EXcisional treatment **C**omparison for **I**n **S**itu **E**ndocervical adenocarcinoma

Paul Cohen

On behalf of PIs: David Wrede, Peter Sykes, Lois Eva, Orla McNally, Alison Brand, Yee Leung, Louise Farrell, Martin Stockler, Aime Powell, Jim Codde, Max Bulsara, Lyndal Anderson, Pennie Stoyles

Acknowledgments

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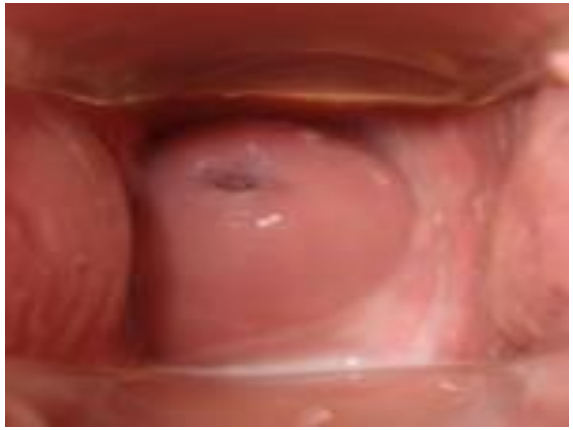
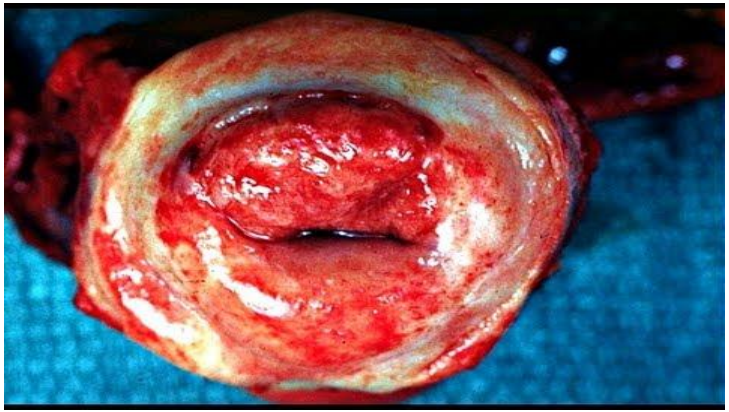
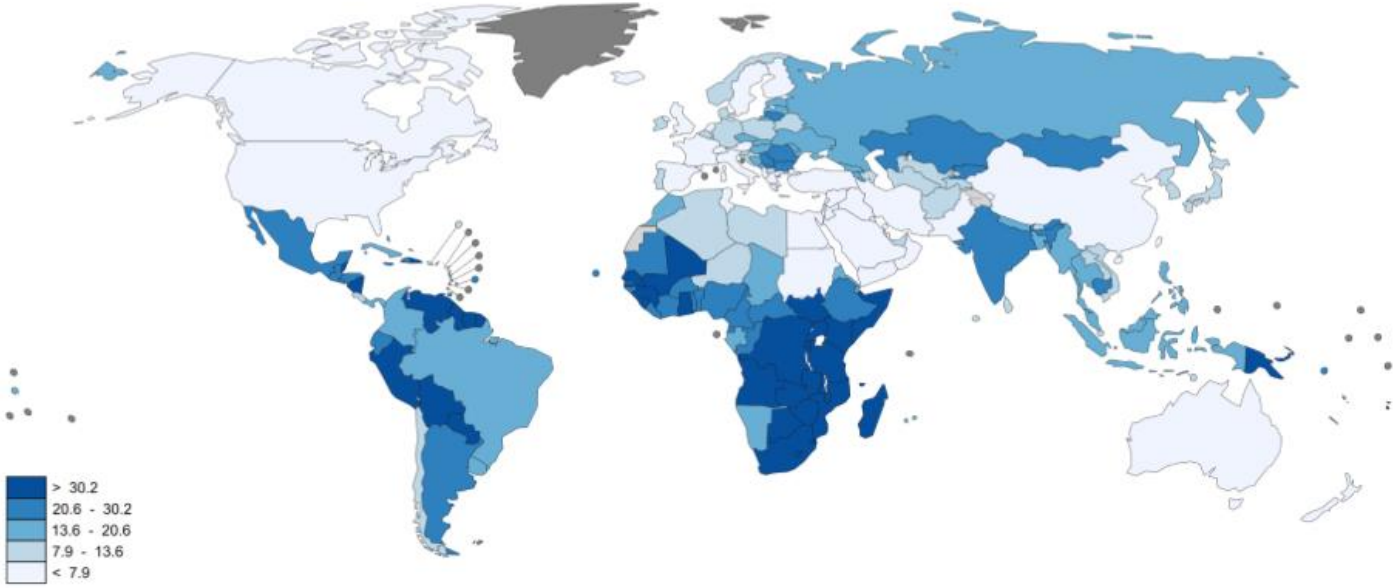
Normal appearance of the cervix



Cervical Cancer



Estimated Cervical Cancer Incidence Worldwide in 2012



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

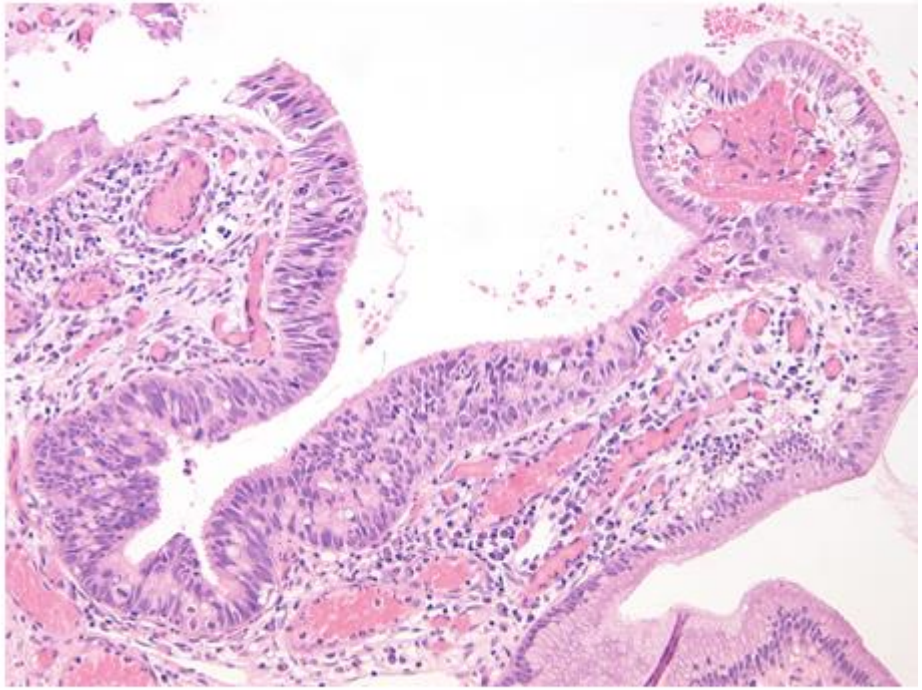
World Health Organization

Estimated age-standardised rates (World) per 100,000

Adenocarcinoma in situ (AIS)

- AIS of the uterine cervix is a precursor to cervical adenocarcinoma
- Cause: persistent infection by high-risk subtypes of HPV
- AIS is the glandular equivalent of CIN3/HSIL

AIS Histopathology



Adenocarcinoma in situ Endocervical type

AIS in Australia

- AIS is rare
- 932 high-grade endocervical cytological abnormalities in 2015
- 678 of these were AIS/AIS+
- Incidence is increasing in absolute terms and relative to HSIL

Table A5.6: Positive predictive value (PPV) of high-grade endocervical cytological abnormalities in women aged 20–69, most serious histology within 6 months of cytology performed in 2009 to 2015

	Cytology prediction			
Year	Possible high-grade E3	Adenocarcinoma in situ E4	Adenocarcinoma in situ plus E5	High-grade
2009	54.1% (139/257)	89.2% (214/240)	78.6% (11/14)	71.2% (364/511)
2010	56.3% (120/213)	88.7% (212/239)	73.9% (17/23)	73.5% (349/475)
2011	55.6% (154/277)	86.0% (228/265)	100.0% (17/17)	71.4% (399/559)
2012	56.1% (143/255)	90.0% (216/240)	92.3% (12/13)	73.0% (371/508)
2013	55.2% (159/288)	85.4% (228/267)	88.2% (15/17)	70.3% (402/572)
2014	55.2% (148/268)	88.8% (215/242)	100.0% (15/15)	72.0% (378/525)
2015	56.1% (128/228)	89.1% (204/229)	77.8% (7/9)	72.7% (339/466)

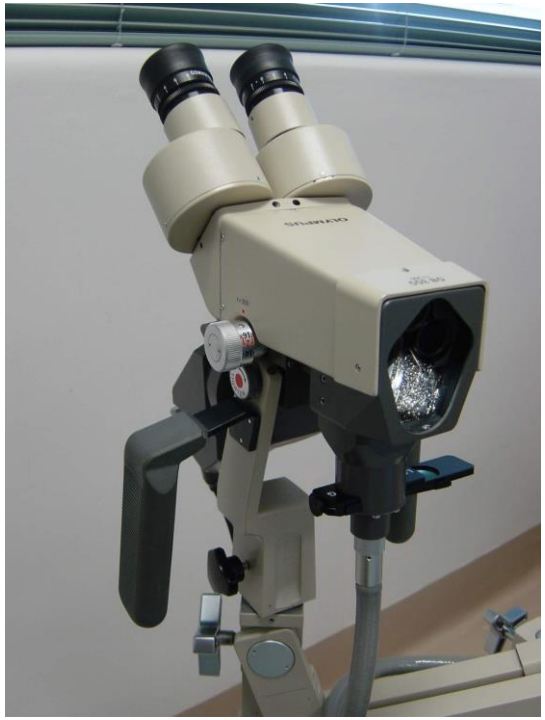
Note: The positive predictive value is calculated as the proportion of endocervical cytology results of 'possible' or 'definite' high-grade that were confirmed on histology to be a high-grade endocervical abnormality or adenocarcinoma. These are prone to variability due to small numbers. Cytology data were included only where histology was performed within 6 months; cytology data not followed by histology, or followed by histology more than 6 months after cytology, are not included in the calculations.

Source: AIHW analysis of state and territory cervical screening register data.

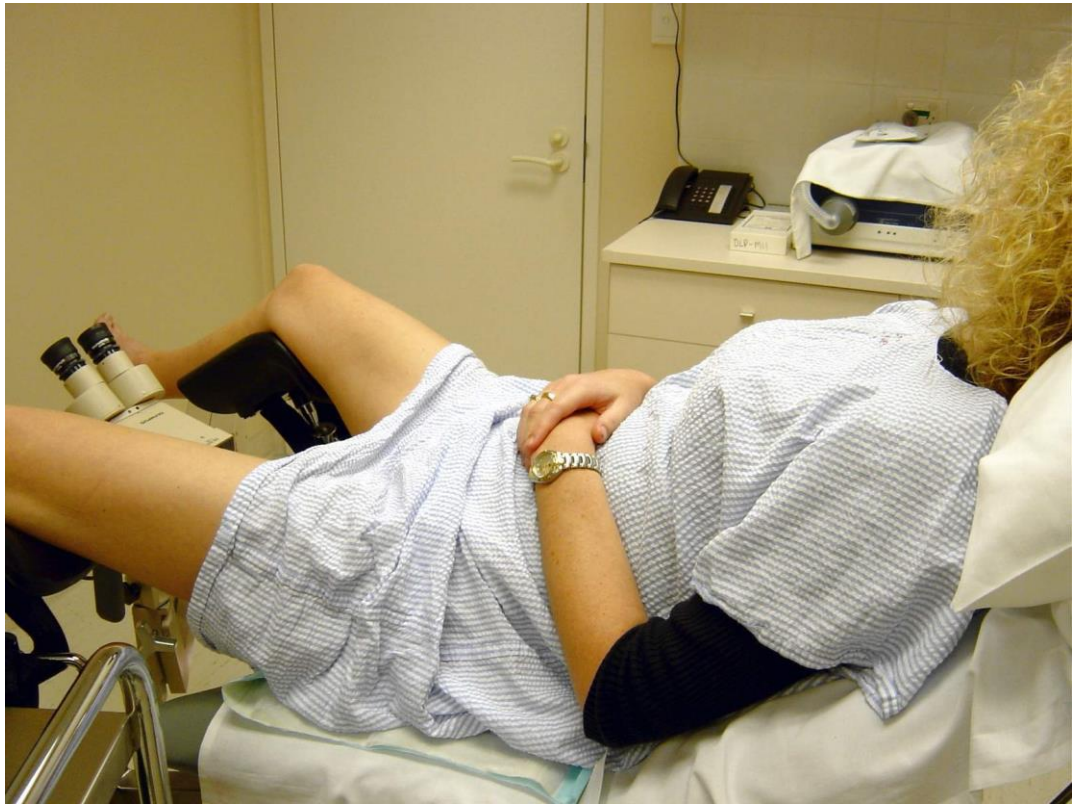
The Clinical Pathway

- Cervical screening test is HPV 16 or 18 or non 16, non 18 +ve
- Reflex cytology predicts AIS or ?high-grade glandular abnormality
- Patient referred for colposcopy

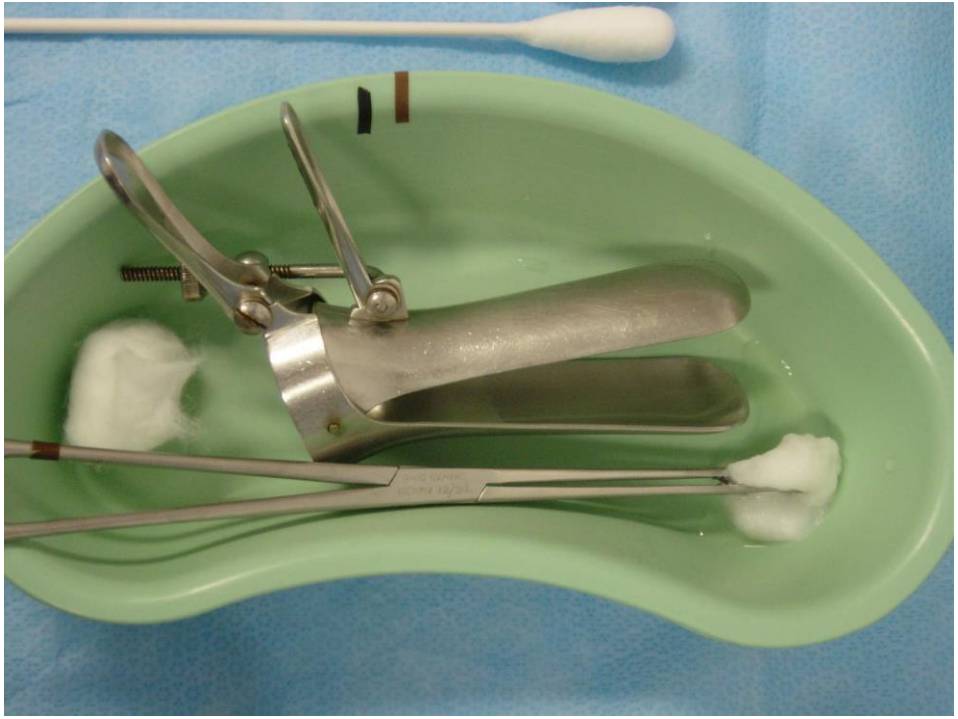
Colposcopy



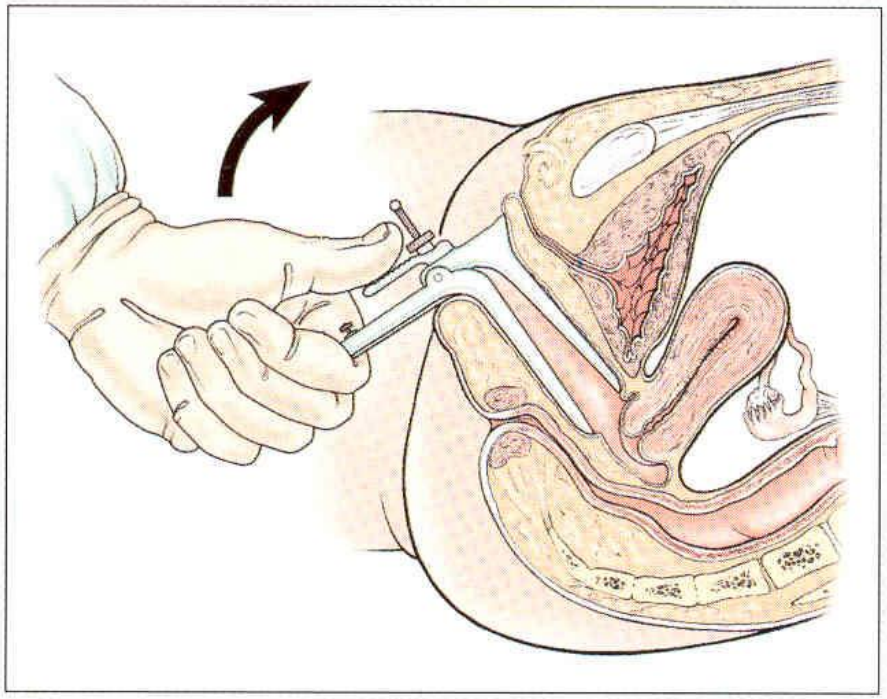
Colposcopy

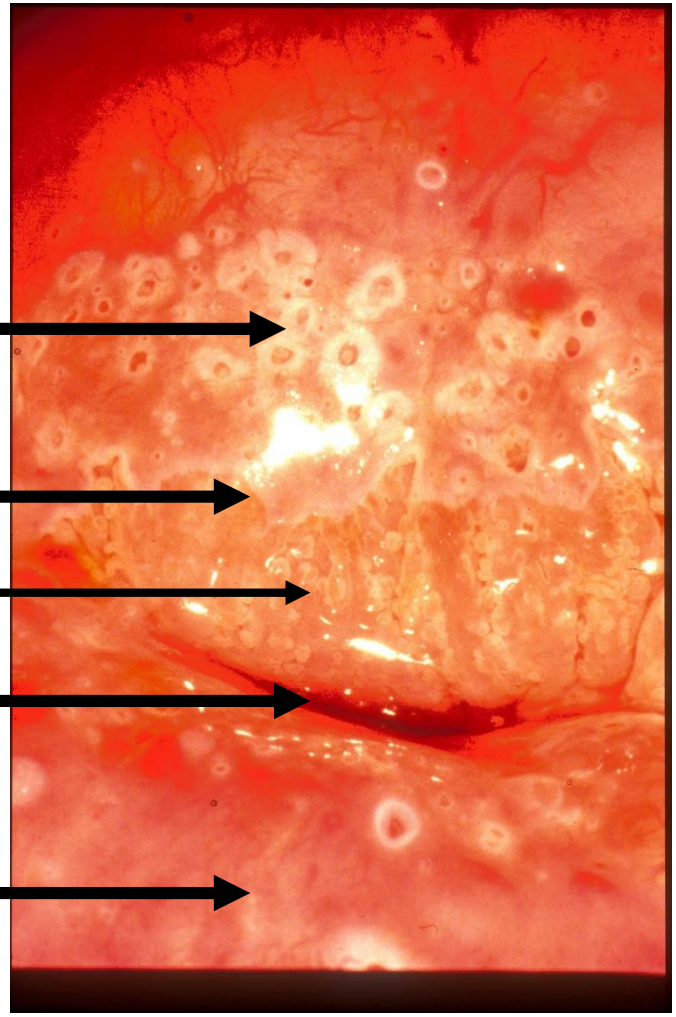


Colposcopy



Colposcopy

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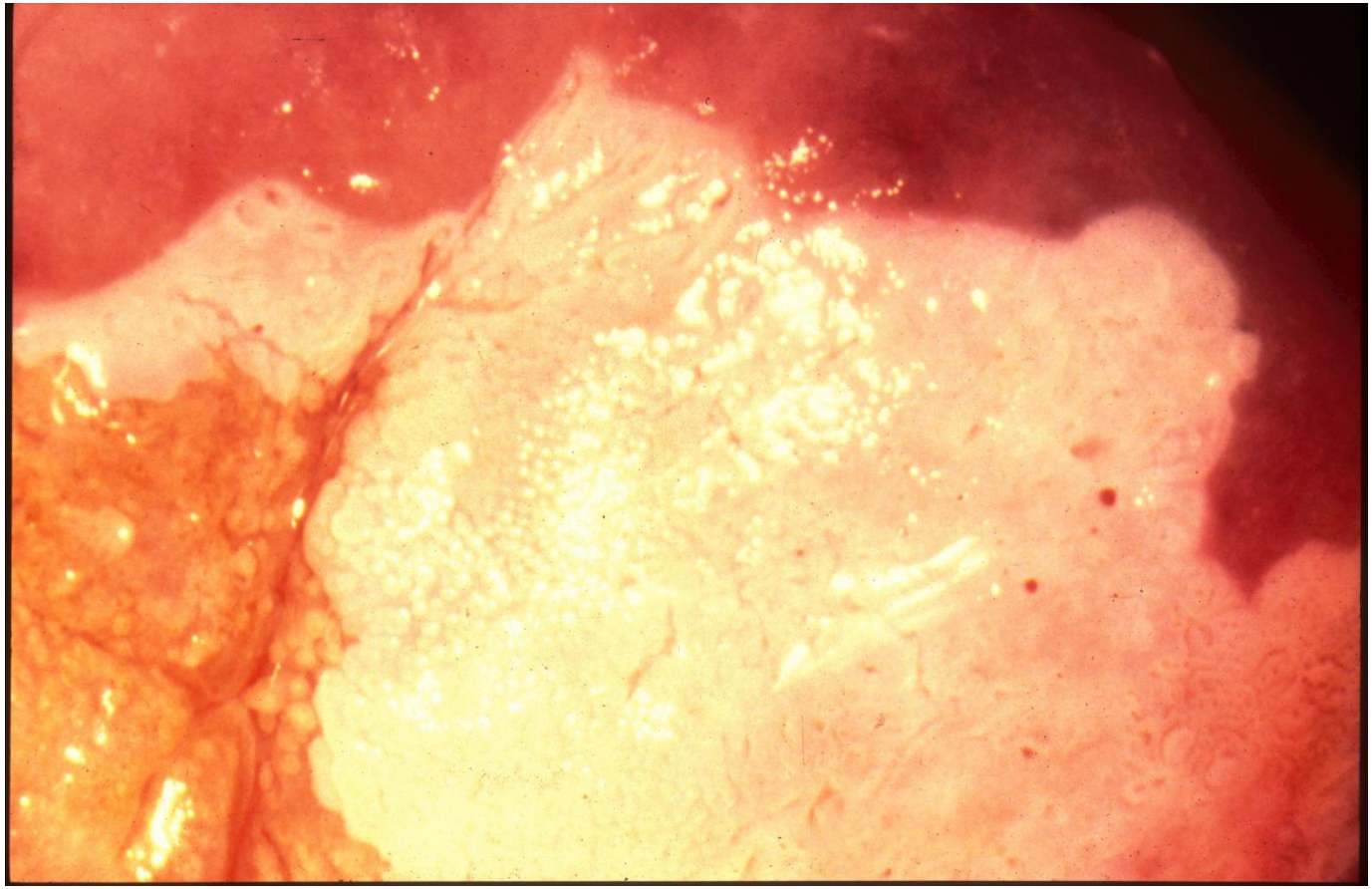

HSIL (CIN3)

Colposcopy

- A biopsy or biopsies are taken of the abnormal appearing areas
- Biopsy confirmed AIS requires an excisional biopsy
- Even if AIS is not confirmed at colposcopy if the cytology predicts AIS or ?AIS an excisional biopsy must be performed
- In Australia usually a cold knife cone biopsy

AIS Challenges

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- AIS can extend into the endocervical canal and colposcopic examination may only show minimal changes

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- The full extent of AIS lesions may not be apparent at colposcopy

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- AIS can extend into the endocervical canal and colposcopic examination may only show minimal changes
- The full extent of AIS lesions may not be apparent at colposcopy
- This makes determination of excisional approaches challenging

AIS Challenges

- An excision biopsy is essential to exclude invasive adenocarcinoma which may coexist in up to 19% of patients with a cytological prediction of AIS

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- An excision biopsy is essential to exclude invasive adenocarcinoma which may coexist in up to 19% of patients with a cytological prediction of AIS
- Negative margins on an excision biopsy do not reliably indicate complete excision of AIS because lesions may be multifocal

AIS Challenges

- Excisional treatments for AIS are mostly curative and prevent progression to invasive disease but….

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- May compromise the structural integrity of the cervix increasing the risk of preterm delivery

AIS Challenges

- Excisional treatments for AIS are mostly curative and prevent progression to invasive disease but….
- May compromise the structural integrity of the cervix increasing the risk of preterm delivery
- Positive margins after excision are associated with residual and recurrent disease

AIS Challenges

- Risk of preterm birth positively correlates with excision dimensions

AIS Challenges

- Risk of preterm birth positively correlates with excision dimensions
- Clinicians need to balance the risks of future obstetric harm and inadequate treatment of AIS

Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis

Maria Kyrgiou,[1,2] Antonios Athanasiou,[3] Maria Paraskevaidi,[1] Anita Mitra,[1,2] Ilkka Kalliala,[1] Pierre Martin-Hirsch,[4,5] Marc Arbyn,[6] Phillip Bennett,[1,2] Evangelos Paraskevaidis[3]

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[2]Queen Charlotte's and Chelsea-Hammersmith Hospital, Imperial Healthcare NHS Trust, London, UK

[3]University Hospital of Ioannina, Ioannina, Greece

[4]Department of Gynaecological Oncology, Lancashire Teaching Hospitals, Preston, UK

[5]Department of Biophotonics, Lancaster University, Lancaster, UK

[6]Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium

ABSTRACT

OBJECTIVE

To assess the effect of treatment for cervical intraepithelial neoplasia (CIN) on obstetric outcomes and to correlate this with cone depth and comparison group used.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

CENTRAL, Medline, Embase from 1948 to April 2016 were searched for studies assessing obstetric outcomes in women with or without previous local cervical treatment.

DATA EXTRACTION AND SYNTHESIS

Independent reviewers extracted the data and performed quality assessment using the Newcastle-

haemorrhage, analgesia, cervical cerclage, and cervical stenosis. Neonatal outcomes comprised low birth weight, admission to neonatal intensive care, stillbirth, APGAR scores, and perinatal mortality.

RESULTS

71 studies were included (6 338 982 participants: 65 082 treated/6 292 563 untreated). Treatment significantly increased the risk of overall (<37 weeks; 10.7% *v* 5.4%; relative risk 1.78, 95% confidence interval 1.60 to 1.98), severe (<32-34 weeks; 3.5% *v* 1.4%; 2.40, 1.92 to 2.99), and extreme (<28-30 weeks; 1.0% *v* 0.3%; 2.54, 1.77 to 3.63) preterm birth. Techniques removing or ablating more tissue were associated with worse outcomes. Relative risks for delivery at <37 weeks were 2.70 (2.14 to 3.40) for cold knife conisation, 2.11 (1.26 to 3.54) for laser conisation, 2.02 (1.60 to 2.55) for excision not otherwise specified,

Why Excisional Biopsy is Important

Aust N Z J Obstet Gynaecol 2018; 1–7

ANZJOG

DOI: 10.1111/ajo.12886

ORIGINAL ARTICLE

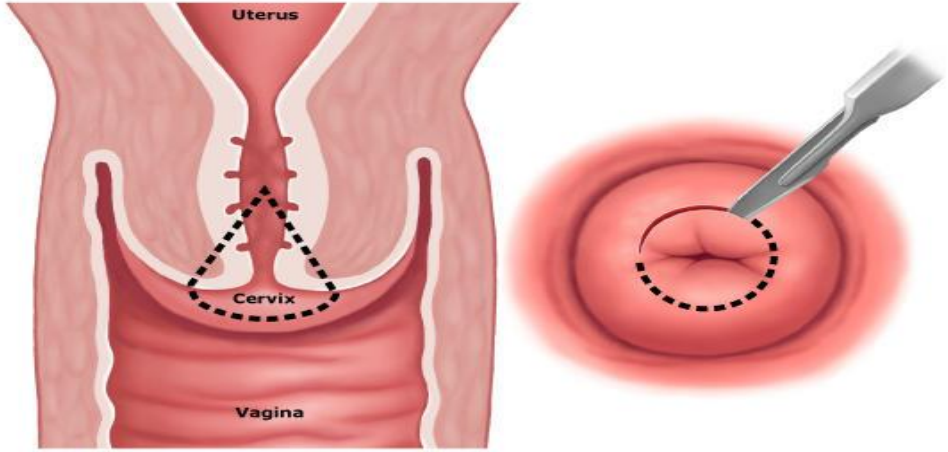
RANZCOG Fellows' adherence to guidelines following cytological prediction of cervical adenocarcinoma-*in-situ*: Cause for concern?

Aime Powell[1,2], Paul A. Cohen[2,3], Katrina Spilsbury[1,4], Nerida Steel[1,5] and Penny Blomfield[6]

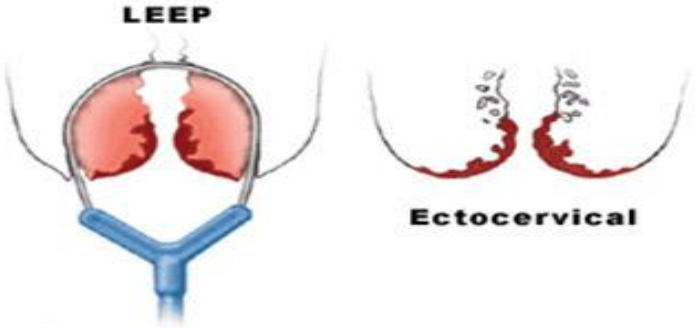
Why Excisional Biopsy is Important

- 321 women from Tasmania and Western Australia
- Retrospective cohort 2001 – 2012 with a smear reporting AIS
- Cervical cancer was diagnosed in 62 (19.3%) patients
- 21 of 321 patients (6.7%) did not have an excisional biopsy
- 2 women were diagnosed with an occult cancer following a simple total hysterectomy
- This is of concern given that nearly one in five women with a smear predicting AIS had a final diagnosis of cervical cancer

Cold Knife Cone Biopsy



LEEP

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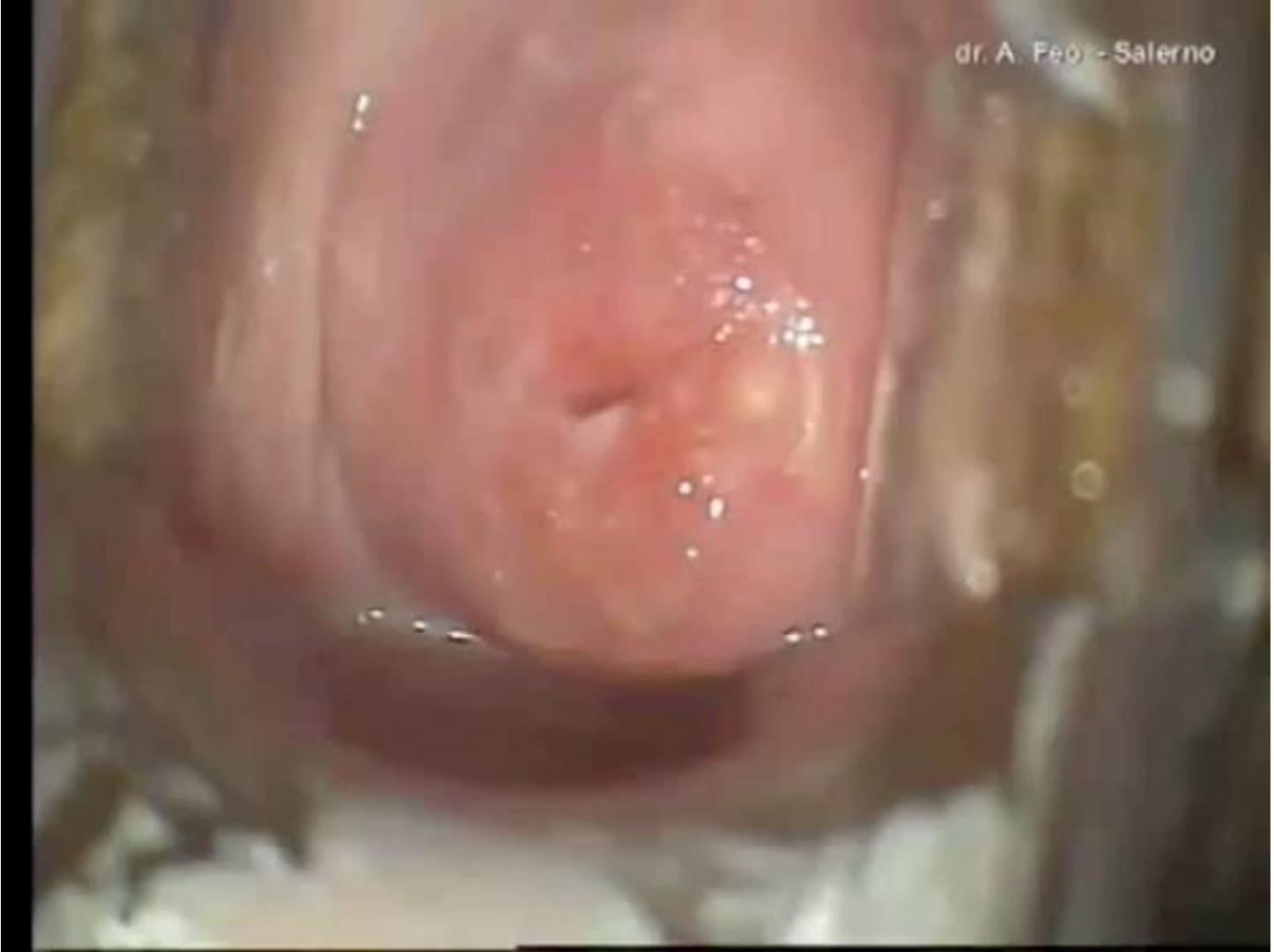
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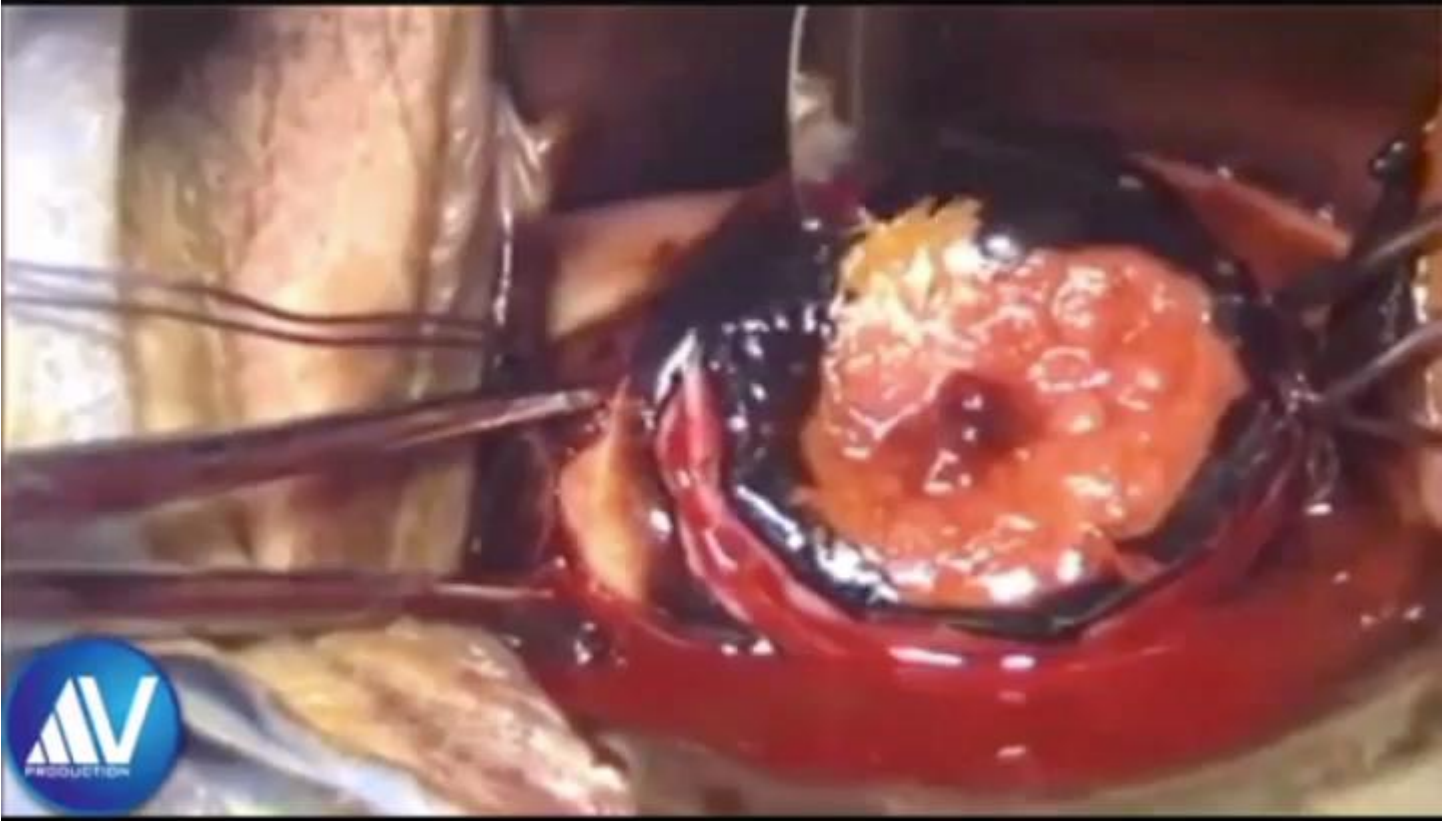
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Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma *in situ*: What is the gold standard?

A. Munro[a,*], Y. Leung[b], K. Spilsbury[c], C.J.R. Stewart[b], J. Semmens[c], J. Codde[c], V. Williams[d], P. O'Leary[e], N. Steel[a], P. Cohen[b]

PlumX Metrics

DOI: https://doi.org/10.1016/j.ygyno.2015.02.024 | Check for updates

338 patients

107 LEEP
231 CKC

2001 – 2012
WA

Table 3
Hazard ratios of persistent or recurrent endocervical neoplasia according to age, socio-economic index, concurrent CIN and margin status.

Variable	Hazard rate ratio	95% confidence interval	p-Value
Age (years)			
≤30	0.7	0.3–1.8	0.477
>30 (base)	1.0		
Socio-economic index			
Least disadvantaged (base)	1.0		
Less disadvantaged	1.6	0.4–5.9	0.469
Middle	1.7	0.5–6.1	0.433
More disadvantaged	3.0	0.9–9.6	0.068
Most disadvantaged	0.6	0.1–5.8	0.689
Initial treatment			
LEEP	0.8	0.3–2.0	0.578
CKC biopsy (base)	1.0		
Number of specimens			
1 (base)	1.0		
>1	0.9	0.3–2.5	0.847
Concurrent CIN			
Absent (base)	1.0		
Present	0.9	0.4–2.2	0.870
Margin status			
Negative (base)	1.0		
Positive	3.4	1.4–7.8	0.004
Indeterminate	1.2	0.1–9.5	0.885
Specimen depth (mm)			
≤10	1.6	0.6–4.0	0.337
>10–15	0.4	0.1–1.5	0.183
>15– ≤ 40 (base)	1.0		

CKC – cold knife cone, LEEP – loop electrosurgical excision procedure.

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RESEARCH ARTICLE

Comparison of Cold-Knife Conization versus Loop Electrosurgical Excision for Cervical Adenocarcinoma In Situ (ACIS): A Systematic Review and Meta-Analysis

Yanming Jiang, Changxian Chen, Li Li

Published: January 26, 2017 • https://doi.org/10.1371/journal.pone.0170587

Table 1. Characteristics of the included studies.

Source	Country	Intervention		Histology	Study design	Study period	Follow-up period	Quality score*
		LEEP	CKC					
Munro 2015 [10]	Austria	107	231	ACIS	retrospective study	2001 to 2012	<1 year to 11.8 years	9
Latif 2015 [2]	USA	30	48	ACIS	retrospective study	1997 to 2011	2–168 months	9
Baalbergen 2015 [17]	Netherlands	45	65	ACIS	retrospective study	1989 to 2012	1–217 months	8
Taylor 2014 [18]	USA	15	37	ACIS	retrospective study	1998 to 2011	mean 32 months	7
Costales 2013 [12]	USA	62	110	ACIS	retrospective study	1983 to 2011	0.3–286.5 months	7
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Kennedy 2002 [23]	USA	30	27	ACIS	retrospective study	1994 to 2001	1–165 months	8
Soutter 2001 [24]	UK	43	10	ACIS	retrospective study	1986–2000	0–543 weeks	6
Kuohung 2000 [25]	USA	9	39	ACIS	retrospective study	1990 to 1999	NA	6
Azodi 1999 [26]	USA	8	25	ACIS	retrospective study	1988 to 1996	mean 38 months	9
Denehy 1997 [27]	USA	13	24	ACIS	retrospective study	1980 to 1996	1–72 months	6
Wolf 1996 [28]	USA	7	47	ACIS	retrospective study	1984 to 1993	17–132 months	9
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* Quality assessment based on the Newcastle-Ottawa Scale.

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Excisional treatment in women with cervical adenocarcinoma in situ (AIS): a prospective randomised controlled non-inferiority trial to compare AIS persistence/recurrence after loop electrosurgical excision procedure with cold knife cone biopsy: protocol for a pilot study

Paul A Cohen[1, 2, 3], Alison Brand[4], Peter Sykes[5, 6], David C H Wrede[7, 8, 9], Orla McNally[10, 11], Lois Eva[12, 13], Archana Rao[14, 15], Michael Campion[16, 17], Martin Stockler[18, 19], Aime Powell[20], Jim Codde[21], Max K Bulsara[22], Lyndal Anderson[23, 24], Yee Leung[25, 26, 27, 28], Louise Farrell[29], Pennie Stoyles[30]

Author affiliations

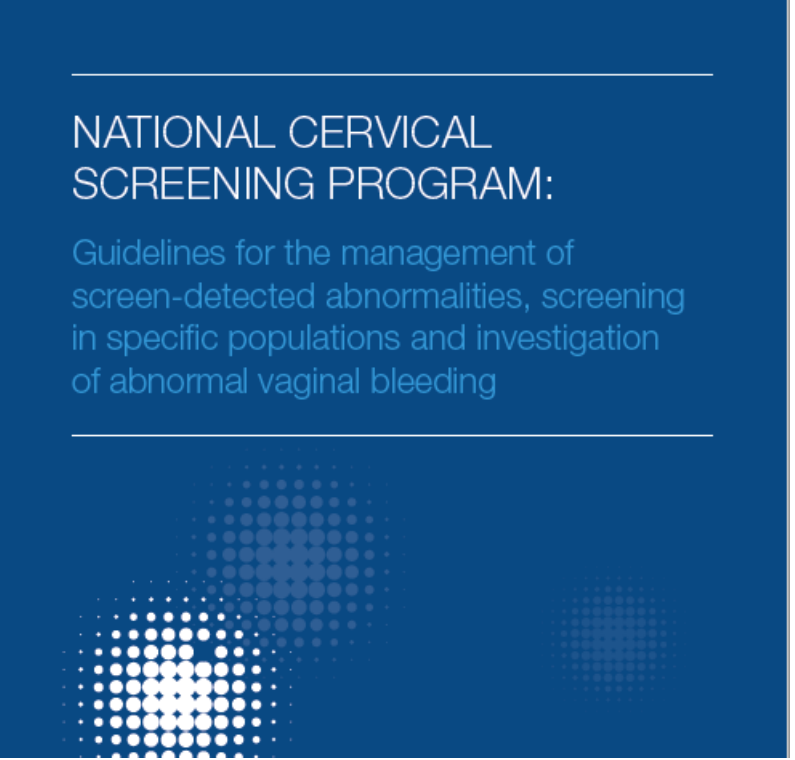
1. Division of Women's and Infants' Health, School of Medicine, University of Western Australia, Crawley, Western Australia, Australia
2. Department of Gynaecological Oncology, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia

Background and rationale

- AIS can persist, recur, co-exist with/progress to adenocarcinoma
- Hysterectomy has been regarded as the definitive treatment but no longer
- AIS affects young women who may wish to preserve fertility
- Conservative excisional treatments

Background and rationale

- AIS on cervical cytology and/or cervical biopsy => a diagnostic excisional procedure to exclude invasive adenocarcinoma
- In Australia cone biopsy regarded as the ‘gold standard’
- There are NO prospective randomised studies to inform practice



- December 1st 2017

NATIONAL CERVICAL SCREENING PROGRAM
A joint Australian, State and Territory Government Program

Australian Government
Department of Health

Cancer Council Australia

ENDORSED BY

RACGP Endorsed clinical guideline

RCPA The Royal College of Pathologists of Australasia

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Australian Society of Gynaecologic Oncologists Inc. Caring for women since 1986

PRACTICE POINT

REC11.10: Cold-knife cone biopsy is the 'gold standard' for glandular abnormalities'

Cold-knife cone biopsy should be considered the 'gold standard' for the diagnostic assessment of glandular lesions. However, a diathermy excisional procedure may be appropriate in some circumstances and could provide an appropriate surgical specimen when performed by a gynaecologist with appropriate training, experience and expertise.

Discussion: Management of histologically confirmed high-grade squamous abnormalities

UNRESOLVED ISSUES

Whilst at this time indefinite co-testing is recommended, the ongoing monitoring of the renewed NCSP may provide data in the future to support the safety of discharging women who have been negative for both HPV and cytology on multiple occasions at an earlier point.

FUTURE RESEARCH PRIORITIES

Well-designed prospective research studies are needed to compare the use of cold knife cone biopsy with diathermy loop excision (LEEP or LLETZ) in the diagnosis and treatment of AIS. If such a study were to show that loop excision was non-inferior to cold-knife cone biopsy for the outcomes of post-treatment recurrent and adenocarcinoma, loop excision could be recommended as an appropriate treatment option for AIS. This would benefit women because, unlike cold-knife cone procedures, loop excision does not require hospital admission and general anaesthesia.

Studies evaluating endocervical curettage would provide useful evidence to determine its role in clinical practice.

Long-term data from the National Cancer Screening Register should be analysed to determine the minimal effective surveillance period for women undergoing annual Test of Cure for post-treatment AIS before returning to routine 5-yearly screening.

EXCISE Study

- Excisional treatment in women with cervical adenocarcinoma-in-situ (AIS): a prospective randomised controlled non-inferiority trial to compare AIS recurrence after loop electrosurgical excision procedure to cold knife cone biopsy.

- Short title**: EXCISE** – **EX**cisional treatment **C**omparison for **I**n **S**itu **E**ndocervical adenocarcinoma

Aim

- To determine if the treatment of cervical AIS by LEEP is non-inferior to Cone Biopsy with regard to treatment failure (disease persistence at 12 months or recurrence by 2 years in women managed conservatively, when treatment is performed in tertiary level colposcopy and gynaecology/gynaecologic oncology centres

Hypothesis

- LEEP will not be inferior to Cone Biopsy with regard to AIS treatment failure in conservatively managed women, when treatment is performed in tertiary centres

Primary Objectives

- To compare the rate of treatment failure after LEEP and Cone Biopsy performed for AIS in conservatively managed women

Secondary Objectives

- Margin status and specimen dimensions
- Early and late complications (including obstetric outcomes)
- QoL
- PRO
- Efficacy, safety and cost-benefits associated with co-testing f/up

Study Population

- Women aged 18 to 45 years diagnosed with AIS on cervical screening and/or colposcopically directed biopsy who are to receive excisional treatment in a tertiary level centre

Inclusion Criteria

- Aged ≥18 to ≤45 years of age at time of study enrollment
- Documented AIS on cervical cytology and/or cervical biopsy
- Lesion amenable to **single pass excision** (serial endocervical excisions including ‘top-hat’ will not be permitted in accordance with American Society for Colposcopy and Cervical Pathology Recommendations)

Exclusion Criteria

- Lesion considered unsuitable for single pass excision by treating specialist
- Previous high-grade cervical abnormality
- Previous excisional or ablative treatment
- Cytology suspicious of invasion or clinical suspicion of invasion
- Presence of a concurrent gynaecological cancer
- Patients unable to comply with follow-up evaluations
- Immunosuppression
- Pregnancy

Procedures

- Randomisation:
- Randomisation will be 1:1 (LEEP: CKC). Sequence generation will be by computer with no blocking or stratification. Randomisation will be by IVRS (interactive voice response system).
- Blinding:
- Study investigators and participants will not be blinded to the intervention. Members of the study team conducting data analysis at the co-ordinating centre will be blinded to the intervention.
- Safety monitoring: DSMB

Procedures

- Only Type 2 and type 3 excisions
- Single pass excision
- For LEEP:
  - electrosurgical unit set to 70 – 80 watts blend 1
  - Avoid excessive coagulation
  - May be performed under local anaesthesia

Sample Size

- Estimated using a 2 group test of non-inferiority of proportions
- Primary end point is the AIS recurrence rate at 5 years and the comparison will be between Cone Biopsy and LEEP, based on a 1-sided test for non-inferiority
- Assumes an 8% rate of AIS recurrence at 5 years after Cone Biopsy, and a 5% non-inferiority margin (so an upper 95% confidence rate of AIS recurrence of 13% is still within the non-inferiority margin)
- Sample size needed is 730 (365 per group). Assuming a 10% drop-out rate, a total sample size of 810 participants (405 per group) would need to be randomised. The one-sided Type I error is set at 5% with 80% power.

Feasibility

- Approximately 900 AIS cases are diagnosed annually in Australia and New Zealand in women <45 years of age. These figures continue to increase in both relative and absolute terms every year but may decrease over the next 5 years due to effects of the nonavalent HPV vaccine.
- Estimated that 60% of these patients would receive treatment in tertiary centres making the total number of eligible patients 600 per year. If 30% of eligible patients enroll in the study, then approximately 200 participants would be randomised per year.
- Will require international collaboration.

EXCISE Pilot Study

- Objective – feasibility
- Primary outcome – pathological margin status
- Sample size = 30 participants
- Randomised 2:1 LEEP: Cone Biopsy
- Central Pathology Review
- Surgeon Accreditation
- 6 sites – SJOG Subiaco, KEMH, Melbourne, Sydney, Christchurch, Auckland
- Funded by an ANZGOG Fund for New Research Grant $50,000

Figure 1. CONSORT Flow Diagram of EXCISE Study

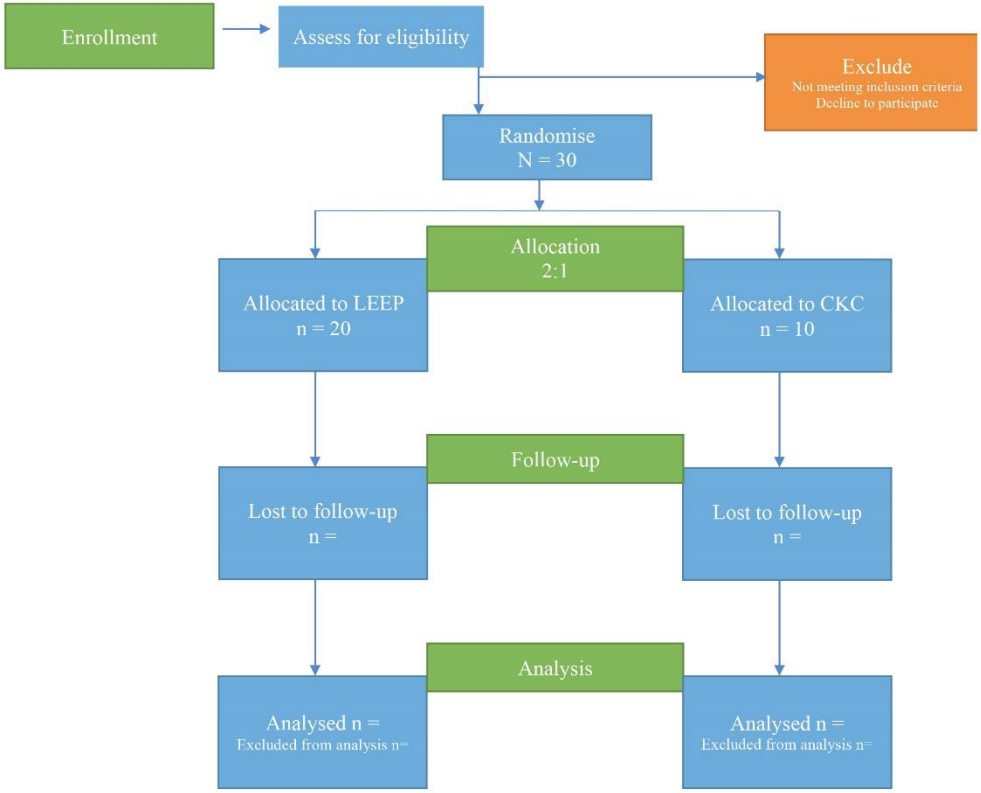


Figure 2.

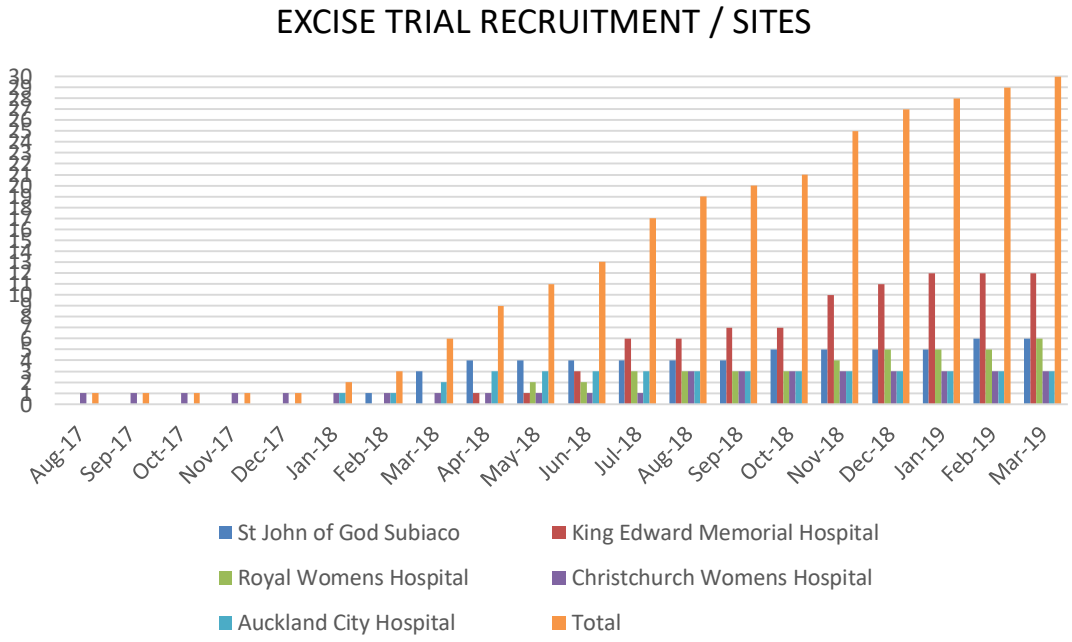
Schedule of enrollment, interventions, and assessments.

	STUDY PERIOD			
	Enrolment	**Allocation**	**Intervention**	**Close-out**
TIMEPOINT	***-t₁***	***0*** **Within 7 days (+4)** (Day 0-11)	***t1*** **Within 8 weeks of allocation** (Day 0-56)	***tx*** ***6 weeks' post intervention (+14 days)***
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
[List other procedures]				
Allocation		X		
INTERVENTIONS:				
[Intervention A]			LEEP	
[Intervention B]			CKC	
[List other study groups]				
ASSESSMENTS:		t1	t2	tx
Baseline variables	Age Parity BMI Smoking status HPV vaccine status STIs Family history Comorbidities AIS on Pap AIS on biopsy Colposcopy findings			
Outcome variables				Histopathology Report Complications Patient Satisfaction Questionnaire Hospital costs of treatment

We have 5 sites open for recruitment with 21 participants recruited to date:
The Mater Hospital, Brisbane and Westmead Hospital, Sydney are expected to open during the second quarter of 2019.

St John of God Hospital, Subiaco, Western Australia, Australia	**6 participants**
King Edward Memorial Hospital, Subiaco, Western Australia, Australia	12 participants
Christchurch Women's Hospital, Christchurch, New Zealand	3 participants
National Women's Health, Auckland City Hospital, Auckland, New Zealand	3 participants
Royal Womens Hospital, Melbourne, Australia	6 participants
TOTAL as of 15.03.2019	30 participants

Recruitment to 18th March 2019



The Future in Australia

Articles

The projected timeframe until cervical cancer elimination in Australia: a modelling study

Michaela T Hall, Kate T Simms, Jie-Bin Lew, Megan A Smith, Julia M L Brotherton, Marion Saville, Ian H Frazer, Karen Canfell

Summary

Background In 2007, Australia was one of the first countries to introduce a national human papillomavirus (HPV) vaccination programme, and it has since achieved high vaccination coverage across both sexes. In December, 2017, organised cervical screening in Australia transitioned from cytology-based screening every 2 years for women aged from 18–20 years to 69 years, to primary HPV testing every 5 years for women aged 25–69 years and exit testing for women aged 70–74 years. We aimed to identify the earliest years in which the annual age-standardised incidence of cervical cancer in Australia (which is currently seven cases per 100 000 women) could decrease below two annual

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