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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Anal Cancer Screening in High Risk Populations: Clinical Effectiveness, Diagnostic Accuracy, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	September 20, 2019
Report Length:	9 Pages

CADTH

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Cite As: *Anal Cancer Screening in High Risk Populations: Clinical Effectiveness, Diagnostic Accuracy, Cost-Effectiveness, and Guidelines*. (CADTH rapid response report: summary of abstracts). Ottawa: CADTH; 2019 September.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Research Questions

1. What is the clinical utility of anal cancer screening in high risk populations?
2. What is the diagnostic accuracy of Pap testing for anal cancer in high risk populations?
3. What is the cost-effectiveness of anal cancer screening in high risk populations?
4. What are the evidence-based guidelines for anal cancer screening in high risk populations?

Key Findings

Four systematic reviews (all with meta-analyses) were identified regarding the diagnostic accuracy of Pap testing for anal cancer in high risk populations. One economic evaluation was identified regarding the cost-effectiveness of anal cancer screening in high risk populations. Three evidence-based guidelines were identified regarding the use of anal cancer screening in high risk populations. No relevant health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials were identified regarding the clinical utility of anal cancer screening in high risk populations.

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were anal cancer screening and high-risk populations. Search filters were applied to limit retrieval health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials or controlled clinical trials, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2014 and Sept 11, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-4: Individuals at high risk of developing anal cancer or patients with anal intraepithelial neoplasia (AIN)
Intervention	Q1,3-4: Anal cancer screening (refers to anal pap test, anal cytology, visualization) Q2: Anal Pap Test
Comparator	Q1-3: Digital rectal exam Anal scope No screening Q4: Not applicable
Outcomes	Q1: Clinical utility Q2: Diagnostic accuracy Q3: Cost-effectiveness Q4: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, and evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, economic evaluations, and evidence-based guidelines.

Four systematic reviews (all with meta-analyses) were identified regarding the diagnostic accuracy of Pap testing for anal cancer in high risk populations.[1-4] One economic evaluation was identified regarding the cost-effectiveness of anal cancer screening in high risk populations.[5] Three evidence-based guidelines were identified regarding the use of anal cancer screening in high risk populations.[6-8] No relevant health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials were identified regarding the clinical utility of anal cancer screening in high risk populations.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Four systematic reviews (all with meta-analyses) were identified regarding the diagnostic accuracy of Pap testing for anal cancer in high risk populations.[1-4] Three systematic reviews with meta-analyses[1-3] suggested that anal cytology (i.e., Pap testing) could be effective in screening for anal precancers (i.e., high grade anal intraepithelial neoplasia) and cancers in high risk populations. Another systematic review with meta-analyses[4] concluded that anal cytology for anal cancer screening differs in sensitivity and specificity when compared to cervical cytology for cervical cancer screening. The investigators suggested that this due to an increased incidence of human papillomavirus infection and higher severity of disease in anal cancer, particularly for HIV-positive men who have sex with men.[4] Detailed study findings are included in Table 2.

One economic evaluation was identified regarding the cost-effectiveness of anal cancer screening in high risk populations.[5] The identified study modeled the cost-effectiveness of anal cytology screening in a population of women with a previous history of cervical

neoplasia versus a population that did not receive screening in Canada. Using Canadian cost estimates, the study concluded anal cytology screening to be cost-effective with respects to overall survival in women with a previous diagnosis of high-grade cervical neoplasia.

Three evidence-based guidelines were identified regarding the use of anal cancer screening in high risk populations.[6-8] The National Comprehensive Cancer Network (NCCN) Anal Carcinoma Guideline suggests that evidence is lacking for regular anal cytology screening in high risk populations (e.g., men who have sex with men, people living with HIV).[6] Despite limited evidence, the NCCN Guideline on Cancer in People Living With HIV suggests that routine anal cytology can be used to detect recurrence in anal cancer survivors living with HIV.[7] The British HIV Association Guideline for HIV-Associated Malignancies suggests that since evidence is lacking for routine anal cytology, people living with HIV should regularly check for lumps in the anal canal.[8]

Table 2: Summary of Findings of the Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Chen, 2019[1]	
Anal cytology for detecting AIN+ • Pooled sensitivity = 0.79 • Pooled specificity = 0.66 • Pooled diagnostic odds ratio = 5.31	*"Our results revealed that the anal cytology might be effective in diagnosing AIN+."*
Dias, 2019[2]	
Anal cytology with the cutoff of any SIL to detect HGAIN • Sensitivity = 82% • Specificity = 45% Anal cytology with the cutoff of HSIL • Sensitivity = 44% • Specificity = 79%	*"Given its sensitivity, cytology with a cutoff of any SIL could be considered as a triaging method, whereas cytology with a cutoff of HSIL had better specificity and could be used for quality assurance."*
Goncalves, 2019[3]	
Anal cytology for detecting AIN2+ versus AIN grade 1 and normal • Pooled sensitivity = 85.0% • Pooled specificity = 43.2% • The accuracy was higher in MSM, and HIV-positive MSM subgroups	*"The study results support the hypothesis that cytology is a good test for the screening of anal cancer."*
Clarke, 2018[4]	
All Studies: Anal cytology for detecting AIN2+ (cutoff of atypical squamous cells of undetermined significance) • Pooled sensitivity = 77.3% • Pooled specificity = 55.5% Subgroup of HIV-positive MSM • Pooled sensitivity = 80.8% • Pooled specificity = 54.0%	*"Our systematic review and meta-analysis demonstrates that the performance of anal cytology differs from cervical cytology in a screening population, both with regard to sensitivity and specificity. This is due to the higher burden of HPV infection and higher degree of disease severity, particularly in HIV-positive MSM. For a population at high-risk for anal cancer, such as HIV-positive MSM, a screening test should have high sensitivity in order to provide adequate reassurance that those testing negative will not develop anal precancer or cancer."*

AIN = anal intraepithelial neoplasia; AIN+ = anal intraepithelial neoplasia or worse; AIN2+ = anal intraepithelial neoplasia grade 2 or worse; HGAIN = high-grade anal intraepithelial neoplasia; HIV = human immunodeficiency virus; HSIL = high-grade squamous intra-epithelial lesion; MSM = men who have sex with men; SIL = squamous intra-epithelial lesion

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Chen CC, Chou YY. Predictive value of the anal cytology for detecting anal intraepithelial neoplasia or worse: A systematic review and meta-analysis. *Diagn Cytopathol*. 2019 Apr;47(4):307-314.
PubMed: PM30605263

2. Dias Goncalves Lima F, Viset JD, Leeflang MMG, Limpens J, Prins JM, de Vries HJC. The Accuracy of Anal Swab-Based Tests to Detect High-Grade Anal Intraepithelial Neoplasia in HIV-Infected Patients: A Systematic Review and Meta-analysis. *Open Forum Infect Dis*. 2019 May;6(5):ofz191.
PubMed: PM31123696

3. Goncalves JCN, Macedo ACL, Madeira K, et al. Accuracy of Anal Cytology for Diagnostic of Precursor Lesions of Anal Cancer: Systematic Review and Meta-analysis. *Dis Colon Rectum*. 2019 Jan;62(1):112-120.
PubMed: PM30451747

4. Clarke MA, Wentzensen N. Strategies for screening and early detection of anal cancers: A narrative and systematic review and meta-analysis of cytology, HPV testing, and other biomarkers. *Cancer Cytopathol*. 2018 Jul;126(7):447-460. PubMed: PM29797691

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

No literature identified.

Economic Evaluations

5. Cromwell I, Gaudet M, Peacock SJ, Aquino-Parsons C. Cost-effectiveness analysis of anal cancer screening in women with cervical neoplasia in British Columbia, Canada. *BMC Health Serv Res*. 2016 Jun 27;16:206. PubMed: PM27349646

Guidelines and Recommendations

6. National Comprehensive Cancer Network. Anal Carcinoma. (NCCN Guidelines v.2.2019) 2019; https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
See: Risk Reduction, p.3

7. Reid E, Suneja G, Ambinder RF, et al. Cancer in People Living With HIV, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018 Aug;16(8):986-1017. PubMed: PM30099375

8. BHIVA Writing Group. British HIV Association guidelines for HIV-associated malignancies 2014. *HIV Medicine* (2014), 15 (Suppl. 2), 1–92: https://www.bhiva.org/file/qUSRLDwncBEYp/MalignancyGuidelines2014.pdf
See: Section 9 Anal cancer

Appendix — Further Information

Randomized Controlled Trials – Alternative Comparator

9. Wiley DJ, Hsu HK, Ganser MA, et al. Comparison of nylon-flocked swab and Dacron swab cytology for anal HSIL detection in transgender women and gay, bisexual, and other men who have sex with men. *Cancer Cytopathol*. 2019 Apr;127(4):247-257. PubMed: PM30913381

Non-Randomized Studies

No Comparator

10. Morency EG, Harbert T, Fatima N, Samolcyzk J, Maniar KP, Nayar R. Anal Cytology: Institutional Statistics, Correlation With Histology, and Development of Multidisciplinary Screening Program With Review of the Current Literature. *Arch Pathol Lab Med*. 2019 Jan;143(1):23-29. PubMed: PM29652190

11. Santorelli C, Leo CA, Hodgkinson JD, Baldelli F, Cantarella F, Cavazzoni E. Screening for Squamous Cell Anal Cancer in HIV Positive Patients: A Five-Year Experience. *J Invest Surg*. 2018 Oct;31(5):378-384. PubMed: PM28644711

12. Pisano L, Tiradritti L, Lorenzoni E, et al. Pap smear in the prevention of HPV-related anal cancer: preliminary results of the study in a male population at risk. *G Ital Dermatol Venereol*. 2016 Dec;151(6):619-627. PubMed: PM26199089

13. Cheng SH, Wang CC, Chang SL, Chu FY, Hsueh YM. Oncogenic human papillomavirus is not helpful for cytology screening of the precursor lesions of anal cancers in Taiwanese men who are infected with human immunodeficiency virus. *Int J Clin Oncol*. 2015 Oct;20(5):943-951. PubMed: PM25712159

14. Sananpanichkul P, Pittyanont S, Yuthavisuthi P, et al. Anal papanicolaou smear in women with abnormal cytology: a thai hospital experience. *Asian Pac J Cancer Prev*. 2015;16(3):1289-1293.
PubMed: PM25735369

Alternative Comparator

15. Pernot S, Boucheron P, Pere H, et al. Comparison of anal cancer screening strategies including standard anoscopy, anal cytology, and HPV genotyping in HIV-positive men who have sex with men. *Br J Cancer*. 2018 Aug;119(3):381-386.
PubMed: PM30026613

16. Maia LB, Marinho LC, Wanderley Paes Barbosa T, et al. A comparative study between conventional and liquid-based cytology in screening for anal intraepithelial lesions in HIV-positive patients. *Diagn Cytopathol*. 2014 Oct;42(10):840-845.
PubMed: PM24591207

Review Articles

17. Diefenthaler VL, de Fatima Pavan Zanella J, Coser J. Screening anal cancer in women living with HIV/AIDS. J Coloproctol (Rio J).2018;38(3):233-239:
http://www.scielo.br/pdf/jcol/v38n3/2237-9363-jcol-38-03-0233.pdf

18. Roberts JR, Siekas LL, Kaz AM. Anal intraepithelial neoplasia: A review of diagnosis and management. *World J Gastrointest Oncol*. 2017 Feb 15;9(2):50-61.
PubMed: PM28255426

19. Wasserman P, Rubin DS, Turett G. Review: Anal Intraepithelial Neoplasia in HIV-Infected Men Who Have Sex with Men: Is Screening and Treatment Justified? *AIDS Patient Care STDS*. 2017 Jun;31(6):245-253.
PubMed: PM28530494

20. Park IU, Introcaso C, Dunne EF. Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. *Clin Infect Dis*. 2015 Dec 15;61 Suppl 8:S849-855.
PubMed: PM26602622

21. Shridhar R, Shibata D, Chan E, Thomas CR. Anal cancer: current standards in care and recent changes in practice. *CA Cancer J Clin*. 2015 Mar;65(2):139-162.
PubMed: PM25582527

Clinical Practice Guidelines – Non-Systematic Methodology

22. Primary Care Guidelines for the Management of HIV/AIDS in British Columbia. Vancouver (BC): British Columbia Centre for Excellence in HIV/AIDS. 2011, revised 2015: http://www.cfenet.ubc.ca/sites/default/files/uploads/primary-care-guidelines/primary-care-guidelines_015-09-15.pdf
See: Section IV, Part 1F (p. 38)