# Anal Cancer: A Multispecialty Disease, a Multispecialty Cure

## Part I: Malignant Precursors

By Gary H. Hoffman, MD

Anal neoplasms are a rare, diverse group of lesions. Each manifests a different behavior. With the recent publicity surrounding anal cancer, attention has focused on screening, early diagnosis and treatment.

The incidence of anal carcinomas has been increasing slowly, with 3,500 cases reported in the United States in 2001, and 5,260 cases reported in 2009.[1] Of these cases, 85% arise in the anal canal. The remainder arise from the perianal skin. Patients presenting with anal carcinomas range in age from 25 to 75, although 95% of patients are older than age 45. In anal canal cancers, there is a marked female to male preponderance of 5:1. However, in locales with a large number of high-risk males, the ratio approaches 1:1. In contrast to anal canal cancers, perianal cancers are found almost equally in men and women.[2]

Homosexual males have up to a 30 times higher risk for developing an anal squamous cell cancer than the general male population. HIV-positive men are at particularly high risk.[3,4]

### Anal Anatomy—The First Step in Understanding the Disease

It is useful to consider the anatomic site of origin when evaluating anal cancers, as tumors arising from differing locations in the anal canal may have different histogenetic origins, may behave differently and may be treated differently.

To best approach the diagnosis and staging of anal tumors, the anal canal first must be defined (Figure 1). The anal canal is small and complex, with differing areas of histology, differing lymph node drainage patterns, an intricate musculature and a complex neural innervation. The canal begins at the upper aspect of the anorectal ring, which is defined by the upper borders of the internal anal sphincter and the puborectalis muscles.[5,6]

The proximal canal contains a columnar epithelium. The mucosa gradually changes to a nonkeratinized-stratified squamous epithelium as it passes through the 1 cm-long anal transition zone above the dentate line.[7] The canal continues distally to the anal verge and then to the mucocutaneous junction, which is that area of change from nonkeratinized-stratified squamous mucosa to a keratinized squamous epithelium of the epidermis, with hair-bearing skin appendages and sebaceous or apocrine sweat glands.[8]

The dentate line, so named because of its edged, tooth-like appearance, is located 1 to 2 cm proximal to the anal verge and is the transition between columnar mucosa and squamous mucosa. It is the remnant of the border between the embryological endoderm and ectoderm. The dentate line is often used as a point of reference when describing the location of anal disease.

Generally, the area proximal to the dentate line, the first centimeter of which is termed the anal transitional zone, has a lymphatic basin which drains into the superior rectal lymphatics and then to the inferior mesenteric nodes. Additionally, lateral drainage occurs through the middle and inferior lymphatics and the ischioanal fossa into the internal iliac nodes. Distal to the dentate line, drainage is primarily to the inguinal nodes. However, secondary drainage may also extend superiorly to the internal iliac nodes. The perianal skin begins at the anal verge and extends for 5 cm outward onto the buttocks. It drains exclusively to the inguinal nodes. Knowledge of the lymphatic drainage is important in guiding therapy of anal cancers so as to ensure that the appropriate nodal basins are included in the treatment.

### Genetics and Genetic Epidemiology—The Next Step in Understanding

There exist many associations between anal cancer and a variety of possible causes such as smoking; the coexistence of sexually transmitted diseases; a history of cervical, vulvar or vaginal carcinoma; the use of solid-organ post-transplant immunosuppressive medications; and various environmental factors. Anoreceptive intercourse is considered to be a risk factor in disease development and there is a suggestion that anoreceptive intercourse beginning at an early age is the specific high risk factor in the promotion of disease. However, most people with anal squamous cell cancers deny anoreceptive intercourse, leading to the idea that other modes of risk transmission may be operative.

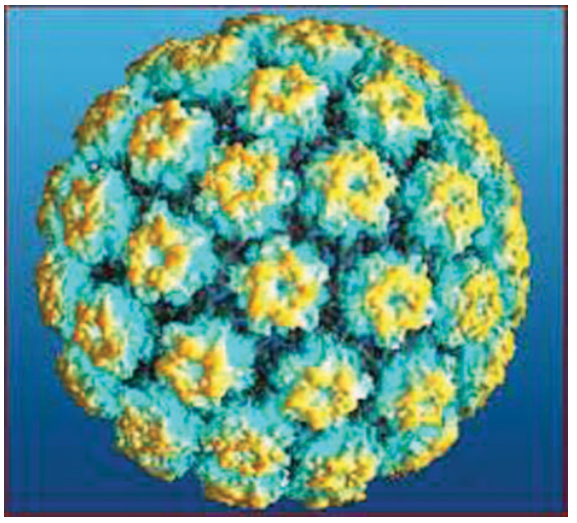

**Figure 2. The human papilloma virus.**

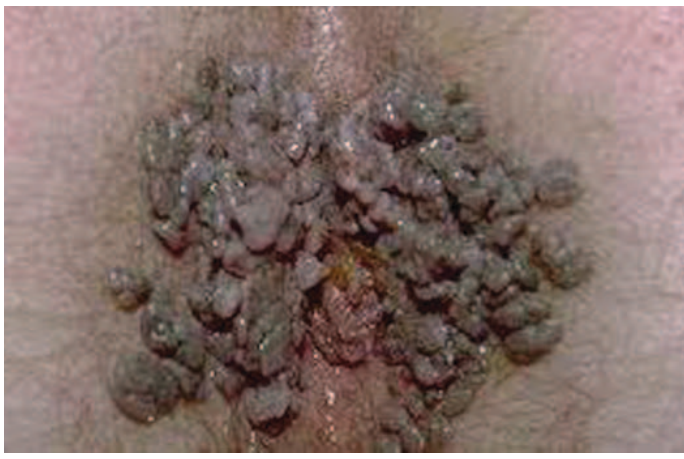

**Figure 3. HPV-associated anal condyloma.**

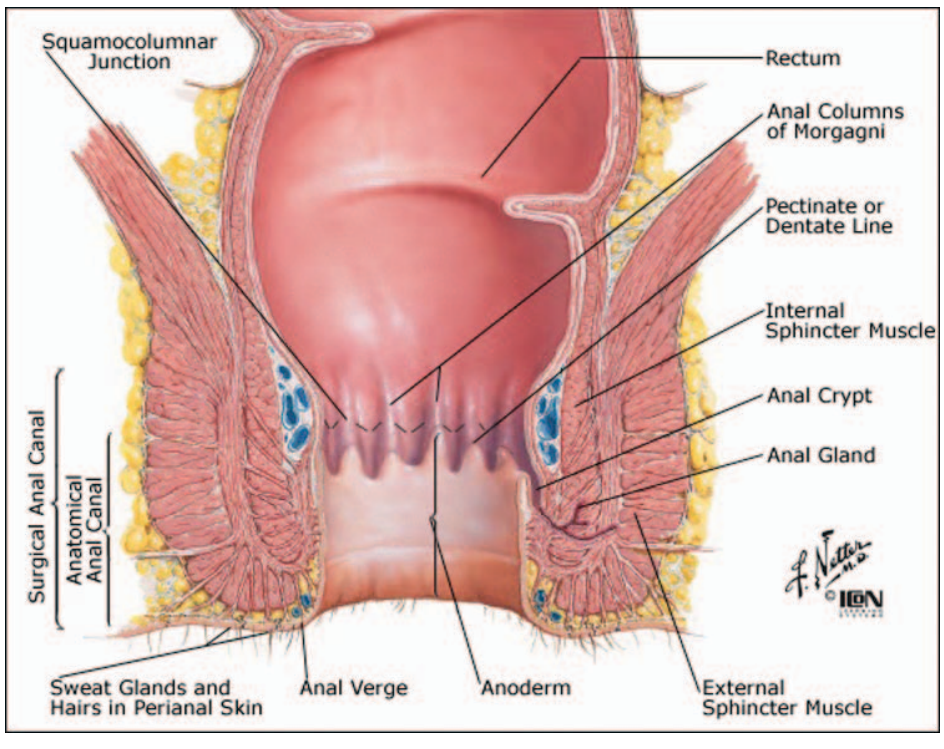


**Figure 1. Anatomy of the anal canal.**



### HPV the Culprit? The Data

Research has focused on data pointing to the human papilloma virus (HPV) in combination with other risk factors as the etiology of many anal cancers (Figure 2). This may be similar to HPV causation in cervical cancer.

HPV is a double-stranded DNA virus which infects stratified epithelium of skin or mucous membranes. At least 20 of the more than 200 HPV genotypes infect the anogenital area. Types 6 and 11 are associated with anal condyloma (warts) and low-grade anal intraepithelial neoplasia (AIN). These rarely become malignant (Figure 3). Genotypes 16, 18, 31, 33 and 35 are associated with high-grade AIN (also called Bowen's disease, carcinoma in situ [CIS], or AIN III) as well as with invasive cancers of the anus and cervix.

The more benign genotypes 6 and 11 are found as episomes. Episomes are pieces of genetic material that exist separately from chromosomal DNA. HPV-6 and 11 are rarely associated with malignancies and this may be

see Malignant Precursors page 16

## Malignant Precursors

Continued from page 14

because of their lack of integration into the host chromosomal DNA. HPV-16 and 18, however, are integrated into the host DNA and thus may promote a neoplastic cascade that ends in malignancy.

The upper anal canal transitional epithelium is composed of a columnar epithelium with an overlay of nonkeratinized squamous metaplasia. Metaplastic nonkeratinized tissue may be unusually susceptible to infection with HPV.[9-11] HPV-16 and 18 are commonly found in anal canal carcinomas, especially proximal to the dentate line. In fact, these upper canal cancers are rarely found without HPV-16 or 18. It is uncommon to find HPV-16 or 18 DNA in the modified skin of the lower anal canal, with its keratinized mucosa. HPV DNA is almost never found in normal, nonmalignant anal tissue, and is rarely found in nonsquamous cell anal cancers such as adenocarcinoma.

Anal cancer pathogenesis may include a combination of an HPV infection in an immunocompromised host, in susceptible tissue, compounded by other, as of yet unknown environmental factors. Bolstering the idea that a faulty immune system is a necessary precondition in anal squamous cell malignancies, it has been noted that immunocompromised transplant patients and those with post-chemotherapy carcinoma have a higher frequency of HPV infections with a greater progression to anal squamous cell carcinoma.[12,13] Additionally, up to 50% of HIV-positive patients harbor detectable levels of HPV DNA, and an immunocompromised state may promote disease in combination with a persistent HPV infection in the anal canal.[2]

### Screening: Alphabet Soup of Acronyms

Those at a higher risk should be screened every one to three years with an anal Papanicolou (Pap) smear. Screening rationale is similar to that in screening women for cervical cancer. Abnormal cells found on an anal Pap smear should prompt further investigation using anal biopsies to identify intraepithelial neoplasia.

Men with a history of homosexual or bisexual activity and/or anoreceptive intercourse, HIV-positive men and women irrespective of an anal intercourse history and women with cervical or vulvar lesion or carcinoma should be evaluated with physical exams and anal Pap smears. A special brush is used to obtain cells from the lower anal canal and anal verge (Figure 4). The specimen is fixed and then evaluated for the presence of abnormal cells. With 95% accuracy, certain abnormal results should prompt a closer evaluation using anoscopy and biopsies of areas targeted by acetic acid staining. Borrowing a page from the Bethesda gynecological grading system,[14] anal Pap smears are graded as follows:

- Normal
- Atypical squamous cells of undetermined significance (ASCUS)
- Low-grade squamous intraepithelial lesion (LGSIL or LSIL)
- High-grade squamous intraepithelial lesion (HGSIL or HSIL).

It is not established whether or not patients with anal ASCUS or LSIL require further evaluation. By analogy to cervical Pap evaluation, many physicians do pursue findings of ASCUS or LSIL. However, it is not clear that this part of the evaluation algorithm is truly similar to anal cytological evaluation. Some physicians do move forward with further evaluation, and some do not. At any rate, in HIV-positive patients with normal anal Pap smears, repeat exams are performed every 12 months. In HIV-negative patients, exams are repeated every two or three years. The examinations are painless, highly accurate, and inexpensive.

**Figure 4. Brush for Anal Cytology.**

For patients with HSIL or those with normal Pap smears for whom the physician has a high level of suspicion that disease may exist, further inquiry with biopsies is initiated looking for AIN or occult malignancies.

Biopsy-proven anal intraepithelial neoplasia is graded as AIN I, II or III. With AIN III, in situ carcinoma is seen microscopically. There are multinucleated giant cells, the so-called bowenoid cells, with some vacuolization, giving a "halo" effect. AIN III is a worrisome finding.

### Perianal Premalignant Disease: Many Names, Many Treatments

Evaluating and treating all forms of AIN may lead to overtreatment. Treating only selected patients such as those with AIN III may lead to undertreatment and a failure to prevent an ominous progression of the disease. Longitudinal studies will be illuminating.

The recommendations for evaluating and treating AIN I and AIN II are not uniform. AIN I or II may be observed and re-evaluated every three to six months. These may regress spontaneously.

Some practitioners do treat AIN I, however, with the rationale that treating AIN I prevents the further spread of disease, reduces the symptoms associated with AIN I and reduces the extent of disease to the point that topical therapy remains possible.

The purported rationale for treating AIN II and AIN III is to prevent cancer. Again, the natural history of the disease is unknown, and the progression to an anal malignancy is not a given.

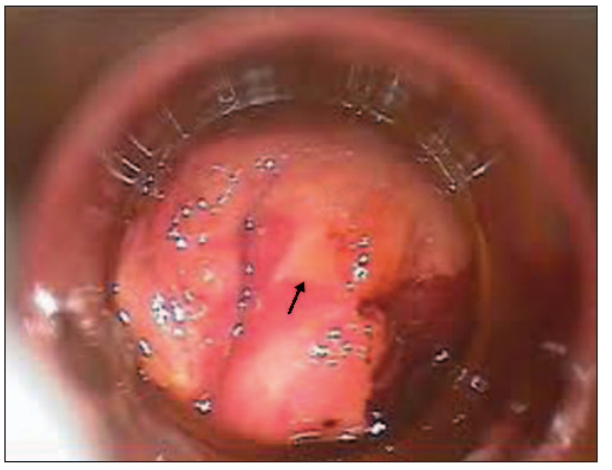

**Figure 5. AIN 3 stained with Lugol's solution (arrow).**

Erring on the side of caution, consideration must be given to eradicating AIN III. High-grade AIN (AIN III) is an intraepithelial squamous cell carcinoma or carcinoma in situ and is the same disease as the older moniker, Bowen's disease, which should be used only in an historical context.

AIN III is strongly associated with the presence of HPV-16 and 18 and is considered to be a premalignant condition that has not yet undergone malignant transformation.[15,16] Observations show a low incidence of malignant transformation of AIN III in patients who are immunocompetent.[17] Definitive proof that AIN III progresses to anal cancer is lacking however, and the natural history of perianal AIN is not firmly established.[18] Studies suggest that up to 28% of patients with AIN III have a synchronous invasive squamous cell carcinoma at the time of diagnosis of AIN III.[16,19-20] Perianal AIN may be associated with malignancies in other organs.[21]

### What Does AIN Look Like?

Crusted plaques with erythema or scales and occasional pigmentation are typical of AIN. Areas of ulceration may signal carcinomatous changes. Circumferential disease is common. Lesions may be accompanied by itching, burning or bleeding and a definitive diagnosis is made by biopsy. The disease may involve the anoderm just above the anal verge, the anal verge itself, the perianal skin or the vulva. Disease borders are notoriously indistinct. Intraoperative localization is aided by using an operating microscope, acetic acid or Lugol's solution (Figure 5). Areas to be biopsied appear white when exposed to acetic acid. AIN III lesions appear yellow or tan when stained with Lugol's solution. Diagnosis may also be made incidentally by finding AIN in hemorrhoidectomy specimens.

### Many Cures: Which Is Best?

There is ample literature supporting a watch-and-wait posture with AIN III. With this approach, patients are followed with regular exams rather than being treated. Any change in symptoms or the appearance of new lesions would prompt further investigation.

However, after evaluating the available data, many physicians have chosen to aggressively treat AIN III. Either way, vigilance is mandatory.

### Topical Therapy

Several modes of treatment are available to treat AIN III. Imiquimod (Aldara, 3M Pharmaceuticals), an immune response modifier, was originally approved as a treatment for genital warts. It had been used for other benign and malignant skin disorders as well. Imiquimod increases the local production of interferon. It is applied as a 5% cream, 3 times weekly at night for up to 3 months and is left in place for 8 hours per treatment.[22] Although safe, imiquimod may cause local itching, pain or burning, or constitutional reactions such as headache, myalgia, or gastrointestinal symptoms. A 2- or 3-week rest period may be necessary if the local reaction may be significant. Although promising, further studies are necessary to determine if it will become the first line treatment for AIN III.

Topical 5% fluorouracil (5-FU) is a well-known antineoplastic agent. When applied to anal disease, it has been shown to be highly effective in treating and eradicating AIN III. In a prospective study conducted over a

see Malignant Precursors page 18

## Malignant Precursors

Continued from page 16

6-year period, a 16-week course of topical 5-FU treatment was given for patients whose disease was greater than one-half the circumference of the anal canal.[23] Patients with lesser involvement of the canal underwent surgical excision. One year after treatment, all patients underwent anal mapping and biopsies. Eight of 11 patients underwent topical treatment and 3 underwent surgical excision. All but one (who was HIV-positive) were free of disease at the conclusion of therapy. All patients were followed yearly for between 12 and 74 months. There were no recurrences and no long-term side effects or morbidity were reported. Topical 5-FU is commonly used as the first line of defense in treating perianal carcinoma in situ.

### Operative Intervention

Both cautery ablation and surgical excision are readily available to experienced surgeons. Ablation has the advantage of causing less long-term damage to the perianal area. Ablation, however, does not allow for tissue diagnosis, and more extensive disease or carcinoma may be overlooked. Thus, ablation should be combined with biopsies. The location of each biopsied area should be noted in detail so as to be able to treat any newly disclosed disease.

When combined with acetic acid visualization, targeted ablation can be performed with a low incidence of nonhealing wounds or stricture. With extensive or circumferential disease, treatment should be performed in stages to avoid stricture development. A caveat: AIN III may involve hair follicles, sweat glands, and sebaceous glands. During cautery ablation, occult disease in these structures may be overlooked and subsequently untreated.[24] Of note, ablation is curative in almost all HIV-negative patients, whereas HIV-positive patients have a recurrence rate close to 100%. Close follow-up is mandatory.[15]

High-resolution anoscopy with guided biopsies has shown promise in improving targeted treatment. However, this technique requires specialized training and may not be available in all operating rooms.

Although it would seem logical that wide local excision (WLE) would be the treatment of choice for extensive disease, this may not be the case. However, most surgeons seem to favor this approach.[25] Excision margins may be difficult to define and normal-appearing skin may harbor HPV, especially genotypes 16 and 18. Diseased areas treated with WLE have a high recurrence rate, even with the use of disclosing agents and mapping. Normal-appearing mucosa may harbor microscopic disease, leading to recurrence.[21] WLE is associated with anal stricture, ectropion and incontinence, occasionally necessitating an ostomy. As an adequate excision might need to include the anoderm up to the dentate line, V-Y island flaps may be needed. The surgeon must be experienced in the anatomy and operative treatment of the anal and perianal areas.

### AIN in a Hemorrhoidectomy Specimen

In the special case where disease is found in a hemorrhoidectomy specimen, treatment recommendations vary from a return to the operating room after sufficient healing, for a WLE with frozen section evaluation of the specimen margins, to topical therapy or watchful waiting. The more radical surgical approach is associated with high recurrence rates and the potential for anal stenosis and continence difficulties.[26]

### What To Do?

AIN evaluation and treatment guidelines are continuing to evolve as new data and research are published.

It appears as if treatment for high-grade disease is shifting away from routine surgical extirpation[24] toward either watchful waiting or topical therapy with imiquimod or 5-FU. Targeted electrofulgeration in patients discovered to have AIN III also is a possible initial treatment option.[16] Surgical extirpation may be reserved for patients with persistent untreatable symptomatic disease or invasive carcinoma. Long-term follow-up is a necessity. As always, physicians should be aware of the possibility of coexisting anal malignant disease or malignant disease in other organs.

Physicians treating AIN should vigilantly follow patients' clinical complaints and physical examinations, and remain cognizant of the ever-changing treatment recommendations.

### Vaccination: Prevention Is Always Best

For women, 2 vaccines are available to prevent cervical HPV infection in those who have not yet been exposed to the disease. It is hoped that immunization between the ages of 9 and 26 will reduce the incidence of cervical neoplasia. What about male vaccination?

Gardasil®, a quadrivalent recombinant vaccine, has the advantage of proven effectiveness against HPV-6 and 11, the viruses associated with anal condyloma, as well as HPV-16 and 18, the genotypes thought to cause AIN and anal cancer. Gardasil contains recombinant virus-like particles that look like HPV virions but lack the viral DNA. The particles cannot induce cancer, but do promote an antibody response, and thus protect against infection with the 4 HPV types represented in the vaccine. Gardasil now has been approved for use in boys and men as well as in women. Its efficacy appears promising.

Vaccination will not prevent disease in those already exposed to one of the genotypes of HPV, although it may prevent disease caused by another one of the 3 remaining genotypes. Vaccination will not cause regression of established disease. Finally, vaccination will not prevent disease caused by any of the more than 16 other genotypes that infect the anogenital region.

Rather than offering vaccination to only high-risk groups, universal immunization may be offered prior to the beginning of sexual experience, as HPV is a sexually acquired pathogen with a ubiquitous presence.[27] Universal vaccination recommendations have not yet been formulated.

With progression to the malignant stage, perianal cancers become more ominous and treatments become more radical. These issues will be the subject of Part 2 of this series.

### References


1. American Cancer Society (ACS). Detailed guide: Anal cancer. What are the key statistics about anal cancer? www.cancer.org/cancer/analcancer/detailedguide/anal-cancer-what-is-key-statistics. Accessed Dec. 28, 2010.

2. Deans GT, McAlee JA, Spence RJ. Malignant anal tumors. *Br J Surg.* 1994;81:501-508

3. Fenger C FM, Marti MC, Parc R. WHO classification of tumors. Pathology and genetics of tumors of the digestive system. In: Hamilton SR, Aaltonen LA, eds. *Tumors of the anal canal.* Lyon, France: International Agency for Research on Cancer [IARC];2002:146-155.

4. Maggard MA, Beanes SR, Ko CY. Anal canal cancer: a population-based appraisal. *Dis Colon Rectum.* 2003;46(11):1517-1524.

5. Nivatvongs S, Stern HS, Fryd DS. The length of the anal canal. *Dis Colon Rectum.* 1981;24(8):600-601.

6. Milligan ETC, Morgan CN. Surgical anatomy of the anal canal: with special reference to anorectal fistulae. *Lancet.* 1934;224(5804):1150-1156.

7. Fenger C. The anal transition zone. *Acta Pathol Microbiol Immunol Scand.* 1987;85(suppl 289):1-42.

8. Morson BC, Dawson IP. *Gastrointestinal Pathology.* Oxford, UK: Blackwell Scientific Publications;1972:603-606.

9. Shroyer KR, Kim JG, Manos MM, Greer CE, Pearlman NW, Franklin WA. Papilloma virus found in anorectal squamous carcinoma, not in colon adenocarcinoma. *Arch Surg.* 1992;127(6):741-744.

10. Palmer JG, Scholfield JH, Coates PJ. Anal cancer and human papillomaviruses. *Dis Colon Rectum.* 1989;32(12):1016-1022.

11. Fisch M, Glimelius B, Van Den Brule AJ. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med.* 1997;337(19):1350-1358.

12. Welton ML. Etiology of human papilloma virus infections and the development of anal squamous intraepithelial lesions. *Semin Colon Rectal Surg.* 2004;15(4):193-195.

13. Mullerat J, Northover J. Human papilloma virus and anal neoplastic lesions in the immunocompromised (transplant) patient. *Semin Colon Rectal Surg.* 2004;15(4):215-217.

14. Solomon D. The Bethesda System: Terminology for reporting results of cervical cytology. *JAMA.* 2002;287(16):2114-2119.

15. Chang GJ, Welton ML. Anal neoplasia. *Semin Colon Rectal Surg.* 2003;14 (2):111-118.

16. Brown SR, Skinner P, Tidy J, Smith JH, Sharp F, Hosie KB. Outcome after surgical resection for high-grade anal intraepithelial neoplasia (Bowen's disease). *Br J Surg.* 1999;86(8):1063-1066.

17. Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. *Br J Surg.* 2005;92(9):1133-1136.

18. Abbasakoor F, Boulos PB. Anal intraepithelial neoplasia. *Br J Surg.* 2005;92(3):277-290.

19. Machesa P, Fazio VW, Oliart S, Goldblum JR, Lavery IC. Perianal Bowen's disease: a clinico-pathological study of 47 Patients. *Dis Colon Rectum.* 1997;40(11):1286-1293.

20. Sarmiento JM, Wolff BG, Burgart LJ, Frizelle FA, Ilstrup DM. Perianal Bowen's disease: associated tumors, human papilloma virus, surgery and other controversies. *Dis Colon Rectum.* 1997;40(8):912-918.

21. Gordon PH, Nivatvongs S. Perianal neoplasms. *Principles and Practice of Surgery for the Colon, Rectum, and Anus.* New York, NY: Informa Healthcare; 2007.

22. Chen K, Shumack S. Treatment of Bowen's disease using a cycle regimen of imiquimod 5% cream. *Clin Exp Derm.* 2003;28(Suppl s1):10-12.

23. 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(3):444-450.

24. Skinner PP, Ogunbiyi OA, Scholefield JH, Starts JF, Smith JHF, Sharp F, Rogers K. Skin appendage involvement in anal intraepithelial neoplasia. *Br J Surg.* 1997;84(5):675-678.

25. Cleary RK, Schaldenbrand JD, Fowler JJ, Schuler JM, Lampman RM. The treatment options for perianal Bowen's disease: survey of American Society of Colon and Rectal Surgeons members. *Am J Surg.* 2000;66(7): 686-688.

26. Scholfield JH. Anal intraepithelial neoplasia. *Br J Surg.* 1999;86:1364.

27. Stanberry LR. A human papilloma virus type 16 vaccine. *N Engl J Med.* 2003;348(14):1402-1405.


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