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REVIEW

Anal intraepitelial neoplasia: A narrative review

Garazi Elorza, Yolanda Saralegui, José María Enríquez-Navascués, Carlos Placer and Leyre Velaz

Department of General and Digestive Surgery. Hospital Universitario Donostia. Donostia, Guipúzcoa. Spain

ABSTRACT

Anal intraepitelial neoplasia (AIN) constitutes a major health problem in certain risk groups, such as patients with immunosuppression of varied origin, males who have sexual relations with other males, and females with a previous history of vaginal or cervical abnormalities in cytology. Its relationship with the human papillomavirus (HPV) infection has been well documented; however, many of the factors involved in the progression and regression of the viral infection to dysplasia and anal carcinoma are unknown. AIN can be diagnosed through cytology of the anal canal or biopsy guided by high-resolution anoscopy. However, the need for these techniques in high-risk groups remains controversial. Treatment depends on the risk factors and given the high morbidity and high recurrence rates the utility of the different local treatments is still a subject of debate.

Surgical biopsy is justified only in the case of progression suggesting lesions. The role of the vaccination in high-risk patients as primary prevention has been debated by different groups. However, there is no general consensus on its use or on the need for screening this population.

Key words: Anal intraepithelial neoplasia. High-resolution anoscopy. Anal carcinoma. Human papillomavirus vaccine.

INTRODUCTION

Anal intraepithelial neoplasia (AIN) is a precursor to anal squamous carcinoma that can arise in the anal canal or anal margin and little is known about its natural history. It has been proven that AIN, as in the case of cervical intraepithelial neoplasia (CIN) and in vulvar intraepithelial neoplasia (VIN), is related with the human papillomavirus (HPV) (1) in more than 90% of cases, particularly with serotypes 16 (85%) and 18 (7%) (2). The presence of HPV in the anal canal is almost universal in HIV-infected patients (3).

The incidence of AIN has increased in the last decade. Major risk groups are males who have sex with other males (MSM), patients with immunesuppression of diverse origin, patients with a previous history of anogenital condylomas, and women with vaginal, vulvar or cervical dysplasia.

AIN is histologically classified as AIN I (low-grade dysplasia) and AIN II-III (high-grade dysplasia) depending on the level of the affected epithelium and cytologically as high and low-grade squamous intraepithelial lesion (SIL) according to the Bethesda classification.

Anal canal cytology and high-resolution anoscopy are the current "gold standard" for the diagnosis of AIN; however, today, the diagnostic and screening methods, along with the treatment used are still very controversial. It is important to recognize these lesions as most of them are not clinically specific and they have very few characteristics. Only a thorough examination with a high intuitive suspicion can prevent delay in the diagnosis.

The importance of this entity centres on selecting the patients that would benefit from a screening program and subsequently may be eligible for a therapeutic strategy.

METHODS

For this narrative review a research has been carried out about the diagnosis, treatment and prevention of anal intraepithelial neoplasia. The research was limited to papers published between January 2005 and January 2015.

Systematic reviews, meta-analysis, cohort studies, randomized clinical trials and guidelines and recommendations of governmental and scientific associations related with the topic were analyzed. The most relevant articles were selected according to the consensus of the authors. A research strategy was undertaken using databases such as Medline, Ovid, EMBASE and Cochrane. Keywords such as "anal intraepithelial neoplasia", "high-resolution anoscopy" "papillomavirus", "screening" and "vaccine" were used.

EPIDEMIOLOGY

Despite its limited length, the anal canal has a very complex histological and anatomical structure and it produces a

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Correspondence: Garazi Elorza. Department of General and Digestive Surgery. Hospital Universitario Donostia. Begiristain Doktorea Pasealekua, 117. 20080 Donostia, Gipuzkoa. Spain
e-mail: garazielorza@gmail.com

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large variety of tumours. Anal cancer is relatively uncommon and accounts for 2% of gastrointestinal cancers (4), so the recommendations based on scientific evidence are scarce and confusing.

Anal cancer is a relatively low occurring entity but its incidence has been increasing, especially in risk groups such as MSM, immunosuppressed patients (HIV, transplanted patients) and women with a previous history of vaginal, vulvar or cervical dysplasia.

It has long been recognized that there is a causal association between anal HPV infection and the development of AIN. HPV is considered to be the most common sexually transmitted disease in the world. Cervical HPV disease is very frequent in sexually active women (5), but the occurrence of anal HPV varies depending on the associated risk factors. HIV-uninfected women with a previous history of cervical dysplasia have a higher rate of anal HPV disease. In women who had no previous history of cervical dysplasia, the prevalence of anal HPV is 6%, and rises to 55% in women with previous microinvasive carcinoma of the cervix (6).

The prevalence of HPV infection, SIL, high-grade AIN and anal carcinoma in male heterosexuals, MSM, and women are summarized in table I. It can be noticed that the risk of having an infection by anal HPV increases in MSM and in those infected with HIV. The prevalence of anal HPV in HIV heterosexual males is 24%, and 6.2% in HIV-infected women. The prevalence of the anal HPV infection is 42-63% in HIV-negative MSM and rises to 80-95% in HIV-infected MSM.

HIV-infected patients have a higher risk of having AIN or of developing anal squamous cell carcinoma, regardless of their sexual activity, and the risk increases in patients with a CD4 count < 200. However, it has been observed that receptive anal intercourse increases the degree of dysplasia (7). Theoretically, it is assumed that the prevalence of AIN would be reduced in the times when anti-retroviral treatment is aggressive. Contrary to this theory, it has been demonstrated that the prevalence is actually increasing. The possible explanation could be a prolonged survival of HIV-positive patients, which allows AIN to develop an invasive carcinoma (9). According to a meta-analysis published by Machalek (3), 93% of the HIV-infected MSM have an anal HPV, 29% of which also show a high-grade AIN. Sixty-three per cent of HIV-uninfected MSM have an anal HPV infection, 21% of which have a high-grade AIN.

Women with HPV-related gynaecologic neoplasm are at higher risk of anal cancer and the highest risk was identified in those with *in situ* vulvar carcinoma (10). The prevalence of anal HPV infection and anal carcinoma and its relation with the coexistence of cervical intraepithelial dysplasia are shown in table II. The fact that the prevalence of high-grade AIN in HIV-uninfected women is 1% indicates that AIN in women is closely related with the synchronous existence of CIN and/or VIN in the absence of HIV infection.

Moreover, Hessol et al. examined 655 women, comparing the prevalence of AIN in HIV-infected and HIV-uninfected. HIV-infected women showed a higher risk of anomalies in the histology or cytology (31% in HIV-infected and 9% in HIV-uninfected), regardless of their sexual activity. Although in this study the proportion of anal sexual relations in both groups was high (47% and 46% respectively), women with a history of receptive anal

Table II. Prevalence of anal HPV in HIV-uninfected women and its relation with cervical cytology abnormalities (10)

	Anal HPV
No cervical dysplasia	6.2%
CIN 1	15.8%
CIN 2	27.8%
CIN 3	48.5%
In situ adenocarcinoma	33.3%
Micro-invasive cervical carcinoma	55.5%

Table I. Prevalence of anal HPV infection, AIN and progression of anal carcinoma per year

	Anal HPV infection (any type)	*Abnormal citology or histology*	*High-grade AIN*	*Progression to anal carcinoma/year*
MSM HIV+	85-95% (3)	48% (7)	29-31% (3.7)	1/600 (3) 1/400 (7) 1/760 (13)
MSM HIV-	42-63% (2.8)		19% (3)	1/4,000 (3) 1/50,000 (13)
Heterosexual males	24% (14)			
HIV+ women	80% (9)	10-31% (7.9)	6% (11)	1/204 (7) 1/3.000 (13)
HIV- women	6.2% (6)	2-9%	1% (11)	1/770 (10) (women with a previous vulvar/ cervical carcinoma)

intercourse were 3.8 times more likely to have AIN than women with no history of such relations, independent of their immune condition (11).

As with CIN and VIN, AIN has been associated with cigarette smoking, promiscuity (8,12) and not being circumcised (15).

PATHOGENESIS

The natural history of anal cancer is not precisely known, although it is understood that its evolution is similar to that of cervical cancer. Anal cancer is usually associated with HPV infection and it has predilection for the squamocolumnar junction. Most of these lesions are located on the anal transitional zone, but as it is a multifocal disease, it could affect both the anal canal and the perianal skin. However, the natural history of CIN and AIN is different probably due to the anatomical, physiological (hormonal activity) and immunological differences between the anus and cervix (16).

HPV infects the keratinocytes of the basal layer through discontinuous areas in the top layer of the epithelium (lesions, micro-wound or micro-abrasions). These micro-wounds allow the access to receptors on the basal cells, which is necessary for the internalization of the virion through endocytosis (17). When the HPV is associated with benign lesions such as condylomas, the replication of the viral genome is extrachromosomal. When the lesion is malignant, viral DNA is integrated into the host cell chromosome. The integration of the HPV is also necessary for the progression from AIN III to an invasive tumour and it is postulated to be the origin of the proliferation of monoclonal cells (18).

A sequential accumulation of molecular changes, the integration of the DNA of the HPV and consequent chromosomal instability characterizes the evolution from an abnormal mucosa to an invasive carcinoma. The instability of chromosomes initiates the sequence of mutation of the carcinogenesis, causing an imbalance in the number of chromosomes and an increase in the rate of heterozygosity loss, which is an important mechanism for deactivating suppressive tumour genes (19). The progression to invasive carcinoma also requires an inactivation of tumour suppressor genes such as APC (5q), 17p (p53) y 18 q (DDC) (20).

NATURAL HISTORY OF AIN

There are very few studies on the persistence, progression and regression of anal HPV infection to AIN or to invasive cancer. The progression rate of an AIN to invasive carcinoma is scarce; however, more studies are required to clarify its natural history. Moreover, most of the studies on AIN are based on males, MSM to be more precise.

A study based on HIV-negative males reported that regression of anal HPV-16 was 66% after 12 months and 90% after 24 months without following any type of treatment (12). The regression rate was considerably lower with a higher number of sexual partners. Furthermore, a lower rate of regression of HPV-16 was observed compared with other types of non-oncogenic HPV (12,21).

The estimated progression of AIN to anal squamous carcinoma is 1/56-600 per year in HPV-infected MSM (3,13) and 1/4,000 per year in HIV-uninfected MSM (3). Among women with a history of cervical or vulvar dysplasia the progression of AIN to anal squamous carcinoma is 1/700 (13) and 1/200-625 (7,13) in HIV-infected women.

This estimated progression of AIN to carcinoma is substantially lower than the rate of progression of CIN to cervical squamous cell carcinoma, which is considered to be 1/80 (22). Hence, we can affirm that there are important differences between the carcinogenesis and natural history of the cervical and anal HPV. The natural history of the HPV in the anus appears to be influenced by the microenvironment, because anal environment is more hostile to the persistence of HPV, the immune response is different and, moreover, the hormonal differences between both locations could help to slow down the carcinogenesis (2).

DIAGNOSIS

Anal HPV infection is asymptomatic, although sometimes exophytic lesions, and palpable or small hyper or hypopigmented areas, generally non-pruritic, may be observed. The diagnosis of AIN may also be incidental, in haemorrhoidectomies and in the removal of "anal strips" and, of course, in resections of anal condylomas.

The goal of the diagnosis is to detect high-grade disease, through cytology and histology. Cytology or histology samples are just a representation of the actual disease. Larger or more biopsies would give a more accurate estimation of the true biology of each lesion.

The recommended terminology for HPV-associated squamous lesions is a dichotomous terminology (high or low-grade), SIL nomenclature for cytology samples and AIN nomenclature for histology lesions, due to the fact that it is biologically more relevant (23) (Table III).

Cytology

Anal cytology should be performed in anal canal and the anal margin. The sample is taken by introducing a cytobrush into the anal canal to a depth of 3 cm and withdrawn in a downward spiral movement after which it is prepared for a cytopathology analysis. This sample will be analyzed under the microscope, in a similar way to the conventional cervical cytology (24).

There must be no lubrication prior to obtaining a cytology sample and the patient should not have a receptive anal intercourse or an enema 24 hours before the sample collec-

tion, as it may interfere with the interpretation of the sample (25). The sample should be taken before performing the high-resolution anoscopy or rectal examination, given that the acetic acid or the lubricant could influence the analysis.

As cervical cytology, anal cytology is graded based on the Bethesda classification as low-grade SIL and high-grade SIL (26).

According to the systematic review of Chiao et al. (27), the sensitivity of anal cytology ranges between 69% and 93% and the specificity between 32% and 59% in the era of highly active antiretroviral therapy. Given its low specificity (28), many patients would have to undergo a high-resolution anoscopy, with the expenses and psychological consequences that this entails. Moreover, there are indications that cytological evaluation may not be fully correlated with the histopathologic evaluation (7) and that the cytology underestimates the grade of the dysplasia (3,11). Indeed, a blind swabbing cytology would be insufficient for the diagnosis of a dysplastic lesion and it should always be confirmed histologically as to determine the integrity of the basement membrane. Biopsies can be taken by simple inspection or using high-resolution anoscopy if possible.

High-resolution anoscopy

High-resolution anoscopy has been shown to be highly effective in the diagnosis of AIN and it appears to be the preferred screening method (29). However, despite its sensibility to identify patients with AIN, there is little debate about its routine use and it has not been proven to be superior to simple inspection and observation (29). Given that the progression from AIN to carcinoma is very infrequent, it is probable that surveillance and periodic control of the suspicious lesions could be the method to follow.

During the high-resolution anoscopy, a microscope similar to a colposcope is used to magnify the view. The perianal skin is treated with 3% acetic acid and left in contact with the mucosa for 2 min followed by the application of Lugol iodine solution. AIN lesions that have been in contact with the acetic acid usually acquire a whitish colour (acetowhite areas), and these are the areas that should be considered for biopsy (the acetowhite areas, ulcerated or with irregular vascular patterns). Suspicious areas are identified as acetowhite and will not take Lugol. Both the colposcopy and high-resolution anoscopy are operator dependent and their quality depends on the experience of the clinician which needs a steep learning curve. In our experience, performing a high-resolution anoscopy seemed difficult for different reasons: A good interpretation of the pectinate line as normal or pathological by acetowhite areas is difficult, taking directed biopsies in the anal canal is technically complex and any biopsy in the anal zone is too painful to be performed in the consultation without the use of some type of anaesthetic. However, bearing in mind the aforementioned difficulties, we have found the application "magnifying glass-app" –the objective of the camera of smart phones connected to a conventional anoscope– useful for monitoring patients with AIN.

Table III. Terminology in anal intraepithelial lesions

	Low-grade lesions	*High-grade lesions*
Cytology	L-SIL	H-SIL
Histology	Low-grade AIN (AIN 1)	High-grade AIN (AIN 2-3)

PRIMARY PREVENTION: VACCINATION

Since the introduction of screening programs, the incidence of cervical cancer has decreased, however the incidence of anal cancer has increased in last decade. Given that HPV infection is the major contributor for anal cancer, vaccination in high-risk groups has been a subject of debate (30).

The quadrivalent HPV vaccine is a recombinant major capsid protein (protein L1) of HPV-6, 11, 16 and 18, and has proven to be effective in the prevention of anogenital lesions related to HPV. The quadrivalent vaccine is a synthetic vaccine, including virus-like particles. The Food and Drug Administration (FDA) approved the quadrivalent vaccine for the prevention of cervical cancer in females between the ages of 9 and 26 years. It protects against HPV-6 and 11, which have a low risk of carcinogenesis and are responsible for 90% of condylomas, and against HPV-16 and 18, responsible for most of the anogenital cancers.

HIV-infected MSM have a high prevalence of high-grade AIN (30%) (31), which indicates that this group would benefit from vaccination before being exposed to HPV. The quadrivalent vaccine has demonstrated a seroconversion in 95% of the patients, even patients who previously had antibodies against HPV show increase in the antibody count (32).

Guiliano et al. (33) compared the quadrivalent vaccine with placebo in a randomized clinical trial. Four thousand and sixty-five males between the ages of 16 and 26 participated, all in good health, without past histories of anal condylomas and the majority of which were heterosexuals. They observed a significant reduction in the number of external anal lesions related with HPV-6 (60%) and HPV-11 (76%). In the intention-to-treat analysis, there was a non-significant reduction in anal lesions related with HPV-16 (70% efficacy) and in HPV-18 (33% efficacy). The global efficacy of the vaccine was higher in male heterosexuals (92% efficacy) than in MSM (79% efficacy).

In another randomized clinical trial by Palefsky et al. (34) the quadrivalent vaccine was compared with a placebo in 200 MSM. The global efficacy was 50% and there was a significant reduction of low and high-grade AIN.

Swedish et al. (35), in an observational study compared MSM with a history of treated high-grade AIN who received a quadrivalent HPV vaccine with those who did not receive the vaccine. The population studied was over 18 years with a mean age of 40 years. The study demonstrated that the vaccine decreased the incidence of the recurrence of high-grade AIN. The incidence of recurring high-grade AIN was 15/100 people per year in those vaccinated and 28/100 people per year in those who weren't vaccinated.

Although there are some data suggesting that HPV vaccination may play a role in preventing HPV infection in males, cost-effectiveness analysis show that it is not cost-effective in the general population (36). However, the analysis of vaccination of MSM or HIV-infected showed that the quadrivalent vaccine may be cost-effective for the prevention of anogenital lesions and anal cancer and is also safe in these patients (37).

HPV infection is rapidly acquired after sexual debut (38). The problem of the prevention of the infection in high-risk groups lies in the fact that it is difficult to recognize MSM among the preadolescent population and the majority of those who are HIV-infected are older than 26 years. Additionally, vaccination in preadolescent females would have no benefit for this group, given that they are infected by other males.

Hence, the US Centre for Disease Control and Prevention (CDC) recommends the HPV vaccine for all HIV-infected patients under 26 years of age (regardless of the CD4 number) and MSM under the age of 26 years (39).

Despite the aforementioned studies, currently in Spain the quadrivalent HPV vaccine is not on the vaccination programs of males or high-risk groups.

SECONDARY PREVENTION: SCREENING

Prevention of anal cancer with screening in high-risk groups (24) has been proposed, however, there is currently no evidence of its effectiveness.

The European AIDS Clinical Society Guidelines (40) recommend screening with anal cytology in MSM every 1-3 years and a high-resolution anoscopy in cases of abnormalities anomalies, although the guidelines acknowledge that the evidence is uncertain.

The New York State Department of Health AIDS Institute (41) recommends a systematic anal cytology screening in HIV-infected MSM, patients with a history of anogenital condylomas and in women with abnormal vulvar or cervical histology.

The Centres for Disease Control and Prevention and the HIV Medicine Association of the Infectious Diseases Society of America (42) do not recommend screening for the prevention of anal cancer, however it does mention that cytology in high-risk patients such as MSM or women with a history of cervical cancer would be useful, and should be followed by a high-resolution anoscopy in cases of abnormalities.

The British guidelines for the management of sexual and reproductive health do not recommend routine screening (43).

TREATMENT

The risk of anal squamous carcinoma in patients with a history of AIN depends on associated risk factors, but, generally, its progression to carcinoma is scarce and slow (44), therefore the less aggressive treatment should be considered. The best treatment for AIN is still controversial. Treatments have been associated with very high rates of morbidity (15% stenosis or faecal incontinence), recurrence (especially in HIV-positive) (45) and metachronous lesions.

At present, there is no evidence that a screening program in the general population can reduce the morbidity and mortality related with anal cancer. Although its progression can be reduced in risk groups (29) there are very few studies and most are case series, only two clinical trials exist comparing different treatments.

Multiple treatments, such as CO_2 laser, electrocautery, infrared (46,47), cryotherapy or topical agents such as Imiquimod, trichloroacetic acid or 5-fluorouracil (5-FU) have been used. Table IV shows the results obtained from the most relevant studies or with a large number of patients, using different treatment techniques.

Fox et al. compared the use of imiquimod (Aldara®) and placebo in a randomized clinical trial (48). There was a complete response in 40% of the patients and a reduction in the degree of dysplasia in 28%, compared with 4% of complete response in the placebo group. In another randomized clinical trial comparing electrocautery, imiquimod cream and topical 5-FU, with high-resolution anoscopy surveillance, Richel et al. (49) concluded that a wait and see policy might be sufficient and that electrocautery is superior to imiquimod and 5-FU topical for the treatment of intra-anal AIN in HIV-infected MSM. They recommend imiquimod cream for the treatment of perianal AIN. Additionally, the recurrence rate was high (67%) five years after treatment. Electrocautery was also analyzed by Marks et al. (50) in a retrospective cohort study that found cure rates of 73% in MSM HIV-negative and 50% in HIV-positive. However, recurrence rates were 53% and 61% respectively.

The American Society of Colorectal Surgeons (51) recommends to treat high or low-grade AIN patients with 5% imiquimod cream, especially in anal margin lesions, or with a 5% 5-FU topical cream (1C Evidence). It also considers local excision as an optional therapy or to "watch and wait" (2C Evidence).

Hence, as described in the research, recurrence is above 60% after six months, regardless of the type of treatment.

Table IV. The results of the different types of treatments

	Study method	*Treated patients*	*Intervention*	*Results*	*Conclusion*
Fox (48)	Double-blind randomized clinical trial (n = 64)	MSM HIV+HG-AIN	Imiquimod (n = 28) ---------- Placebo (n = 25)	Imiquimod: – Complete response: 14% – Partial response: 28% ---------- Placebo Complete response: 4%	Imiquimod is a safe and well tolerated treatment which can be useful for the treatment of HG-AIN
Richel (49)	Randomized clinical trial (n = 148)	HIV+, MSM, > 18 years LG-AIN or HG-AIN	Imiquimod (n = 54) ---------- 5-FU (n = 48) ---------- Electrocautery (n = 46)	Complete response: 24% Recurrence: – At week 24: 19% – At week 48: 50% – At week 72: 71% Side-effects: 91% Stopped treatment: 9% ---------- Complete response 17% Recurrence: – At week 24: 38% – At week 48: 50% – At week 72: 58% Side-effects: 92% Stopped treatment 4% ---------- Complete response 39% Recurrence: – At week 24: 14% – At week 48: 43 % – At week 72: 68% Side-effects: 93% Stopped treatment: 7%	In cases of LG-AIN "watch and wait" could be adequate. Electrocautery is superior to topical Imiquimod or to topical 5-FU in the treatment of AIN in HIV-infected MSM. Imiquimod is the best option for perianal lesions
Marks (50)	Retrospective (n = 232)	MSM Intra-anal HG-AIN	Electrocautery	HIV- (n =100) Complete response 73% Recurrence 53% (after first treatment) HIV+ (n = 132) Complete response: 58% Recurrence 61% No important side-effects	Electrocautery is a safe procedure the treatment of HG-AIN and could be performed in the consultation
Weis (46)	Prospective cohort study (n = 124)	HIV + men and women HG-AIN	Infrared coagulation	Treatment (n = 98) HG-AIN persistence: 26% LG-AIN: 71% Complete response: 3% Progression to anal carcinoma: 0% No treatment/delay treatment (n = 42) HG-AIN persistence: 88% LG-AIN: 7% Complete regression: 0% Progression to anal carcinoma: 5%	Infrared coagulation is an effective treatment for HG-AIN

Continued on the next page

Table IV (Cont.). The results of the different types of treatments

	Study method	*Treated patients*	*Intervention*	*Results*	*Conclusion*
Goldstone (47)	Retrospective cohort study (n = 143)	MSM HG-AIN	Infrared coagulation	HIV+ (n = 68) Recurrence: After the 1st treatment: 91% After the 2nd treatment: 63% After the 3rd treatment: 85% After the 4th: 47% Progression to anal carcinoma: 0% HIV- (n = 75) Recurrence: After the 1st treatment: 62% After the 2nd treatment: 48% After the 3rd treatment: 57% Progression to anal carcinoma: 0%	Infrared coagulation is an effective treatment for HG-AIN in HIV-infected and HIV-uninfected. HIV-infected patients have higher recurrence rates and recurrence occurred more rapidly in these patients

Considering that the rate of progression from high-grade lesions to invasive squamous carcinoma is only 1/400-600 in HIV-infected MSM and 1/4,000 in HIV-uninfected MSM, we believe that it may be more prudent to maintain a wait-and-see attitude with anal examinations and ordinary anoscopy before considering carrying out a high-resolution anoscopy in a routine way.

CONCLUSIONS

The natural history of anal illness by HPV infection is still undetermined due to the fact that the regression factors and/or progression of the illness towards invasive cancers are still unknown. All patients with AIN should be followed-up and have a periodical control of their suspicious lesions, either by a simple inspection and a biopsy of the suspicious lesions or through a high-resolution anoscopy in centres of expertise. The procedure of high-resolution anoscopy is complex and entails a steep learning curve.

We believe that AIN should not be treated in a routine way given the high rate of recurrence and its low progression to invasive cancers. We believe that a surgical biopsy should only be accomplished in cases of macroscopically progressing lesions.

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