

High-resolution anoscopy: Uncharted territory for gastroenterologists?

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Abstract

High-resolution anoscopy (HRA) is a procedure where patients with an increased risk of anal cancer, like men who have sex with men, human immunodeficiency virus infected individuals, transplant patients and women with a history of lower genital tract neoplasia, with abnormal anal cytology results, are submitted to anal and perianal visualization under magnification. This will

allow for a better detection of anal high-grade lesions that can be treated, in an effort to prevent anal cancer. Anal cancer screening follows the same principles that cervical cancer screening. During this procedure, an anoscope is inserted and a colonoscope is used to examine systematically the squamocolumnar junction, the transformation zone and the perianal skin. Initially the observation is done with no staining and then with the application of acetic acid and Lugol's iodine solution, allowing for better lesion identification and characterization. Any suspicious lesion seen should be carefully evaluated and biopsied. Without HRA only a small percentage of suspicious lesions are identified. High-grade lesions that are detected can be ablated under HRA. This is a challenging exam to perform, with a long learning curve and the number of clinicians performing it is limited, although the growing number of patients that need to be screened. Specific equipment is required, with these patients ideally followed by a multidisciplinary team, in a reference centre. HRA remains unfamiliar for many gastroenterologists.

Key words: High-resolution anoscopy; Anal cytology; High-grade squamous intraepithelial lesions; Low-grade squamous intraepithelial lesions; Anal cancer

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Core tip: High-resolution anoscopy is a procedure where high-risk patients are submitted to anal and perianal visualization under magnification, allowing detection of anal high-grade lesions that can be treated. Anal cancer is histologically and biologically very similar to cervical cancer and the screening follows the same principles. The importance, difficulties and the description of the technique will be discussed. This is a difficult exam to perform, with a long learning curve that requires specific equipment and the need for a multidisciplinary team, ideally in a reference centre. It remains unfamiliar for many gastroenterologists.

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DEFINITION AND PRINCIPLES OF HIGH RESOLUTION ANOSCOPY

High-resolution anoscopy (HRA) is a procedure where high-risk patients are submitted to anal and perianal visualization under magnification, allowing detection of anal high-grade lesions that can be treated. HRA can simply be defined as a colposcopy applied to the anal canal and perianal region.

Men who have sex with men (MSM), human immunodeficiency virus (HIV) infected individuals, transplant patients and women with a history of lower genital tract neoplasia have an increased risk of anal cancer. HIV-negative MSM have an estimated incidence rate of 35 per 100000 person-year and anal cancer incidence rates in HIV-positive MSM are two times higher (about 70-100 per 100000 person-year)^[1]. Anal cancer has become one of the most common non-AIDS-defining tumors in HIV-infected individuals^[2]. Human papillomavirus (HPV) infection is almost always present in HIV-positive MSM, and infections with multiple HPV types are common^[3]. Concerning transplantation, most data come from renal transplant recipients, and the relative risk of anal cancer in these patients is 10 fold^[4,5].

Anal cancer screening follows the same principles that cervical cancer screening. Both tumors are caused by infection with oncogenic HPV strains, occur at the squamocolumnar transition zone and arise from same precancerous dysplastic lesions, anal intraepithelial neoplasia or cervical intraepithelial neoplasia^[6]. Women are screened through cervical cytology and those with abnormal results are then referred for colposcopy. Abnormalities are biopsied, and if high-grade squamous intraepithelial lesions (HSIL) are present, the patient is treated, thereby preventing progression to cervical cancer. Cervical cancer rates have dramatically decreased through cytology screening^[7,8], from 40-50 cases per 100000 individuals to about 8-10 cases per 100000 individuals. Anal cancer is likely preceded by HSIL, a colposcope may similarly be used to visualise it and permit biopsy and treatment in an effort to prevent anal cancer.

Progression of biopsy-proven anal HSIL to cancer in a group of 27 HIV-infected MSM has been recently reported^[9] and confirmed that individual HSIL lesions can progress to cancer.

High-risk patients like HIV-positive men and women regardless of sexual orientation or HIV-negative MSM submitted to anal cytology as a screening test, that have an abnormal result should be refer to HRA. The prevalence of anal squamous intraepithelial lesions

(SIL) has remained high among HIV-positive MSM after the introduction of highly active antiretroviral therapy (HAART); HAART is not associated with a reduced prevalence of anal SIL^[10]. Other groups who should be considered for screening include women with cervical cancer, high-grade vulvar disease or cancer, individuals with perianal condyloma acuminata; and transplant recipients^[11].

Anal cytology is classified on the basis of the 2001 revised Bethesda System of cervical cytology classification^[12]. There is no specific terminology for anal cytology. The specificity and predictive value for anal high-grade lesions on biopsy are highest for HSIL, atypical squamous cells which cannot exclude high-grade squamous intraepithelial lesion(ASC-H), low-grade squamous intraepithelial lesions (LSIL) and atypical squamous cells of undetermined significance (ASC-US).

The severity of cytological findings and infection with high-risk HPV are the most significant predictors of significant predictors for HSIL, underscoring the importance of anal dysplasia screening^[13]. A systematic review described that anal cytology has a sensitivity from 69% to 93% and a specificity from 32% to 59%, that is similar to those reported for cervical cancer screening^[1]. Abnormal anal cytology seems highly predictive of anal dysplasia on biopsy, in a previous study by Cranston *et al*^[14] 2007, the positive predictive value of anal cytological abnormality to predict any degree of anal dysplasia was 95.7%. Both sensitivity and specificity of anal cytology are higher for internal disease as compared to external disease (perianal region)^[3].

HIGH RESOLUTION ANOSCOPY TECHNIQUE

Normally, during HRA the patient is in the left lateral position, in the foetal position, with the buttocks at the edge of the table. Bowel preparation is not needed. An anoscope is inserted and a colposcope is used to examine the squamocolumnar junction, the anal canal including the transformation zone and the perianal skin in a systematic manner. The inspection should be performed first with no staining and then with the topical application of acetic acid (3% or 5%), that will allow for better lesion identification and characterization. Most of the anal exam is done under 16 × magnification, once specific areas of interest are visualised, they should be examined under 25 × magnification and the anal verge is viewed with 10 × magnification^[15]. After examination with acetic acid, application of Lugol's iodine solution may help to distinguish HSIL from LSIL, to assist the clinician in deciding where to biopsy, as well as to define the margin of the lesion^[15].

Lesions seen during HRA should be carefully described concerning localization, contour, margins, acetic acid induced whitening, Lugol's staining, epithelial pattern, vascular pattern (mosaic pattern, punctation, warty vessels, atypical). This will help to distinguish between

low-grade and high-grade lesions. HSIL may be flat or thickened, and often have vascular changes including punctuation or a mosaic pattern, are acetowhite, with a poor uptake of Lugol's solution. In a study by Camus *et al*^[16], the positive predictive value for HSIL increased to 68.6% with the following combination of criteria: Acetic acid-induced whitening, no Lugol staining, irregular epithelial pattern, and vascular changes. Many of these anal suspicious lesions have similar aspects to that initially describe in cervical colposcopy^[7,8]. Cancers are often friable or ulcerated lesions with atypical vessels. Any suspicious lesion, namely of HSIL or anal cancer should be biopsied.

IMPORTANCE OF HIGH RESOLUTION ANOSCOPY

HRA is fundamental for high-grade lesion detection and subsequently guided treatment. Anal HSIL ablation treatment under HRA may reduce the rate of anal cancer^[17].

Previous studies revealed that before HRA is performed, only a small percentage of suspicious lesions are identified. Camus *et al*^[16], show that only 38.7% of the lesions were visible with the naked eye before HRA.

Few data are available on the progression of anal SIL to anal squamous-cell carcinoma (ASCC), the true rate of progression from high-grade dysplasia to invasive anal cancer remains unclear^[1]. There are clearer data concerning perianal intraepithelial neoplasia or Bowen disease in which approximately 5% of lesions undergo malignant change^[18].

Devaraj *et al*^[19], published a series of 98 HIV-positive patients, with 40 patients with a follow-up of more than one year, with expectant management of anal squamous dysplasia. In this series, 28 of 40 patients had anal HSIL and three of these patients (11%) developed invasive carcinoma while under surveillance (expectant management). Scholefield *et al*^[20] described a series of 35 non-infected HIV patients, all with anal HSIL. In this series, 7 patients were submitted to expectant management due to extensive or multifocal disease and three of these patients (9%) developed invasive ASCC during follow-up, median of 5 years after the initial diagnosis of anal HSIL. In a study by Sobhani *et al*^[21], including 199 patients who were successfully treated for anal warts (HIV positive and HIV negative patients included), 38 (19%) later developed anal HSIL, and of these, seven (18%) developed ASCC, 13 to 108 mo after entry in the study.

Wide excision is a morbid procedure that also removes uninvolved healthy tissues to achieve widely clear margins. Nevertheless, there is still a risk of recurrence^[22]. HRA guided ablation of anal HSIL has several advantages: It permits a full evaluation of the anorectal anatomy, detection of grossly invisible disease, allowing target therapy with protection of normal tissues, minimal morbidity and reducing the risk

of anal stenosis^[22]. Cervical HSIL is usually treated with the loop electrosurgical excision procedure, removing the squamocolumnar transformation zone where most dysplasia develops. This is not possible for anal HSIL and treatment most often relies on ablation of individual lesions with laser, electrocautery (ECA), and infrared coagulation (IRC). There is no significant difference in treatment success between IRC and ECA^[17]. A recent study by Goldstone *et al*^[17] showed that patients undergoing ablation of anal HSIL have high recurrence, but the probability of developing anal cancer is low. The recurrence 1 year after the first ablation for HIV-positive and -negative patients was 53% and 49%, respectively; at 2 and 3 years, the rate of recurrence was 68% and 77% for HIV-positive patients and 57% and 66% for HIV-negative patients. The probability of cancer 3 years post-ablation was 1.97%.

Perianal high-grade dysplasia (Bowen disease) it is traditionally treated with mapping (blind biopsies) and wide excision. A recent study by Johnstone *et al*^[23], showed that perianal dysplasia can be successfully treated with HRA-guided targeted ablation (ECA, laser or IRC) with no morbidity, although recurrence remains high. Almost all of these patients have anal canal dysplasia and HIV-positive patients are at the greatest risk for disease and recurrence.

Recommendations on post-treatment follow-up intervals are lacking.

DIFFICULTIES IN PERFORMING HIGH RESOLUTION ANOSCOPY, CAN WE DO IT?

Probably due to the long learning curve, the number of clinicians performing HRA is limited. Although the similarities of HRA and colposcopy, HRA is a more challenging and demanding technique due to the anal anatomy, anal pathology and difficulties in the treatment (excision is not a real option). Previous training in colposcopy is important to understand how to work with the colposcope and detect the aspect of the lesions. To perform this technique, a colposcope is required, and this equipment is not normally available outside a gynaecology clinic. In some cases, patients have not been referred to this technique due to the lack of knowledge of the indications or trained clinicians that can observe these patients. These patients need to be followed by a multidisciplinary team, including the clinicians performing HRA, pathologists, infectiologists, and colon and rectal surgeons.

This is extremely important because there is a growing number of patients, namely, HIV and MSM who need to be screened. It will be a long journey until all of these high-risk patients are referred for screening and more clinicians feel motivated to learn this technique. Recently the results of an internet-based survey on attitudes and practice of Colon and Rectal surgeons (United States members of the American Society of

Colon and Rectal Surgeons) on anal dysplasia revealed that, although most of them treated patients at risk for anal cancer and had read research on HSIL, only one-third had performed HRA and of these less than half (46%) were formally trained. When evaluating patients for HSIL in surgery, only 31% used acetic acid with magnification^[24]. Another internet-based survey to members of international surgical and dermatological societies concerning diagnosis, treatment and surveillance of patients with HPV-related anal diseases revealed that to detect dysplastic lesions, 42.0% of surgeons used acetic acid only, 23.2% used this in combination with HRA and 19.5% applied intra-anal cytological smears. Likewise, 64.6% of dermatologists applied acetic acid only, 16.5% combined acetic acid with HRA and 30.2% performed intra-anal cytological smears^[25].

It is fundamental to have more and better trained clinicians performing it. This will never be a technique that can be performed by all.

Several clinicians can perform anal cytology, especially those involved with high-risk patients, namely infeciologists, dermatologists, gynaecologists, nephrologists. If an abnormal result is detected, patients should be referred, ideally to a reference centre, to a clinician properly trained in HRA and with a multi-disciplinary team. Thus, regarding anal cancer screening, we should inform all clinicians, cytology should be performed by most and HRA by some.

HRA was developed in the 90's, but remains unfamiliar to many, including gastroenterologists, although in some countries gastroenterologists are also proctologists. Much of the gastroenterology daily routine involves diagnostic and interventional therapeutic procedures. These are central concepts of HRA. Basic knowledge regarding the technique and even proper training may well be in the present and future realm of gastroenterologists.

HRA is fundamental for high-grade anal and perianal lesion detection and subsequently guided treatment in an effort to prevent anal cancer in high-risk patients.

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