Excisional treatment comparison for in situ endocervical adenocarcinoma (EXCISE): a phase 2 pilot randomised controlled trial to compare histopathological margins status, specimen size and fragmentation after loop electrosurgical excision procedure and cold knife cone biopsy.

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Abstract

Objective

Adenocarcinoma in situ (AIS) of the cervix is a precursor to cervical adenocarcinoma. When AIS is detected by cervical screening an excision biopsy is mandatory to exclude invasion. We aimed to compare margins status, specimen size and fragmentation after loop electrosurgical excision procedure (LEEP) and 'cold knife cone biopsy' (CKC).

Methods

The EXCISE Trial was an investigator-initiated, multicentre, open-label, parallel-group, phase 2, randomised study. Patients were enrolled at seven hospitals in Australia and New Zealand. We randomly assigned women aged ≥18 to ≤45 years with screen detected AIS to LEEP or CKC. Co-primary endpoints were margin status, specimen size and fragmentation. Analysis was by intention-to-treat.

Results

Between August 2, 2017 and September 6, 2019, 40 patients were randomly assigned 2:1 to LEEP or CKC. Margin status was evaluable in 36 cases. The proportion of patients with involved margins did not differ between groups. 25 of 26 LEEP and all 14 CKC biopsies were excised as single specimens (p=1·00). There were no differences in specimen dimensions. Patients in the CKC group had more post-operative complications (64.3% compared to 15.4% for LEEP p=·00). There were no differences in grade three complications (p=·65).

Conclusions

LEEP was not associated with a greater likelihood of positive margins, specimen fragmentation or smaller excision compared to CKC when performed according to a standardised protocol. However, the study was not powered to establish non-inferiority of LEEP and a definitive phase 3 trial to compare margin status and rates of treatment failure after LEEP and CKC is warranted.

Introduction

Adenocarcinoma in situ (AIS) of the uterine cervix is a precursor to, and may coexist with, endocervical adenocarcinoma in approximately 15% of cases.[1] When AIS is detected by cervical screening, examination by a clinician with expertise in colposcopic evaluation of the cervix is mandatory and, if malignancy is not identified, an excision biopsy should be performed to exclude invasive disease.[2] A cervical excision biopsy can be performed by various techniques including 'cold knife cone biopsy' (CKC) and large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excision procedure (LEEP), and these are the two procedures most commonly used in Australia and New Zealand.[3,4] These techniques have been described in detail elsewhere and are fertility-preserving alternatives to hysterectomy in women of reproductive age in whom AIS is prevalent.[5,6] Excisional treatments (typically International Federation of Cervical Pathology and Colposcopy type two or type three excisions[7]) for AIS are mostly curative and prevent progression to invasive disease but they may compromise the structural integrity of the cervix increasing the risk of preterm delivery.[8] Risk of preterm birth positively correlates with excision dimensions and the number of excisions.[9,10]

In many settings LEEP is the preferred modality because it offers advantages compared to CKC including the ability to perform the procedure in an outpatient setting under local anesthesia, and lower morbidity, including fewer adverse obstetric outcomes.[4] However, the role of alternative excisional modalities to CKC in the management of AIS is controversial and in Australia CKC is considered the 'gold standard'.[11]

Single-specimen excision biopsies with minimal thermal damage and epithelial disruption are essential for accurate histopathological assessment of AIS. However, tissue margins in a LEEP biopsy may show significant thermal artefact, which can interfere with assessment of margin status.[12,13] Positive histopathological margins are associated with an increased risk of treatment failure (residual or recurrent AIS).[14] Two systematic reviews have reported higher rates of incomplete excision with LEEP

(44%-51%) than with CKC (29%-30%) but concluded that LEEP had acceptable safety and was comparable to CKC when negative margins were achieved.[4,15] However, both systematic reviews concluded that larger prospective studies with longer follow-up are required to determine the superiority of either procedure.

No prior randomised trial has compared excision biopsy techniques for cervical AIS, a gap that was highlighted in the 2016 Australian NHMRC clinical management guidelines for the prevention of cervical cancer.[11] A definitive phase 3 non-inferiority trial would require 810 participants to demonstrate non-inferiority of LEEP with a primary outcome of an AIS treatment failure rate of 8% in women treated by CKC, and a 5% non-inferiority margin.[16] The specific objectives of this phase 2 study were to compare histopathological margins status, and specimen size and fragmentation, after LEEP and CKC when treatment was performed in tertiary level cervical dysplasia and gynaecologic oncology centres, prior to conducting a definitive phase 3 non-inferiority trial. Secondary objectives were to compare rates of early postoperative complications and patient satisfaction.

Methods

Study design and participants

The Excisional treatment comparison for in situ endocervical adenocarcinoma (EXCISE) Trial was an investigator initiated, multicentre, international, open-label, parallel-group, phase 2, randomised study. The trial is registered with the Australia and New Zealand Clinical Trials Registry (ANZCTR registration number ACTRN12617000132347). Patients with pre-treatment, screen detected AIS were randomly assigned with an allocation ratio of 2:1 in favour of the intervention (LEEP: CKC). The trial protocol has been published elsewhere and is available in the Supplementary Appendix.[16] Ethical approval for the study was granted by the St John of God Healthcare Human Research Ethics Committee (Reference number #1137) and approvals were obtained at all participating sites. There were no changes to the methods after trial commencement. Women aged ≥18 to ≤45 years diagnosed

with AIS on cervical screening or colposcopically directed biopsy who were to receive excisional treatment in a tertiary level centre were eligible to participate. Patients were required to have lesions that were amenable to a single-pass excision as assessed by the treating specialists who were all senior colposcopists and study investigators. Exclusion criteria were a prior history of a high-grade cervical abnormality or cervical cancer; previous excisional or ablative treatment; cytology suspicious for invasion; clinical/colposcopic suspicion of invasion, presence of a concurrent gynaecological cancer; inability to comply with follow-up evaluations; immunosuppression; and pregnancy. Participants were enrolled at seven academic hospitals in Australia and New Zealand (Supplementary Appendix 2) and were identified from new patient referrals by study nurses and lead investigators at each site. Eligible patients were provided with information brochures and counselled about the trial by study nurses and site investigators. All participants provided written, informed consent.

Randomisation and masking

Allocation: participants were randomised to undergo LEEP or CKC (2:1 ratio). Unequal randomisation was chosen because this pilot trial was primarily assessing histopathological margin status as a surrogate for safety (treatment failure) of the intervention (LEEP) compared to the control treatment (CKC). Generation of the allocation sequence was by computer generated random numbers. The allocation sequence was implemented by central telephone (interactive voice response system) and generated by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney. Enrolment and assignment were performed by a trial coordinator who was not involved in clinical management. Participants and investigators, who were the treating specialists, were not masked to treatment allocation.

Procedures

LEEP and CKC were conducted according to techniques described in detail in the protocol (Supplementary Appendix 1). Local anesthetic (5-10ml of lignocaine) with adrenaline (1 in 100,000)

was injected into the subdermal tissue of the ectocervix at 3, 6, 9 and 12 o'clock prior to LEEP and CKC. Coagulation of the surface and application of ferric subsulphate (Monsel's solution) was performed in both arms. Patient management followed Australia's NHMRC 2005 Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen-detected abnormalities and the revised 2016 guidelines.[2,11] Participants randomised to LEEP had their procedure performed under local anesthesia in an outpatient setting or operating theatre, or under general anesthesia in an operating theatre, at the discretion of the treating specialist as per local routine practice. Participants randomised to CKC had their procedure performed under general anesthesia in an operating theatre. The trial was conducted in academic tertiary level dysplasia/gynaecologic oncology units. To mitigate surgical performance bias, a potential issue in surgical trials, patients with lesions not amenable to a single-pass excision were excluded, and the procedures were only performed by the named study investigators who are highly experienced providers, certified under the Colposcopy Quality Improvement Program (CQUIP) of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). Participants had one follow up visit with a study coordinator at 6 weeks' post procedure. This visit was conducted either face to face or via telephone and involved collection of information regarding post procedure complications, return to hospital, GP visits and completion of the European Organisation for Research and Treatment of Cancer (EORTC) Patient Satisfaction Questionnaire PATSAT-C33 and the EORTC Outpatient Satisfaction Questionnaire OUT-PATSAT 7.

Outcomes

Co-primary endpoints were the histopathological margin status, and size and fragmentation of the excised specimen (specimen dimensions and single specimen vs. more than one piece). Central pathology review of all cases was conducted in Australia (LA) and New Zealand (RvdG). Prespecified secondary outcomes were frequency of early complications including pain, infection, primary and delayed haemorrhage, readmission to hospital and return to the operating theatre, as assessed using

184 the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; the EORTC
185 PATSAT-C33 and EORTC OUT-PATSAT7 at 6 weeks post-procedure.[17]
186
187 The EORTC PATSAT-C33 satisfaction with cancer care core questionnaire and cancer outpatient
188 satisfaction complementary module OUT-PATSAT7 are composed of 33 and seven items respectively
189 (Supplementary Appendix 1). The core questionnaire encompasses three sections addressing the
190 perceived quality of care provided by doctors, nurses and services/care organisation. The doctor
191 section comprises three scales addressing technical skills (three items), information exchange (three
192 items), and affective behaviour (four items). The nurses section encompasses two scales addressing
193 information provision and responsiveness three items) and affective behaviour (four items). The
194 service and care organisation section comprise three scales including coordination (four items),
195 interaction with health care team (seven items), and five single items. The complementary specific
196 outpatient satisfaction module includes two scales addressing care convenience (three items) and
197 transition (three items) and a single item on care continuity. Instructions invite patients to assess the
198 most recent experience of care, and to specify the cancer care setting and the professionals to be
199 evaluated. Internal consistencies (Cronbach's α) computed for each hypothesized scale range from
200 0·85 (Convenience scale) to 0·95 (Coordination scale).[17]
201
202 The resulting satisfaction with cancer care core questionnaire and cancer outpatient
203 satisfaction complementary module are composed of 33 and 7 items respectively. These
204 require validation in a phase IV field study. The core questionnaire encompasses three
205 sections addressing the perceived quality of care provided by doctors,
206 nurses/radiotherapy technicians, and services/care organization. The doctor section
207 comprises three scales addressing technical skills (3 items), information exchange (3
208 items), and affective behaviour (4 items). The nurses/radiotherapy technicians section
209 encompasses two scales addressing information provision and responsiveness (3 items)

and affective behaviour (4 items). The service and care organization section comprise three scales including coordination (4 items), interaction with health care team (7 items), and five single items. The complementary specific outpatient satisfaction module includes two scales addressing care convenience (3 items) and transition (3 items) and a single item on care continuity.

Instructions invite patients to assess the most recent experience of care, and to specify the cancer care setting and the professionals among nurses or radiotherapy technicians to be evaluated.

Internal consistencies (Cronbach's α) computed for each hypothesized scale range from 0.85 (Convenience scale) to 0.95 (Coordination scale).

Sample size

The sample size for this phase 2 pilot study was pragmatic, hence all eligible patients in routine clinical practice were invited to participate.[18,19]

Statistical methods

All analyses were by intention to treat. IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA) was used to analyse the data with an alpha of ·05 considered statistically significant. Categorical variables were described using frequency and percent, and variations in sample noted. Continuous scale variables were described using mean and standard deviation. Group differences between treatments (LEEP/CKC) and each categorical variable were examined using Fisher's Exact and Chi-square tests. Group differences for scale variables were examined using the independent t-test for age at enrolment, PATSAT33 organisation rating score, histopathological specimen dimensions, distance of AIS to margins; and the non-parametric Mann-Whitney U Test for body mass index (BMI), time from diagnosis to treatment, PATSAT33 doctors, nurses and total scores, OUT-PATSAT7, and procedure time (based on the Shapiro-Wilk test for normality).

Role of the funding source

The study was funded by the Australia New Zealand Gynaecological Oncology Group [Grant number #FNR2016/03]. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The first author (PAC), statisticians (PC and MB) and project manager (SB) had full access to the data, vouch for the integrity of the data and the adherence to the study protocol. All authors are responsible for the final decision to submit for publication.

Results

Between August 2, 2017 and September 6, 2019, 40 patients were randomly assigned 2:1 to the LEEP group or CKC group. Twenty-six participants underwent LEEP and 14 underwent CKC. All participants were included in the analysis. A CONSORT flow diagram is shown in Figure 1 with participants' baseline characteristics shown in Table 1. All participants (n=40) were premenopausal. The groups were well balanced for baseline factors (Table 1). Two participants in the LEEP group and one participant in the CKC group had type one excision specimens (≤10mm in length) on histopathology. Ten of 26 (38·5%) participants in the LEEP group had their procedure performed under local anesthesia.

Histopathological margin status was evaluable in 36 cases and the proportion of participants with involved margins did not differ between the LEEP and CKC groups (Table 2). Twenty five of 26 LEEP biopsies and all 14 CKC biopsies were excised as single specimens (p=1·000) (Table 2). Sixteen of 26 patients in the LEEP group had a general anesthetic. No difference in margin status was reported by type of anesthesia (p=·66). There were no significant between group differences in histopathological specimen dimensions (Table 3). Distance from AIS to the margins did not differ between groups (Table 3). Tissue artefact was more common in the LEEP group (88·4%) compared to the CKC group (21·4%) (p=·00) (Table 2) although this was mostly minimal and did not impact diagnosis. No other statistically significant differences were detected. Four of 40 (10%) patients had concurrent invasive cervical tumours. Two of 14 (14·3%) patients in the CKC group had adenocarcinomas and two of 26 (7·7%)

patients in the LEEP group had invasive disease (one adenocarcinoma and one squamous cell carcinoma).

Patients in the CKC group had significantly more post-operative complications (64·3% compared to 15·4% for LEEP p=·00), although there were no differences in grade three complications between groups (p=·65) (Table 4). For the CKC group complications were higher for all complication types compared to LEEP (p=·00). There were no differences in all patient satisfaction scores between groups (Table 5). Procedure times were significantly longer for CKC compared to LEEP (p<·001) (Table 5).

Discussion

This is the first randomised comparison of LEEP and CKC in women with cervical AIS. LEEP was not associated with a greater likelihood of positive histopathological margins, specimen fragmentation or smaller excision compared to CKC. These findings are not consistent with previous systematic reviews and meta-analyses of retrospective data that showed higher rates of incomplete excision with LEEP compared to CKC. A 2017 systematic review and meta-analysis of 18 retrospective studies that included 1559 patients reported positive margins in 44% of LEEP and 29% of CKC biopsies (RR, 1·55; 95% CI, 1·34 - 1·80, P<0·00001).[4]

Our findings should be considered in the context of the trial's limitations, particularly its modest sample size, which was not powered to assess non inferiority of LEEP compared to CKC. However, rates of incomplete excision were comparable in both groups. Involved endocervical and stromal margins have consistently been shown to predict AIS recurrence and mandate repeat excision. In the current study positive endocervical margins were found in 11·5% and 7·1% of patients in the LEEP and CKC groups respectively, and positive stromal margins in 4·2% and 7·1% of the LEEP and CKC groups respectively. These proportions in the LEEP group are considerably lower than rates reported in previous retrospective studies (23%-51%).[4,15,20] A potential explanation for the lower rate of

incomplete excision in women undergoing LEEP in our study is that surgery was conducted at high-volume tertiary level dysplasia centres, by highly experienced providers with knowledge that patients were participating in a trial to compare dimensions, which may have influenced the way that LEEP was performed. Hence our findings may not be applicable outside of high-volume tertiary level dysplasia centres. Further, a majority of patients had LEEP performed under general anesthesia, which is routine practice in some Australian centers, and this may also limit the external validity of our findings. An additional limitation was the short follow-up period that does not allow assessment of test of cure and long-term treatment sequelae including cervical stenosis and adverse obstetric outcomes. A strength of our study was the attempt to mitigate surgical performance bias by excluding patients with lesions that were not amenable to a single-pass excision and ensuring that procedures were only performed by the named study investigators to ensure consistency of surgical technique. Our findings are consistent with those of a 2016 meta-analysis of mostly non-randomised studies that compared LEEP and CKC for the treatment of squamous dysplasia, which found that post-operative complications such as bleeding occurred more frequently after CKC.[21]

In contrast to cervical squamous dysplasia, the incidence of AIS and cervical adenocarcinoma has been increasing since the early to mid 2000's, although the introduction of HPV vaccination and HPV-based screening in Australia will likely reduce future disease burden.[22,23] It is essential that women with cervical AIS are treated in tertiary level dysplasia and gynaecologic oncology centres by specialists with expertise in its management because almost one in five women with AIS will have a concurrent cervical malignancy.[24] There are also important implications of an incomplete initial excision for younger women wishing to preserve fertility because a further excision will be required, which increases the risk of a subsequent pre-term birth.[10]

In conclusion, this is the first randomised trial to compare LEEP and CKC in the management of cervical AIS. Our findings suggest that LEEP may be a safe alternative to CKC when performed in a tertiary

dysplasia or gynaecologic oncology centre. LEEP was associated with fewer post-operative complications. A definitive phase 3 randomised non-inferiority trial to compare margin status and rates of treatment failure after LEEP and CKC is warranted. However, given the slow accrual in the current study, and the required sample size to demonstrate non-inferiority of LEEP, a phase 3 trial would not be feasible in Australia and New Zealand and would require international collaboration.

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Conflict of interest statement

PAC and CDHW have received honoraria from Seqirus unrelated to this work. MRS has received grants from Astellas, Amgen, Astra Zeneca, Bayer, Bionomics, Bristol-Meyers-Squibb, Celgene, Medivation, Merck Sharp & Dohme, Pfizer, Roche, Sanofi, Specialised Therapeutics and Tilray unrelated to this work. All other authors declare no competing interests.

Author Contributions

PAC, YL, AB, MS, PS, CDHW contributed to trial conception and design.
PAC and PC contributed to data analysis.
PAC and CDHW wrote the initial draft of the manuscript.
LA and RvdG performed central pathology review.
The first author (PAC), senior author (CDHW), statisticians (PC, MB) and project manager (SB) had full access to the data, vouch for the integrity of the data and the adherence to the study protocol, and are responsible for the decision to submit the manuscript.
All authors contributed to data collection, data interpretation, and revised the manuscript for critically important content.

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Legends

Figure 1. CONSORT Flow Diagram of EXCISE Study

Table 1. Participant Characteristics

Table 2. Histopathology outcomes – categorical variables

Table 3. Histopathology outcomes – continuous variables

Table 4. Post-operative complications

Table 5. Patient satisfaction and procedure time

Supplementary Files

Supplementary Appendix 1. Study Protocol

Supplementary Appendix 2. Participant recruitment by site

Figure 1. CONSORT Flow Diagram of EXCISE Study

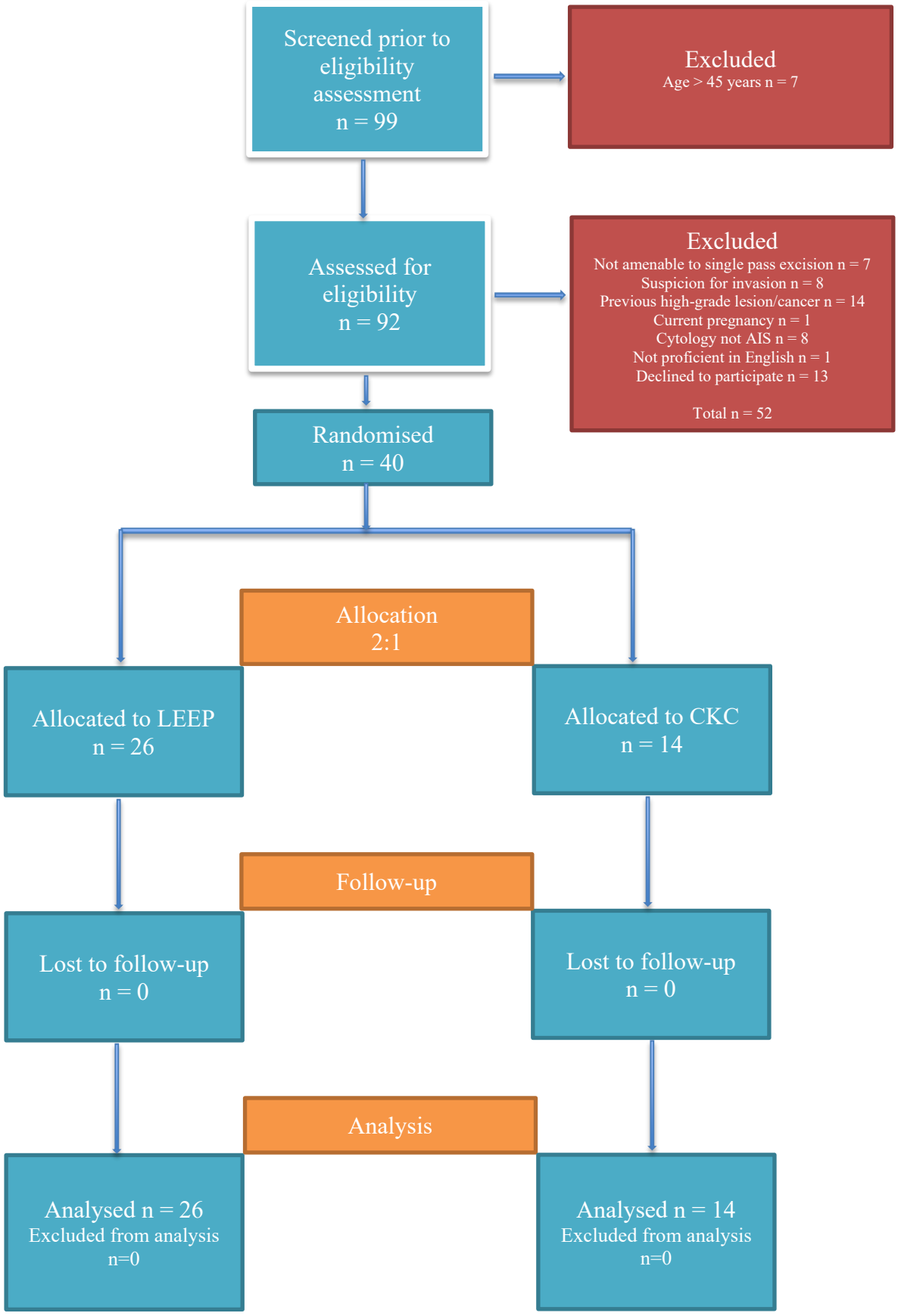

Table 1. Participant Characteristics

		Total sample	LEEP	CKC	
Participant characteristic					
Continuous variables	N	Mean (SD)	Mean (SD)	Mean (SD)	p-value
Age at Enrolment	40	33·67 (4·44)	33·35 (4·37)	34·27 (4·69)	·54
Body Mass Index[a]	40	26·09 (5·72)	26·51 (6·03)	25·31 (5·22)	·69 [b]
Time from AIS diagnosis to treatment (days) [a]	40	73·38 (65·39)	79·35 (77·74)	62·29 (31·69)	·73[b]
		ƒ	ƒ	ƒ	p-value
Categorical variables					
Current Smoker	40	11	7	4	1·00
Previous STI	40	11	7	4	1·00
Current or previous contraceptive use	40	8	4	4	·42
HPV Vaccinated	40	14	9	5	1·00 [c]
Method of AIS diagnosis	40				1·00 [c]
Cytology		5	3	2	
Colposcopic biopsy		25	16	9	
Cytology and Colposcopic biopsy		10	7	3	
Gravidity	40				·74
Nulligravid		17	12	5	
Gravid		23	14	9	
Parity	40				1·00
Nulliparous		20	13	7	
Parous		20	13	7	

[a] Not normally distributed as per Shapiro Wilk test, [b] Mann Whitney U test, [c] Fisher's Exact test. Exact 2-sided p-values reported.
LEEP= loop electrosurgical excision procedure, CKC= cold knife cone biopsy, STI= sexually transmitted disease, HPV= human papilloma virus, AIS=adenocarcinoma in situ, SD= standard deviation, ƒ=frequency.

Table 2. Histopathology outcomes – categorical variables

		Total Sample (N=40)		LEEP		CKC		
VARIABLE		ƒ	%	ƒ	%	ƒ	%	p-value
AIS involved ectocervical margin[a]	36	2	5·6	0	0	2	14·3	·08
AIS involved endocervical margin[a]	36	4	11·1	3	11·5	1	7·1	·84
AIS involved stromal margin[a]	36	2	5·6	1	4·2	1	7·1	·65
Single pass specimen[b]	40	39	97·5	23	95·8	14	100	1·00
Excision type	40							·67
Type 1		3	7·5	2	7·7	1	7·1	
Type 2		10	25	8	30·8	2	14·3	
Type 3		27	67·5	16	61·5	11	78·6	
Invasion present[a]	40	4	10	2	7·7	2	14·3	·60
SMILE type AIS present[c]	40	5	12·5	4	15·4	1	7·1	·64
Thermal artefact	40							·00*
Absent		14	35	3	11·5	11	78·6	
Minimal		25	62·5	22	84·6	3	21·4	
Extensive (impacting diagnosis)		1	2·5	1	3·8	0	0	
Epithelial loss	40							1·00
Absent		1	2·5	1	3·8	0	0	
Minimal		36	90	23	88.5	13	92·9	
Extensive (impacting diagnosis)		3	7·5	2	7·7	1	7·1	
HSIL present in excision specimen[b]	40	17	42·5	11	45·8	6	42·9	1·00
AIS present in excision specimen	40	36	90	24	92·3	12	85·7	·60

[a] alternate group not involved, [b] alternate group specimen in more than one piece, [c] alternate group absent, *statistically significant p<·05

LEEP= loop electrosurgical excision procedure, CKC= cold knife cone biopsy, HSIL = high grade squamous intraepithelial lesion, AIS= adenocarcinoma in situ, SMILE= Stratified mucin producing intraepithelial lesion,

Note one decimal place rounding sometimes results in cumulative sum of % not equal to 100. Exact 2-sided p-values reported.

Table 3. Histopathology outcomes – continuous variables

	N	Total sample	LEEP	CKC	
		Mean (SD)	Mean (SD)	Mean (SD)	p-value
VARIABLE					
Histopathology specimen length (mm)	40	17 (4·19)	16·19 (3·60)	18·5 (4·90)	·10
Histopathology specimen width (mm)	40	20·9 (4·51)	21 (4·83)	20·71 (3·99)	·85
Histopathology specimen height (mm)	40	17·98 (4·38)	18·88 (3·96)	16·29 (4·76)	·07
Distance from AIS to ectocervical margin (mm)	36	4·25 (2·82)	4·42 (2·97)	3·92 (2·97)	·62
Distance from AIS to endocervical margin (mm)	36	5·92 (3·38)	5·71 (3·56)	6·33 (3·08)	·61
Distance from AIS to stromal margin (mm)	36	4·08 (2·45)	4·45 (2·54)	3·35 (2·17)	·21

LEEP= loop electrosurgical excision procedure, CKC= cold knife cone biopsy, mm = millimetres, AIS= adenocarcinoma in situ, SD= standard deviation.

Table 4. Post-operative complications

	Total Sample (N=40)		LEEP (N=26)		CKC (N=14)		
VARIABLE	ƒ	%	ƒ	%	ƒ	%	p-value
Any post-operative complication	13	32·5	4	15·4	9	64·3	·00*[b]
Grade 3 complication	6	15	3	11·5	3	21·4	·65 [b]
Type of post-operative complication							·00*[b]
None	27	67·5	22	84·6	5	35·7	
Pain	1	2·5	0	0	1	7·1	
Infection	3	7·5	0	0	3	21·4	
Bleeding	8	20	4	15·4	4	28·6	
Bilateral upper limb paraesthesia	1	2·5	0	0	1	7·1	

[b] Fisher's Exact test statistic reported, *statistically significant p<·05, Exact 2-sided p-values reported.

Table 5. Patient satisfaction and procedure time

	N	Total Sample	LEEP	CKC	
		Mean (SD)	Mean (SD)	Mean (SD)	p-value
VARIABLE					
PATSAT33 Rating Doctors Total Score [a]	38	43·13 (8·15)	43·08 (9·25)	43·21 (6·12)	·45[b]
PATSAT33 Rating Nurses Total Score [a]	38	30·79 (4·66)	31·29 (4·81)	29·93 (4·43)	·39 [b]
PATSAT33 Rating Organisation Total Score	38	64·55 (9·55)	64·67 (10·42)	64·36 (8·19)	·93
PATSAT33 Total Score [a]	38	138·47 (20·21)	139·04 (22·95)	137·50 (15·12)	·56 [b]
OUT-PATSAT7 Total Score	34	27·85 (4·84)	27·71 (4·76)	28·08 (5·17)	·84
Procedure time (minutes)[a]	40	17·95 (9·69)	12·81 (5·09)	27·50 (8·99)	·00*

[a] Not normally distributed as per Shapiro Wilk test. [b] Mann Whitney U test, *statistically significant p<·05, LEEP= loop electrosurgical excision procedure, CKC= cold knife cone biopsy, PATSAT33 = Patient Satisfaction Questionnaire C33, OUT-PATSAT7 = Outpatient Satisfaction Questionnaire C7, AIS= adenocarcinoma in situ, SD= standard deviation.

EXCISE Supplementary Appendix 2

Participant recruitment by site

	Participants (n)	%
St John of God Subiaco Hospital Perth, Western Australia, Australia	5	12.5
King Edward Memorial Hospital, Perth, Western Australia, Australia	15	37.5
Royal Womens Hospital Melbourne, Victoria, Australia	10	25.0
Christchurch Womens Hospital, Christchurch, New Zealand	4	10.0
National Womens Health Auckland City Hospital, Auckland, New Zealand	4	10.0
Hollywood Private Hospital Perth, Western Australia, Australia	1	2.5
Westmead Hospital Sydney, New South Wales, Australia	1	2.5
Total	40	100