Post-hysterectomy AIS – evidence summary

PICO: For women who have had a total hysterectomy after adenocarcinoma in situ (AIS)

i) Who have been treated for AIS by excision with clear margins and are under surveillance, and subsequently had a total hysterectomy (either as completion therapy or for other benign indications) OR

ii) Who have had incomplete excision of AIS with clear margins on total hysterectomy OR

iii) Who had a total hysterectomy as initial treatment for AIS with clear margins on hysterectomy

AND have had i. 2 consecutive negative annual HPV and cytology co-tests ii. 10 consecutive negative annual HPV and cytology co-tests, what is the safety of cessation of annual co-testing compared to continued annual co-testing?

A systematic review was conducted in 2023 for the above PICO and did not find any RCTs or pseudo-RCTs comparing ceasing with continuing annual co-testing if negative on either 2 or 10 consecutive annual co-tests for women have undergone a hysterectomy following a diagnosis of AIS. Therefore, on the advice of the Working Party, an evidence review was undertaken to address this question.

Evidence review for 2023 guidelines update

Searches: EMBASE and Medline databases were searched on 15 May 2023 by combining terms for adenocarcinoma in situ and hysterectomy. The search was limited to English language articles published from 2015 onwards. Full details of the search strategy are included in the Appendices. To cover the pre 2015 literature we also considered studies included in an evidence summary in the previous guidelines which addressed different questions regarding the management of women post hysterectomy who have been treated for high-grade squamous intraepithelial lesions or AIS.

Results: No comparative or single arm studies were identified that reported on risks or rates of cervical or vaginal cancers or dysplasia for women who have undergone a hysterectomy following a diagnosis of AIS and followed up with HPV testing or co-testing

Existing guidelines Current (2017) Australian guidelines

Women who have had a total hysterectomy, have been treated for AIS, and are under surveillance, should have a co-test on a specimen from the vaginal vault at 12 months and annually thereafter, indefinitely†

Women who have a total hysterectomy, as completion therapy or following incomplete excision of AIS at cold-knife cone biopsy or diathermy excision, should have a co-test on a specimen from the vaginal vault at 12 months and annually thereafter, indefinitely.

† Until sufficient data become available to support cessation of testing

Other existing potentially relevant consensus-based guidelines

Guideline	Organisation	Recommendation
2016 Genital Tract Cancers in Females: Human Papillomavirus Related Cancers (Cervical, Vaginal & Vulvar)	British Columbia Medical Association	Hysterectomy with the cervix removed and a history of pre-cancerous lesions or cervical cancer: History of invasive cervical cancer Histologically proven CIN2+, screening recommendation vaginal vault smear annually – for 25 years after the most recent histological evidence of CIN2+ or vaginal intraepithelial neoplasia (VAIN) 2+. History of HSIL: CIN 1 or negative at colposcopy, screening recommendation vaginal vault smear annually – for 25 years after the most recent HSIL. *Age to Stop Screening for Higher Risk* History of pre-cancerous lesions or cervical cancer OR a hysterectomy with the cervix removed and a history of pre-cancerous lesions or cervical cancer. Cessation of screening recommendation age 69 or 25 years since diagnosis with at least 5 negative Pap test with no significantly abnormality in the last 10 years whichever occurs later.
2016 Cervical cancer screening: Clinical Practice Guideline	Towards Optimized Practice (TOP Alberta doctors)	*After Hysterectomy* Women with a history of proven biopsy-confirmed high-grade squamous intraepithelial lesion (HSIL), adenocarcinoma in situ (AIS), or invasive cervical cancer should have vault smears annually thereafter as they are at higher risk for vaginal neoplasia.
2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors (Perkins 2020)	American Society of Colposcopy and Cervical Pathology	*1.6 Management of AIS: Adoption of Society of Gynecologic Oncology Recommendations*. After hysterectomy, surveillance per the ASCCP surveillance guidelines for treated CIN 2+ is recommended (Section J3) *J3 Guidance for Long-Term Follow-up After Treatment for High-Grade Histology or Cytology* In patients treated for histologic or cytologic HSIL, after the initial HPV-based test at 6 months, annual HPV or co-testing is preferred until 3 consecutive negative tests have been obtained. After the initial intensive surveillance period, continued surveillance at 3-year intervals is recommended for at least 25 years after treatment of high-grade histology (histologic HSIL, CIN 2, CIN 3, or AIS) or high-grade cytology (HSIL or persistent ASC-H) even if this is beyond the age of 65 years. When patients with a history of treated high-grade histology or cytology reach the age of 65 years, if they have completed the initial 25-year surveillance period, continued surveillance at 3-year intervals is acceptable and may continue as long as the patient is in reasonably good health. Discontinuation of screening is recommended if a patient has a limited life expectancy. Management according to the highest-grade abnormality found on histology or cytology is recommended. *K.4 Managing Patients After Hysterectomy* Guideline: After a diagnosis of high-grade histology or cytology, patients may undergo hysterectomy for reasons related or unrelated to their cervical abnormalities. If hysterectomy is performed for treatment, patients should have 3 consecutive annual HPV-based tests before entering long-term surveillance. Long-term surveillance after treatment for histologic HSIL (CIN2 and CIN3) or AIS involves HPV-based testing at 3-year intervals for 25 years, regardless of whether the patient has had a hysterectomy either for treatment or at any point during the surveillance period. Among patients who have undergone hysterectomy but either have no previous diagnosis of CIN2+ within the previous 25 years or have completed the 25 year surveillance period, screening is generally not recommended. However, if performed, abnormal vaginal screening test results should be managed according to published recommendations.

Guideline	Organisation	Recommendation
Diagnosis and Management of adenocarcinoma in situ (Teoh 2020)	Society of Gynecologic Oncology	*Recommendation 5.1* For patients who undergo definitive management with hysterectomy, surveillance per the ASCCP Risk-Based Management Consensus guidelines (http://www.asccp. org/consensus-guidelines) is recommended for at least 25 years after diagnosis, even if that extends the testing period beyond the age of 65 years .
2019 Adenocarcinoma in situ of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV) (Ciavattini 2019)	Italian society of colposcopy and cervical pathology	Post-hysterectomy follow-up for AIS is not standardized. It is reasonable to recommend colposcopy, cervical cytology and high-risk human HPV testing every 6 for the first 2 years, and then every 12 months for the following 3 years. Colposcopy can effectively identify possible residual disease or early disease progression (such as high-grade vaginal intraepithelial neoplasia or invasive carcinoma in HPV related cases)
Prevention of cervical carcinoma Part 2 (Hillemanns 2019)	The Oncology Guidelines Program of the Association of Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG) and German Cancer Aid (DKH).	*Follow-up with HPV testing and cytology after treatment for CIN* Follow-up after treatment for CIN/ACIS must consist of examinations combining HPV testing and cytology. Differential colposcopy should be performed if the findings at follow-up are abnormal (at least 1 of the test results is positive). Follow-up examinations combining HPV testing and cytology should be performed at 6, 12 and 24 months after completing treatment. The patient must continue to participate in regular screening, even if the findings at follow-up are unremarkable.

References

British Columbia Medical Association. Genital Tract Cancers in Females: Human Papillomavirus Related Cancers (Cervical, Vaginal & Vulvar) https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/hpv-cancers Accessed March 2023

Ciavattini A, Giannella L, Delli Carpini G, Tsiroglou D, Sopracordevole F, Chiossi G et al. Adenocarcinoma in situ of the uterine cervix: Clinical practice guidelines from the Italian society of colposcopy and cervical pathology (SICPCV). Eur J Obstet Gynecol Reprod Biol 2019; 240:273-277.

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Teoh D, Musa F, Salani R, Huh W, Jimenez E. Diagnosis and Management of Adenocarcinoma in situ. Obstet Gynecol 2020; 135:869-878.

Towards Optimized Practice (TOP Alberta doctors). Cervical cancer screening 2016 https://actt.albertadoctors.org/media/w3vpspf2/cervical-cancer-screening-cpg.pdf accessed March 2023.

APPENDICES

Appendix A: Medline and Embase database (via Ovid platform) search strategy

#	Searches
1	AIS.tw.
2	adenocarcinoma in situ.tw.
3	(adenocarcinoma adj3 situ).tw.
4	Adenocarcinoma in Situ/
5	(adenocarcinoma* adj3 (cervi* or endocervix*)).tw.
6	glandular.tw.
7	1 or 2 or 3 or 4 or 5 or 6
8	hysterectomy.tw.
9	(post hysterectomy or post-hysterectomy).tw.
10	8 or 9
11	7 and 10
12	limit 11 to conference abstract status [Limit not valid in Ovid MEDLINE(R); records were retained]
13	11 not 12
14	limit 13 to human
15	limit 14 to english language
16	limit 15 to yr="2015 -Current"
17	remove duplicates from 16