

# Clinicopathological Review Of Adenocarcinoma In-Situ Of The Uterine Cervix

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## ABSTRACT

**Objective.** This study aims to evaluate the clinicopathological correlates of adenocarcinoma-in-situ of the cervix (ACIS) according to treatment modality, and to provide recommendations for clinical management of this condition.

**Materials and Methods.** A retrospective review of 94 consecutive cases of ACIS diagnosed from January 1990 to January 2005 was conducted. Data was extracted from clinical records and all cases underwent central pathology review. The mean duration of follow-up was 48 months.

**Results.** The mean age was 43.8 years (range 26-80 years). Abnormal smear was the presenting problem in 84 patients (89.4%), of which 38 (45.2%) were glandular lesions. Excisional procedure was performed in 86 patients and ACIS was present in 94.2%. Positive resection margins were detected in 19 patients (35.8%) who underwent laser cone biopsy, 8 patients (36.4%) who had knife cone biopsies and 4 patients (36.4%) who underwent LEEP. Among those whose cone length (laser and cone) measured less than 2.5cm, 34 (56.7%) had negative resection margins compared to 11 (73.3%) in those with cone length of 2.5cm or more. 54.5% of the patients with positive cone margins had residual disease on hysterectomy compared to 10.0% in those whose cone resection margins were clear ( $p < 0.01$ ). There was no case of recurrent ACIS or overt adenocarcinoma developing following cone biopsy or hysterectomy.

**Conclusions.** Conization is essential for diagnosis of ACIS. Knife and laser cone biopsy appeared to have comparable results in terms of rate of negative margin. A cone length of 2.5cm or more had better yield in terms of negative margin and absence of residual disease in eventual hysterectomy specimen. We recommend repeat conization for positive margins, and hysterectomy in patients with negative margins not desirous of fertility. All others require stringent follow-up including endocervical sampling.

**Key Words.** cervix, adenocarcinoma; adenocarcinoma in situ; cone biopsy

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## INTRODUCTION

Adenocarcinoma in-situ (ACIS) of the uterine cervix was first described by Hepler in 1952. [1] It is a premalignant condition and is considered to be the precursor lesion of most cases of invasive carcinoma. The last few decades have seen an increase in the incidence of ACIS, due in part to improved recognition of the lesion by pathologists, increase in the use of oral contraceptives and increased prevalence of HPV 18. Because of its relative rarity, conflicting data regarding the status of cone biopsy margins and the incidence of residual disease in the uterus, the management of ACIS of the uterine cervix remains controversial. [2, 3, 4, 5, 6] In addition, there is lack of agreement for colposcopic diagnostic criteria for this entity. [6, 7, 8, 9] Various surgical procedures ranging from LEEP to even radical

hysterectomy have been described. Traditionally, the definitive treatment for ACIS is hysterectomy. However, a proportion of patients, in particular those diagnosed at a younger age, will not have completed childbearing and thus there is a desire for more conservative treatment. A few recent studies show excellent results with cone biopsy alone. Nevertheless, concern regarding patients' compliance and reported cases of multifocal or skip lesions with risk of residual disease after cone biopsies render some physicians hesitant about using a conservative approach. [3, 4, 10-17]

The objectives of this study are to evaluate the clinicopathological correlates of ACIS according to treatment modality, assess the role of cone length and margin status in relation to residual status and to provide a recommendation for the clinical management of this condition.

### Materials and methods

Ninety-four cases of adenocarcinoma in-situ of the cervix registered on the database of Gynecological Oncology Unit in KK Women's and Children's Hospital from January 1990 to January 2005 were included in this retrospective studies. Data was extracted from clinical records, consisting of hospital and day-surgery charts, cytology and pathology reports and operative reports. Patients with coexisting squamous intraepithelial lesion were included. Those with invasive carcinoma were excluded. The method of conization was individually selected by the treating gynecologist. All subsequent management was determined by our tumour board's decision after undergoing central pathologic review. The diagnosis of ACIS was based on the finding of glandular epithelial abnormalities- pseudostratified epithelial cells, enlarged hyperchromatic nuclei, mitotic figures and no stromal reaction or stromal invasion.

The mean duration of follow-up was 48 months and 17 patients were lost to follow up. After conization, patients were followed up with colposcopy and cytology. Subsequent follow-up regime would depend on whether cone margins were involved and results of cytology, biopsy or colposcopic findings during follow-up. The two-tailed Fisher's exact test was used for statistical analysis of the data.

### Results

The mean age was 43.8 years (range 26-80 years) with 87% of the patients aged 35 and above. Mean parity was 3.2 years. Majority of patients (62.5%) were asymptomatic. Abnormal smear was the presenting problem in 84 patients (89.4%), of which 38 (45.2%) were glandular lesions, 40 (47.6%) were squamous

and 6 (7.2%) were mixed glandular and squamous. A history of smoking was found in 8 (8.5%) patients.

Colposcopy was performed on 86 patients. Only 4 (4.7%) were suspected to have glandular lesion based on colposcopy. Among 55 patients who underwent colposcopic-guided cervical biopsies, 13 (23.7%) showed adenocarcinoma in-situ, 18 (32.7%) showed CIN, 11 (20%) showed both ACIS and CIN, and 13 (23.6%) had no histological evidence of ACIS or CIN.

Endocervical curettage was performed for 36 patients prior to cervical conization. Of these, only 33% (12/36) of patients indicated a glandular lesions whereas 67% (24/36) were negative.

Excisional procedure was performed in 86 patients. 22/86 (26%) had a knife cone biopsy, 53/86 (61%) had a laser cone biopsy and 11/86 (13%) had LEEP conization. ACIS was present in 94.2% of the cone specimens.

For the 5 'negative' cones, 2 had ACIS only in the initial punch biopsies, while the other 3 had ACIS only in the final hysterectomy specimen.

Positive resection margins were detected in 35.8% (19/53) of patients who underwent laser cone biopsy, 36.4% (8/22) of patients who had knife cone biopsies and 36.4% (4/11) of patients who underwent LEEP.

Among those whose cone length (laser and cone) measured less than 2.5cm, 56.7% (34/60) of patients had negative resection margins compared to 73.3% (11/15) in those with cone length of 2.5cm or more.

A total of 62/75 patients who had initial cone biopsy (LEEP excluded) subsequently underwent a repeat cone biopsy or hysterectomy. 72% (54/75) of patients underwent hysterectomy, 10.7% (8/75) of patients had a second conization and 17.3% (13/75) of patients had no additional therapy. All patients with no additional therapy had negative endocervical and ectocervical margins with negative endocervical curettage after the cone biopsy. All patients who underwent a second cone desired future fertility. All of the second cones had negative endocervical and ectocervical margins with negative endocervical curettage.

54.5% (12/22) of the patients with positive cone margins had residual disease on eventual hysterectomy specimen or reconization specimen compared to 10.0% (4/40) in those whose cone resection margins were clear ( $p < 0.01$ ).

90.9% (10/11) of the patients with cone length  $\geq 2.5$ cm had no residual disease in the eventual hysterectomy

specimen or reconization specimen compared to 70.6% (36/51) in patients with cone length < 2.5cm.

ACIS was found to be associated with concurrent CIN in 33.3% and malignancy in another 36.1% of patients. There was no case of recurrent ACIS or overt adenocarcinoma developing following cone biopsy or hysterectomy.

### Discussions

Our data shows, as in previous studies, that pre-conization diagnosis of ACIS using PAP smear, colposcopy and cervical biopsy is difficult. Endocervical curettage indicated a glandular lesion in only 33%. Cone biopsy is essential for the diagnosis of ACIS.

Laser cone biopsy, knife cone biopsy and LEEP cone biopsy have comparable rates of negative resection margins (64.2% vs. 63.6% vs. 63.6%). This is surprising, especially when comparing to previous data in the literature. Wolf et al. showed 62% negative margins in cold knife cones compared to 29% in LEEP cones.[3] In addition, Denehy et al. showed 67% negative margins in cold knife cones compared with 31% in LEEP cones. [18] Two randomized controlled trials ( Girardi et al. and Mathevet et al.) have demonstrated significantly greater depth and larger volume of cold knife cone specimens compared with LEEP. [19, 20] In addition, coagulation artifact induced by the LEEP may make surgical margins difficult to evaluate. Because depth of excision and evaluation of margin status are among the most important clinical prognosticators in the management of ACIS, cold knife cone has been traditionally advocated as a cone biopsy technique superior to LEEP. [21]

A cone biopsy of length of 2.5cm or more had better yield in terms of negative resection margins (73.3% vs. 56.7%) and absence of residual disease on eventual hysterectomy or reconization specimen (90.9% vs. 70.6%). This is consistent with current literature where there seems to be an agreement that cone biopsies in cases of ACIS should have length of at least 2.5cm which would result in the adequate removal of the majority of ACIS lesions and provide a considerable margin of safety in younger patients. [22]

Patients with positive resection margin on cone biopsy were associated with higher rates of residual disease (54.5% vs. 10.0%) ( $p < 0.01$ ). These rates are comparable to previous studies in the literature. (range of 0 to 80% for positive margins vs. 0 to 50% for negative margins). ACIS was found to be associated with concurrent CIN in 33.3% and malignancy in another 36.1% of patients.

The decision of the type of treatment is strongly influenced by the status of cone margin and desire for future fertility. We recommend a repeat conization in patients with positive margins or postcone endocervical curettage due to the importance of negative endocervical cone margin to exclude persistent ACIS or underlying invasive adenocarcinoma. Care should be taken to remove the cone specimen in a single piece in order to facilitate careful evaluation by the pathologist. Hysterectomy is recommended in patients with negative margins not desirous of fertility. Those who wish to retain their fertility and opt for conservative management must be counseled regarding possibility of residual disease in the cervix and risk for persistent and recurrent including invasive adenocarcinoma. The follow-up of such patients should include stringent colposcopic and cytological follow-up including endocervical sampling.

**Table 1. Cone Biopsies**

<b>Modality</b>	<b>Number</b>	<b>%</b>
Knife	22	26
Laser	53	61
LEEP	11	13
Total	86	100

**Table 2. Presence of ACIS on cone biopsy**

<b>ACIS</b>	<b>Number</b>	<b>%</b>
Present	81	94.2
Absent	5	5.8

**Table 3. Margin status according to excisional modality**

	<b>Laser cone (n=53)</b>		<b>Knife cone (n=22)</b>		<b>LEEP (n=11)</b>	
<b>Positive margins</b>	19	35.8%	8	36.4%	4	36.4%
<b>Negative margins</b>	34	64.2%	14	63.6%	7	63.6%

**Table 4. Relationship between cone length and resection margin (LEEP excluded)**

N= 75	Cone length <2.5cm	Cone length ≥2.5cm
<b>Positive margins</b>	26 (43.3%)	4 (26.7%)
<b>Negative margins</b>	34 (56.7%)	11 (73.3%)

**Table 5. Residual disease status according to initial excisional modality**

Laser cone/ knife cone/ LEEP – Recone/ hysterectomy (N=62)	Residual disease		No residual disease	
	<b>Positive margins</b>	12	54.5%	10
<b>Negative margins</b>	4	10.0%	36	90.0%

**Table 6. Relationship between residual disease status, cone length and margins**

Laser cone/ Knife cone (LEEP excluded) – Recone/ Hysterectomy (N=62)	Cone length <2.5cm		Cone length ≥2.5cm	
	Residual disease	No residual disease	Residual disease	No residual disease
<b>Positive margins</b>	11	9	1	1
<b>Negative margins</b>	4	27	0	9

## REFERENCES

1. Hepler TK, Dockerty MB, Randall LM. Primary adenocarcinoma of the cervix. *Am J Obstet Gynecol* 1952;63:800-8
2. Masoud Azodi, Setsuko K. Chambers, Thomas J. Rutherford, Ernest I. Kohorn, Peter E. Schwartz, Joseph T. Chambers. Adenocarcinoma in Situ of the Cervix: Management and Outcome. *Gynecol Oncol* 73:348-353, 1999
3. Wolf JK, Levenbeck C, Malpica A, Moris M, Burke T, Mitchell MF: Adenocarcinoma in situ of the cervix: significance of cone biopsy margins. *Obstet Gynecol* 88:82-86, 1996
4. Hopkins MP, Roberts JA, Schmidt RW: Cervical adenocarcinoma in situ. *Obstet Gynecol* 71:842-844, 1988
5. Im DD, Duska LR, Rosenshein NB: Adequacy of conization margins in adenocarcinoma in situ of cervix as a predictor of residual disease. *Gynecol Oncol* 59:179-182, 1995
6. Wildrich T, Alexander D, Kennedy W, et al.: Adenocarcinoma in situ of cervix: management and outcome. *Gynecol Oncol* 61:304-308, 1996

7. Luesley DM, Jordan JA, Woodman CB, et al.: A retrospective review of adenocarcinoma in situ and glandular atypia of uterine cervix. *B J Obstet Gynecol* 94:699-703, 1987
8. Anderson ES, Arffman E: Adenocarcinoma in situ of cervix: a clinicopathologic of 36 cases. *Gynecol Oncol* 35:1-7, 1989
9. Cartier R: *Practical Colposcopic Textbook*, Farmington, CT, S. Karger AG, pp 154-156
10. Quizilbash AH. In situ and microinvasive adenocarcinoma of the uterine cervix. *Am J Clin Pathol* 64:155-170, 1975
11. Christopherson WM, Nealon N, Gray LA. Noninvasive precursor lesions of adenocarcinoma of cervix and mixed adenosquamous carcinoma of the cervix uteri. *Cancer* 44:975-83, 1979
12. Christine H. Shin, M.D., John O. Schorge, M.D., Kenneth R. Lee, M.D., Ellen E. Sheets, M.D.: Conservative Management of Adenocarcinoma in Situ of the Cervix. *Gynecol Oncol* 79:6-10, 2000
13. Wolk BM, Kime W, Albites V. Simultaneous in situ squamous cell carcinoma and microinvasive adenocarcinoma of the cervix. *Int J Gynaecol Obstet* 1981;19:69-72
14. van Roon E, Boon ME, Kurver PJH, Baak JPA. The association between precancerous-columnar and squamous lesions of the cervix: a morphometric study. *Histopathology* 1983;7:887-96
15. Buschema J, Woodruff JD. Significance of neoplastic atypicalities in endocervical epithelium. *Gynecol Oncol* 1984;17:356-62
16. 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
17. Nicklin JL, Wright RG, Bell JR, Samaratunga H, Cox NC, Ward BG. A clinical pathological study of adenocarcinoma in situ of cervix. The influence of cervical HPV infection and other factors, and the role of conservative surgery. *Aust N Z J Obstet Gynaecol* 1991;2:179-83
18. Denehy TR, Gregori CA, Been JL. Endocervical curettage, cone margins and residual adenocarcinoma in situ of the cervix. *Obstet Gynaecol* 1997;90:1-6
19. Girardi F, Heydarfadai M, Koroschetz F, Peckel H, Winter R. Cold knife conization versus loop excision: Histopathologic and clinical results of a randomized trial. *Gynecol Oncol* 55:368-370, 1994
20. Mathevet P, Dargent D, Roy, Beau G. A randomized prospective study comparing three techniques of conization: Cold knife, laser and LEEP. *Gynecol Oncol* 54:175-179, 1994
21. Shin CH, Schorge JO, Lee KR, Sheets EE. Cytologic and biopsy findings leading to conization in ACIS. *Obstet Gynaecol* 2002;100:271-6
22. Bertrand M, Lickrish GM, Colgan TJ: The anatomic distribution of cervical adenocarcinoma in situ: Implications for treatment. *Am J Obstet Gynaecol* 157: 21-25;1987