

# Management of Adenocarcinoma In Situ (ACIS) of the Uteri Cervix – A Clinical Dilemma

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## ABSTRACT

**Objective:** We retrospectively reviewed 24 cases of adenocarcinoma in-situ (ACIS) of the cervix, managed at KK Hospital, with the objective of determining our local approach to its treatment, the consequent clinical outcome and problems encountered.

**Methods:** Except for one case, all patients were treated between 1991 – 1996. Nineteen cone biopsies (17 laser and 2 cold knife) and eleven hysterectomies were performed. The mean follow-up duration was 20.5 months (range: 1 – 75 months).

**Results:** The mean age was 44.2 years (range: 32 – 68) with 80% of the cohort being more than 35 years old and the mean parity was 2.2. Six (25%) patients were symptomatic. Majority (21/23) had an abnormal initial Pap smear. Glandular lesions were found in 39% (9/23) of Pap smear, 28% (6/21) of colposcopy, 58% (8/14) of cervical biopsies and in 3 of 4 endocervical curettage. Of the 17 laser cone biopsy specimens, lesion involved the surgical margin in 6 patients (35%). ACIS was found in conjunction with CIN in 14 patients (58%). Five hysterectomies were performed for involved surgical margin and one for dubious surgical margin of the prior cone biopsy, of which 3 had residual ACIS. At the time of the study, there was no case of recurrent ACIS or overt adenocarcinoma developing following cone biopsy.

**Conclusion:** Preconisation diagnosis of ACIS using Pap smear, colposcopy and cervical biopsy was found to be difficult in our series. Concurrent CIN occurred in a sizeable portion of patients. Laser cone biopsy was the preferred method employed. Total hysterectomy was frequently employed following cone biopsy for treating possible residual disease. We recommend greater vigilance for this condition especially in patients with CIN and the need for regular endocervical sampling in the follow-up of patients treated by cone biopsy.

**Keywords:** adenocarcinoma in-situ, uteri cervix, cone biopsy

## INTRODUCTION

Although adenocarcinoma in-situ (ACIS) of the cervix

was first described in 1952<sup>(1)</sup>, it only gained greater recognition as a distinct disease entity in the last one to two decades. Being uncommon and often under-diagnosed, its natural history is still not fully understood. Hence, it is not surprising that several issues concerning the management of ACIS remains controversial, namely: the difficulty of pre-conisation diagnosis; the adequacy of a conservative therapeutic procedure (cone biopsy); the advantage of cold-knife technique over laser cone biopsy and the ideal follow-up procedure following conservative surgery.

More recently, there has been a trend towards conservative management of ACIS, departing from previous radical procedures like extrafascial hysterectomy and even radical hysterectomy. While cervical conisation for ACIS is the preferred procedure for women who desire to preserve their fertility, its safety is still a matter of controversy, largely due to the detection of residual disease in subsequent hysterectomy specimen in a sizeable portion of patients.

We present the findings of a review on 24 cases with histological diagnosis of ACIS of the cervix, managed at the KK Gynaecological Cancer Centre, KK Women's & Children's Hospital with the objective of determining: (1) the problems of diagnosis and follow-up; (2) the local practices in the management of ACIS and (3) the clinical outcome of treatment.

## PATIENTS AND METHODS

The computerised Tumour Registry database at our Gynaecological Cancer Centre, KK Hospital, was searched for patients with the diagnosis of ACIS, either as the sole condition or co-existing with another condition. The case records were reviewed and the relevant information were extracted. Except for one case managed in 1989, all patients were treated between 1991 – 1996.

All the diagnosis of ACIS were made largely on cone biopsies and hysterectomy specimens apart from 2 cases who had large loop excision of transformation zone (LLETZ) of the cervix. All cases were managed at our Centre.

Altogether, 24 case records of patients with the diagnosis of ACIS were analysed. There were 21 patients who had ACIS alone or in conjunction with adjoining CIN (cervical intra-epithelial neoplasia). In

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the remaining 3 patients, ACIS were found in the hysterectomy specimens, performed for adenocarcinoma of the cervix (2 patients) and adenocarcinoma of the fallopian tube (1 patient).

The use of standard LLETZ, laser or cold knife cone biopsies were decided individually by the surgeon in charge, as was the decision for subsequent hysterectomy. In general, laser conisation was the preferred procedure at our hospital in the last 10 years.

## RESULTS

### Patients' profile and clinical presentations

The mean age was 44.2 years (range: 32 – 68), the median age was 44 years with 80% of the cohort being 35 years or older. Only one patient was nulliparous and the mean parity was 2.2. The majority of patients were symptom-free, presenting with an abnormal Pap smear. Only 6 (25%) patients were symptomatic, presenting with a complaint of abnormal vaginal bleeding.

### Pre-conisation investigations and diagnosis

Of the 23 patients who had Pap smears performed prior to the diagnosis of ACIS, 21 of them were abnormal. However, only 39% (9/23) had indicated suspicion of a glandular lesion. Colposcopy were performed for 21 patients and 28% (6/21) had indicated suspicion of a glandular lesion. Of the 14 cervical biopsies taken, only 57% (8/14) confirmed the presence of ACIS. Endocervical curettage was infrequently performed (4 patients), and 3 out of these 4 specimens denoted a strong suspicion of an endocervical lesion (Table I).

For the 21 patients who had cone biopsies or LLETZ performed, the initial pre-conisation diagnoses were ACIS for 10 patients and CIN for 11 patients. ACIS was later found to be present in the histopathological specimens of the latter group of patients. Overall, a total of 14 patients (58%) had ACIS found in conjunction with CIN. Two cases of ACIS were associated histological findings of patients with adenocarcinoma of the cervix and one with adenocarcinoma of the Fallopian tube.

## Treatment

Of the 21 patients with a diagnosis of ACIS or in conjunction with CIN, 19 patients had cone biopsies (17 laser cone and 2 knife cone) and 2 had loop electrical excision of the cervical transformation zone. The latter 2 patients had a primary diagnosis of CIN but with a small focus of ACIS found on the histological specimen, with one of them having CIN involving the surgical margin. A repeat cone biopsy was performed for this patient and no residual disease was found (Fig 1).

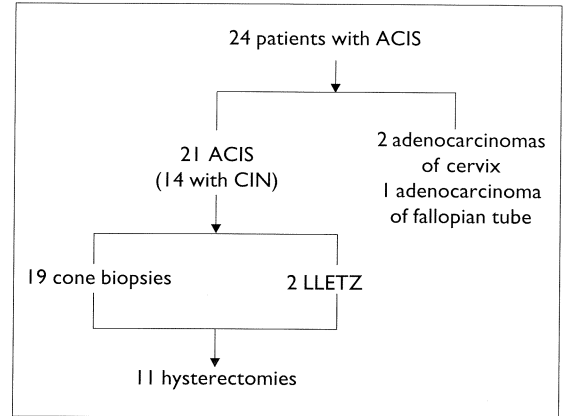


Fig 1 – Overview of patients' management

The mean procedure time for the cone biopsies was 38 minutes (range: 15 – 133 minutes). Five cases encountered complications with 2 secondary haemorrhages needing conservative management without transfusion, 2 mild infections and one with bladder perforation. Of the 17 laser cone biopsy specimens, 6 (35%) had surgical margin involvement, while one specimen had a dubious surgical margin. Both cold knife cone biopsies had clear surgical margins.

Following cone biopsy, 11 patients subsequently had total hysterectomy; 5 were performed for involved surgical margin in the preceding cone biopsies and one for dubious surgical margin. Three of the 6 patients had residual ACIS. Of the 8 patients who did not have hysterectomy following their cone biopsy, all but one had clear cone surgical margins. The latter patient had ACIS which involved the endocervical margin but refused further surgical treatment against medical advice and is currently undergoing close clinical surveillance.

Table I – Pre-conisation investigations and diagnosis

	Glandular abnormalities <sup>(2)</sup>	All abnormalities <sup>(1)</sup>
	n (%)	n (%)
Pap smears (n = 23)	9 (39)	21 (91)
Colposcopy (n = 21)	6 (29)	17 (81)
Cervical biopsies (n = 14)	8 (57)	13 (93)
Endocervical curettage (n = 4)	3 (75)	3 (75)

(1) include all results that warranted further investigation leading to the diagnosis of ACIS

(2) include results that specifically indicated glandular abnormalities

## Follow-up

Excluding the 3 cases of ACIS associated with adenocarcinoma, the mean follow-up duration for the group of 21 patients with ACIS alone or in conjunction with a CIN lesion was 20.5 months (range: 1 – 75 months). At the time of the study, none of these patients was known to have developed recurrent ACIS or adenocarcinoma. At follow-up, apart from symptom review and a routine examination, all patients had Pap smears done. Among the patients with conserved uterus, the use of endocervical brush was not specified and endocervical curettage was only performed in one patient.

## DISCUSSION

Being a lesion of the endocervical glandular epithelium, the diagnosis of ACIS is usually difficult. Diagnosis is usually made with the help of a cone biopsy. Often, it is diagnosed following the treatment of a high grade CIN or as a coincidental finding on a hysterectomy specimen of a patient treated for another condition. In our study, only 10 out of 24 patients had ACIS alone. In another 11 patients, cone biopsy was initially performed for CIN and ACIS was subsequently found to be present in the surgical specimen. Most of these patients were asymptomatic and an abnormal Pap smear was usually the reason for their referral. Other authors have reported a similar experience. In the study by Widrich et al<sup>(2)</sup>, 45 of 46 patients were asymptomatic and presented with an abnormal Pap smear, while in the series of Poynor et al<sup>(3)</sup>, 68% of their patients were asymptomatic.

Although the presentation leading to the diagnosis of ACIS is usually an abnormal Pap smear, only 39% of the latter (9/23) in our series suggested a glandular lesion, with the rest of them showing squamous cell lesions. A subsequent colposcopy detected a glandular lesion in only 28% (6/21) of the cases. This is not surprising as the latter was designed primarily to survey the ectocervix and the endocervical canal is usually obscure especially in nulliparous women. While it is evident that endocervical curettage (ECC) is not a regular practice in our Centre, 3 out of the 4 cases that had ECC proved positive for glandular abnormality. Although one could argue that a routine endocervical curettage may contribute more to the diagnosis of ACIS, this was not borne out in the study by Poynor et al<sup>(3)</sup>. In this study, of the 21 patients who had a pre-conisation ECC, 7 showed ACIS and 2 showed endocervical glandular dysplasia making a total of only 9 of the 21 patients, revealing a glandular lesion in the ECC specimens. However, until a better method becomes available, ECC and cytobrush will remain the most direct method of sampling the endocervical epithelium.

Fourteen of our patients (58%) had an associated squamous CIN lesion, a finding which is consistent with other studies<sup>(2,4)</sup>. This fact lends support to the fact that while a routine ECC performed together with a screening Pap smear may not be cost-effective, there may be a role for it to be done routinely in patients where CIN is evident.

The mean age of the patients in our series was 44.2 years old, which is older than those of other series<sup>(2,3)</sup>. Most of our patients were parous (mean parity of 2.2) and had completed their child-bearing. These two findings have significant bearing on the choice of treatment of the patients as the preservation of fertility is no longer a major consideration. This may explain a less conservative approach to their subsequent treatment, as evident by the significant number of hysterectomy performed for our patients.

The management of this condition used to be fairly radical, with hysterectomy being recommended<sup>(5)</sup> to be performed for a patient with ACIS on a cone biopsy. But as the understanding of the disease progressed, there is now a trend towards

conservative management, chiefly by cone biopsy. Laser cone biopsy is the preferred method over cold knife cone biopsy in the treatment of CIN, due to its lower morbidity and complication rate. However recently, Widrich and colleagues<sup>(2)</sup> recommended a cold knife cone biopsy for the treatment of ACIS. In their study, it was shown that cold knife cone biopsy was associated with a higher rate of negative surgical margin and a lower rate of recurrence of cervical adenocarcinoma in-situ compared to LLETZ. In our series, there were 6 out of 17 laser cone specimens which showed positive surgical margin and 1 with dubious margin. However, only 2 cold knife cone biopsies were performed; this number is too small for any comment.

Although there is no proper study comparing cold knife cone biopsy with laser cone biopsy for treating ACIS, it is conceivable that the former would possibly be superior for 2 reasons: a cold knife cone biopsy is done with our naked eyes visualising the cervix and one would tend to take a wider margin from the lesion and the cervical transformation zone (TZ). With the aid of the magnification of a colposcope, this margin tends to be closer when a laser beam is used. The latter also allows greater surgical flexibility that enables one to follow the contours of the lesion more accurately. The second possible explanation, is perhaps that the latter tends to be conical, tapering towards its apex. The glandular crypts usually dip from the surface epithelium into the cervical stroma which is unlike the squamous lesion that remains at the surface of the ectocervix. The tapering apex of a laser cone biopsy will hence cut across these glandular crypts, resulting in a positive margin being seen in the specimen. One way to circumvent this problem is to perform a more cylindrical cone biopsy using the laser beam and transecting the apex of the cone specimen with a pair of scissors to complete the procedure (Fig 2).

The decision on the consequent management of patients following the diagnosis of ACIS in the cone biopsy specimens was very much left to the surgeon in-charge. It was interesting to find that 11 patients subsequently had total hysterectomy, 5 of whom had positive surgical margins and 1 with dubious margin in the cone biopsy specimens. Only 3 showed evidence

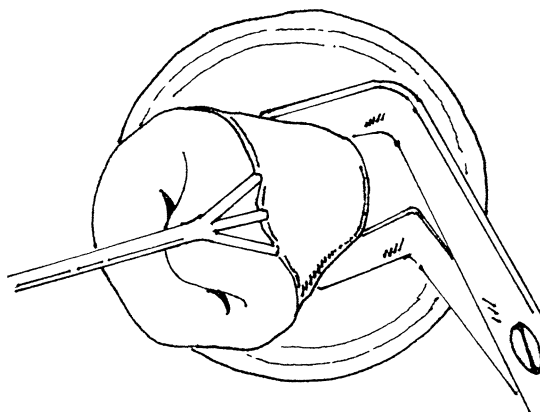


Fig 2 – Cone biopsy using scissors to transect the upper margin.

of residual disease in the hysterectomy specimens. As alluded to earlier in the discussion, the greater use of hysterectomy could be due in part to the nature of our cohort of patients, who are older and have no wish for more children. The preference for a cone biopsy alone in treating ACIS in younger women who desire to preserve their fertility, remains a viable course of action provided that the specimen shows an adequate negative margin and the patients consent to close follow-up surveillance<sup>(3)</sup>.

While there was no case of recurrence, including one patient with a positive surgical margin who refused further surgery, the follow-up period was short (mean of 20.5 months). However, the frequent employment of hysterectomy may have weeded out patients likely to develop a recurrence. Even then, the long follow-up of these patients remains relevant as the majority of them had associated squamous lesions. It was also evident that the use of ECC was not a routine procedure in their surveillance. It is the recommendation of the author that every attempt should be made in the follow-up of such patients to obtain endocervical samples (either an ECC or using an endocervical brush) to detect recurrence, in the light that diagnosis can be difficult to begin with.

#### **CONCLUSION**

In summary, we found that pre-conisation diagnosis of ACIS using Pap smear, colposcopy and cervical biopsy was difficult in our series. Concurrent CIN occurred in a sizeable portion of patients and hence should deserve appropriate attention. Laser cone biopsy was the preferred method employed at our

Centre. For laser cone biopsy, there was a sizeable proportion of specimens showing surgical margin involvement although residual ACIS was found in less than half of these patients who consequently underwent total hysterectomy. The frequent employment of total hysterectomy for treating possible residual disease, may have contributed to the absence of recurrence observed, in addition to the relatively short period of follow-up.

We recommend greater vigilance of this condition, especially in patients with CIN and the need for regular endocervical sampling in the follow-up of patients treated by cone biopsy.

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