HHS Public Access

Author manuscript

J Low Genit Tract Dis. Author manuscript; available in PMC 2021 April 01.

Published in final edited form as:

J Low Genit Tract Dis. 2020 April ; 24(2): 192–196. doi:10.1097/LGT.0000000000000508.

The utility of Digital Anal Rectal Examinations (DARE) in a public health screening program for anal cancer

Alan G. Nyitray, PhD[1], **Gypsyamber D'Souza, PhD**[2], **Elizabeth A. Stier, MD**[3], **Gary Clifford, PhD**[4], **Elizabeth Y. Chiao, MD MPH**[5,6]

[1]Clinical Cancer Center and Center for AIDS Intervention Research, Medical College of Wisconsin, Milwaukee, WI, USA

[2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA

[3]Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston MA, USA

[4]International Agency for Research on Cancer, Lyon, France

[5]Section Infectious Diseases, Department of Medicine, Baylor College of Medicine

[6]Center for Innovations in Quality, Effectiveness, and Safety, Michael E. DeBakey VA Medical Center, Houston, TX, USA

Abstract

Objectives: There are no uniform screening recommendations for anal cancer. Medical practice guidelines are now available on the use of Digital Anal Rectal Examinations (DARE) for the detection of anal cancer; however, since screening can result in more harm than benefit, our objective was to assess the evidence for use of DARE as a public health screening tool.

Methods: We conducted a current critical appraisal of anal cancer literature using World Health Organization (WHO) criteria for assessing the potential utility of a public health screening program.

Results: DARE satisfies most, but not all, WHO criteria for a public health program that seeks to detect early invasive anal cancer in populations at high risk for anal cancer, most notably HIV-positive men who have sex with men; however, DARE is not appropriate when facilities for treatment are nonexistent. In addition, there are insufficient data on DARE sensitivity and specificity.

Conclusions: The mildly-invasive nature of DARE, limited likelihood of adverse procedure-related events, cost-effectiveness and patient acceptability, as well as, wide availability of DARE

Corresponding author: Dr. Alan G. Nyitray, Clinical Cancer Center and Center for AIDS Intervention Research, Medical College of Wisconsin, 8701 Watertown Plank Road, Suite C5400, Milwaukee, WI 53226, Ph: 414-805-3312, Fax: 414-287-4209, anyitray@mcw.edu.

Institutional Review Board permission was not sought as the article does not present original research on humans.

Potential conflicts of interest: AGN-no conflicts; GD-no conflicts; EAS-no conflicts; GC-no conflicts; EYC-no conflicts.

support consideration of its integration into screening for populations at high risk of anal cancer, especially HIV-positive men who have sex with men.

Précis:

DARE satisfies most public health screening criteria for detecting early invasive anal cancer among HIV-positive men who have sex with men.

Keywords

Digital Anal Rectal Exam; DARE; anal cancer; anal neoplasms; mass screening; HIV; men who have sex with men

INTRODUCTION

Anal cancer incidence is stable or increasing in the general population[1,2] and highest in men who have sex with men (MSM) with HIV;[2,3] however, no uniform screening recommendations for anal cancer exist for this population or others with increased anal cancer incidence[4] including other persons with HIV, other immunosuppressed persons,[5] HIV-negative MSM,[6] and women with a history of human papillomavirus (HPV)-associated ano-genital dysplasia.[7]

While HPV vaccines are highly efficacious, their full impact on anal cancer incidence will take decades to be realized;[8,9] thus, secondary prevention utilizing screening methods have been suggested in several regional and national guidelines for persons living with HIV (PHIV).[4]

One method cited by these recommendations for PHIV is the Digital Anal Rectal Examination (DARE)[10] whose goal is to detect early stage (preferably Stage 1) anal cancer. Currently, anal canal tumors average >3.0 cm in diameter at first presentation. These larger tumors result in poorer 5-year survival, and higher morbidity.[11] Given that DARE can detect abnormalities smaller than 1.0 cm,[12] and new medical practice guidelines are now available for DARE,[13] it may be helpful to evaluate DARE as a public health screening tool for anal cancer.

The current article assesses the evidence for use of DARE according to the application of established World Health Organization criteria for public health screening.[14] Much of this evidence focuses on HIV-positive MSM; however, we will also address data from other populations with elevated risk, when available.

Of note, other proposed screening algorithms target putative precancerous lesions, rather than invasive cancer, and rely upon high-resolution anoscopy (HRA)-directed biopsy to detect anal high-grade squamous intraepithelial lesions (HSIL).[15] While utility of HRA has been suggested,[16] and is being used to assess anal precancer therapeutics in a current trial (NCT02135419), currently there is limited capacity for HRA even in high-resource settings and several challenges in scaling up HRA, including cost, specialized technical training required, and participant discomfort.[15,17] DARE may be an option for health programs in areas without access to HRA if the benefits of screening with DARE outweigh the harms.

DIGITAL *ANAL* RECTAL EXAMINATION - DARE

The purpose of DARE is to detect abnormalities of the perianus, anal canal, distal rectum and, in women, the rectovaginal septum. DARE is different than the Digital Rectal Exam (DRE) which has emphasized palpation of the posterior surface of the prostate gland.[18] A health care provider performs DARE by first inquiring about anal symptoms, e.g., anal bleeding, pain, and palpable masses, and then inspecting the perianus (a radius of 5 cm from the anal verge), followed by a 360-degree palpation of the anal canal and distal rectum. The procedure is short, usually taking no more than one minute to complete. Detailed instructions, standards, training, competencies and quality assurance metrics for DARE have been recently published.[13]

WORLD HEALTH ORGANIZATION CRITERIA

Screening is the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly.[14] Screening can result in more harm than benefit, for example, if there is no treatment to give screen-positive individuals, or if the number of false positives is high and results in substantial morbidity through unnecessary tests and examinations. The WHO publication "Principles and Practice of Screening for Disease" proposed a set of 10 criteria which can be a useful lens in which to consider potential harms and benefits of DARE for anal cancer screening.[14] Each criterion is considered in light of the evidence for cancer detection using DARE.

1. The condition should be an important health problem for the individual or community.

Late detection of squamous cell carcinoma of the anus carries substantial morbidity and mortality including sphincter dysfunction, permanent colostomy, and low probability of age-standardized 5-year survival when diagnosed in regional or distant stages (58.5% and 31.7%, respectively).[19,20]

Population-based cancer registries identify anal cancer as a very rare cancer (annual age-adjusted incidence approximately 0.5–2/100,000) with incidence generally 1.5- to 2-fold higher in women than men.[1,2] Risk increases with age, reaching a maximum of 4–8 annual cases per 100,000 women and 3–5 cases per 100,000 men, aged ≥70 years.[21] However, some sub-populations are known to be at vastly higher risk, most notably persons living with HIV.[22,23]

Among MSM with HIV, anal cancer is a common cancer (table 1) with more than a 40-fold higher risk than the rest of the general population.[2,3,24,26] Annual incidence among MSM with HIV ranges from 88–131 cases per 100,000 in the antiretroviral therapy era in some high-income settings,[3,24] and is highest in HIV-positive MSM ≥ 60 years old.[24] Indeed, Colon-Lopez et al. observed that in the United States, the 5-year cumulative incidence of anal cancer among HIV-positive MSM ≥ 45 years is at least as high as that of colorectal cancer in persons aged ≥50 years, for which routine, population-based screening is standardized and recommended.[24]

While incidence is lower than in HIV-positive MSM, anal cancer incidence is also well established to be highly elevated among female PHIV whose annual incidence is 18–30 per 100,000 persons and non-MSM male PHIV whose annual incidence 32–46 per 100,000 persons.[24,25,28]

Cancer registry data and linkage studies identify other sub-populations with an excess incidence of anal cancer compared to the general population. They include HIV-negative MSM (17–19 annual cases per 100,000 persons, although anal cancer incidence data remain sparse).[3,6,30] Anal cancer incidence is also elevated among persons with iatrogenic immune suppression (12 cases per 100,000)[5] and among women with prior ano-genital HPV-associated neoplasia.[7,27] For example, incidence is (4–6/100,000) among women with cervical intraepithelial neoplasia III[27, 29–31] and 10/100,000 among those with cervical cancer.[31] These incidence data are lower than those seen for PHIV, and more similar to incidence seen among women aged ≥70 years in the general population.

Anal cancer incidence data outside of high-resource countries are sparse, although recent studies indicate that in some middle income countries anal cancer incidence is also increasing.[1] High-risk anal HPV infection and anal precancers have also been shown to be very common among PHIV and HIV-negative MSM in some middle and low-income countries;[32,33] thus, increased anal cancer incidence in these sub-populations may not be restricted to high-resource settings.

2. There should be an accepted treatment for persons with recognized disease.

Excisional biopsies with adequate margins is an appropriate treatment for perianal squamous cancers of less than 2 cm or anal canal cancers with less than 3 mm invasion and less than 7 mm horizontal spread. Treatment with chemoradiation for non-metastatic invasive anal canal tumors is non-controversial with treatment protocols established 45 years ago.[34,35] A majority of patients treated with chemoradiation experience low morbidity and mortality with better prognosis the earlier the cancer is detected.[19]

There are reports of high survival rates for small tumors. For example, one publication reported 100% disease-specific survival in 66 persons with tumors ≤1 cm at 5 years.[36] Another study used local excision only for squamous cell carcinomas below the dentate line. For 15 PHIV with tumors ≤2 cm, the publication reported 100% survival at 4 years.[37]

3. Facilities for diagnosis and treatment should be available.

While diagnostic and treatment resources for anal cancer are widely available in high-income countries, the extent of training needed to perform an accurate DARE is unknown, but may require some or all of the following: knowledge of anal anatomy and physiology, training on clinical features of anal disease, experience performing the procedure, and feedback from patients undergoing the exam.[13] The training could conceivably be accommodated in medical or nursing schools or specialized training courses using in-person or online formats.[38] Initial research suggests under-utilization of DARE by clinicians is associated with a lack of training and other factors.[39]

Access to surgery and radiotherapy resources may be very limited or absent in many low- and middle-income countries.[40,41] Use of DARE for anal cancer screening is *not* appropriate when diagnostic and treatment resources are not available.

4. There should be a recognizable latent or early symptomatic stage.

Most anal cancers are visible at the perianus and/or have palpable tumors in the anal canal.[42,43] In one study, palpable masses as small as 0.3 cm were recognized during DARE;[12] thus, a DARE public health screening program may detect invasive cancers in an early stage when the tumor may not be obvious to the patient. Provider questions about anal symptoms, e.g., anal bleeding and pain, may increase detection of anal cancer.[13]

5. There should be a suitable test or examination.

To be a suitable screening test, DARE should recognize very early invasive disease, for example, tumors ≤2 cm. While robust sensitivity and specificity data for DARE are lacking, some data shed light on DARE accuracy. In a prospective study of progression of HSIL to invasive anal cancer, a total of 23 of 27 anal cancers (85%) were detected by palpation.[43] In a retrospective chart review of 128 anal cancers in a single radiotherapy center in Australia, 52% were visible at the perianal region which may act as a lower bound for sensitivity.[42]

Other data imply there may be a low number of unnecessary referrals after a DARE. The Anal Cancer Examination Study included 327 MSM with HIV and resulted in referral of 30 persons to a colorectal surgeon after a total of 862 DARE exams over 2 years. Of 24 men who completed the referral, 5 had no lesion upon a colorectal surgeon's examination, 1 had anal cancer, 8 had incidental HSIL lesions after biopsy of an abnormality, and the remining 10 had benign warts, skin tags, polyps, or anal fissures. Adverse events after DARE were rare.[44] Thus, the potential for substantial morbidity among MSM with HIV from unnecessary DARE follow-up may be low.

6. The test should be acceptable to the population.

Multiple studies observe DARE to be well tolerated and acceptable among HIV-positive and HIV-negative MSM in western countries.[44,45] Nevertheless, some providers incorrectly believe the procedure is generally unacceptable among MSM and thus avoid using it.[46]

Studies of DARE acceptability among other populations are lacking.[45], It is worth noting that DRE, which is also a mildly invasive manual procedure involving the anal canal, may be somewhat less acceptable among the overall population of African American men.[47]

7. The natural history of the disease should be adequately understood.

Unlike the natural history of HPV infection, the natural history of anal cancer is well known in that smaller tumors usually become larger and the smaller tumors are more easily treated than larger tumors; thus, smaller tumors can be targeted for detection and yield a better prognosis.[11] While the median age at presentation is approximately 60 years in HIV-negative persons,[48] the median age at presentation for HIV-positive MSM is approximately 10 years younger.[49]

8. There should be agreement on whom to treat as patients.

There is agreement that suspicious masses detected on DARE, regardless of lesion location, size, or patient age, should be further evaluated.[13]

9. Cost-effectiveness should be established.

Using mathematical modeling, an Australian study determined that DARE is likely to be cost-effective when conducted on a regular basis among HIV-positive MSM ≥ 50 years of age. The investigators found that biennial screening resulted in incremental cost-effectiveness ratios of $45,484 per quality-adjusted life year gained.[50]

10. Screening should be a continuing process.

DARE's high acceptability among MSM likely facilitates repeated use of DARE. In one study that used screening reminders that mimicked standard clinical reminders, 71% of participants returned for 3 DAREs scheduled at 0, 12, and 24 months. Of the remainder, 22% of men returned for 2 DAREs, and 7% had one DARE.[44]

Repeat screening will be affected by recommended screening intervals and currently, only expert opinion guides the recommended intervals. For example, a minimum of an annual DARE among HIV-positive MSM ≥ 37 years has been suggested[13] while other intervals are recommended for other populations at increased risk for anal cancer.[13,51,52]

CONCLUSION

DARE satisfies most, but not all, WHO criteria for detecting an outcome of early invasive anal cancer in sub-populations at high risk for anal cancer, most notably HIV-positive MSM, followed by other persons with HIV. The mildly-invasive nature of DARE, limited likelihood of adverse procedure-related events, and wide availability of the test (compared to HRA) supports consideration of its integration into screening for these populations at high risk of anal cancer. However, lack of facilities for treatment in some low and middle-income regions, insufficient data on sensitivity and specificity of DARE, also caution that DARE may not be appropriate in all settings.

While DARE might also be considered for other groups with elevated anal cancer risk in comparison to the general population, such as recipients of solid organ transplants, HIV-negative MSM, and women with prior HPV-associated ano-genital disease, their absolute anal cancer incidence rates are lower. In addition, fewer published data regarding some WHO screening criteria among these populations provides less support for their inclusion in DARE public health screening programs at this time.

Nevertheless, there is evidence that the following WHO criteria are supported for anal cancer screening among these high-risk populations:

- anal cancer is an important health problem;
- non-controversial treatment modalities exist for invasive anal cancer;

- resources for conducting DARE may be available in most places (but should only be used when there is access to diagnostic and treatment facilities);
- invasive anal cancer has a recognizable early symptomatic phase;
- DARE may recognize common anal cancer signs and symptoms including palpable anal canal tumors and visible perianal lesions;
- the natural history of invasive anal cancer is well understood, in comparison to HPV infection natural history;
- there is agreement on whom to treat;

Among MSM with HIV, the use of DARE is further supported by its acceptability, cost-effectiveness, and patient compliance with repeated screening.

To support implementation of DARE screening, further studies are needed, most importantly to better understand sensitivity and specificity of DARE for anal cancer. Cost-effectiveness data are needed in additional populations and more data are needed on barriers to physician use. In addition, better anal cancer incidence data are needed for HIV-negative MSM.[53] But given the potential for rapidly educating clinicians and the lack of need for technical and costly equipment, it may be possible to rapidly scale up the infrastructure for a DARE public health screening program for HIV-positive MSM.

There are few ongoing studies whose primary outcomes include the assessment of DARE to detect early invasive anal cancer. The Prevent Anal Cancer (PAC) Study will use modeling strategies to evaluate the cost-effectiveness of DARE among HIV-positive and HIV-negative MSM and the impact of DARE on survival and quality of life (1R01CA232892–01). This study will also assess compliance with anal cancer screening among MSM and provide additional data on the clinical utility of DARE (7R01CA215403–02). While not a screening study, the ANCHOR Study, designed to assess if treatment for anal HSIL prevents progression to anal cancer, may provide data that supports a better understanding of DARE's utility.

In summary, while these studies' forthcoming data may shed more light on public health screening strategies that incorporate DARE, we believe there is substantial evidence at hand that supports its use in high-risk populations now.

Acknowledgments

Financial support: National Cancer Institute, National Institutes of Health (USA), 1R01CA232892 [AGN]; U01-HL146193 [NIH, GD]. Publication and report contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCI, or of the International Agency for Research on Cancer/World Health Organization.

List of all Abbreviations and Acronyms

DARE	Digital Anal Rectal Exam
HIV	Human Immunodeficiency Virus

WHO	World Health Organization
MSM	Men who have sex with men
HPV	Human papillomavirus
PHIV	Persons living with HIV
HRA	High-resolution anoscopy
HSIL	High-grade squamous intraepithelial lesions
DRE	Digital Rectal Exam

References

1. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. Int J Epidemiol. 2017;46(3):924–938. [PubMed: 27789668]
2. van der Zee RP, Richel O, de Vries HJ, Prins JM. The increasing incidence of anal cancer: can it be explained by trends in risk groups? The Netherlands journal of medicine. 2013;71(8):401–411. [PubMed: 24127500]
3. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: A systematic review and meta-analysis. The Lancet Oncology. 2012;13(5):487–500. [PubMed: 22445259]
4. Ong JJ, Chen M, Grulich AE, Fairley CK. Regional and national guideline recommendations for digital ano-rectal examination as a means for anal cancer screening in HIV positive men who have sex with men: A systematic review. BMC Cancer. 2014;14(1):557. [PubMed: 25081485]
5. Madeleine MM, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-related cancers after solid organ transplantation in the United States. American Journal of Transplantation. 2013;13(12):3202–3209. [PubMed: 24119294]
6. Aldersley J, Lorenz DR, Misra V, Uno H, Gabuzda D. Increased risk of anal squamous cell carcinoma in HIV-positive men with prior hepatitis B virus infection. AIDS. 2019;33(1):145–152 (Dana Gabuzda personal communication). [PubMed: 30325778]
7. Gilbert DC, Wakeham K, Langley RE, Vale CL. Increased risk of second cancers at sites associated with HPV after a prior HPV-associated malignancy, a systematic review and meta-analysis. Br J Cancer. 2019;120(2):256–268. [PubMed: 30482913]
8. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. New England Journal of Medicine. 2011;365(17):1576–1585. [PubMed: 22029979]
9. Woestenberg PJ, King AJ, Van Benthem BHB, et al. Bivalent vaccine effectiveness against anal human papillomavirus positivity among female sexually transmitted infection clinic visitors in the Netherlands. J Infect Dis. 2019.
10. Steele SR, Varma MG, Melton GB, et al. Practice parameters for anal squamous neoplasms. Diseases of the colon and rectum. 2012;55(7):735–749. [PubMed: 22706125]
11. Madeleine MM, Newcomer LM. Cancer of the Anus In: Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, eds. SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988–2001, Patient and Tumor Characteristics, Pub. No. 07–6215 Bethesda, MD: National Cancer Institute, SEER Program; 2007.
12. Nyitray AG, Hicks JT, Hwang LY, et al. A phase II clinical study to assess the feasibility of self and partner anal examinations to detect anal canal abnormalities including anal cancer. Sex Transm Infect. 2018;94(2):124–130. [PubMed: 28835533]
13. Hillman RJ, Berry-Lawhorn JM, Ong JJ, et al. International Anal Neoplasia Society guidelines for the practice of digital anal rectal examination. J Low Genit Tract Dis. 2019.

14. Wilson JMG, Jungner G. Public Health Papers, #34: Principles and Practice of Screening for Disease. Geneva: World Health Organization;1968.
15. Hillman RJ, Cuming T, Darragh T, et al. 2016 IANS international guidelines for practice standards in the detection of anal cancer precursors. Journal of Lower Genital Tract Disease. 2016;20(4):283–291. [PubMed: 27561134]
16. Panther LA, Wagner K, Proper J, et al. High resolution anoscopy findings for men who have sex with men: Inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. Clinical Infectious Diseases. 2004;38(10):1490–1492. [PubMed: 15156490]
17. Neukam K, Milanes Guisado Y, Fontillon M, et al. High-resolution anoscopy in HIV-infected men: Assessment of the learning curve and factors that improve the performance. Papillomavirus research. 2019;7:62–66. [PubMed: 30716543]
18. Reis LO, Simao AF, Baracat J, Denardi F, Gugliotta A. Digital rectal examination standardization for inexperienced hands: teaching medical students. Adv Urol. 2013;2013:797096.
19. Shridhar R, Shibata D, Chan E, Thomas CR. Anal cancer: Current standards in care and recent changes in practice. CA Cancer J Clin. 2015;65(2):139–162. [PubMed: 25582527]
20. Razzaghi H, Saraiya M, Thompson TD, Henley SJ, Viens L, Wilson R. Five-year relative survival for human papillomavirus-associated cancer sites. Cancer. 2018;124(1):203–211. [PubMed: 29105738]
21. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer Published 2018. Accessed July 6, 2019.
22. Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative incidence of cancer among persons with HIV in North America: A cohort study. Ann Intern Med. 2015;163(7):507–518. [PubMed: 26436616]
23. Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: The Swiss HIV Cohort Study. Br J Cancer. 2010;103(3):416–422. [PubMed: 20588274]
24. Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis 2012;54:1026–34. [PubMed: 22291097]
25. Piketty C, Selinger-Leneman H, Bouvier AM, et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the French Hospital Database on HIV. J ClinOncol 2012;30:4360–6.
26. Colon-Lopez V, Shiels MS, Machin M, et al. Anal cancer risk among people with HIV infection in the United States. J Clin Oncol 2018;36:68–75. [PubMed: 29140774]
27. Ebisch RMF, Rutten DWE, IntHout J, et al. Long-lasting increased risk of human papillomavirus-related carcinomas and premalignancies after cervical intraepithelial neoplasia grade 3: a population-based cohort study. J ClinOncol 2017;35:2542–50.
28. Evans HS, Newnham A, Hodgson SV, et al. Second primary cancers after cervical intraepithelial neoplasia III and invasive cervical cancer in Southeast England. Gynecol Oncol 2003;90:131–6. [PubMed: 12821353]
29. Tomassi MJ, Abbas MA, Klaristenfeld DD. Expectant management surveillance for patients at risk for invasive squamous cell carcinoma of the anus: a large US healthcare system experience. Int J Colorectal Dis 2019;34:47–54. [PubMed: 30244347]
30. D'Souza G, Wiley DJ, Li X, et al. Incidence and epidemiology of anal cancer in the Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr 2008;48:491–9. [PubMed: 18614927]
31. Pan J, Kavanagh K, Cuschieri K, et al. Increased risk of HPV-associated genital cancers in men and women as a consequence of pre-invasive disease. Int J Cancer 2019;145:427–34. [PubMed: 30650180]
32. Nowak RG, Gravitt PE, He X, et al. Prevalence of anal high-risk human papillomavirus infections among HIV-positive and HIV-negative men who have sex with men in Nigeria. Sex Transm Dis. 2016;43(4):243–248. [PubMed: 26967301]
33. Cranston RD, Carballo-Dieguez A, Gundacker H, et al. Prevalence and determinants of anal human papillomavirus infection in men who have sex with men and transgender women. Int J STD AIDS. 2019;30(2):154–162. [PubMed: 30336747]

34. Nigro ND, Vaitkevicius VK, Considine B Jr., Combined therapy for cancer of the anal canal: A preliminary report. Diseases of the colon and rectum. 1974;17(3):354–356. [PubMed: 4830803]
35. Benson AB, Venook AP, Al-Hawary MM, et al. Anal Carcinoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(7):852–871. [PubMed: 30006428]
36. Ortholan C, Ramaioli A, Peiffert D, et al. Anal canal carcinoma: Early-stage tumors ≤10 mm (T1 or Tis): Therapeutic options and original pattern of local failure after radiotherapy. International Journal of Radiation Oncology Biology Physics. 2005;62(2):479–485.
37. Alfa-Wali M, Dalla Pria A, Nelson M, Tekkis P, Bower M. Surgical excision alone for stage T1 anal verge cancers in people living with HIV. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2016;42(6):813–816.
38. Nensi A, Chande N. A survey of digital rectal examination training in Canadian medical schools. Canadian Journal of Gastroenterology. 2012;26(7):441–444. [PubMed: 22803019]
39. Ong J, Chen M, Temple-Smith M, et al. The inside story. Physicians' views on digital ano-rectal examination for anal cancer screening of HIV positive men who have sex with men. J Med Screen. 2013;20(4):188–191. [PubMed: 24307004]
40. Alkire BC, Raykar NP, Shrime MG, et al. Global access to surgical care: A modelling study. The Lancet Global health. 2015;3(6):e316–323. [PubMed: 25926087]
41. Zubizarreta EH, Fidarova E, Healy B, Rosenblatt E. Need for radiotherapy in low and middle income countries - the silent crisis continues. Clinical oncology (Royal College of Radiologists (Great Britain)). 2015;27(2):107–114. [PubMed: 25455407]
42. Read TR, Huson KL, Millar JL, et al. Size of anal squamous cell carcinomas at diagnosis: A retrospective case series. Int J STD AIDS. 2013;24(11):879–882. [PubMed: 23970608]
43. Berry JM, Jay N, Cranston RD, et al. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. Int J Cancer. 2014;134(5):1147–1155. [PubMed: 23934991]
44. Ong JJ, Walker S, Grulich A, et al. Incorporating digital anorectal examinations for anal cancer screening into routine HIV care for men who have sex with men living with HIV: A prospective cohort study. Journal of the International AIDS Society. 2018;21(12):e25192.
45. Davis TW, Goldstone SE, Chen G. Tolerability of anal dysplasia screening. J Low Genit Tract Dis. 2013;17(4):404–408. [PubMed: 23609591]
46. Ong JJ, Temple-Smith M, Chen M, et al. Why are we not screening for anal cancer routinely - HIV physicians' perspectives on anal cancer and its screening in HIV-positive men who have sex with men: a qualitative study. BMC Public Health. 2015;15(1):67. [PubMed: 25636181]
47. Lee DJ, Consedine NS, Spencer BA. Barriers and facilitators to digital rectal examination screening among African-American and African-Caribbean men. Urology. 2011;77(4):891–898. [PubMed: 21477716]
48. Ouhoummane N, Steben M, Coutlee F, et al. Squamous anal cancer: Patient characteristics and HPV type distribution. Cancer Epidemiol. 2013.
49. Jin F, Vajdic CM, Law M, et al. Incidence and time trends of anal cancer among people living with HIV in Australia. Aids. 2019.
50. Ong JJ, Fairley CK, Carroll S, et al. Cost-effectiveness of screening for anal cancer using regular digital ano-rectal examinations in men who have sex with men living with HIV. Journal of the International AIDS Society. 2016;19(1):20514.
51. Wright JL, Patil SM, Temple LK, Minsky BD, Saltz LB, Goodman KA. Squamous cell carcinoma of the anal canal: Patterns and predictors of failure and implications for intensity-modulated radiation treatment planning. Int J Radiat Oncol Biol Phys. 2010;78(4):1064–1072. [PubMed: 20350793]
52. Moscicki AB, Darragh TM, Berry-Lawhorn JM, et al. Screening for anal cancer in women. J Low Genit Tract Dis. 2015;19(3 Suppl 1):S27–42. [PubMed: 26103446]
53. Institute of Medicine. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Washington, DC: The National Acadamies Press; 2011.

Table 1.

Anal squamous cell carcinoma risk estimates in selected populations

	Incidence Rate*
HIV-positive persons	
Men who have sex with men	
Silverberg et al. (2012)[24]	131
Piketty et al. (2012)[25]	95
Colón-López et al. (2018)[26]	88
Women	
Silverberg et al. (2012)[24]	30
Colón-López et al. (2018)[26]	24
Piketty et al. (2012)[25]	18
Non-MSM males	
Silverberg et al. (2012)[24]	46
Piketty et al. (2012)[25]	45
Colón-López et al. (2018)[26]	32
HIV-negative persons	
U.S. General Population	
Women	
GLOBOCAN (2018)[21]	2
Men	
GLOBOCAN (2018)[21]	1
Men who have sex with men	
Aldersley et al. (2019)[6]	19
Women with prior CIN3	
Ebisch et al. (2017)[27]	6
Evans et al. (2003)[28]	5
Tomassi et al. (2019)[29]	4
Women with prior cervical cancer	
Evans et al. (2003)[28]	12
Tomassi et al. (2019)[29]	10
Immunosuppressed transplants	
Madeleine et al. (2013)[5]	12

CIN, Cervical intraepithelial neoplasia

*annual incidence per 100,000