[21] A postconization endocervical curettage (ECC) was performed above the conization bed after the cone specimen was removed. Histology was reviewed by a pathologist with particular expertise in gynecologic pathology (JCF). The diagnosis of ACIS was made on the basis of the morphologic appearance of the lesion including: endocervical glands lined by a stratified layer of enlarged endocervical cells that exhibit nuclear enlargement, marked nuclear atypia, increased mitotic activity, and/or apoptotic bodies. The architectural conformation of the glands involved had to be compatible with the conformation of benign endocervical glands. Complex glandular patterns, stromal desmoplasia, vascular or neural invasion all precluded the diagnosis of an in situ lesion, and classified the lesion as invasive adenocarcinoma.

Data were summarized using standard descriptive statistics. The association between categorical variables was tested using Fisher exact test. The 95% confidence intervals, negative and positive predictive values were also calculated.

We conducted a comprehensive English literature review of articles available on ACIS. We conducted a MEDLINE search from 1950 to 2012. All articles referenced in the retrieved articles were also reviewed to ensure that relevant publications were not missed. We excluded case reports and metaanalyses.

RESULTS

Seventy-eight patients were identified in this review. The median age at diagnosis of ACIS was 40 years old (range, 21−64). Approximately one-third of patients were under the age of 35 years at time of diagnosis. The majority of the population was Hispanic comprising 73% of the total. The remaining patients described themselves as white (10%), Asian (8%), and African American (5%); in 3 (4%) race was unknown. Inconsistent information regarding use of oral contraception was available and, thus, that data could not be analyzed. Cervical cytology findings were as follows: 9 (12%) atypical squamous cells of undetermined significance, 1 (1%) atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion, 16 (20%) high-grade squamous intraepithial lesion, 2 (3%) low-grade squamous intraepithial lesion, 1 (1%) suspicious for squamous cell carcinoma, 21 (27%) atypical glandular cells of undetermined significance, 2 (3%) atypical endometrial cells, 5 (6%) ACIS, 6 (8%) suspicious for adenocarcinoma, 12 (15%) were unknown, and 3 (4%) were normal. Of 78 women, 32 (41%) had ACIS found on cervical biopsy, 27 (35%) had ACIS found in the ECC done at the time of colposcopy, and the remaining 19 cases of ACIS (24%) were diagnosed after cone biopsy for squamous dysplasia. The method used for the initial conization procedure was cold knife conization (CKC) in 26 (33%) women and LEEP conization in 52 (67%) women. A concurrent diagnosis of cervical intraepithelial neoplasia was made in 37% of the cases (Table 1). Postconization ECC status could be assessed in 69 patients. Those that were not assessed were insufficient for evaluation at the time of pathologic interpretation.

The second procedures consisted of 40 conizations, and 38 hysterectomies. Four of the 38 hysterectomies were radical or modified radical hysterectomies. Third procedures included 2 conizations and 25 hysterectomies. Overall, the outcome after the subsequent procedures revealed 45 (58%) without residual ACIS, 28 (36%) with residual ACIS, and 5 (6%) with invasive adenocarcinoma.

On univariate analysis, the presence of ACIS at the internal conization margin or in the postconization ECC correlated with residual glandular neoplasia (Table 2), although conization method, presence of squamous neoplasia and age did not. A margin positive for ACIS was associated with residual ACIS in 19 (56%) of the cases and was associated with invasive adenocarcinoma in 4 (12%) of the cases. An ECC positive for ACIS was associated with residual ACIS in 14 (78%) of the cases and was associated with invasive adenocarcinoma in 3 (17%) of the cases. If both the margins and the ECC were positive for the presence of ACIS, 1 (8%) specimen did not have residual disease, 10 (77%) had residual ACIS, and 2 (15%) had invasive adenocarcinoma. On the other hand, if both the internal conization margin and the postconization ECC were negative for the presence of ACIS, only 5 (14%) of the final specimens had residual ACIS and none had invasive cancer.

Invasive adenocarcinoma was diagnosed in 5 patients at the time of follow-up procedure. All cases of invasive adenocarcinoma were microinvasive (no more than 3 mm of stromal invasion and no lymphovascular space invasion). These patients were 40, 40, 53, 58, and 64 years old. Three patients had a simple hysterectomy after the initial cone biopsy and were found to have invasive adenocarcinoma in the hysterectomy specimen. Two patients were diagnosed with

TABLE 2
Association between conization margin/ECC status and outcome

Variable	Outcome in subsequent procedure			
	Negative	ACIS	Cancer	*P* value
Cone technique				
CKC	16 (62%)[a]	9 (35%)	1 (4%)	.87
LEEP	29 (56%)	19 (37%)	4 (8%)	
Margin status				
Negative	34 (77%)	9 (20%)	1 (2%)	< .001
Positive	11 (32%)	19 (56%)	4 (12%)	
ECC status				
Negative	39 (76%)	11 (22%)	1 (2%)	< .001
Positive	1 (6%)	14 (78%)	3 (17%)	
Margin/ECC				
Both negative	31 (86%)	5 (14%)	0	< .001
Margin+ ECC−	8 (53%)	6 (40%)	(7%)	
Margin− ECC+	0	4 (80%)	1 (20%)	
Both positive	1 (8%)	10 (77%)	2 (15%)	
Margin/ECC				
Both negative	31 (86%)	5 (14%)	0	< .001
Either positive	11 (28%)	23 (59%)	5 (13%)	
Squamous dysplasia on cone				
Negative	25 (51%)	19 (39%)	5 (10%)	.12
Positive	20 (69%)	9 (31%)	0	
Squamous dysplasia on cone margin				
Negative	40 (57%)	25 (36%)	5 (7%)	>.99
Positive	4 (67%)	2 (33%)	0	
Squamous dysplasia on postconization ECC				
Negative	38 (59%)	22 (34%)	4 (6%)	.67
Positive	4 (50%)	4 (50%)	0	

ACIS, adenocarcinoma in situ; *CKC*, cold knife cone; *ECC*, endocervical curettage; *LEEP*, loop electrosurgical conization.

[a] %s in parentheses are row %s.

Tierney. Predictors of residual ACIS. Am J Obstet Gynecol 2014.

invasive disease on a follow-up cone biopsy after their initial cone biopsy. One of these women was counseled extensively on her options, however, declined surgery for reasons that remain unclear and opted for radiation rather than definitive surgical management. The other woman underwent a modified radical hysterectomy.

COMMENT

There is significant controversy in the literature regarding the safety of conservative treatment in women with ACIS found at the time of cone biopsy (Table 3). Multiple studies have reported that a conization margin negative for ACIS is not reliably predictive of the absence of residual glandular neoplasia.[6,10,13,14,20,22-25] Other studies have concluded the contrary; that margin status is highly reliable in predicting the absence of residual disease.[4,5,7-9,11,12,17,18,25] In our study, 56% of those with positive margins had residual ACIS. However, we found that the negative predictive value of margin status alone may not be as reliable as the positive predictive value in that 20% of those with a negative margin had residual ACIS and 1 woman (2%) had invasive cancer. As shown in Table 3, these findings are further validated by the combined results from 18 studies showing that 18% of those with negative margins had residual ACIS and 2% had cancer. Only a paucity of studies have evaluated the role of postconization ECC, alone or in combination with conization margin status, as a predictor of residual neoplasia. A summary of studies correlating postconization ECC status with residual disease in women undergoing conization for ACIS is summarized in Table 4. As demonstrated in the table, a positive ECC incurred a significant risk of residual ACIS (95%) when the data from these studies is combined. A negative ECC, when not accounting for margin status, was somewhat reassuring, however, 28% of women were still found to have residual neoplasia. Only 1 study, that of Lea et al,[7] gave complete information regarding the risk of residual ACIS based on both margin status and postconization ECC. These authors reported that 1/9 women had residual ACIS if both the margin and postconization ECC were negative, 0/8 women had residual ACIS if the the conization margin was positive and postconization ECC was negative, 5/5 cases had residual ACIS if the margin was negative and postconization ECC was positive and 7/7 cases had residual ACIS if both the margin and postconization ECC were positive. When both margin and ECC were negative, the risk of residual neoplasia was low; although if postconization ECC was positive, regardless of margin, the rate of residual glandual neoplasia was high (100%).[7]

Our study, involving a larger number of women, yielded similar findings in that the risk of residual glandular neoplasia was very low (14% risk of ACIS, no cases of invasive cancer) if both the conization margin and

TABLE 3
Summary of studies reporting residual ACIS and correlation with margin status

Source	n	Residual ACIS/Pos margins	Cancer/Pos margins	Residual ACIS/Neg margins	Cancer/Neg margins
Ostor, 1984[9]	9	4/6 (67%)	0/6 (0%)	0/3 (0%)	0/3 (0%)
Bertrand, 1987[5]	5	0/1 (0%)	0/1 (0%)	0/4 (0%)	0/4 (0%)
Luesley, 1987[16]	10	4/8 (50%)	0/8 (0%)	1/2 (50%)	0/2 (0%)
Hopkins, 1988[13]	12	4/5 (80%)	0/5 (0%)	1/7 (14%)	0/7 (0%)
Andersen, 1989[4]	4	2/4 (50%)	0/4 (0%)	0 (0%)	0 (0%)
Nicklin, 1991[15]	22	5/11 (45%)	0/11 (0%)	2/11 (18%)	0/11 (0%)
Muntz, 1992[8]	22	7/10 (70%)	0/10 (0%)	1/12 (8%)	0/12 (0%)
Im, 1995[14]	15	4/6 (67%)	0/6 (0%)	4/9 (44%)	0/9 (0%)
Poynor, 1995[10]	18	3/8 (38%)	1/8 (13%)	4/10 (40%)	0/10 (0%)
Wolf, 1996[22]	40	10/19 (53%)	0/19 (0%)	4/21 (19%)	3/21 (14%)
Denehy, 1997[6]	17	7/10 (70%)	0/10 (0%)	2/7 (29%)	0/7 (0%)
Goldstein, 1998[20]	61	8/18 (44%)	1/18 (6%)	13/43 (30%)	0/43 (0%)
Azodi, 1999[24]	32	7/16 (44%)	2/16 (13%)	5/16 (31%)	0/16 (0%)
Shin, 2000[17]	37	13/21 (62%)	0/21 (0%)	1/16 (6%)	0/16 (0%)
Bryson, 2004[18]	11	0/6 (0%)	0/6 (0%)	0/5 (0%)	0/5 (0%)
Young, 2007[23]	31	7/18 (39%)	3/18 (17%)	0/13 (0%)	1/13 (8%)
Van Hanegem, 2012[19]	40	6/25 (24%)	0/25 (0%)	0/15 (0%)	0/15 (0%)
Costales, 2013[25]	65	2/13 (15%)	1/13 (8%)	6/52 (12%)	1/52 (2%)
Total	451	93/205 (45%)	8/205 (4%)	44/246 (18%)	5/246 (2%)
Present study	78	19/34 (56%)	4/34 (12%)	9/44 (20%)	1/44 (2%)

ACIS, adenocarcinoma in situ; *Pos*, positive; *Neg*, negative.

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TABLE 4
Summary of studies reporting residual ACIS after conization with endocervical curettage

Source	n	Residual ACIS/Pos ECC	Cancer/Pos ECC	Residual ACIS/Neg ECC	Cancer/Neg ECC
Goldstein, 1998[20]	48	6/6 (100%)	0/6 (0%)	10/42 (24%)	0/42 (0%)
Azodi, 1999[24]	20	0/1 (0%)	0/1 (0%)	11/19 (58%)	0/19 (0%)
Lea, 2002[7]	29	12/12 (100%)	0/12 (0%)	1/17 (6%)	0/17 (0%)
Total	97	18/19 (95%)	0/19 (0%)	22/78 (28%)	0/78 (0%)
Present study	69	14/18 (78%)	3/18 (17%)	11/51 (21%)	1/51 (2%)

n = total cone biopsies including those who did not have a second CKC/HYST and excluding invasive adenocarcinoma on initial conization.

ACIS, adenocarcinoma in situ; *CKC*, cold knife cone; *ECC*, endocervical curettage; *HYST*, hysterectomy; *Neg*, negative; *Pos*, positive.

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postconization ECC were negative but was very high (94%) if postconization ECC was positive. Although some practitioners consider postconization ECC standard practice, the data to support such practice has been very limited. Our data validates the use of ECC at the time of conization, used in conjunction with margin status, to predict the presence of residual disease. One of the concerns that has been expressed in allowing conservative follow-up of women is that cervical cytology is not as effective in detecting glandular lesions as is it in detecting high-grade squamous lesions, and thus cannot be counted on to detect those women with persistent or recurrent ACIS postconization.[26] In this regard, there is emerging data that use of HPV testing is of significant value in predicting who will recur after conization for ACIS.[27] Costa et al[27] recently reported on 166 women treated conservatively after cone biopsy for ACIS. These authors found that high-risk HPV positivity at any time during the follow-up period was the single most powerful independent predictor of both disease recurrence and of disease progression to invasive cancer on multivariate analysis.[27] The use of cotesting will likely increase the safety of conservative follow-up of women with a history of ACIS.

The strengths of our study include a consistent approach used to treat ACIS and the availability of expert pathologic review. Limitations include that the study is retrospective, over a long span of time and limited to a single institution. However, a prospective study model would be difficult given the relative rarity of this entity.

In conclusion, we advise that a postconization ECC be performed in all women undergoing cervical conization for ACIS to provide guidance regarding the safety of conservative treatment. If either the conization margin or postconization ECC is involved, we recommend a repeat conization regardless of desire for future fertility to determine the extent and degree of disease. If both conization margin and postconization ECC are negative, we recommend simple hysterectomy for those not desiring uterine retention and conservative follow-up with cervical cytology every 6 months. Strong consideration should be given to concurrent HPV testing in light of recent data supporting its value in prediction of recurrent ACIS.[27] ■

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