INFECTIOUS DISEASE

Forging the framework for anal cancer detection among high-risk populations: The IANS consensus guidelines for anal cancer screening

Stier EA, Clarke MA, Deshmukh AA, Wentzensen N, Liu Y, Poynten IM, Cavallari EN, Fink V, Barroso LF, Clifford GM, Cuming T, Goldstone SE, Hillman RJ, Rosa-Cunha I, La Rosa L, Palefsky JM, Plotzker R, Roberts JM, Jay N. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Int J Cancer. 2024; 1-9.

Anal cancers are predominantly preceded by screening-detectable high-grade squamous intraepithelial lesions (HSILs).[1] Despite being relatively uncommon in the general population, possessing an incidence rate of 1.7 per 100,000 person-years, anal cancers disproportionately affects specific groups of individuals, particularly people with human immunodeficiency virus (HIV), solid organ transplant recipients and women with a history of vulvar cancer or precancer.[1]

Given the recent establishment that treating anal HSIL reduces the risk of anal cancer in people with HIV, and the emergence of data on the risk of anal cancer among other groups and the performance of anal cancer screening tests, pre-existing anal cancer screening guidelines would benefit from an update.[1-2] As such, the International Anal Neoplasia Society (IANS) developed consensus guidelines for anal cancer prevention and early detection to assess the needs, develop evidence-based guidance, and address knowledge gaps in anal cancer screening.[1]

The initial IANS task force comprised 17 international experts representing 6 countries with a wide range of professional expertise including epidemiology, decision science, pathology, public policy, infectious diseases, gynecology, colorectal surgery and high-resolution anoscopy (HRA) providers. To account for variability in discipline, geography, and under-represented populations, the IANS task force was expanded to a total of 60 experts, which represents 19 countries.[1] Priority areas for guideline improvement included establishing **(1)** the populations to screen based on the evaluation of anal cancer incidence in each group (table 1), **(2)** the screening tools to recommend (table 2), and **(3)** the management of results and threshold for HRA referral (table 3).[1] Recommendation strength (A-E) and quality of evidence (I-III) using the same grading system applied to the US multi-organizational cervical cancer screening and management guidelines were assigned where applicable.[1]

Risk category	Population	Recommended screening initiation	Anal cancer incidence per 100,000 person-years
A (incidence ≥10-fold compared to the general population)	MSM and TW with HIV	Age 35	>70 in age 30-44 >100 in age ≥45
	Women with HIV	Age 45	>25 in age ≥45
	MSW with HIV	Age 45	>40 in age ≥45
	MSM and TW not with HIV	Age 45	>18 in age 45-59 >34 in age ≥60
	History of vulvar HSIL or cancer	Within 1 year of diagnosis	>40
	Solid organ transplant recipient	10 years post-transplant	>25
B (incidence ≤10-fold compared to the general population)	Cervical/vaginal cancer	Shared decision age 45*	9
	Cervical/vaginal HSIL	Shared decision age 45*	8
	Perianal warts (male or female)	Shared decision age 45*	Unknown
	Persistent cervical HPV16 (>1 year)	Shared decision age 45*	Unknown
	Other immunosuppression (e.g., rheumatoid arthritis, lupus, Crohn's, ulcerative colitis, on systemic steroid therapy)	Shared decision age 45*	6

Table 1. Recommended anal screening initiation timing for each high-risk population

HPV16: Human papillomavirus 16; HSIL: High grade squamous intraepithelial lesion; MSM: Men who have sex with men; MSW: Men who have sex with women; TW: Transgender women

**Shared decision-making was defined as the process in which a health care provider and patient work together to make a health care decision. The optimal decision considers evidence-based information regarding available options, the provider's knowledge and experience, and the patient's values and preferences*

Primary screening test	Triage test	Level of evidence	Special considerations/rationale
Cytology	None	BII	• Anal cytology is the most widely used and evaluated test for anal cancer screening. Providers may consider using different thresholds for referral to HRA depending on capacity (see table 3)
	hrHPV testing*	CII	• hrHPV testing to triage ASC-US (or other results, see table 3) could be used to reduce HRA referral rates. This strategy has not been widely evaluated in the literature
hrHPV testing*	None	BII	• The efficiency of primary testing with a pooled hrHPV test is limited in populations with high HPV prevalence (e.g. MSM with HIV). This strategy could be considered in settings with no cytology infrastructure or to reduce HRA (for patients testing hrHPV-) in practices providing HRA on all patients. In most settings, additional triage will be needed for individuals who hrHPV+ • The use of hrHPV genotyping, specifically for HPV16, may help identify patients with a high risk of HSIL or cancer. Performance does not seem to improve with the addition of HPV18
	Cytology	CII	• Triage of hrHPV+ results with cytology (e.g., at an ASC-US or worse threshold) can improve the specificity of hrHPV-testing and reduce HRA referral. However, observational data on this approach are lacking in the literature
Cytology/ hrHPV* co-test	None	BII	• Currently, available data suggest that anal co-testing does not provide any benefit over primary hrHPV testing for anal HSIL. However, anal co-testing may be especially beneficial for its negative predictive value. Co-testing may be less efficient in populations with high hrHPV prevalence
DARE	None	BII	• All populations at-risk for anal cancer receive DARE at the time of screening tests (or in lieu of screening tests in the absence of HRA availability)

Table 2. Consensus review of currently used anal cancer screening strategies that show acceptable performance

+: Positive; -: Negative; ASC-US: Atypical squamous cells of undetermined significance; DARE: Digital anal rectal examination; HIV: Human immunodeficiency virus; HPV18: Human papillomavirus 18; HRA: High resolution anoscopy; hrHPV: High-risk human papillomavirus; HSIL: High grade squamous intraepithelial lesion; MSM: Men who have sex with men

**hrHPV testing (with or without genotyping)*

Primary screening test	Triage test	Test results/scenarios	Recommended actions	Modification for low HRA capacity*
Cytology	None	NILM	Repeat screening at 12 months	• Repeat screening at 12-24 months
		ASC-US or worse	HRA referral	• Repeat screening at 12 months for ASC-US/LSIL • HRA referral for HSIL and ASC-H
	hrHPV testing for ASC-US or worse	ASC-US/hrHPV-	Repeat screening at 12 months	• Repeat screening at 24 months
		LSIL/hrHPV-	Provider discretion – either HRA referral or repeat screening in 12 months	• Repeat screening at 12 months
		ASC-US or LSIL/hrHPV+	HRA referral	• Repeat screening at 12 months for ASC-US/LSIL/hrHPV+ (non-16) • HRA referral for hrHPV16+ (regardless of cytology)
		ASC-H/HSIL (regardless of HPV)	HRA referral	• HRA referral
hrHPV testing	None	hrHPV-	Repeat screening at 12-24 months	• Repeat screening at 24 months
		hrHPV+	HRA referral	• Repeat screening at 12 months for hrHPV+ (non-16) • HRA referral for hrHPV16+
	Cytology for hrHPV+	NILM/hrHPV+ [hrHPV+ (non-16)]	Provider discretion – either HRA referral or repeat screening in 12 months	• Repeat screening at 12 months
		ASC-US or worse/ hrHPV+ [HPV16+/ regardless of cytology]	HRA referral	• Repeat screening at 12 months for ASC-US/LSIL/hrHPV+ (non-16) • HRA referral for HSIL, ASC-H (regardless of hrHPV) or hrHPV16+ (regardless of cytology)
Cytology + hrHPV co-testing	None	NILM/hrHPV-	Repeat screening at 12-24 months	• Repeat screening at 24 months
		ASC-US/hrHPV-	Repeat screening at 12 months	• Repeat screening at 24 months
		NILM/hrHPV+ [NILM/hrHPV+ (non-16)]	Provider discretion – either HRA referral or repeat screening in 12 months	• Repeat screening at 12 months
		LSIL/hrHPV-	Provider discretion – either HRA referral or repeat screening in 12 months	• Repeat screening at 12-24 months
		ASC-US or LSIL/ hrHPV+ HSIL, ASC-H (regardless of HPV) [HPV16+, regardless of cytology]	HRA referral	• Repeat screening at 12 months for ASC-US/LSIL/hrHPV+ (non-16) • HRA referral for HSIL, ASC-H (regardless of hrHPV) or hrHPV16+ (regardless of cytology)

Table 3. Recommended management strategies and HRA referral thresholds

ASC-H: Atypical squamous cells cannot exclude high grade; ASC-US: Atypical squamous cells of undetermined significance; HRA: High-resolution anoscopy; hrHPV-: High-risk human papillomavirus negative; hrHPV+: High-risk human papillomavirus positive; HSIL: High grade squamous intraepithelial lesion; LSIL: Low grade squamous intraepithelial lesion; NILM: Negative for intraepithelial lesion or malignancy

**Low HRA capacity is defined as >6 months of waiting period for HRA referral in response to an abnormal screening test result*

Q&A

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In an interview with *Omnihealth Practice*, Dr. Wong, Tin-Yau Andrew, an infectious disease specialist, shared his insights on the current local practices in managing patients with anal high-grade squamous intraepithelial lesions (HSILs) or anal cancer, and potential challenges in anal cancer prevention.

01. Current anal cancer management strategies in Hong Kong

Anal cancer is relatively uncommon in the general population of Hong Kong. However, specific populations face a higher risk of developing anal cancer such as people living with human immunodeficiency virus HIV (PLHIV), men who have sex with men (MSM), transgender women, and individuals with a weakened immune system (e.g. solid organ transplant recipients and patients with autoimmune disorders who are treated with immunosuppressants). According to statistics from the Hong Kong Cancer Registry, the incidence rate of anal cancer has also been consistently higher in women compared to men (figure 1 and table 1), which may be attributed to cervical and vulvar cancer being closely associated with anal cancer.

Chemoradiation (CR) therapy and surgery are the cornerstones of treating anal cancer. In the case of anal HSILs, while topical treatment such as imiquimod cream may be used to enhance mucosal immunity against infections, additional methods such as electrocautery or laser therapy may be necessary for lesion removal. It is crucial to emphasize that the success of these treatment modalities greatly relies on prompt initiation, underscoring the significance of early detection and intervention in managing anal cancer effectively.

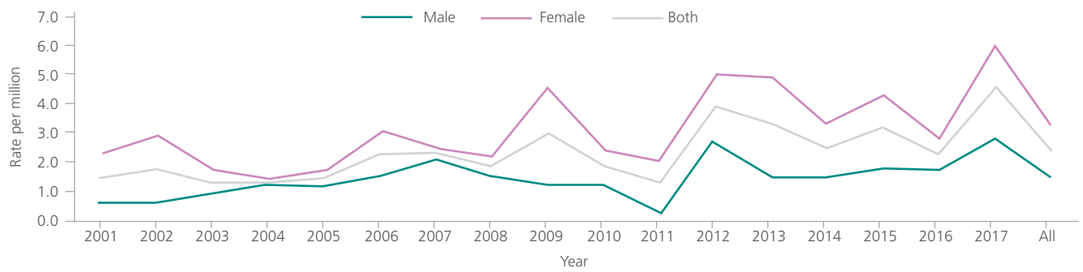


Figure 1. Crude rate of anorectal and perianal squamous cell carcinoma in Hong Kong

Gender	Cases	Median age
Male	82	66.5
Female	200	66

Table 1. Median age of anorectal and perianal squamous cell carcinoma cases in Hong Kong between 2001 and 2017

02. Potential hurdles in local anal cancer screening implementation

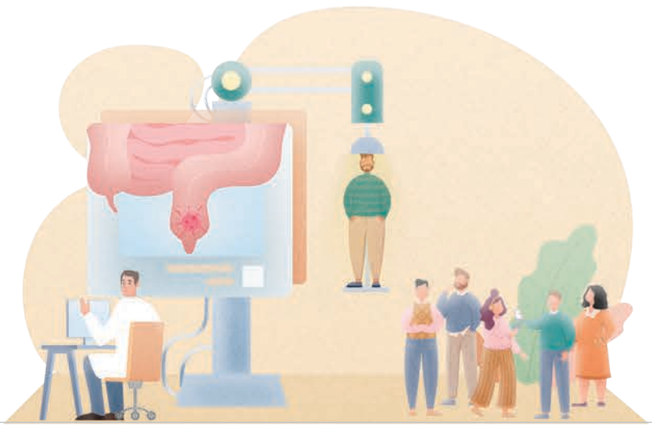
Regardless of the choice of screening modality (cytology, HPV-typing tests or cytology-HPV co-test), high-resolution anoscopy (HRA) should be performed in individuals with abnormal screening results to verify the diagnosis of anal HSILs and cancer. However, the accessibility of HRA has been a bottleneck in the screening and diagnosis of anal cancer. In Hong Kong, resources and expertise to perform HRA are limited, with HRA facilities only available in a few institutions, resulting in long HRA referral times.

Given the inadequate HRA resources and long HRA referral time in Hong Kong, digital anal rectal examination (DARE) should be performed, such as at regular check-ups and when symptoms appear in at-risk populations, to detect early anal lesions via palpation. Integrating anal cancer screening protocols as an extension to the cervical screening program in Hong Kong may also be feasible, given the close association between cervical and anal cancers, and the similarities in risk factors and screening algorithms.

03. The significance of physician training and patient education

In addition to technical limitations, the inadequate awareness among the local healthcare community also poses a significant challenge to the effectiveness of anal cancer screening which often leads to delayed diagnosis. For instance, some physicians may misinterpret the early signs of anal cancers, such as rectal bleeding, as hemorrhoids. Moreover, there are common misconceptions prevalent among the general public regarding anal cancer. These include the belief that anal cancer is primarily associated with anal sex, overlooking hygiene-related risk factors (such as post-toilet wiping behavior), and assuming that colorectal cancer screening results are sufficient for detecting anal cancer. Addressing these misconceptions and increasing awareness among the public is crucial for improving the detection of anal cancer.

To facilitate these improvements, it is essential to prioritize patient education and physician training. By providing accurate information and raising awareness about the symptoms, risk factors, and screening methods for anal cancer, individuals can be better equipped to seek timely medical attention. Additionally, fostering collaborations between infectious disease specialists, gynecologists, organ transplant physicians and colorectal surgeons can enhance their collective awareness and vigilance towards anal cancer, leading to more proactive and effective detection and management strategies.



References
1. Stier EA, et al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. *Int J Cancer.* 2024; 1-9 **2.** Palefsky JM, et al. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. *N Engl J Med* 2022;386:2273-2282.