Adenocarcinoma In Situ of the Cervix: Significance of Cone Biopsy Margins

JUDITH K. WOLF, MD, MS, CHARLES LEVENBACK, MD, ANAIS MALPICA, MD, MITCHELL MORRIS, MD, THOMAS BURKE, MD, AND MICHELE FOLLEN MITCHELL, MD, MS

Objective: To evaluate the treatment and outcome of patients with adenocarcinoma in situ of the cervix, with special emphasis on cone biopsy margins.

Methods: Sixty-one women with adenocarcinoma in situ of the cervix treated between April 1984 and December 1993 were identified. Medical records and histologic material were reviewed. Mixed lesions with both adenocarcinoma in situ and squamous cervical intraepithelial neoplasia (CIN) were included.

Results: The mean age of the patients was 35.9 years. Fifty-five of the 61 (90%) patients had cone biopsies, and 44 of these 55 (80%) subsequently had hysterectomies. Eight women (13%) had associated invasive cancer. Among 50 patients in whom the status of the margins was confirmed, 23 (46%) had positive margins and 27 (54%) had negative margins. Of 23 women with positive margins, 19 had hysterectomies and ten of the 19 (53%) had residual disease in the uterus. Of 27 patients with negative cone margins, 21 had hysterectomies, and seven of the 21 (33%) had residual disease in the uterus. Two women with negative margins who did not have hysterectomies developed recurrent disease. Fifty-five of the total series of 61 patients followed-up for a median of 57 months (range 17–132) had no evidence of disease at last follow-up.

Conclusion: Women with adenocarcinoma in situ of the cervix often have residual disease in the uterus, regardless of whether the margins on cone biopsy are positive or negative. *(Obstet Gynecol 1996;88:82–6)*

The concept of preinvasive adenocarcinoma of the uterine cervix was first introduced by Hepler et al[1] in 1952, from a review of invasive cervical adenocarcinomas. Adenocarcinoma in situ of the uterine cervix, first described in detail in two patients by Friedell and McKay in 1953,[2] is now a well-described pathologic entity characterized by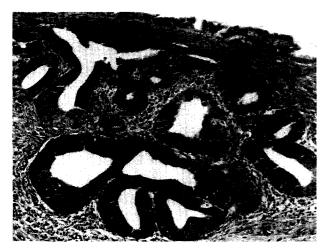 the presence of pseudostratified epithelial cells with enlarged and hyperchromatic nuclei and frequent mitotic figures, but with no stromal invasion. Adenocarcinoma in situ is thought to be a precursor of invasive adenocarcinoma.[3-6] The management of adenocarcinoma in situ of the cervix and the role of cone biopsy in its treatment remain controversial. The purpose of this study was to evaluate the treatment and outcome of patients with adenocarcinoma in situ of the cervix, particularly as it is related to cone biopsy margins.

Materials and Methods

Ninety-four patients with the diagnosis of adenocarcinoma in situ of the cervix made between April 1984 and December 1993 were identified from data bases at the M.D. Anderson Cancer Center. This period was chosen because it was during the mid-1980s that pathologists began to define more clearly the changes associated with adenocarcinoma in situ. Mixed lesions with adenocarcinoma in situ and squamous intraepithelial neoplasia were included. Sixty-one patients had complete clinical and pathologic material for review and are included in this study.

The medical records of the 61 patients identified were reviewed for clinical, treatment, and follow-up information. The diagnosis of adenocarcinoma in situ of the cervix was confirmed by one of the authors (AM) by review of cervical biopsies and/or cone biopsies, using the definition given previously. Figure 1 is a photomicrograph showing the typical changes of adenocarcinoma in situ. The status of margins on cone biopsy was of particular interest; however, in five cases, the available material did not allow for evaluation of the margins.

During the period covered by this review, there was no protocol for treating patients with adenocarcinoma in situ. Abnormal Papanicolaou smears were evaluated

Figure 1. Adenocarcinoma in situ in a cone biopsy specimen. Figure shows pseudostratified epithelial cells with enlarged and hyperchromatic nuclei and mitotic figures, without stromal invasion. (Hematoxylin-eosin, original magnification × 100.)

at the discretion of the individual attending physician, and colposcopy, ectocervical biopsies, and endocervical curettage may have been done. Likewise, the type of cone biopsy and type of hysterectomy for adenocarcinoma in situ were determined at the discretion of the individual attending physician.

Results

Table 1 lists the clinical characteristics of the 61 patients with adenocarcinoma in situ. Human papillomavirus typing was not performed on all patients and was not evaluated in this study.

Fifty-four of the 61 patients had records of Papanicolaou smears done at diagnosis. In 52 of 54 cases, the Papanicolaou smear was abnormal. Twenty-seven patients (50%) had a Papanicolaou smear with a glandular abnormality. Seven Papanicolaou smears included the diagnosis of adenocarcinoma in situ; however, another ten were read as atypical glandular cells and ten as suggestive for adenocarcinoma. Twenty-one (39%) smears had squamous atypia or dysplasia, either alone or mixed with glandular changes.

Nineteen patients had colposcopic descriptions, 18 of which were abnormal; these included five with white epithelium, seven with abnormal vessels, two with punctation, two with hypertrophied columnar epithelium, one with mosaicism, and one described as suggestive of invasion. No description mentioned atypical vessels.

The diagnosis of adenocarcinoma in situ was made by cervical biopsies (five patients), incidental finding at hysterectomy (one), or cone biopsy (55). Fifty-five of the 61 patients had at least one cervical biopsy. Endocervi-

cal curettage was performed in 43 patients, ectocervical biopsies in 37, and both in 32 patients. Fifteen of the 43 endocervical biopsies (35%) showed some abnormality of the glandular epithelium, including adenocarcinoma in situ (two), adenocarcinoma and cervical intraepithelial neoplasia (CIN) (three), adenocarcinoma without invasion (six), and glandular atypia (four). Glandular atypia is characterized by the presence of an increment in the nuclear size accompanied by hyperchromasia in the absence of pseudostratification or nuclear pleomorphism. Mitotic activity is absent or rare. Twenty-three of the 37 ectocervical biopsies (62%) showed some abnormality of glandular epithelium, including adenocarcinoma in situ (seven), adenocarcinoma and CIN (seven), adenocarcinoma without invasion (five), and glandular atypia (four).

Cervical cone biopsies were performed in 55 of the 61 patients. Forty-seven (85%) had a cold-knife conization, seven (13%) had a loop electrical excision procedure conization, and one (2%) had a laser conization. Nineteen of the 55 patients (35%) who had a cone biopsy had both adenocarcinoma in situ and CIN. Forty-four of the 55 patients (80%) who had cone biopsies underwent hysterectomy as part of their treatment. In 50 patients (91%), the status of the margins of the cone biopsy was determined. Of these 50 patients, 23 (46%) had positive margins and 27 (54%) had negative margins. Table 2 summarizes the outcomes of patients who had cone biopsies.

Nineteen of the 23 patients (83%) with positive cone biopsy margins had hysterectomies (14 simple and five radical). Four declined hysterectomy after extensive consultation; three desired future fertility, and one was pregnant at the time of cone biopsy. Ten of the 19 patients (53%) with positive cone biopsy margins who underwent hysterectomy had residual disease in the uterine specimen: five had invasive cancer, four had residual preinvasive disease, and one had glandular atypia. Two of the patients for whom invasive disease was found in the uterine specimen had radical hysterectomies and no further treatment. The other patients with invasive disease in the uterine specimen had

Table 1. Clinical Characteristics of Patients With Adenocarcinoma In Situ of the Cervix

Mean age at diagnosis (y)	35.9 (range 23.5–63.9)
Median parity	2 (range 0–9)
Smoking*	12 (20%)
Oral contraceptive use*	14 (23%)
Race	
White	46 (75%)
Hispanic	12 (20%)
African-American	3 (5%)

* Within 6 months of diagnosis.

Table 2. Outcomes of Patients Who Had Cone Biopsies

Type of cone biopsy	Margins	Hysterectomy			No hysterectomy	
		Total no.	No. with residual disease	No. with invasive cancer	Total no.	No. with recurrent disease
Cold knife (n = 47)	18 pos.	14	8	4	4	0
	24 neg.	19	6	2	5	2
	5 unk.	4	1	0	1	0
LEEP (n = 7)	5 pos.	5	2	1	0	0
	2 neg.	2	1	1	0	0
Laser (n = 1)	0 pos.	0	0	0	0	0
	1 neg.	0	0	0	1	0
Total	55	44	17	8	10	2

pos. = positive; neg. = negative; unk. = unknown; LEEP = loop electrical excision procedure.

simple hysterectomies and were treated postoperatively with pelvic radiotherapy.

Five of the 23 patients with positive margins on cone biopsy had loop electrical excision procedure cone biopsies; subsequently, all five underwent simple hysterectomy. Two of these five had residual adenocarcinoma in situ in the uterine specimen; one had invasive adenocarcinoma and was treated postoperatively with pelvic radiotherapy. The other 18 patients with positive margins had cold-knife cone biopsies.

Three of the four patients who had positive cone biopsy margins and no further treatment have been followed-up for 2–9 years and have had no recurrence. The fourth patient was pregnant at the time of cone biopsy, and she was lost to follow-up after 6 months.

Twenty-one of the 27 patients with negative cone biopsy margins had hysterectomies (14 simple and seven radical). Four had no further treatment, and two were lost to follow-up after cone biopsy. All four of the patients who refused hysterectomy desired future fertility. Seven of the 21 patients (33%) with negative cone biopsy margins who underwent hysterectomy had residual disease in the uterine specimen: three had invasive cancer, three had residual preinvasive disease, and one had focal glandular atypia. All three of the patients with invasive disease found at hysterectomy had simple hysterectomies. Two had 2 mm or less of invasion and therefore had no further treatment. One had 5 mm of invasion and was treated postoperatively with pelvic radiotherapy.

Two of the 27 women with negative cone biopsy margins had loop electrical excision procedure cone biopsies; both had simple hysterectomies. One had no residual disease in the uterus. The other was the patient who had 5 mm of invasive adenocarcinoma. The one patient who had a laser cone biopsy had negative margins and no further treatment. This woman had no evidence of disease at last follow-up.

Two of the four women with negative cone biopsy margins who did not undergo hysterectomy have been followed-up for 4 and 7 years, with no evidence of recurrent disease. One of the four developed invasive adenocarcinoma 2 years after her cone biopsy, diagnosed by cervical biopsy after a Papanicolaou smear showed cells suggestive of adenocarcinoma. She underwent radical hysterectomy with pelvic lymph node dissection. The final pathologic analysis revealed 5 mm of invasive adenocarcinoma. The last patient who did not have a hysterectomy recently had a Papanicolaou smear showing cells suggestive of adenocarcinoma; however, evaluation with colposcopy, ectocervical and endocervical biopsies, and cold-knife cone biopsy revealed only focal glandular atypia.

Fifty-five of the 61 patients had follow-up ranging from 17–132 months (median 57). Two women treated only with cone biopsy with negative margins have recurred: one with invasive adenocarcinoma and one with glandular atypia. Both were described earlier. Two patients with invasive adenocarcinoma died of metastatic disease: one after radical hysterectomy, radiotherapy, and chemotherapy, and the other after radiotherapy.

Discussion

Adenocarcinoma in situ is rare, with an estimated frequency ranging from 1:25,000 to 1:475,000.[7-10] Ostor et al[11] suggested that adenocarcinoma in situ may be underdiagnosed because it may be focal and is frequently associated with squamous lesions that are more striking.

Patient characteristics in our series were similar to those in other series with regard to age at diagnosis,[5,12-15] contraceptive use,[5,14,15] and parity.[12,15] The typical findings of adenocarcinoma in situ in Papanicolaou smears have been described. These include a history of inflammatory cells and/or blood, many hyperchromatic groups or sheets containing epithelial cells with marked crowding, and high nuclear-cytoplasmic ratios, with some groups exhibiting glandular features.[4,9,15,16] The results of Papanicolaou smears in our patients were similar to others reported, most showing some abnormality and 50–60% showing glandular abnormalities.[8,14,17] Colposcopic findings of adenocarcinoma in situ are difficult to recognize. Few patients in our series had recorded colposcopic examinations, so no conclusion can be drawn.

Endocervical curettage would appear to be important in the evaluation of patients with a lesion arising from the endocervix; however, in our study, endocervical curettage was not consistently done in all patients, and

Table 3. Proportion of Patients With Residual Disease in
Uterine Specimen

| | Proportion with residual disease | | | |
| | Negative margins | | Positive margins | |
First author [reference]	No.	%	No.	%
Squamous CIN/CIS				
Ostergard (CIN) [18]	28/172	16	33/96	34
Paterson-Brown (CIN) [19]	4/32	12	40/51	78
Garcia (CIS) [20]	21/68	31	38/47	81
Total	53/272	19	111/194	57
Adenocarcinoma in situ				
Poynor [12]	4/8	50	3/8	38
Muntz [13]	1/12	8	5/10	50
Hopkins [5]	1/7	14	4/5	80
Ostor [11]	0/3	0	4/6	67
Bertrand [21]	0/4	0	0/1	0
Anderson [15]	0/4	0	2/4	50
Wolf [this series]	7/21	33	10/19	53
Total	13/59	20	28/53	53

CIN = cervical intraepithelial neoplasia; CIA = carcinoma in situ.

it showed glandular abnormalities in only 35% of the 43 women in whom it was done. In 1989, Anderson and Affmann[15] reported a 78% incidence of malignant changes of columnar epithelium on endocervical curettage in patients with adenocarcinoma in situ. One-third to one-half of adenocarcinoma in situ lesions of the cervix have been reported as being associated with CIN[12-14]; 35% of our patients showed mixed lesions on cone biopsy.

Other authors have commented on the presence or absence of disease at cone biopsy margins. A summary of results from previous reports of the incidence of residual uterine disease after cone biopsy for patients with squamous or adenocarcinoma in situ is shown in Table 3.[18-21] We found that patients with positive cone biopsy margins had a high incidence of residual disease in the uterus (53%), and this is similar to findings of other studies of adenocarcinoma in situ.[5,10-13] In addition to those noted in the table, Christopherson et al[10] reported that eight of 12 patients had residual disease in the hysterectomy specimen after cone biopsy; however, margin status is not addressed specifically in their paper. These proportions are similar to those reported for squamous intraepithelial neoplasia when a cone biopsy has positive margins.[18-21]

In the present study, we found that seven of 21 patients (33%) with negative margins on cone biopsy had residual disease in the uterine specimen. This finding is similar to that of Poynor et al,[12] who found that four of ten patients (40%) with negative cone biopsy margins had residual adenocarcinoma in situ in the uterus. In our series, four of 21 patients (19%) had residual preinvasive disease in the uterine specimen,

and three of the 21 patients (14%) had residual invasive carcinoma in the uterus. None of the other studies report invasive disease in the uterus after cone biopsy with negative margins.

We found that five of 19 patients (26%) had invasive adenocarcinoma in the uterus after cone biopsy with positive margins. Previous reports[22-25] of the association of invasive carcinoma with squamous carcinoma in situ and adenocarcinoma in situ are summarized and compared with our findings in Table 4.

Seven of our patients had loop electrical excision procedure cone biopsies, and four of these (57%) had residual disease in the uterus. Two women with invasive disease underwent simple hysterectomies after the loop electrical excision procedure cone and required pelvic radiotherapy postoperatively. Other authors have not reported treating adenocarcinoma in situ with loop electrical excision procedure cone biopsy. Based on our findings in this limited number of patients, we would not recommend a loop electrical excision procedure cone biopsy alone in patients with known or suspected adenocarcinoma in situ.

In 1972, Weisbrot et al[26] reported residual disease in a patient with negative cone biopsy margins and recommended hysterectomy as the treatment of choice for patients with adenocarcinoma in situ. In 1979, Christopherson et al[10] reiterated this. More recently, cone biopsy alone has been proposed as adequate therapy for adenocarcinoma in situ if the margins are negative.[11,13-15,21,27] Several studies have reported managing patients this way with rare or no recurrence. In our series, two of the four patients treated only with cone biopsy who had negative margins have had recurrent

Table 4. Invasive Carcinoma in Patients Treated for
Carcinoma in Situ with Cone Biopsy Followed by
Hysterectomy or Cone Biopsy Alone

| | No. patients with invasive carcinoma (%) | | | |
| | Cone biopsy followed by hysterectomy | | Cone biopsy alone | |
First author [reference]	No.	%	No.	%
Squamous CIS				
Bjerre [22]			8/156	5
Villasanta [23]	3/52	6		
Killackey [24]	18/393	5		
Kolstad [25]			7/795	1
Total	21/445	5	15/951	2
Adenocarcinoma in situ				
Wolf (this series)	8/40	20	1/10	10
Poynor [12]	1/8	12	2/15	13
Muntz [13]	2/10	20	0/18	0
Total	11/58	19	3/43	7

CIS = carcinoma in situ.

disease. Both recurrences were diagnosed after an abnormal Papanicolaou smear. Poynor et al[12] reported a similar experience, with two of six patients managed conservatively with cone biopsy alone having recurrence of glandular lesions. This is in contrast to outcomes reported for squamous carcinoma in situ with negative cone biopsy margins. In 1976, Bjerre et al[22] reported a less than 1% recurrence of disease for patients with squamous carcinoma in situ after treatment with cone biopsy only.

We believe that women with known or suspected adenocarcinoma in situ from an abnormal Papanicolaou smear should be evaluated with colposcopically directed biopsies and endocervical curettage. If biopsies confirm adenocarcinoma in situ, a cone biopsy 2.5–3.0 cm deep should be done to try to exclude invasive adenocarcinoma. In our experience, a cold-knife cone is best to get a biopsy of this depth. If the cone biopsy margins are positive, another cone biopsy and D&C should be done to further rule out invasive disease before proceeding with hysterectomy. We recommend radical hysterectomy for patients with proven invasive disease only.

In our study, negative cone biopsy margins did not offer complete security regarding absence of invasive disease; one-third of patients had residual disease in the uterus, 14% with invasive carcinoma. Therefore, treatment of these patients should be similar to guidelines for those with positive cone biopsy margins. Patients who refuse hysterectomy should be counseled carefully on the potential risks of recurrent disease. For patients refusing hysterectomy, minimum follow-up should include Papanicolaou smear with cytobrush every 3–4 months for at least 2 years.

References

1. Hepler TK, Dockerty MB, Randall LM. Primary adenocarcinoma of the cervix. Am J Obstet Gynecol 1952;63:800–8.
2. Friedell GH, McKay DG. Adenocarcinoma in situ of the uterine cervix. Cancer 1953;6:887–97.
3. Buscema J, Woodruff JD. Significance of neoplastic atypicalities in endocervical epithelium. Gynecol Oncol 1984;17:356–62.
4. Bestill WL, Clark AH. Early endocervical glandular neoplasia. I. Histomorphology and cytomorphology. Acta Cytol 1986;30:115–26.
5. Hopkins MP, Roberts JA, Schmidt RW. Cervical adenocarcinoma in situ. Obstet Gynecol 1988;71:842–4.
6. Brown JV, Peters WA, Corwin DJ. Invasive carcinoma after cone biopsy for cervical intraepithelial neoplasia. Gynecol Oncol 1991; 40:25–8.
7. Boon ME, de Graaff Guilloud JC, Kok LP, Olthof PM, van Erp EJM. Efficacy of screening for cervical squamous and adenocarcinoma. Cancer 1987;59:862–6.
8. Nguyen GK, Jeannot AB. Exfoliative cytology of in situ and microinvasive adenocarcinoma of the uterine cervix. Acta Cytol 1984;28:461–7.
9. Ayer B, Pacey F, Greenburg M, Bousfield L. The cytologic diagnosis of adenocarcinoma in situ of the cervix uteri and related lesions: I. Adenocarcinoma in situ. Acta Cytol 1987;31:397–411.
10. Christopherson WM, Nealon N, Gray LA Sr. Noninvasive precursor lesions of adenocarcinoma and mixed adenosquamous carcinoma of the uterine cervix. Cancer 1979;44:975–83.
11. Ostor AG, Pagano R, Davoren RAM, Fortune DW, Chanen W, Rome R. Adenocarcinoma in situ of the cervix. Int J Gynecol Pathol 1984;3:179–90.
12. Poynor EA, Barakat RR, Hoskins WJ. Management and follow-up of patients with adenocarcinoma in situ of the uterine cervix. Gynecol Oncol 1995;57:158–64.
13. Muntz HG, Bell DA, Lage JM, Felman S, Rice LW. Adenocarcinoma in situ of the uterine cervix. Obstet Gynecol 1992;80:935–9.
14. Luesley DM, Jordan JA, Woodman CBJ, Watson DR, Waddel C. A retrospective review of adenocarcinoma-in-situ and glandular atypia of the uterine cervix. Br J Obstet Gynaecol 1987;94:699–703.
15. Anderson ES, Affmann E. Adenocarcinoma in situ of the uterine cervix: A clinico-pathologic study of 36 cases. Gynecol Oncol 1989;35:1–7.
16. Krumins I, Young Q, Pacey F, Bousfield L, Mulhearn L. The cytologic diagnosis of adenocarcinoma in situ of the uterine cervix. Acta Cytol 1977;21:320–9.
17. Lee KR, Manna EA, Jones MA. Comparative cytologic features of adenocarcinoma in situ of the uterine cervix. Acta Cytol 1991;35:117–26.
18. Ostergard DR. Prediction of clearance of cervical intraepithelial neoplasia by conization. Obstet Gynecol 1980;56:77–80.
19. Paterson-Brown S, Chappatte OA, Clark SK, Wright A, Maxwell P, Taub NA, et al. The significance of cone biopsy resection margins. Gynecol Oncol 1992;46:182–5.
20. Garcia RL, Bigelow B, Demopoulos RI, Beckman EM. Evaluation of cone biopsy in the management of carcinoma in situ of the cervix. Gynecol Oncol 1975;3:32–9.
21. Bertrand M, Lickrish GM, Colgan TJ. The anatomic distribution of cervical adenocarcinoma in situ: Implications for treatment. Am J Obstet Gynecol 1987;157:21–5.
22. Bjerre B, Eliasson G, Linell F, Soderberg H, Sjoberg NO. Conization as only treatment of carcinoma in situ of the uterine cervix. Am J Obstet Gynecol 1976;125:143–52.
23. Villasanta U, Durkan JP. Indications and complications of cold conization of the cervix. Obstet Gynecol 1966;27:717–23.
24. Killackey MA, Jones WB, Lewis JL. Diagnostic conization of the cervix: Review of 460 consecutive cases. Obstet Gynecol 1986;67:766–70.
25. Kolstad P, Klem V. Long-term follow-up of 1121 cases of carcinoma in situ. Obstet Gynecol 1976;48:125–9.
26. Weisbrot IM, Stabinsky C, Davis AM. Adenocarcinoma in situ of the uterine cervix. Cancer 1972;29:1179–87.
27. Gloor E, Ruzicka J. Morphology of adenocarcinoma in situ of the uterine cervix: A study of 14 cases. Cancer 1982;49:294–302.

Address reprint requests to:
Judith K. Wolf, MD, MS
Department of Gynecologic Oncology, Box 67
The University of Texas M. D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030