ANAL CYTOLOGY AS A SCREENING TEST FOR ANAL CARCINOMA

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Introduction

Anal cytology was first included in the 2001 Bethesda System for Reporting Cervical Cytology. It has gained acceptance as a tool for anal cancer screening in conjunction with high-resolution anoscopy. The 2014 update incorporates epidemiology, the role of Human Papillomavirus (HPV) testing and biomarkers, and addresses clinical management in addition to original guidance on sampling, adequacy and use of terminology.

Anal squamous intraepithelial lesions, particularly anal high grade squamous intraepithelial lesions (HSIL), are considered anal squamous cell carcinoma (SCC) precancerous lesions. Anal SCC and cervical cancer share several similarities, including the HPV aetiological role. Several differences also exist, especially related to prevalence of disease.

Anal cytology is normally used as the first screening test and, in case of abnormalities, patients are then referred for high-resolution anoscopy (HRA).

Anal cancer

Anal cancer is uncommon in the general population. The vast majority of anal carcinomas are SCC and about 90% are attributed to HPV and in particular HPV-16. In America, there are more new cases per year in women than men.

Screening and anal cytology

Screening is defined as a medical test which serves as a medical consultation providing an interpretation that contributes to a diagnosis when integrated with patient history, clinical findings and the results of other laboratory tests such as biopsy. Anal cytology is used as a screening test for anal squamous intraepithelial lesion (ASIL), mirroring the use of the Pap test in cervical cytology. The digital rectal examination remains an essential component to anal screening, especially in symptomatic patients with painful, palpable lesions. When screening high risk populations, cytologic abnormalities are common. Sensitivity and specificity of a single anal cytologic specimen are comparable to that of a single cervical cytology test.

There is poor correlation between ASIL grading on cytology and histology. Cytology often underestimates the grade of SIL. A large proportion of patients with any level of abnormal cytology have histopathologically verifiable HSIL.

Glandular abnormalities are uncommon on anal cytology. HPV-associated glandular lesions of the anus have not been convincingly described. Glandular abnormalities due to colonic lesions (polyps, adenocarcinoma) are occasionally seen on anal cytology.

The role of Human Papillomavirus

It is currently recognised, that in addition to the major impact HPV infection has in females, HPV causes considerable disease in men, in the genitals, anal canal and oropharynx. High-risk (HR) HPV is aetiologically associated with 90% - 96% of all anal cancers.

HPV infects the stratified squamous epithelia, both mucosal and cutaneous, and preferentially target mitotically active cells of the basal layer. HPV is strongly linked to the development of tumours in the anal canal in both genders. HPV positivity in anal SCC seems to have a prognostic value, with better survival in those patients with HPV positive tumours. Testing for anal HPV is not routinely done in anal canal screening because of the very high prevalence of HPV in high-risk populations.

HPV infection in one site is often associated with other sites of infection. Anal SCC survivors have an increased risk of HPV-related second primary malignancies (anal, genital, oral), occurring in men and women across all HPV-related sites.

Who to screen?

High risk groups for anal squamous cell carcinoma and anal HPV infection include:

- HIV-positive patients
- Men who have sex with men
- Women with genital tract neoplasia
- Solid organ transplant recipients
- Patients with auto-immune disease who are immunosuppressed
- Patients with genital warts. Although caused by low-risk HPV, co-infection with HR HPV occurs in approximately one third of cases. There is evidence supporting that patients with warts belong to a high-risk group with regard to subsequent HPV-related cancer.

Sampling

At Lancet Laboratories we use the BD SurePath™ LBC system. The sample is collected with the Rovers® Anex® brush and placed in the BD CytoRich™ Clear collection vial.

BD CytoRich™ Clear

Anal Cytology with BD CytoRich Clear Collection Vial

The target of sampling includes the entire anal canal from the distal rectal vault to the anal verge, including the anal transformation zone and the non-keratinised and keratinised squamous epithelium of the anal canal. Samples are usually obtained without direct visualisation. Liquid-based preparations increase cell yield and reduce compromising factors such as obscuring faecal material, air-drying and mechanical artefacts.

Specimen Collection-Materials required

Sampling Device

Rovers® Anex® Brush with remover tube

Collection Vial

BD CytoRich Clear Collection Vial

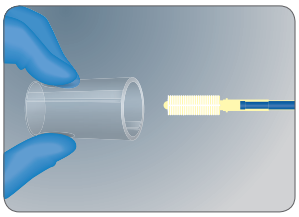
Specimen Collection – General instructions

The Rovers® Anex® Brush is for one use only and a fresh brush and vial must be used for each patient. Reuse causes contamination and misdiagnosis.

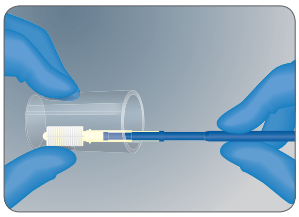
Place the patient in a dorsal lithotomy (feet above or at the same level as the hip) or lateral recumbent position (e.g. patient lying on the left side with the right thigh and knee drawn up).

BD

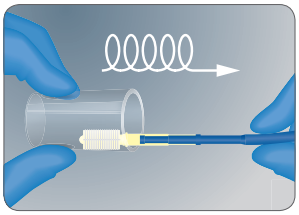
Specimen Collection-Step by step instructions



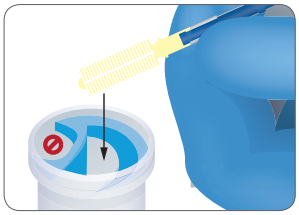
1. Insert the collection device 5-7 cm into the anal canal.



2. Maintain firm lateral pressure on the device.



3. Begin to rotate the entire device while slowly extracting it from the anal canal. The motion will generate a spiraling effect beginning at the anal-rectal transformation zone to the anal os.



4. Using the remover tube, push the device head **into the larger opening of the collection vial.**

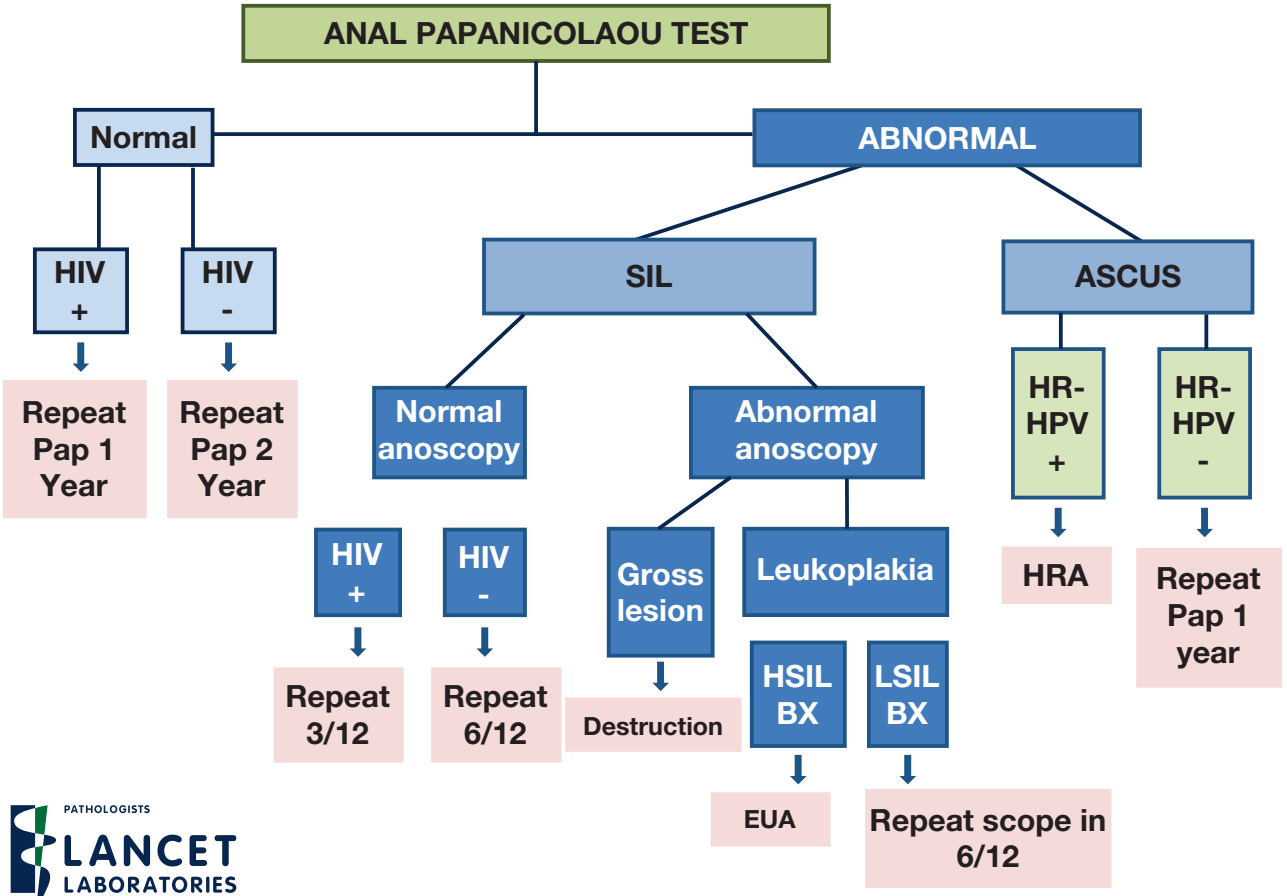
The cytology report

Anal Pap tests are reported in a similar fashion to cervical Pap tests.

- **Adequacy**
  - There is a paucity of reference material as to what constitutes an adequate anal cytology sample.
  - Generally the cellularity of adequate anal samples is similar to cervical samples.
  - Nucleated squamous cells are necessary for evaluation.
  - The presence or absence of anal transformation zone components (rectal columnar cells/squamous metaplastic cells) are reported as an indicator of sampling above the keratinised portion of the canal.
  - As with cervical cytology, the presence of transformation zone components is a quality indicator, not a measure of overall specimen adequacy.
  - Contamination with bacteria and faecal material may hamper interpretation.

- **Interpretation**
  - Bethesda terminology that parallels cervical cytology is used, i.e. NILM, ASC, LSIL, HSIL, Malignant.
  - The Bethesda system has been modified to reflect the anatomy, i.e. rectal columnar cells are substituted for endocervical cells as a measure of transformation zone sampling.
  - A variety of organisms can be seen on anal cytology including viruses, protozoa, fungi and helminths.
    - *Candida* and Herpes simplex virus are similar to the organisms seen on cervical tests.
    - A large number of amoebae can parasitise the human intestinal tract. All but *Entamoeba histolytica* are considered non-pathogenic commensals.
    - The range of pathogens are larger in the immunocompromised population.

- **Recommendation / Clinical management**
  - Because the role of cytology screening for anal cancer is still developing, there are neither standardised international nor national guidelines to screen for this disease. However, with the rising incidence of anal cancer in high-risk populations, anal cytology is more frequently being used as a screening test in a manner similar to the Pap test in cervical cancer screening.
  - Uncertainty still remains regarding the natural history of HPV in the anus and the role of anal cytology and HRA as screening tests for anal cancer.
  - Two major studies, Anal Cancer HSIL Outcomes Research (ANCHOR) and the Study of the Prevention of Anal Cancer (SPANC), are currently in progress to evaluate the potential value of anal screening, early detection, and destruction of anal intraepithelial neoplasia for the prevention of invasive squamous cell carcinoma.
  - Meta-analyses have shown anal cytology to have a high abnormal rate and sensitivity, but low positive predictive value and specificity for the detection of HSIL.
  - Please see the proposed algorithm from Northwestern Memorial Hospital, Chicago, below. As more data becomes available in South Africa, we propose multi-disciplinary input for our own clinical guidelines and management.



Nortwestern Memorial Hospital Clinical Algorithm

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