

## **Management and long-term outcomes of women with Adenocarcinoma-in-situ of the cervix: a retrospective study**

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### **Contribution to Authorship**

JT, CDW, MS, DG, MQ conceived and developed the protocol to perform this retrospective analysis. JT, KD, RT, MM were involved in collecting, retrieving and analysing the data. All authors have reviewed the manuscript and have approved the final version. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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**Abstract**

**Background**

Adenocarcinoma-in-situ of cervix is increasingly managed by local excision rather than hysterectomy and this study will ascertain if conservative management by excision alone is adequate.

**Aims**

To evaluate the long term outcomes of conservative management of Adenocarcinoma-in-situ of cervix, particularly in relation to excisional margin status.

**Materials and Methods** Retrospective analysis of women diagnosed with Adenocarcinoma-in-situ and their management between 1992 and 2010 retrieved from the Victorian Cervical Cytology Registry, Australia. Failure of conservative treatment is defined by histologically-proven Adenocarcinoma-in-situ or Adenocarcinoma at follow up after negative excisional margins.

### **Results**

Adenocarcinoma-in-situ of the cervix was managed primarily with cold knife cone biopsy or loop electro-surgical excision of cervix. Most excisions were in one piece (83.4%) with average depth of 16.1mm and 21.9% had involved excisional margins. Women with Adenocarcinoma-in-situ on any excisional margin were more likely to have residual or recurrent disease (28.7%) compared with negative excisional margins (4.3%). Residual Adenocarcinoma-in-situ was twice as common if Adenocarcinoma-in-situ was present at endocervical (29.6%) and stromal (23.1%) margins compared with an ectocervical margin (13.6%). Cancer incidence at follow up was 2.3% for women with positive excisional margins compared to 1.3% with negative margins.

### **Conclusions**

Women with Adenocarcinoma-in-situ of cervix can be managed with local excisional procedures, best in single pieces to provide the important information on excisional margins. Adenocarcinoma-in-situ at endocervical and stromal excisional margins needs re-excision or where appropriate, hysterectomy, whilst negative excisional margins have a low rate of recurrence and can be followed up with test of cure.

### **Short communication**

Adenocarcinoma-in-situ of the cervix is increasingly managed conservatively by local excision rather than hysterectomy. This study showed that cervical Adenocarcinoma-in-situ can be managed with excisional procedures, cold knife cone biopsy or electrosurgical loop excision (LEEP or LLETZ). Adenocarcinoma-in-situ at endocervical and stromal excisional margins needs re-excision or where appropriate, hysterectomy, whilst negative margins has low recurrence rate and can be followed up with test of cure.

## **Introduction**

Adenocarcinoma-in-situ of the cervix (AIS) was first described by Hepler et al<sup>1</sup> in 1952 and considered a precursor of adenocarcinoma. In the State of Victoria, Australia, the reported incidence of glandular cytological abnormality is less than 0.1% and 926 women had histologically confirmed AIS over a period of ten years between 2001 and 2010.<sup>2</sup>

Hysterectomy has been traditionally the recommended management of confirmed AIS but many authors now advocate a more conservative approach with cold knife cone biopsy (CKC) or loop electrosurgical excision procedure (LEEP), also known as LLETZ.<sup>3,4</sup> The excision should preferably be in one piece to aid pathological interpretation. Margin status is an important predictor of recurrence as involved margins are significantly associated with persistent disease<sup>5</sup> whereas with negative margins, the likelihood of recurrence is low.<sup>6</sup> Recurrence as late as 12 years has been reported and long term follow up is considered necessary.<sup>7</sup> We wished to ascertain if conservative management is adequate when excisional margins are clear and to question the necessity for hysterectomy after completion of childbearing.<sup>8</sup>

## **Materials and Methods**

This is a retrospective analysis of a cohort of women with histological diagnosis of AIS between 1992 and 2010 in the state of Victoria and managed initially with CKC or LEEP. Data were collected routinely by the Victorian Cervical Cytology Registry (VCCR) for virtually all cytology, histopathology, treatment of screened abnormalities and follow up. Coding of all histopathology reports was routinely conducted internally by Registry staff according to an in-house coding schedule and was subject to regular quality assurance. Record linkage was conducted between the VCCR and Victorian Cancer Registry on an annual basis hence ascertainment of cancer diagnoses was complete for all women on the register. Prior to 2008, however, histopathological reports were not routinely scanned by the register and were thus unavailable for a more detailed analysis of excisional margins and treatment modality. To try to obtain complete records for cases diagnosed prior to 2008, we obtained management records and histology data via a questionnaire to known treating medical practitioners and pathology centres. We were able to retrieve hard-copy histopathology reports for 646 (64.0%) women from the chosen cohort but not all of these had complete data. The other 364 women (36.0%) only had diagnosis and method of

treatment in the Registry. Depth of excision was recorded in 559 (55.3%) and excisional margins in 589 (58.3%) women.

Eligible population: All women on the VCCR database who had histologically confirmed AIS between the period January 1, 1992 and December 31, 2010.

Exclusion criteria:

- i. Women who had associated malignancy detected on their histology at pre-excision punch biopsy or at first excisional treatment,
- ii. Women whose initial AIS diagnosis was only at hysterectomy.
- iii. Women with a past history of cervical cancer.
- iv. Women with AIS diagnosed on punch biopsy or curetting but no record of treatment or no AIS at subsequent excision.

Follow-up and Outcome definitions: Failure of conservative treatment was defined as histologically-proven AIS or adenocarcinoma at follow up after clear margins were confirmed on histology at initial excisional treatment. We characterised AIS at repeat excision or hysterectomy up to 12 months following positive AIS margins as residual disease.

Method of analysis: A descriptive analysis of the data was undertaken to determine frequency of treatment type, treatment failures and key covariates. The chi-squared test and Fisher's exact test were used to assess associations between categorical variables. Fisher's exact test was applied when categories had less than 10 observations. For continuous variables, the Student T-test or Wilcoxon-rank-sum was applied. Spearman's correlation was run to assess the relationship between age at excision and depth of specimen. Univariate and multivariate logistic regression was used to examine variables associated with residual or recurrent AIS. Backward stepwise regression and likelihood ratio tests were applied to determine the factors that were significantly associated in multivariate model as well as assessing effect modification. Variables adjusted in the multivariate analysis were age at excision, depth of specimen excised and excisional margins status. All 95% confidence intervals were calculated using the robust estimator of variance. The statistical program STATA/SE 12.1 ® (StatCorp, LP, College Station, TX, USA) was used for data analyses.

Censoring: Date of death, date of migration from state of Victoria, at diagnosis of cancer or AIS after first excisional treatment, at hysterectomy, at date of last follow-up episode or at end of study.

This study was approved by the Human Research Ethics Committee, Department of Health in the State of Victoria in 2012 (Ref: 19/11).

## Results

Initial extraction from the VCCR database yielded 1,766 cases with histological diagnosis of AIS or glandular abnormality and after exclusions, a final cohort of 1010 women for analysis. (Figure 1) The mean age at diagnosis of AIS was 35.1 years and median age 33.3 years, with a range from 17.1 to 76.3 years. One hundred and ten (10.9%) women were under 25 years of age. LEEP was the excisional procedure for 281 (27.8%) women and CKC for 729 (72.2%) women. Of the 646 women with hard-copy histopathology reports, 267 (41.3%) had AIS with associated CIN. AIS, residual or recurrence, was noted in 37 (9.8%) women with no associated CIN and 35 (13.1%) with associated CIN. No association was found between the presence of squamous CIN lesions and AIS recurrence (Pearson  $\chi^2(1) = 1.77$ ,  $P = 0.18$ ). Excisional specimens were in one piece for 83.4% (489/586) of women, with average depth of 16.1mm (sd 7.4mm) and median of 15.0mm (range 2.0mm - 44.0mm). Three excisional margins were reported, endocervical (endo-), stromal and ectocervical (ecto-). In the five hundred and eighty-nine women who had their excisional margins recorded, there were no AIS in any of the 3 margins in 460 (78.1%) women whilst AIS was present in any one of the 3 margins or in combinations in 129 (21.9%) women. Seventy-one women (12.1%) had AIS on endocervical margins, 13 (2.2%) had AIS on stromal margins and 22 (3.7%) had AIS on ectocervical margins. Twenty-three (3.9%) had AIS on more than one margin. Twenty-six of the 559 women with depth of excision had no record of their excisional margins. For the remaining 533 women, AIS was found more often at endocervical margins with shallower depth of excision, 27.5% (<10mm), 15.3% (>10mm-15mm) and 6.6% (>15mm). Using greater than 20mm as reference, we found that for women less than 40 years old, the odds of AIS at the endocervical margin were greater if the depth of excision was 10mm or less, (Odds ratio (OR) 5.02 [95% CI: 1.45-17.37],  $P = 0.011$ ), with AIS noted at endocervical margins in 22.7% of women compared with 4.5% when greater than 10mm. For those women forty years or older, the odds of involved AIS margins were greater even when the depth of excision was between 10mm to 15mm, (OR 7.86 [95% CI: 1.59-38.82],  $P = 0.011$ ), with AIS noted at endocervical margins in 42.9% and still at 19.4% between 15mm and 20mm. (Table 1)

The median follow up after the first excision was 8.8 years (range: 0.03–22.6 years), 76.6% for at least 2 years and 56.5% over five years. Hysterectomy was performed in 323 (32.0%)

women after the first excisional treatment, 51.2% of those with AIS positive margin and 24.8% with AIS negative margin. The median time to hysterectomy was 8 months after the first excision (range: 0.4–238.6 months) with 41.6% in the first six months. There were eighty five women (8.4%) who were found to have an AIS event, defined as recurrence or residual AIS confirmed on histopathology. For the women with AIS on any excisional margins, 37 (28.7%) had residual or recurrent AIS at further excisional procedures or hysterectomy, 34 (91.9%) of them within the first twelve months. The median duration after initial treatment leading to an AIS event was 2.5 months. Twenty (4.3%) women with negative margins had AIS recurrence with thirteen (65.0%) diagnosed within the first year, ten of these were incidental findings at hysterectomy. The median interval to recurrence was 5.9 months, range 0.03 to 189.5 months (Figure 2). AIS events were twice as common if AIS was present at the endocervical (29.6%) and stromal (23.1%) margins as compared with ectocervical margins (13.6%). AIS events were also more common with shallower excisions, 11.6% with a depth of excision 15mm or less compared with 6.4% if greater than 15mm depth. AIS events for women in 10-year age groupings (at age of excision) indicate a higher incidence of residual AIS with increasing age when positive AIS margins are found. This was also evident in the first year in women with negative excision margins, 9.4% when over forty years of age compared with 1.4% in the younger women. Following the first year, risk of AIS recurrence was lower at 1.8% (7/386), all occurring in women under forty years of age. (Figure 3) There were fourteen women (1.4%) diagnosed with cancer within 0.1 to 14.8 years after the first excisional treatment, four within the first year and ten within 5 years. For those with known excisional margins, this was 2.3% (3/129) for women with AIS at excisional margin/s and 1.3% (6/460) with negative excisional margins. Seventy-four women with negative margins had a distance of AIS from the negative endocervical margin of less than 5mm. They were followed up to 18.7 years with a median of 3.8 years. Six (8.1%) had a second excision of cervix by LEEP or CKC and 13 (17.6%) had hysterectomy, one after her second excisional procedure. Among these, 4 had AIS and 1 with adenocarcinoma, the majority was diagnosed within one year of initial excision. The rest of this group of 74 women had cytological or cervical punch biopsy at follow up and none had AIS. The proportion of AIS recurrence was 6.5% (2/31) when AIS was within 2mm of excision, 4.7% (2/43) when between 2 and 5mm distance and 2.5% (2/79) when greater than 5mm from the excision. However, AIS recurrence was not found to be associated with distance of AIS from the excision margin ( $P=0.557$ ).

Multivariate analysis found strong evidence of increased risk of AIS events with positive AIS excisional margins (Adjusted Odds Ratio (AOR) 6.25 [95%CI: 3.39-11.51],  $P < 0.001$ ). This was also noted with increasing age at first treatment (AOR 1.03 [95%CI: 1.01-1.06],  $P = 0.003$ ) and depth of excised specimen (AOR 0.95 [95%CI: 0.92-0.98],  $P = 0.002$ ).

## Discussion

Our study has shown that women with AIS can be managed by local cervical excision, best in one piece with clear margins with the depth of excision tailored according to the women's age. For women under 40 years of age desiring further children, excision at 15mm depth is adequate as the positive AIS endocervical margin rate is about 5.9%. In contrast, for women over 40 years of age, the excision depth should be at least 20mm. We did not have colposcopy data to indicate how colposcopy could have influenced the depth of excision. Margin status is an important predictor of recurrence as involved margins were significantly associated with persistent disease. In one systematic review, residual AIS lesions were found in 49% of re-cone or in the uterus when positive margins were seen in initial excisions.<sup>9</sup> The importance of positive margin status was also shown in another study with a 3.4 times increased risk of AIS persistence and/or recurrence.<sup>10</sup> Just under 29% of our women with AIS on any excisional margins had persistent AIS and 2.3% were found to have cancer at follow up. If AIS is present at the endocervical or stromal margins, these women need repeat cervical excision and where appropriate, hysterectomy. Our results are similar to a study in which 2.6% of cases with negative margins and 19.4% with positive margins developed recurrent disease.<sup>11</sup>

One issue that remains unanswered is how commonly AIS occurs after negative excisional margins. In our study, 4.3% of women with negative margins had recurrence of AIS, slightly higher if AIS is less than 2mm from excision margin (6.3%), but no association was found between distance of AIS from the excision margin and AIS recurrence. Other studies have also suggested that negative margins are no guarantee against persistent or recurrent disease.<sup>10,12-14</sup> We have no specific indicators as to which women is more at risk of AIS recurrence after negative excisional margins. Most of our AIS recurrences were incidental findings at hysterectomy. Twenty-five percent of our women with AIS negative margin had hysterectomy, reasons unspecified and most within the first year. Although there is no doubt that hysterectomy will confer protection against recurrence, the risk for the remaining women in this group after one year is low, 1.8% spanning over fifteen years.

We identified three groups of women that have intermediate risk of AIS recurrence of

between 6 and 14%: i) women with AIS less than 2mm from excision margins (6.3%); ii) women over 40 years old with negative margins (9.4%); and iii) women with positive ectocervical margins (13.6%). We would recommend follow up at 6 months post treatment initially and not wait till 12 months for review per screening guideline, as the majority of the recurrent AIS occur within the first year (65% of women with negative margins who had recurrence). The 6-month follow up should consist of colposcopy, test of cure (with oncogenic HPV test and liquid based cytology) and endocervical curettage if possible. Endocervical curettage has been shown to be of value in predicting persistent disease at conisation for AIS<sup>15</sup> and we should consider it for its usefulness only when AIS is detected at follow up, realising a negative result does not exclude presence of disease. However, some of these women at intermediate risk may need further excision after initial treatment and this decision will need to be individualised.

Hysterectomy had been recommended in the past for women who have completed childbearing after a diagnosis of AIS<sup>8</sup> but this is now not a routine recommendation in practice guidelines. In the United Kingdom, women with completely excised cervical glandular Intra-epithelial neoplasia (CGIN), equivalent to AIS, are followed up with test of cure (TOC) and return to routine screening after two normal TOC.<sup>16</sup> We have shown that the risk of recurrence in women with completely excised AIS is less than 5% and thus follow up is sufficient in most cases. As the majority of recurrence is in the first twelve months after treatment, we would recommend follow up with an additional test of cure and colposcopy at six months after initial excision and then annual test of cure at twelve months as per guidelines in Australia.<sup>17</sup> As there is now a National Cancer Screening Register<sup>18</sup> in Australia, prospective collection of these data will help to further refine the management for AIS and whether we can eventually discharge women from indefinite annual co-testing to routine screening.

This study has several strengths and limitations. It reflects clinical and histopathological practice across the public and private health care systems, includes a large cohort of patients, has a long follow up and includes accurate data on subsequent malignancy. In contrast, limitations include its retrospective nature, lack of centralised pathology review and missing data, particularly on margin status and how close the AIS were to the excision margins. However, despite the missing data, the group with unknown excisional margins only had marginal increase in residual or recurrent AIS compared with the group with negative

margins (Figure 2). Thus, it would not have significantly affected the results from the AIS negative margin group.

The many issues and challenges outlined in our report showed the importance of these women being adequately counselled and properly managed. We strongly support our Australian guidelines recommendation that this care be provided by a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or a gynaecological oncologist.

## References

1. Hepler TK, Dockerty M, Randall LM. Primary adenocarcinoma of the cervix. *Am J Obstet Gynecol.* 1952; 63: 800–808.
2. VCCR Statistical report 2001–2010. Available from: <http://www.vccr.org/data-research/statistical-reports/annual-statistical-reports>
3. Kim ML, Hahn HS, Lim KT, et al. The safety of conisation in the management of adenocarcinoma in situ of the uterine cervix. *J Gynecol Oncol.* 2011 Mar 31; 22(1): 25–31.
4. Bull-Phelps SL, Garner EI, Walsh CS et al. Fertility-sparing surgery in 101 women with adenocarcinoma in situ of the cervix. *Gynecol Oncol.* 2007 Nov; 107(2): 316–9.
5. Taylor JS, Panico V, Caputo T, et al. Clinical outcomes of patients with adenocarcinoma in situ treated by conization. *Eur J Gynaecol Oncol.* 2014; 35(6): 641–5.
6. Östör AG, Duncan A, Quinn M, Rome R. Adenocarcinoma in situ of the uterine cervix: an experience with 100 cases. *Gynecol Oncol* 2000; 79; 207–210.
7. Hwang D, Lickrish G, Chapman W, Colgan T. Long-term surveillance is required for all women treated for cervical adenocarcinoma in situ. *J. Lower Gen Tract Dis.* 2004; 8: 125–131.
8. NHMRC (National Health and Medical Research Council) 2005. Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen-detected abnormalities. Canberra: NHMRC
9. Baalbergen A and Helmerhorst T. Adenocarcinoma in situ of the uterine cervix--a systematic review. *Int J Gynecol Cancer* 2014; 24: 1543–1548.
10. Munro A, Leung Y, Spilsbury K et al. Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma in situ:

What is the gold standard? *Gynecol Oncol*. 2015; 137:258–63.

11. Salani R, Puri I, Bristow RE. Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1,278 patients evaluating the predictive value of conization margin status. *Am J Obstet Gynecol*, 2009, 200(2): 18.e1–5.
12. Soutter W, Haidopoulos D, Gornall R, et al. Is conservative treatment for adenocarcinoma in situ of the cervix safe? *BJOG*. 2001 Nov; 108(11): 1184–9.
13. Azodi M, Chambers S, Rutherford T et al. Adenocarcinoma in situ of the cervix: management and outcome. *Gynecol Oncol* 1999; 73: 348–353.
14. DeSimone CP, Day ME, Dietrich CS 3<sup>rd</sup> et al. Risk for residual adenocarcinoma in situ or cervical adenocarcinoma in women undergoing loop electrosurgical excision procedure/conisation for adenocarcinoma in situ. *J Reprod Med*. 2011 Sep–Oct; 56(9-10): 376–80.
15. Tierney KE, Lin PS, Amezcua C et al. Cervical conization of adenocarcinoma in situ: a predicting model of residual disease. *Am J Obstet Gynecol*. 2014;210(4):366.e361–366.e365.
16. UK NHS Cervical Screening Program Available from: [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/515817/NHSC\\_SP\\_colposcopy\\_management.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/515817/NHSC_SP_colposcopy_management.pdf)
17. National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding. Available from: [https://wiki.cancer.org.au/australia/Guidelines:Cervical\\_cancer/Screening](https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening)
18. National Cancer Screening Register. Available from: <https://www.ncsr.gov.au/>

Table 1. Adenocarcinoma-in-situ (AIS) on endocervical margins by modalities, age and depth of excision and Odds ratio according to depth of excision

	Depth of excision				
	≤10mm	>10-15mm	>15-20mm	>20-25mm	>25mm
LEEP n=126	30/80 (37.3%)	4/32 (12.5%)	2/11 (18.2%)	0/2	0/1
CKC n=407	8/58 (13.8%)	17/105 (16.2%)	8/113 (7.1%)	5/83 (6.0%)	2/48 (4.2%)
Total	38/138 (27.5%)	21/137 (15.3%)	10/124 (8.1%)	5/85 (5.9%)	2/49 (4.1%)
AGE					
<40yo	25/110 (22.7%)	6/102 (5.9%)	4/93 (4.3%)	3/61 (4.9%)	0/30
≥40yo	13/28 (46.4%)	15/35 (42.9%)	6/31 (19.4%)	2/24 (8.3%)	2/19 (10.5%)
Odds ratio of AIS at endocervical margins according to depth of excision					
Depth of Excision	<40yo		≥40yo		
	OR (95% CI)	P	OR (95% CI)	P	
>20 – 25mm	Ref		Ref		
≤10mm	5.02 (1.45,17.37)	0.011	7.15 (1.43,35.87)	0.017	
>10 – 15mm	1.23 (0.30,5.11)	0.777	7.86 (1.59,38.82)	0.011	
>15 – 20mm	0.85 (0.18,3.92)	0.831	2.54 (0.46,13.95)	0.284	
>25mm	-	-	1.29 (0.16,10.22)	0.807	

Figure 1. Flow chart in selecting final cohort for analysis

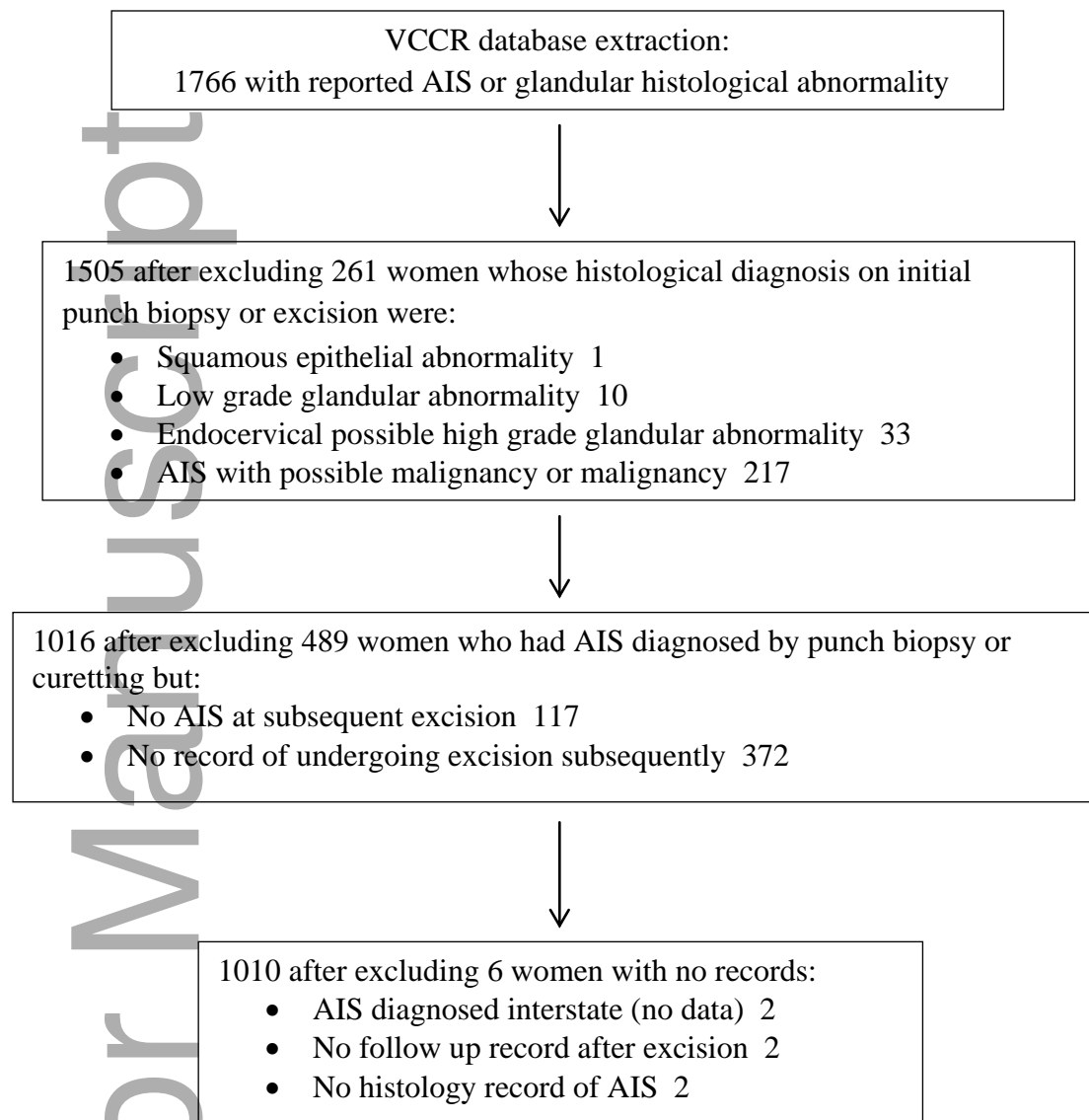


Figure 2. Flow chart of management of Adenocarcinoma-in-situ (AIS)

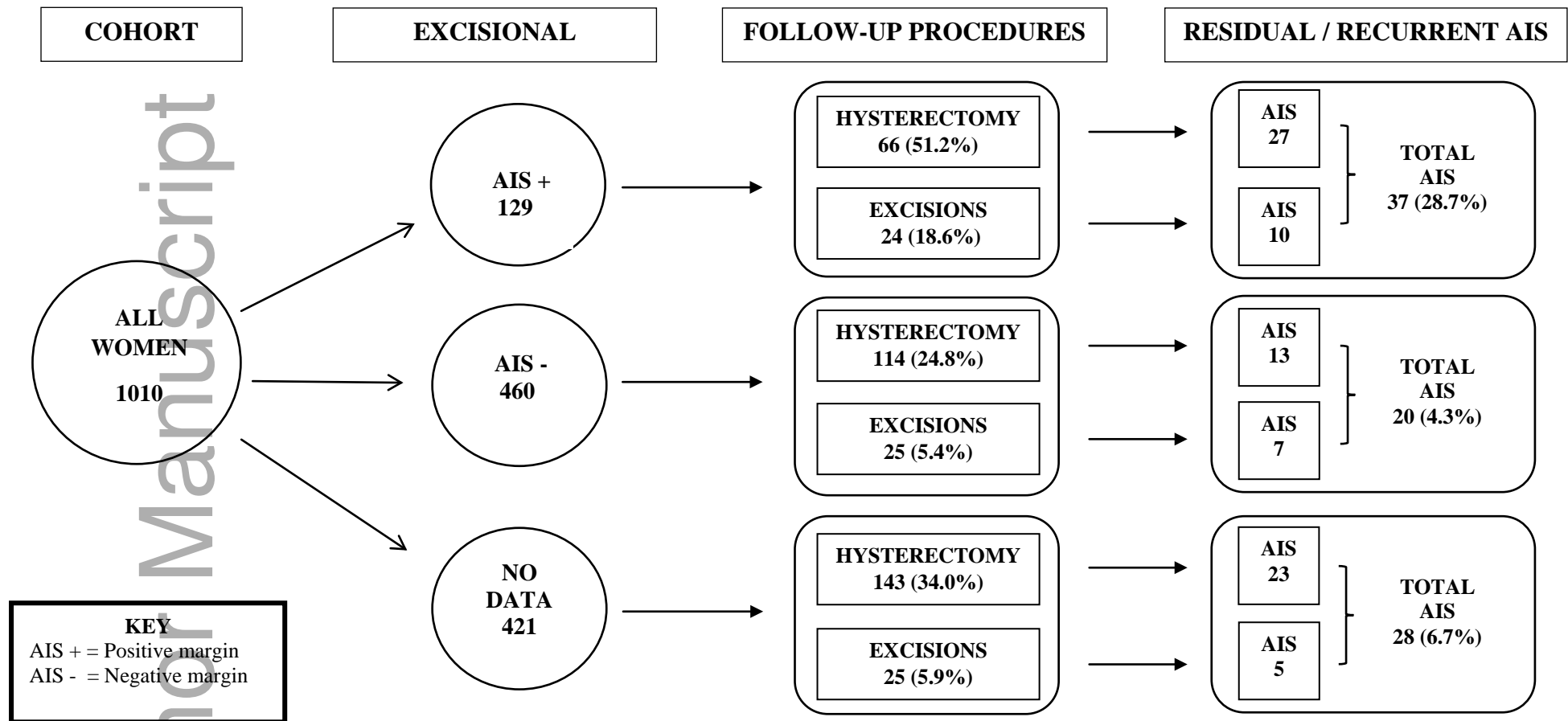
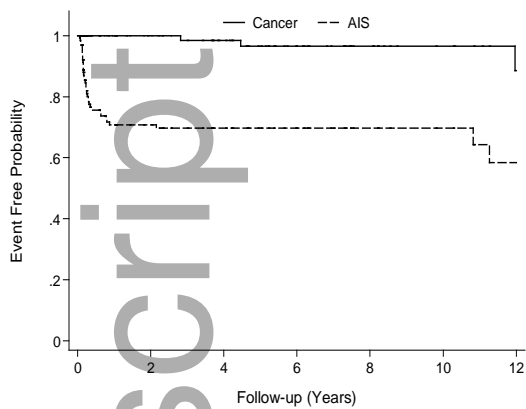


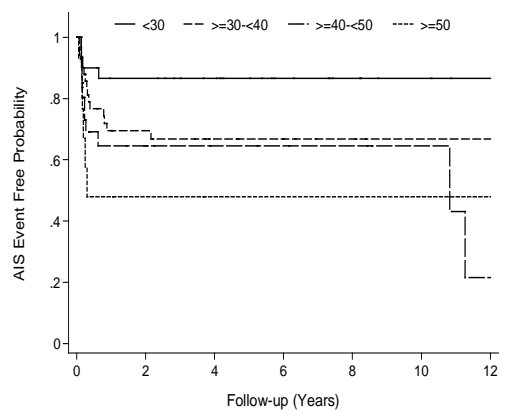
Figure 3. AIS Events correlated to excisional margins

(a) Excisional margins positive (AIS+)

(i) All Age

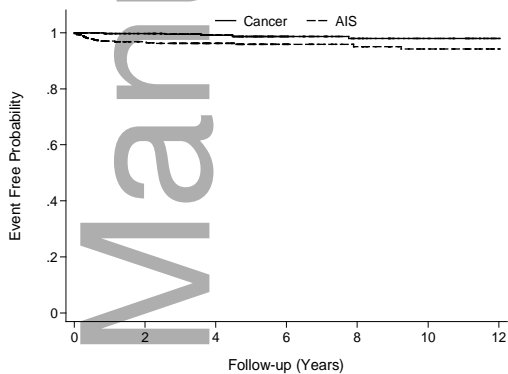


(ii) Age in 10-year groupings

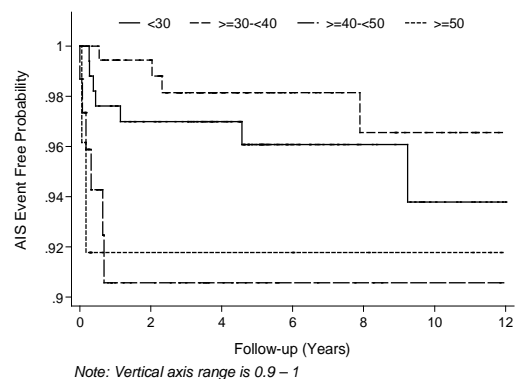


(b) Excisional margins negative (AIS-)

(i) All Age



(ii) Age in 10-year groupings



		Time to Cancer and AIS Events (Years)							
		0.5	1	2	3	4	5	10	20
AIS+ Margin (N=129)	Cancer	0 (92)	0 (82)	0 (72)	1 (65)	1 (58)	2 (49)	2 (18)	3 (2)
	AIS	29 (82)	34 (72)	34 (65)	35 (57)	35 (50)	35 (43)	35 (15)	37 (2)
AIS- Margin (N=460)	Cancer	0 (418)	1 (388)	1 (365)	2 (329)	3 (273)	4 (224)	5 (106)	6 (9)
	AIS	10 (414)	13 (386)	14 (361)	16 (324)	16 (268)	17 (219)	19 (103)	20 (9)
Hysterectomy (Cumulative)		134	188	214	243	260	266	297	322

Cumulative events of Cancer and AIS with number of women left at follow up after censoring in bracket.