Anal Intraepithelial Neoplasia and Squamous Cell Cancer of the Anus

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Abstract

Keywords

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- wide local excision
- photodynamic therapy
- human papilloma virus

Anal intraepithelial neoplasia (AIN) is the premalignant condition of the anal squamous tissue. It is associated with the human papilloma virus and is considered the transition prior to the invasive anal squamous cell carcinoma. It is typically asymptomatic and can be either an incidental finding after anorectal surgery or identified when high-risk patient populations are screened. Once AIN is diagnosed, the optimal management remains controversial, partly because the natural history of the disease is unclear. Surgical management of the disease has essentially been replaced by more conservative treatment options and can range from expectant management to topical therapy to photodynamic therapy. The aim of this article is to review the varied treatment options and to briefly review prevention strategies.

Anal intraepithelial neoplasia (AIN) is considered the pre-invasive phase of anal squamous cell carcinoma (SCC) which is a very uncommon gastrointestinal malignancy, although the incidence has steadily risen in the United States over the past few decades.¹ The increase in incidence of anal SCC has been linked to a change in sexual practice in the United States. This includes an increase in the number of sexual partners for both men and women, more participation in ano-receptive intercourse, and an increase in the number of men having sex with men (MSM).^{2,3}

Although there is a known causal relationship between AIN and anal SCC, the transition to cancer risk is not well known. The precursor condition of AIN is the preinvasive condition and must be identified in a timely fashion for appropriate treatment and follow-up prior to the progression of the disease. The diagnosis, treatment, and follow-up of AIN are not entirely standardized among providers and the ultimate recommendation can vary significantly. The goal is to discuss the currently available and studied treatment strategies for patients with AIN.

Background

Invasive anal SCC has been shown to have a relationship between genital conditions like human papilloma virus (HPV) and anal warts with the precursor condition being AIN.⁴ Anal dysplasia was initially described in 1981 and the adoption of similar terminology to cervical intraepithelial neoplasia (CIN) was proposed.^{1,5} Since these initial studies describing AIN, there is now conclusive evidence between the association of HPV and AIN and the likelihood of developing high-grade squamous dysplasia and eventually the invasive carcinoma component.^{6,7} AIN lesions associated with HPV, or anal intraepithelial HPV-associated squamous lesions, are classified as low-grade squamous intraepithelial lesion (LGSIL) or high-grade squamous intraepithelial lesion (HGSIL) according to the American Joint Committee on Cancer. These terms will be mentioned throughout the article with the broad heading as AIN.

Most patients who are diagnosed with AIN are asymptomatic. The diagnosis is oftentimes found as an incidental

histologic finding after benign anorectal surgery or when high-risk patients are screened.^{8–10} The methods for AIN screening are similar to the management of CIN and include anal cytology and high-resolution anoscopy (HRA) with biopsies.^{8,9} If patients present with nonspecific symptoms like pruritus and/or bleeding, and are found to have visible clinical findings on exam, then a biopsy to determine AIN is imperative.

Treatment of Anal Intraepithelial Neoplasia

The optimal management of AIN remains controversial. Treatment options vary between very conservative measures like watchful waiting or more aggressive treatment with extensive surgical intervention including wide local excision (WLE) and skin flaps. The debate regarding the ideal treatment for AIN is due to the subclinical nature of the condition and unclear disease progression. Despite the unknowns, the primary goal of AIN treatment is to prevent anal SCC.

The prognosis of anal SCC is strongly associated with stage of the disease at diagnosis.^{11,12} It is accepted that high-grade AIN or HSIL is the precursor to anal SCC, but the actual risk of anal cancer is based on relatively small patient population studies.^{13–15}

Another goal in the treatment of AIN, besides the prevention of anal SCC, is to recommend management with the lowest morbidity. Since the risk of anal SCC is somewhat uncertain, many patients opt for the least aggressive treatment option with the lowest side effect profile.

Expectant Management

Close monitoring and “watchful waiting” can be an option in certain patient populations with AIN. This involves periodic office evaluations with thorough digital anal examinations that can enable early detection and treatment of anal SCC which is associated with an improved overall outcome.^{11,12} Intervention and biopsy are then reserved only for those clinically identifiable lesions seen during office evaluation. “Watchful waiting” requires a physical examination every 4 to 6 months and therefore, it is imperative to have a compliant patient.¹⁶

“Watchful waiting” can be a good option in those patients at low risk for transformation to anal SCC but may not apply to those individuals at high risk. Several studies of HIV-positive patients with HSIL found that 11 to 16% of patients progressed to anal cancer within 1 to 7 years who were initially managed with watchful waiting. Surgical intervention was then reserved only for palpable lesions identified on examination.^{13,14,17} The cancer transformation risk in this patient population may prohibit an option for watchful waiting. Therefore, expectant management may be better suited for lower risk individuals, HIV-negative patients, or patients with LGSIL, where lower rates of disease progression have been found.

It has been shown that anogenital HPV infection can be a precursor to other intraepithelial neoplasias located in the penis, vulva, and/or cervix; therefore, AIN typically does not

occur in isolation. Anogenital HPV infection does have an increased prevalence in the immunosuppressed patient population; so, a generalized examination must be performed with a strong consideration for preemptive AIN screening. It is therefore recommended that all females with AIN undergo a complete gynecologic evaluation.⁹

Topical Imiquimod

Imiquimod is a topically applied agent with both antiviral and antitumor activity and has been shown to be effective in patients with AIN.⁹ Imiquimod is currently approved by the United States Food and Drug Administration (FDA) for the treatment of genital and perianal condyloma, actinic keratosis, and superficial basal cell carcinoma.¹⁸ Imiquimod, however, has been an off-label use for several different conditions. It has been heavily studied in the treatment of AIN with relatively effective results.^{19–24} The typical recommended application is three times per week for a total of 16 weeks. Side effects can include burning, itching, irritation, pain, and infection which may adversely affect patient compliance.

A study published from Germany revealed regression of the AIN grade by at least two grades with the application of Imiquimod in 10 HIV-positive males (MSM). In addition to disease regression, it was found that HPV 16, one of the types specifically linked to anal SCC, was not detected by polymerase chain reaction (PCR) in any of the patients at follow-up.²⁰ Other studies have also found that the numbers and types of HPV were significantly reduced in patients treated with Imiquimod along with regression of the disease in 61% of patients studied at a median follow-up of 33 months.^{22,23} These studies have demonstrated that topical Imiquimod is useful in patients with multifocal AIN and can be used as the initial primary therapy in many cases.

The side effect profile of Imiquimod has been shown to limit patient compliance in many studies.^{19,20} Treatment adherence due to the significant treatment-related discomfort can be difficult to achieve and unfortunately, it has been shown that patients who do not comply with topical treatment instructions do not show any clinical response. The rate of compliance has been reported to be as high as 21%.²⁰ Flulike symptoms have also been reported following the start of Imiquimod therapy. Patient education, including the off-label usage, known side effects, and concern for compliance, is essential once this regimen is recommended to treat AIN.

Topical 5-Fluorouracil

Topical 5-fluorouracil (5-FU) has an established role and FDA approval in the treatment of actinic keratosis and nonmelanoma skin cancers, like superficial basal cell carcinoma.¹⁸ 5-FU is an antimetabolite that interferes with the synthesis of DNA and also inhibits the formation of RNA. Topical 5-FU was originally used in the treatment of extramammary Paget's disease but has been described for use in AIN since 1986.²⁵

Several case series reporting on the outcome of 5-FU for the treatment of AIN demonstrate some initial clinical

response rates that approach up to 90%.²⁶ Graham et al prospectively reviewed 11 patients with AIN using 5-FU twice daily for 16 weeks. Ten patients remained without evidence of AIN at a mean follow-up of 39 months. The only person who did not respond to this therapy was a patient with HIV. The results, however, are based on some interruptions in the treatment regimen and some patients had excision of macroscopic disease in addition to the topical therapy.²⁷ Another retrospective study looked at the efficacy of 5-FU in 11 HIV-infected MSM patients with AIN and found that the area of AIN was reduced in 6 of the 11 patients (55%), and also the grade of dysplasia was reduced in 3 of 11 patients (27%). The treatment duration was variable from 7 to 36 weeks, mainly due to patient adherence due to the side effects.²⁸

Treatment periods typically range from 9 to 16 weeks, although recurrence can be minimized with extended application.^{29,30} A prospective trial with enrollment of 46 HIV-infected MSM found that approximately 75% had multifocal high-grade AIN or HGSIL. Side effects were frequent, including skin irritation, burning and ulcerations, and hypopigmentation, and similar to the side effects reported for topical Imiquimod therapy. It was found that approximately 85% of participants experienced some side effects and the majority experiencing moderate to severe side effects. Treatment interruptions were common and found to occur in 5 of the 46 participants (10.8%). They found that 39% (18/46) had complete clearance of the AIN, 17% (8/46) had partial response, and 37% (17/46) patients did not respond. In this study, the authors do suggest that topical 5-FU might help facilitate subsequent surgical intervention by lessening the burden of the disease. Although the efficacy of 5-FU was identified, the optimal dose, frequency, and duration of treatment are still uncertain.²⁶

Another concern for the treatment for AIN with topical agents like 5-FU is the risk of recurrence. Risk factors for recurrence of AIN include poorly defined areas of involvement, poor immune response, dense scar tissue, persistent or recurrent HPV, and poor compliance with therapy.²⁷ The recurrence rate for AIN has been shown to approach 50%.^{9,26}

Topical 5-FU, like topical Imiquimod, has the benefit of treating widespread, multifocal disease; however, extended treatment regimens and the inflammatory side effects can be prohibitive. Therefore, 5-FU, like topical Imiquimod, can work well for patients with extensive multifocal disease who are highly motivated, but intensive counseling must occur to discuss the expected side effects which are also the symptoms of success.³¹

High-Resolution Anoscopy

High-resolution anoscopy is a screening technique that can include anal cytology with biopsies and also targeted therapeutic destruction. It was initially described in 1997.³² The goal of HRA is to identify high risk individuals with AIN who could benefit from more intensive screening or possibly therapeutic treatment with targeted destruction. HRA will be described in more detail by Cho et al.³³

Topical Trichloroacetic Acid

Topical 85% trichloroacetic acid (TCA) is a cytotoxic therapy that destroys tissue by chemical coagulation of proteins. TCA is considered a first-line therapy for condyloma acuminatum.²⁴ TCA can be used in combination with HRA for targeted tissue destruction and control of AIN lesions. Some benefits of TCA include availability, cost, no systemic side effects, and safe in pregnancy. Because of the low profile side effects and ease of use, TCA has been applied to both AIN patients and patients with condyloma.

The initial step is identification of the AIN lesions by HRA. This is then followed by direct application of the TCA to the AIN lesions until it turns white in color. One study reviewing the role of TCA in patients with AIN has been published which studied 54 patients with AIN and 65% of these patients were HIV positive. Patients were treated with topical TCA at month intervals with up to four applications. The response of the AIN lesions to TCA was found to be better in patients with two or fewer lesions and therefore, the authors concluded that TCA could be a reasonable first-line therapy in patients with minimal AIN disease.³⁴

Photodynamic Therapy

Photodynamic therapy, or infrared coagulation, which has been used in the treatment of condyloma and internal hemorrhoids, was initially described to treat patients with AIN in 1992.³⁵ Goldstone et al later elaborated on the role of photodynamic therapy for AIN because standard surgical techniques had associated morbidity that was unsuitable for the multifocal nature of AIN and possibly too aggressive. They discussed that the intraepithelial nature of AIN would be amenable to infrared coagulation therapy with its ablative effects as an outpatient experience offering a good patient safety profile.³⁶

Infrared coagulation uses topical photosensitizing agents, like aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), which is applied as a cream to the affected area followed by treatment with the infrared coagulation at a specific desired wavelength. Identification of the areas of concern is the initial first step by using HRA. Once the areas are confirmed with biopsy and identified, the infrared coagulation occurs under local anesthesia. The coagulated tissue is then removed and if necessary, repeat infrared coagulation is performed until the submucosal vessels are identified and coagulated. The depth of tissue coagulation is equal to the length of the pulse applied; therefore, deeper tissue damage can be avoided. Most patients can continue their normal activities after the procedure with analgesics and instructed local wound care. This technique has many advantages to the patient, namely, no anorectal preparation, local anesthesia, and an outpatient procedure with very little effect to normal activity. Infrared coagulation provides both hemostasis and tissue coagulation simultaneously.

There are many benefits to the use of infrared coagulation in patients with AIN. First, the successful technique can occur after only one outpatient session unlike the duration needed

for success using topical agents. In addition, adherence is better after the outpatient procedure compared with the prohibitive side effects of topical agents like Imiquimod and 5-FU. Also, there is less risk of adverse outcomes, like anal stenosis, fecal incontinence, sexual dysfunction, and pain, compared with surgical intervention.

Several small case series have demonstrated the safety and feasibility of photodynamic therapy for the treatment of AIN with both a regression in the grade of AIN and remission in short-term follow-up.^{37–41} There are multiple studies that discuss the role and efficacy of infrared coagulation for the treatment of AIN, but these studies are difficult to compare as there are many variables including different patient populations, no standardization to the infrared coagulation methods, variation in extent of the disease, different methodology, and different follow-up; therefore, each study should be scrutinized. Despite some of these differences, there is similar efficacy in patients with AIN treated with infrared coagulation, which was consistently in the range of 64 to 87%.^{10,35,42–45}

Infrared coagulation is an ideal treatment option for patients with AIN due to the adherence to treatment, low side effect profile, and less morbidity than surgical intervention; however, additional studies are needed to determine its role.

Operative Treatment

Surgical treatment for AIN has been described in the past to be managed with mapping biopsies and subsequent WLE. Mapping biopsies were used to understand the extent of the disease, followed by WLE which would be used to obtain negative margins in this patient population.⁴⁶ A survey performed in 2000 of the members of the American Society of Colon and Rectal Surgeons found that 87% of respondents chose surgical excision as their treatment of choice for patients with AIN.⁴⁷ At the time of the survey, however, the epidemiology of AIN was changing and the patient population affected was changing to a very different and very diverse subset. Initially, AIN was identified in nonimmunosuppressed patients, whereas currently, AIN is most commonly identified in the high-risk patient populations, that is, immunosuppressed patients, HIV-positive patients, and MSM patients. Since these studies, there have been multiple reports of incomplete efficacy, recurrence, and surgical complications with the wound following aggressive surgical excisional treatment.^{3,13,14}

Surgical treatment outcomes have consistently showed recurrence rates that range from 9 to 63%, with many cases treated with the need for repeat WLE and an 11% risk of progression to an invasive carcinoma, specifically in the high-risk patient population.^{8–10,13} Despite these aggressive surgical approaches with significant potential morbidity including anal stenosis, fecal incontinence, nonhealing wounds, the recurrence rates remain high. Due to the recent data with both high surgical morbidity and surgical wound complications and with questionable efficacy and unacceptable recurrence rates, alternative treatments have been

developed and mainly include the nonsurgical treatment options with good, if not better, overall results.

The most recent studies have changed the role of surgical therapy in patients with AIN. The key results that have changed most clinicians' minds include incomplete surgical excisions, frequent recurrences, and postsurgical morbidity. Surgical treatment specifically in the immunocompromised patient population with the frequent recurrences and progression to invasive anal cancer can be unsuccessful despite aggressive surgical therapy.^{14,15} This has led to a more nonsurgical approach to AIN including watchful waiting, topical therapies, or photodynamic therapy. Aggressive surgical treatment is considered currently not to be an ideal treatment option for most patients with AIN.

Vaccination

Certain strains of HPV have been shown to be the cause of both premalignant and malignant squamous tumors of the anogenital tract. HPV has the capability to induce transformation from AIN to invasive cancer and the HPV prevalence in patients with AIN, both high grade and low grade, has been reported at 91 and 88%, respectively.^{48,49} The prevention of the HPV infection would have the expectation to prevent AIN and then the transformation to invasive anal carcinoma.

There are two HPV vaccines available that prevent infection with the HPV 16 and HPV 18 strains, the strains which are responsible for the majority of cervical and anal cancers. Trials of these HPV vaccines have shown nearly 100% efficacy against high-grade lesions of the cervix, vulva, and vagina and against anogenital disease in uninfected women.⁵⁰ The Centers for Disease Control and Prevention (CDC) currently recommends the HPV vaccine for preteen boys and girls at age 11 or 12 years to protect them prior to any exposure to the HPV virus.

A randomized, double-blinded trial with the quadrivalent HPV vaccination (HPV 6, 11, 16 and 18) revealed that persistent anal infection with HPV 6, 11, 16, or 18 was reduced by 59.4% in the intention to treat group and 94.9% in the protocol cohort. The rate of HGSIL related to infection with the HPV was also reduced by 54.2 and 74.9%, respectively.⁵¹ It appears that the HPV vaccination can reduce persistent anal HPV infection and therefore decrease the risk of AIN and progression to anal SCC. Thus, vaccination seems promising; however, the exact vaccine composition, overall indications, and timing of administration need further investigation.

Summary

The goals of screening and treatment for patients with AIN are prevention of an invasive anal carcinoma and reduction of morbidity. The natural history of AIN in the immunocompetent population appears to be more indolent than the high-risk patient populations. The last two decades have shown a transition in the patient population affected by AIN with the majority of patients having immunosuppression. In the high-risk patient populations, progression of AIN to a more advanced grade can be as high as 50% with a lifetime

risk of progression to invasive cancer as high as 10 to 50%.⁹ The American Society of Colon and Rectal Surgeons recommends that patients with AIN be monitored with surveillance examinations at 3- to 6-month intervals as long as dysplasia is present.⁹ Close follow-up is imperative in the high-risk populations, but the optimal surveillance strategy is still under debate.

The current treatment strategies, including watchful waiting, topical therapy, or photodynamic therapy, aim to treat the complication of the HPV infection and resultant AIN. Surgical intervention is no longer an ideal strategy in most patients with AIN and the role of the HPV vaccine is still under investigation. Ongoing research is imperative to develop the optimal algorithm for treatment for patients with AIN.

References

- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(01):10–29
- Palefsky JM. Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women. *J Natl Cancer Inst Monogr* 1998;23(23):15–20
- 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. *Lancet Oncol* 2012;13(05):487–500
- Oriel JD, Whimster IW. Carcinoma in situ associated with virus-containing anal warts. *Br J Dermatol* 1971;84(01):71–73
- Fenger C, Nielsen VT. Dysplastic changes in the anal canal epithelium in minor surgical specimens. *Acta Pathol Microbiol Scand [A]* 1981;89(06):463–465
- Darragh TM, Winkler B. Anal cancer and cervical cancer screening: key differences. *Cancer Cytopathol* 2011;119(01):5–19
- Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med* 1997;337(19):1350–1358
- Abbasakoor F, Boulos PB. Anal intraepithelial neoplasia. *Br J Surg* 2005;92(03):277–290
- Steele SR, Varma MG, Melton GB, Ross HM, Rafferty JF, Buie WD; Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for anal squamous neoplasms. *Dis Colon Rectum* 2012;55(07):735–749
- Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience. *Dis Colon Rectum* 2008;51(06):829–835, discussion 835–837
- Goldman S, Auer G, Erhardt K, Seligson U. Prognostic significance of clinical stage, histologic grade, and nuclear DNA content in squamous-cell carcinoma of the anus. *Dis Colon Rectum* 1987;30(06):444–448
- Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973–2000. *Cancer* 2004;101(02):281–288
- Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. *ANZ J Surg* 2006;76(08):715–717
- Devaraj B, Cosman BC. Expectant management of anal squamous dysplasia in patients with HIV. *Dis Colon Rectum* 2006;49(01):36–40
- Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. *Br J Surg* 2005;92(09):1133–1136
- Duong TH, Flowers LC. Vulvo-vaginal cancers: risks, evaluation, prevention and early detection. *Obstet Gynecol Clin North Am* 2007;34(04):783–802, x
- Sobhani I, Walker F, Roudot-Thoraval F, et al. Anal carcinoma: incidence and effect of cumulative infections. *AIDS* 2004;18(11):1561–1569
- Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermatol* 2009;145(12):1431–1438
- Ganjian S, Ourian AJ, Shamtoub G, Wu JJ, Murase JE. Off-label indications for imiquimod. *Dermatol Online J* 2009;15(05):4
- Gutzmer R, Kaspari M, Vogelbruch M, et al. Successful treatment of anogenital Bowen's disease with the immunomodulator imiquimod, and monitoring of therapy by DNA image cytometry. *Br J Dermatol* 2002;147(01):160–165
- Kreuter A, Hochdorfer B, Stücker M, et al. Treatment of anal intraepithelial neoplasia in patients with acquired HIV with imiquimod 5% cream. *J Am Acad Dermatol* 2004;50(06):980–981
- Wieland U, Brockmeyer NH, Weissenborn SJ, et al. Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006;142(11):1438–1444
- Fox PA, Nathan M, Francis N, et al. A double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. *AIDS* 2010;24(15):2331–2335
- Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015;64(RR-03):1–137
- Schmidt KU, Wiskemann A, Mensing H. Etretnate and 5-fluorouracil in intra-anal Bowen's disease [in German]. *Hautarzt* 1986;37(05):278–280
- Richel O, Wieland U, de Vries HJ, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. *Br J Dermatol* 2010;163(06):1301–1307
- Graham BD, Jetmore AB, Foote JE, Arnold LK. Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach. *Dis Colon Rectum* 2005;48(03):444–450
- Snyder SM, Siekas L, Aboulafia DM. Initial experience with topical fluorouracil for treatment of HIV-associated anal intraepithelial neoplasia. *J Int Assoc Physicians AIDS Care (Chic)* 2011;10(02):83–88
- Cox NH, Eedy DJ, Morton CA; Therapy Guidelines and Audit Subcommittee, British Association of Dermatologists. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol* 2007;156(01):11–21
- Bargman H, Hochman J. Topical treatment of Bowen's disease with 5-Fluorouracil. *J Cutan Med Surg* 2003;7(02):101–105
- Weis SE. Current treatment options for management of anal intraepithelial neoplasia. *Onco Targets Ther* 2013;6:651–665
- Jay N, Berry JM, Hogeboom CJ, Holly EA, Darragh TM, Palefsky JM. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. *Dis Colon Rectum* 1997;40(08):919–928
- Cho SD, Groves E, Lao VV. History of high-resolution anoscopy. *Clin Col Rec Surg* 2018;31(06):336–346
- Singh JC, Kuohung V, Palefsky JM. Efficacy of trichloroacetic acid in the treatment of anal intraepithelial neoplasia in HIV-positive and HIV-negative men who have sex with men. *J Acquir Immune Defic Syndr* 2009;52(04):474–479
- Petrelli NJ, Cebollero JA, Rodriguez-Bigas M, Mang T. Photodynamic therapy in the management of neoplasms of the perianal skin. *Arch Surg* 1992;127(12):1436–1438
- Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum* 2005;48(05):1042–1054
- Allison RR, Sheng C, Cuenca R, Bagnato VS, Austerlitz C, Sibata CH. Photodynamic therapy for anal cancer. *Photodiagn Photodyn Ther* 2010;7(02):115–119

- 38 Kruijt B, van der Snoek EM, Sterenberg HJ, Amelink A, Robinson DJ. A dedicated applicator for light delivery and monitoring of PDT of intra-anal intraepithelial neoplasia. *Photodiagn Photodyn Ther* 2010;7(01):3–9
- 39 van der Snoek EM, Amelink A, van der Ende ME, et al. Photodynamic therapy with topical metatetrahydroxylchlorin (Fosgel) is ineffective for the treatment of anal intraepithelial neoplasia, grade III. *J Acquir Immune Defic Syndr* 2009;52(01):141–143
- 40 Hamdan KA, Tait IS, Nadeau V, Padgett M, Carey F, Steele RJ. Treatment of grade III anal intraepithelial neoplasia with photodynamic therapy: report of a case. *Dis Colon Rectum* 2003;46(11):1555–1559
- 41 Strauss RJ, Fazio VW. Bowen's disease of the anal and perianal area. A report and analysis of twelve cases. *Am J Surg* 1979;137(02):231–234
- 42 Stier EA, Goldstone SE, Berry JM, et al. Infrared coagulator treatment of high-grade anal dysplasia in HIV-infected individuals: an AIDS malignancy consortium pilot study. *J Acquir Immune Defic Syndr* 2008;47(01):56–61
- 43 Cranston RD, Hirschowitz SL, Cortina G, Moe AA. A retrospective clinical study of the treatment of high-grade anal dysplasia by infrared coagulation in a population of HIV-positive men who have sex with men. *Int J STD AIDS* 2008;19(02):118–120
- 44 Goldstone RN, Goldstone AB, Russ J, Goldstone SE. Long-term follow-up of infrared coagulator ablation of anal high-grade dysplasia in men who have sex with men. *Dis Colon Rectum* 2011;54(10):1284–1292
- 45 Weis SE, Vecino I, Pogoda JM, Susa JS. Treatment of high-grade anal intraepithelial neoplasia with infrared coagulation in a primary care population of HIV-infected men and women. *Dis Colon Rectum* 2012;55(12):1236–1243
- 46 Cleary RK, Schaldenbrand JD, Fowler JJ, Schuler JM, Lampman RM. Perianal Bowen's disease and anal intraepithelial neoplasia: review of the literature. *Dis Colon Rectum* 1999;42(07):945–951
- 47 Cleary RK, Schaldenbrand JD, Fowler JJ, Schuler JM, Lampman RM. Treatment options for perianal Bowen's disease: survey of American Society of Colon and Rectal Surgeons Members. *Am Surg* 2000;66(07):686–688
- 48 Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. *Int J Cancer* 2009;124(10):2375–2383
- 49 Gohy L, Gorska I, Rouleau D, et al; HIPVIRG Study Group. Genotyping of human papillomavirus DNA in anal biopsies and anal swabs collected from HIV-seropositive men with anal dysplasia. *J Acquir Immune Defic Syndr* 2008;49(01):32–39
- 50 Garland SM, Hernandez-Avila M, Wheeler CM, et al; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356(19):1928–1943
- 51 Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011;365(17):1576–1585