Most anal cancers are classified histologically as squamous cell carcinoma (SCC) with a smaller proportion classified as adenocarcinoma and small cell/neuroendocrine carcinoma. While most studies have not distinguished among these histologic types when identifying risk factors, given the predominance of squamous cell cancer, most of the data available reflect risk factors associated with it.

Like cervical cancer, most anal cancers are associated with human papillomavirus (HPV). The HPV types associated with anal cancer are similar to those found in cervical cancer, but HPV 16 may be even more dominant in anal cancers than it is in cervical cancer. Approximately 90% of anal cancers are associated with HPV, and it is possible that this number will increase even further with future studies. As with other HPV-associated cancers, the proportion of anal cancers associated with HPV has varied from study to study, with the more recent studies tending to show a higher prevalence, most likely due to improvements in molecular detection techniques. Overall, the evidence suggests that the relationship between HPV and anal cancer is the same for both men and women; however, one study showed a lower prevalence of HPV infection in anal cancers obtained from men.

As in the cervix, anal cancer is likely preceded by anal intraepithelial neoplasia (AIN), which is morphologically analogous to cervical intraepithelial neoplasia (CIN), and like CIN, AIN is strongly associated with HPV infection. Both cervical and anal cancers commonly develop in regions of metaplastic squamous epithelium of the transformation zones. Given the concordance between their histology, association with HPV, and similarity of their precursor lesions, anal cancer and cervical cancer are very similar diseases.

While anal cancer strongly resembles cervical cancer, there are substantial biologic differences between the anus and the cervix, including their physiologic functions and hormonal and microflora environments. As described later, anal HPV infection is very common in some populations of men and women, and among some female populations, anal HPV infection is more common than cervical HPV infection. Given the relatively lower incidence of anal cancer compared with cervical cancer, the incidence of anal cancer on a per-HPV infection basis is substantially lower than that of the cervix. It would thus appear that the anal epithelium is less susceptible to HPV-associated oncogenic transformation than the cervix. The reason for this discrepancy is not clear but may reflect differences in hormonal influences and other differences in the microenvironment such as microflora, and pH.
The overall incidence of anal cancer in the United States between 1998 and 2003 was 1.52/100,000, with the incidence of squamous cell cancer, adenocarcinoma, and small cell/neuroendocrine cancer being 1.28/100,000, 0.22/100,000, and 0.02/100,000, respectively. In the general population, anal squamous cell cancer is more common among women than men, while adenocarcinomas are more common among men. During this time period, the average annual incidence among males in the United States was 1.0/100,000 and among females was about 50% higher. Among men, the median age of diagnosis of anal cancer was 57 years and among women, 68 years. The incidence of anal cancer increased with age among men, with the highest incidence (3.1/100,000) among those over 70 years of age. The incidence of anal cancer among women followed the same age-related pattern with a peak incidence of 5.2/100,000 among those over 70 years of age. In 2010, there were estimated 2000 cases of anal cancer among men and 3260 cases among women in the United States. In comparison, in 2010 there were an estimated 12,200 cases of cervical cancer in women in the United States or an age-adjusted incidence of 6.7/100,000.

While the incidence of anal cancer is relatively low compared with cervical cancer, the incidence of this disease has been increasing among both men and women by about 2% per year (Figure 17.1). Thus in the 2003 to 2007 time period, the incidence of anal cancer was 1.8/100,000 in women and 1.4/100,000 in men. The reason for this increase is not well understood.

Prior to the human immunodeficiency virus (HIV) epidemic, the main risk factors identified for anal cancer were smoking, history of male homosexual contact, and history of genital warts and other sexually transmitted infections (presumably reflecting exposure to HPV). Other risk factors found include chronic irritation in the form of hemorrhoids, fissures, and fistulas. Men who have sex with men (MSM) have been shown to be one of the populations at highest risk for anal cancer, with an estimated incidence as high as 36.9/100,000 prior to the onset of the HIV epidemic. Although the exact reasons for this high incidence in MSM are not fully understood, it likely reflects high rates of receptive anal intercourse that expose them to anal HPV infection, as well as risk of other sexually transmitted infections and chronic anal irritation. Overall, the incidence of anal cancer among HIV-uninfected MSM is greater than the incidence of cervical cancer in the general population of women. In the United States, most women are screened for cervical cancer. MSM remain largely unscreened for anal cancer and its precursor, AIN.

While it is clear that having receptive anal intercourse is a risk factor, many men and women diagnosed with anal cancer report no history of anal intercourse. Other sexual practices such as exposure to HPV-infected skin surfaces without anal penetration could lead to HPV inoculation of the anal canal. Theoretically, shedding from other genital surfaces could also lead to autoinoculation. Consistent with this, a history of HPV-associated lesions at genital sites other than the anus is associated with anal cancer, presumably reflecting common exposure to HPV.

Finally, an increasingly important risk factor for anal cancer is immunosuppression. At least some of the population-based increase in anal cancer, described above, may reflect growing numbers of immunosuppressed individuals. Solid organ transplant recipients, including kidney, heart, and lung transplants, are at increased risk of anal cancer.

Individuals with HIV-associated immunosuppression are also at increased risk of anal cancer. This was true prior to the availability of highly active antiretroviral therapy (HAART), and there is evidence that the incidence of anal cancer has not declined since HAART became widely available. On the contrary, in some HAART-treated populations, the incidence of anal cancer may be continuing to increase. Several reports describe a higher incidence of anal cancer post-HAART compared with pre-HAART. One recent report showed that the incidence of anal cancer increased from the pre-HAART era to the early post-HAART era, but that the incidence did not continue to increase beyond that in the later post-HAART era. In another report, however, the incidence of anal cancer has continued to rise into the later post-HAART era, with the incidence among HIV-infected MSM on HAART as high as 128/100,000. The risk of anal cancer may correlate with duration of immunodeficiency and high viral load prior to initiation of HAART. Given that most HIV-positive individuals currently do not undergo screening or treatment for high-grade AIN (HGAIN), the longer survival time afforded by HAART gives an untreated HGAIN lesion more time to potentially progress to cancer. Notably, the incidence of anal cancer among HIV-positive individuals is significantly higher than that in the general population, and these individuals are more likely to have squamous cell carcinoma.

Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

A larger number of new sexual partners after the age of 30 years among MSM compared with women in the general population. In that study, anal HPV infection was independently associated with receptive anal intercourse during the preceding 6 months and with having more than five sex partners during the preceding 6 months.

Most studies of HIV-infected MSM show that a very high proportion (>90%) have detectable anal HPV infection. Most of the men have at least one oncogenic HPV type, and many have multiple HPV types; this is also true for men on HAART. Detection of HPV and number of HPV types correlated with lower CD4+ level in the pre-HAART era, but the relationship with CD4+ level in the post-HAART era is not as clear, most likely due to HAART-associated increases in CD4+ level. In one study, the highest incidence rates among HIV-infected MSM were found for HPV 16, HPV 52 and HPV 53, with cumulative incidences at 36 months of approximately 30%.

In the recently reported Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN) study of HIV-infected individuals from the United States, the prevalence of anal HPV infection among HIV-infected MSM was 96%.

Risk factors for anal HPV infection in HIV-infected MSM have been difficult to determine since the proportion infected with HPV is so high. One report showed that oncogenic anal HPV infection was associated with receptive anal intercourse. Interestingly, in contrast to the steep age-related decline in the prevalence of cervical HPV infection seen in most studies in women over the age of 30 years, the age-related anal HPV prevalence curve was flat over this age range in MSM (Figure 17.2). The reasons for this difference are unknown but may partially reflect a larger number of new sexual partners after the age of 30 years among MSM compared with women in the general population. In that study, anal HPV infection was independently associated with receptive anal intercourse during the preceding 6 months and with having more than five sex partners during the preceding 6 months.

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2.5%, and about one-third of the HPV-infected men had an oncogenic HPV type.38 Risk factors for anal HPV infection in this population included lifetime number of female sex partners and frequency of sex with females during the preceding month.

The prevalence of anal HPV infection in women is lower than in MSM yet still surprisingly high; in several studies, it was similar to or higher than the prevalence of cervical HPV infection. Studies from a cohort of healthy, presumably HIV-uninfected Hawaiian women show that 27% were positive for anal HPV DNA compared with 29% with cervical HPV DNA.39 Women with cervical HPV infection had greater than a threefold increased risk of concurrent anal infection. Concurrent anal and cervical HPV infection was most prevalent among the youngest women and steadily declined through age 50 years. However, similar to results described above for HIV-uninfected MSM, the prevalence of anal infection alone remained relatively steady in all age groups. The overall distribution of HPV genotypes in the anus was more heterogeneous than in the cervix and included a greater proportion of nononcogenic types. The investigators reported a high degree of genotype-specific concordance among women with concurrent anal and cervical infections, consistent with a common source of infection through sexual activity or spread from one site to the other. Among women followed prospectively, half had an incident anal HPV infection and of these, 58% cleared during a follow-up period of approximately 1 year.40 The median duration of an incident infection was 150 days, with factors associated with persistence being duration of sexual activity, tobacco smoking, and anal intercourse.

Among HIV-infected women and women at high risk for HIV infection, anal HPV infection is even more common than cervical HPV infection.41 In one study among HIV-infected women in San Francisco, anal HPV infection was detected in 79%, compared with cervical HPV infection in 53%.31 Among HIV-uninfected, high-risk women, anal HPV infection was found in 43%, compared with cervical HPV infection in 24%. Among the HIV-infected women, anal HPV infection was associated with lower CD4+ level, cervical HPV infection, and younger age. Receptive anal intercourse was not associated with anal HPV infection in the HIV-infected women in this study. In the SUN study from the United States, the prevalence of anal HPV among HIV-infected women was 90%.42 Transplant recipients also have a high prevalence of anal HPV infection. In one recent study,42 anal HPV infection was found in 21% of male and female renal transplant recipients with a mean age of 58.1 years.

Overall, these data indicate that anal HPV infection is common even among those with no history of receptive anal intercourse. Among women, anal infection is associated with cervical infection, consistent with the relationship between anal and cervical cancer. Clearly, however, as with cervical HPV and cervical cancer, most anal HPV infections do not lead to anal cancer, and as described above, it is likely that the anus is less susceptible to malignant transformation on a per-HPV infection basis than is the cervix. In contrast, the prevalence of anal HPV infection is even higher among HIV-uninfected MSM, and higher still among HIV-infected MSM. Given the very high prevalence of anal HPV infection in these two groups, the incidence of anal cancer on a per-HPV infection basis in these groups is relatively low. However, the incidence of anal cancer in MSM and HIV-infected men and women is high enough to warrant consideration of screening programs to detect and treat the anal cancer precursor, HGAIN, to reduce the risk of progression to cancer.43

### 17.1.2 Epidemiology of AIN in Men and Women

Similar to cervical cancer which is preceded by high-grade CIN (CIN 2,3), anal cancer is preceded by AIN, with HGAIN (AIN 2,3), specifically, being the cancer precursor. Several reports describe progression of HGAIN to anal cancer, often in the setting of immunosuppression among transplant recipients.44,45 There is also long-standing experience with perianal HGAIN, in the form of perianal intraepithelial neoplasia, grade 3 (PAIN 3) or Bowen’s disease, progressing to anal cancer.46 Consistent with its role as a cancer precursor, HGAIN has a profile of HPV types similar to that of CIN 2,3.2

Although many individuals in research studies have undergone anal cytology testing as a measure of AIN prevalence or incidence, anal cytology screening has limited sensitivity and specificity.47 Consequently, like CIN, the diagnosis of HGAIN requires histologic confirmation. This is accomplished using high-resolution anoscopy (HRA) with treatment based on HRA-guided biopsy (discussed later in this chapter). Optimal performance of HRA requires a lengthy training process, and many studies that report prevalence or incidence of anal neoplasia rely solely on cytology, due to the difficulties in performing HRA and biopsy, particularly in the setting of prospective cohorts. As a result, many studies that use anal cytology without HRA-guided biopsy may substantially underestimate the true prevalence or incidence of AIN.

Overall, the prevalence of AIN and risk of HGAIN, specifically, mirrors that of anal HPV prevalence in various populations. The prevalence of AIN is highest among HIV-infected MSM, followed by HIV-uninfected MSM. The effect of HAART on the prevalence and incidence of HGAIN has varied in different studies. In studies performed in the pre-HAART era, the prevalence and incidence of HGAIN were very high.33,48 A study of San Francisco HIV-infected MSM conducted after the introduction of HAART showed that 81% had AIN of any grade and 52% had HGAIN.49 These figures were even higher than those seen in pre-HAART era studies, suggesting that HAART had little or no beneficial effect in reducing the incidence of HGAIN.49 Risk factors for detection of HGAIN included having more than six HPV types and using HAART. In a study from New York, the investigators reported that 40% of participants had AIN on biopsy.50 Risk factors included history of receptive anal intercourse and lower nadir CD4+ cell count. In contrast, the San Francisco findings, being on HAART was associated with lower risk of AIN. In the only population-based data reported, a post-HAART study in San Francisco showed that the prevalence of any grade of AIN was 57% in HIV-infected MSM and the prevalence of HGAIN was 43%.50 Among HIV-uninfected MSM, the prevalence of any grade of AIN was 35% and the prevalence of HGAIN was 25%. Overall, it is clear that the prevalence of AIN, including HGAIN, is very high in both HIV-uninfected and HIV-infected MSM, and if HAART is reducing the incidence of HGAIN or accelerating its regression, its effect is very limited.

There is one report on the prevalence of AIN in HIV-infected men who have sex only with women, and in this study from Paris, the prevalence of HGAIN (18%) was similar to that seen in a cohort of HIV-infected MSM.37 To date, there are no published reports of the prevalence or incidence of AIN in HIV-uninfected men who only have sex with women.

Consistent with the detection of anal HPV infection at frequencies similar to or higher than in the cervix, AIN is also common in high-risk women in the post-HAART era. In a multisite study from the Women’s Interagency HIV Study...
had biopsy-proven AIN. In that study, 8% of women had CIN or AIN. A recent analysis of healthy women with CIN or AIN in high-risk populations has been proposed. The program of cervical cancer screening and management of abnormal cervical cytology is used as the model for cancer prevention and is based on the triad of cytologic screening, colposcopy, and directed biopsy. In an analogous manner, anal cytology is used in combination with HRA and HRA-directed biopsy, to identify HGAIN and early cancer. As with cervical disease, treatment of HGAIN aims to prevent invasive anal SCC, thus reducing its morbidity and mortality.

In summary, anal HPV is common in a wide range of populations, including healthy women and men. Populations at particularly high risk include MSM and men and women immunosuppressed due to HIV infection or organ transplantation. Relatively little is known about AIN in other populations. The incidence of anal cancer tracks closely with those populations at risk for anal HPV infection and AIN. With high incidences of anal cancer in high-risk populations, and the growing incidence of anal cancer in the general population, it is clear that more information is needed about the natural history of anal HPV infection and AIN in all of these populations. To date, no prospective, randomized studies comparing treatment of HGAIN to observation have been conducted, demonstrating that treatment prevents the development of anal cancer. However, since the populations at highest risk of anal cancer are well known, initial efforts to screen and treat HGAIN to prevent anal cancer should be focused on these populations. Additional evidence supporting the treatment of HGAIN will be presented in a following section on the rationale for treating HGAIN.

**17.2 ANAL CANCER SCREENING**

Anal cancer screening is in its infancy. There are no national screening guidelines for anal cancer, and no randomized clinical trials have been conducted to validate the efficacy of any type of screening. Anal cancer screening is not yet a standard of care in the United States. However, given the similarities between HPV-related cervical and anal disease and the increasing incidence of anal cancer and high-grade precursor lesions in the populations at risk, focusing anal cancer screening to these populations has been proposed. The program of cervical cancer screening and management of abnormal cervical cytology is used as the model for cancer prevention and is based on the triad of cytologic screening, colposcopy, and directed biopsy. In an analogous manner, anal cytology is used in combination with HRA and HRA-directed biopsy, to identify HGAIN and early cancer. As with cervical disease, treatment of HGAIN aims to prevent invasive anal SCC, thus reducing its morbidity and mortality.

An integral addition to the anal evaluation, which differs from routine cervical cancer screening, is the regular use of the digital anorectal examination (DARE) to detect palpable masses and areas of pain, induration, or thickening that may reflect early invasive cancers. DARE is used in conjunction with colposcopy and directed biopsy, to identify HGAIN and early cancer. As with cervical disease, treatment of HGAIN aims to prevent invasive anal SCC, thus reducing its morbidity and mortality.

In experienced hands, anal cytology has operational characteristics similar to the Pap test. However, since these samples are collected without direct visualization of the anal canal, sampling errors may play a larger role than in cervical cytology. In addition, the interpretation of anal cytology often underrepresents the grade of disease ultimately found on HRA-guided biopsy.

The sensitivity of anal cytology for biopsy-proven HGAIN in HIV-positive patients ranges from 69% to 93%, and the specificity ranges from 32% to 59% using atypical squamous cells of undetermined significance (ASC-US) or worse as the threshold for triage to HRA. In a 2010 study reported by Salit et al., anal cytology had a sensitivity of 84% and a specificity of 39% using ASC-US or worse as the threshold; high-grade squamous intraepithelial lesion (HSIL) on anal cytology had 91% specificity for high grade AIN but a correspondingly lower sensitivity. Overall, these test statistics are comparable to those for cervical Pap tests.

17.3.1 Sensitivity and Specificity

The goal of anal cytology is to sample the surface epithelium of the entire anal canal—from the distal rectal vault to the anal verge. Due to the normal resting tone of the anal sphincters, the epithelium of the anal canal is apposed, with much of its surface hidden inside the folds and invaginations of the canal. For an adequate cytologic specimen, all these areas need to be sampled. The technique for collecting anal cytologic samples is detailed in a section below. In the laboratory, either liquid-based cytology or direct smears are prepared and stained in a manner analogous to cervical Pap tests. Modified Bethesda System terminology is used to report the findings on anal cytology. Anal cytology is evaluated using criteria similar to a cervical Pap test. The interpretive categories, morphologic criteria, and terminology parallel cervical cytology and are discussed in brief below.

**17.3 PATHOLOGY OF HPV-RELATED DISEASE OF THE ANAL CANAL AND PERIANUS**

The morphologic changes, caused by HPV infection in either the cervix or the anus, are similar on both cytology and histopathology. The spectrum of HPV-related cutaneous perianal disease is essentially identical to vulvar neoplasia. The basic morphologic manifestations of HPV infection on anal mucosa and perianal skin are described below.

The morphologic changes, caused by HPV infection in either the cervix or the anus, are similar on both cytology and histopathology. The spectrum of HPV-related cutaneous perianal disease is essentially identical to vulvar neoplasia. The basic morphologic manifestations of HPV infection on anal mucosa and perianal skin are described below.
The sensitivity of anal cytology for the detection of HGAIN is highest in HIV-infected MSM, presumably due to the larger lesion size and burden of disease frequently seen in this population. In studies of both HIV-positive and HIV-negative MSM, the sensitivity of ASC-US or greater for the detection of HGAIN on conventional smear cytology was 87% in HIV-positive MSM and 55% in HIV-negative MSM; specificity was 42% and 81%. The sensitivity, using low-grade squamous intraepithelial lesion (LSIL) or greater as the threshold, was 77% and 50% in HIV-positive and HIV-negative MSM, respectively; the specificity was 53% and 85%, respectively. In HIV-positive MSM, the specificity and positive predictive value (PPV) of HSIL cytology was high at 93% and 89%.

17.3.1.2 Anal Cytology: Benign Findings and Specimen Adequacy

An anal cytology test samples surface epithelial cells from the entire anal canal—the distal rectal vault to the anal verge; this includes the anal transformation zone (AnTZ) and the non-keratinized and keratinized portions of the canal. As such, rectal columnar cells, squamous metaplastic cells, nucleated squamous cells, and anucleated squames are normal components of anal cytology (Figure 17.4). Similar to cervical-vaginal cytology, a variety of organisms can be identified on anal cytology; these may be pathogenic or nonpathogenic. As with the Pap test, clinical correlation is needed to determine whether or not evaluation or treatment is warranted. Some of these organisms detected on anal cytology are similar to those seen on Pap tests: for example, *Candida* and herpes virus infection (Figures 17.5 and 17.6). Others, such as ameba and pinworm eggs, are more common to the gastrointestinal tract and are rarely encountered on cervical-vaginal cytology.

Per the 2001 Bethesda System, the minimal cellularity for an adequate anal cytology is approximately 2000 to 3000 cells, or 1 to 2 nucleated squamous cells per high-power field (hpf) for ThinPreps® and 3 to 6 nucleated squamous cells per hpf for SurePath™ preparations. Little is known about how cellularity influences sensitivity and specificity of anal cytology. Some studies have indicated that more cellular specimens have better performance characteristics. The presence or absence of transformation zone components (rectal columnar cells and squamous metaplastic cells) is reported as a quality indicator. When no abnormal cells are identified, samples...
that are composed predominately of anucleate squames or fecal material and that lack the minimal number of nucleated squamous cells should be designated as unsatisfactory for evaluation.

17.3.1.3 Anal Cytology: Squamous Cell Abnormalities

The interpretive categories used for anal cytology are the same as for Pap tests: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC). The alterations seen in squamous cells of the anal canal caused by HPV are remarkably similar to those seen in cervical cytology and are summarized here.

LSIL is characterized by dysplastic nuclear changes (enlargement, hyperchromasia, chromatin, and contour abnormalities) in mature squamous cells with abundant cytoplasm (Figure 17.7). In HSIL, the nuclear changes are often more pronounced than those in LSIL. The cells resemble basal-type squamous cells with scant, often metaplastic cytoplasm. HSIL with metaplastic cytoplasm is derived from the AnTZ (Figure 17.8). Keratinizing HSIL, with evidence of cytoplasmic keratinization, is also frequent on anal cytology.57,58 Cytologically, anal SCC is a challenging diagnosis; features of invasion, such as tumor diathesis, can be difficult to distinguish from fecal material. Similar to cervical cytology, ASC can be subdivided into ASC-US and ASC-H. When they are designated ASC-US, they are usually suggestive of LSIL. When designated as ASC-H, they are suggestive of HSIL. Glandular abnormalities are uncommon on anal cytology; they are not discussed here.

17.3.2 Histopathology of HPV-Related Disease of the Anal Canal and Perianus

There are a variety of classification schemes used to describe HPV-related disease of lower anogenital mucocutaneous
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

squamous epithelia. Here, for the anus and perianus, AIN will be categorized as either low-grade (LGAIN) or high-grade (HGAIN). LGAIN is considered the histopathologic manifestation of HPV infection; it can be caused by either low-risk or high-risk HPV types. It consists of the low-grade spectrum of lesions: condyloma and mild dysplasia or AIN 1. These appear to have little if any potential for cancer and do not require therapy unless symptomatically or cosmetically troubling. HGAIN is a potential cancer precursor and, like HSIL on anal cytology, is usually associated with high-risk HPV types. It is also referred to as moderate dysplasia, severe dysplasia, carcinoma in situ, and AIN 2, AIN 2,3, or AIN 3. On perianal skin, clinical terms such as Bowen’s disease or bowenoid papulosis are sometimes used; morphologically, these are high-grade squamous intraepithelial neoplasms.

The squamous epithelium of the anal canal is stratified (Figure 17.9). The distal canal is a keratinized mucosa, devoid of epidermal appendages. LGAIN and HGAIN may be either keratinized or nonkeratinized. Mucosal lesions with prominent keratinization are more commonly encountered in the anal canal than on the cervix (Figure 17.10). The morphologic features of HPV infection are identical to those of other anogenital mucosal and cutaneous surfaces. Architecturally, LGAIN can be flat or have a warty profile. In LGAIN, abnormal cells are seen throughout the epithelial thickness, though cells in the superficial layer have appreciable cytoplasm, often with the prominent cytoplasmic cavitation or koilocytosis associated with HPV. Many HPV-related lesions, particularly HGAIN, arise in the metaplastic squamous epithelium of the AnTZ near the squamocolumnar junction (SCJ) (Figure 17.11). In HGAIN, the immature-appearing dysplastic cells fill even the upper levels of the epithelium; mitotic figures can be seen well above the basal layers (Figure 17.12).

The vast majority of anal canal cancers are squamous (Figure 17.13); histologic subclassification of anal SCC has little clinical value. Currently, about 93% are associated with high-risk HPV types, particularly HPV 16 and 18, with type 16 predominating. The equivalent of cervical microinvasion, with its specific histologic depth and lateral spread measurements and management and prognostic implications, is not defined for minimally invasive anal SCC. The role, if any, of HPV in glandular neoplasia in the anus is not known. Approximately 10% of anal canal cancers are adenocarcinomas. Most have a colorectal phenotype and probably arise from the distal rectum or glandular epithelium of the AnTZ.

FIGURE 17.8. HSIL on anal cytology. Note the cells with enlarged, hyperchromatic nuclei and scant, dense cytoplasm characteristic of HSIL arising in immature squamous metaplasia of the AnTZ (Anal ThinPrep®, high magnification).

FIGURE 17.9. Benign nonkeratinized squamous mucosa of the anal canal (H&E, medium magnification).

FIGURE 17.10. Low-grade AIN. This biopsy at the anal SCJ shows surface hyperkeratosis and parakeratosis at arrows (H&E, low magnification).

FIGURE 17.11. HGAIN arising in AnTZ. Note extension of HGAIN down the rectal glands (H&E, low magnification).
The histopathology of perianal disease mirrors vulvar disease. HPV-related cytopathic changes are frequently not prominent on keratinized squamous epithelium but may be seen, particularly in low-grade PAIN (Figure 17.14). High-grade perianal lesions are characterized by abnormal maturation with dysplastic keratinocytes occupying the majority of the epithelial thickness. Morphologically, Bowen’s disease and bowenoid papulosis are high-grade PAIN (Figure 17.15).

17.4 EVALUATION OF THE ANUS AND PERIANUS

17.4.1 Assessment of New Patients

The first step in evaluating a new patient is to obtain a HPV-focused history (see Table 17.1 for the new patient questionnaire used in the University of California San Francisco [UCSF] Anal Neoplasia Clinic). The questions are designed to elicit information about specific anal symptoms such as painful bowel movements, pain during sex, irritation, or bleeding. It is important to ask whether the patient has ever been treated for HPV-related lesions and if so, how they were treated.
TABLE 17.1 UCSF ANAL NEOPLASIA CLINIC NEW PATIENT QUESTIONNAIRE

Anal Neoplasia Questionnaire

Please answer the following questions as accurately as you can.

What is the reason for your visit today? ________________________________________

How are you feeling in general today? ________________________________________

Are you having any anal symptoms such as:
- itching
- diarrhea
- bleeding when you have a bowel movement
- feel a lump or bumps
- blood on the toilet paper when wiping
- inability to have receptive sex due to pain or discomfort

Have you had any anal warts? ☐ YES ☐ NO If Yes, where were these treated?
- Office Procedure
- Surgery in the operating room
- Other__________

Have you ever been diagnosed with potentially pre cancerous lesions in the anus (also referred to as moderate to severe dysplasia, AIN, high-grade lesions, carcinoma in situ, or Bowen's disease)?
- YES ☐ NO If yes, when? _______ How were they treated?__________________________

If you are a woman, have you even had an abnormal cervical Pap? ☐ YES ☐ NO

Ever been treated for cervical pre cancerous lesions or lesions on your vulva? ☐ YES ☐ NO
If yes, when? _______ How were they treated?__________________________

Have you ever been diagnosed with anal cancer? ☐ YES ☐ NO
If yes, when? _______ How were they treated?__________________________

Did you receive radiation and chemotherapy? ☐ YES ☐ NO
If yes, when was the last day of your radiation treatment? _______

Have you ever been diagnosed or treated for any other anal problems including hemorrhoids, fissures, fistulas, perianal abscess, or Incontinence? ☐ YES ☐ NO
If yes, please document and explain when and how it was treated? ______________________

Has your sexual partner(s) even been treated for HPV (human papilloma virus) related pre cancerous changes or warts? ☐ YES ☐ NO

(continued)
<table>
<thead>
<tr>
<th>Have you been treated with any of the following drugs?</th>
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<tbody>
<tr>
<td>☐ Aldara (5% imiquimod)</td>
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<tr>
<td>☐ Veregen</td>
</tr>
<tr>
<td>☐ Condylox</td>
</tr>
<tr>
<td>☐ Efudex (5% fluorouracil cream)</td>
</tr>
<tr>
<td>☐ Other ________</td>
</tr>
<tr>
<td>If yes, please give details as to when, for how long, did it help, and if you experienced any side effects?</td>
</tr>
</tbody>
</table>

| Are you HIV positive? ☐ YES ☐ NO                     |
| If yes, what was your lowest CD4 lymphocyte or t-cell count ever? ____________ |
| When was that? ________________                      |
| What was your most recent CD4+ count? ____________    |
| When was that test done? ________________             |
| Are you taking antiretroviral drugs for HIV, also known as HAART? ☐ YES ☐ NO |
| How long have you been taking HAART? ________________|
| What was your highest HIV viral load? ________________|
| When? ________________                              |
| What was your most recent HIV viral load? ____________|
| When was that test done? ________________             |
| Have you ever had any opportunistic infections, KS (Kaposi Sarcoma), HD or NHL (Hodgkin or non-Hodgkin lymphoma)? ☐ YES ☐ NO |
| If yes, please specify which ________________________|
| Are you immunocompromised for any other reason? ☐ YES ☐ NO |
| If yes, please explain ______________________________|
| Have you had an organ transplant? ☐ YES ☐ NO          |
| If yes, when ______________ Have you had any rejection episodes? ____________ |

Instructions to Attending Physician: Your signature below indicates that you have reviewed the information contained in the entire questionnaire and that you have reviewed the pertinent or key finding(s) with the patient and/or family. Key finding(s) must be summarized in your progress note, however the questionnaire may be referenced for additional details.

Attending Provider Signature ______________________ Date ______

Anal Neoplasia Questionnaire ______________________

Page 2 of 2
intercourse. Routinely ask about tobacco, drug, and alcohol use. Smoking may play a role in facilitating progression of lesions as well as hindering treatment response by increasing the likelihood of recurrent or persistent disease. It is imperative that these questions be asked in a nonjudgmental manner. Assisting patients to create a plan for tobacco cessation, in addition to the obvious health benefits, makes them active participants in their treatment. An educated and motivated patient is more likely to adhere to follow-up recommendations and tolerate treatment-related side effects, both of which are necessary parts of effective therapy regimens.

17.4.2 The Anal and Perianal Examination

Distinction is made between the anus (or anal canal) and the perianus (or anal margin). The basic anatomic landmarks of the anal canal are indicated in Figure 17.16. The anal canal is approximately 4 to 6 cm long, but varies in length from individual to individual; it tends to be shorter in women. The proximal end of the anal canal begins anatomically where the rectum enters the puborectalis sling at the internal edge of the anal sphincter complex. This is palpable as the anorectal ring on DARE. The resting tone of the sphincter muscles keeps the walls of the anal canal apposed. The anal canal extends distally to the point where the squamous mucosa blends with the perianal skin of the anal verge. The anal verge is the opening to the anus as seen on external examination and roughly coincides with the band of cutaneous tissue over the external sphincter at the anal opening. The palpable intersphincteric groove or the outermost boundary of the internal sphincter muscle is the proximal edge of the verge. The anal canal is divided by the undulating dentate line, a macroscopically visible landmark that marks the transition from anodermal mucosa to the squamous mucosa of the anal canal.
squamous mucosa, which is firmly attached to the underlying fibromuscular tissue of the distal canal, from the anal mucosa that loosely overlies the internal hemorrhoidal plexus. The anal transformation (or transition) zone and anal SCJ are proximal to the dentate line. The SCJ is located approximately 1 to 2 cm above the dentate line; its location varies. The perianus or anal margin is the circumferential region extending laterally 5 cm from the anal verge.

The goal of evaluating the anus and perianus is to determine the presence, extent, or absence of HPV-associated disease by systematically examining the entire SCJ, anal canal including AnTZ, and perianal skin. A complete examination includes cytology collection, a thorough DARE, HRA using the colposcope with vinegar and Lugol’s solution to visualize lesions, and biopsies to determine the extent and grade of disease. A thorough examination, requiring biopsies of both intra-anal and perianal areas, typically will take 20 to 30 minutes to complete. New patients, unfamiliar with the procedures, will require additional time for teaching and counseling.

The equipment for HRA is similar to that used for evaluation of the cervix with the following differences: synthetic polyester fiber swabs are recommended for anal cytology collection, not cytobrushes or spatulas; metal or disposable plastic anoscopes instead of specula; and smaller biopsy forceps with bites that are \( \leq 3 \) mm, such as the baby Tischler or ENT laryngeal forceps. HRA also requires higher magnification than cervical colposcopy. The colposcope should magnify to at least 25x. Colposcopes that only magnify to 10x are not adequate for HRA. It is also important to have angled eyepieces, as the straight-on view colposcopes are ergonomically difficult to use for HRA (Figure 17.17).

Patients can be examined in any of several positions including left or right lateral, dorsal lithotomy, or prone. Most patients and providers prefer the left lateral recumbent position. Following a cervical examination in women, the patient is repositioned from lithotomy to her left side. When describing the location of lesions and the position used, it is important to be clear and consistent. The anal clock is different from the gynecologic clock (Figure 17.18); note that the patient is in the left lateral decubitus position. Based on the convention used in colorectal surgery, with patients in the prone position, the posterior anal aspect is 12 o’clock; this is in contrast to the gynecologic convention, with the patient in dorsal lithotomy position, where anterior is 12 o’clock. Describing lesion location both anatomically (e.g., right posterior-lateral) and with the anal clock, for shorthand, should reduce communication errors regarding lesion location between clinicians of various disciplines.

### 17.4.3 Anal Cytology Collection

Collection of anal cytology is a simple procedure and is done first, before any lubrication is used, to increase the yield of cell collection. In addition, patients are instructed to refrain from inserting anything per anus for 24 hours before the procedure; this includes no enemas, douching, or receptive anal intercourse. Anal cytology is collected without direct visualization of the anal canal using a tap-water–moistened synthetic polyester fiber swab, such as Dacron\textsuperscript{TM}. Do not use a prescored swab; it may snap at the score line when using adequate pressure during sample collection. The cytobrush is uncomfortable and unnecessary since adequate sampling can be obtained using synthetic swabs. Cotton swabs should not be used; cells adhere more to the cotton and are not as easily transferred to the glass slide or vial for liquid-based cytology. In addition, the wooden handle of cotton swabs may fracture and splinter with the lateral pressure applied during the sample collection process.

To collect the sample for anal cytology, the buttocks are gently separated; patients in the left lateral recumbent position can retract their upper cheek to facilitate the view of the
17.4.4 Digital Anorectal Examination

The DARE is an essential part of anal cancer screening. It is performed after the collection of the anal cytology and before HRA. The goal of the DARE is to detect any palpable abnormalities; it may help guide further evaluation, including the anoscopic examination and biopsies.

Using a mixture of water-soluble lubricant gel and 2% to 5% lidocaine gel (3/4 lube to 1/4 lidocaine gel) for lubrication, insert a gloved finger slowly into the anus. Apply firm pressure on the external sphincter, allowing it to relax before advancing into the rectum. Systematically palpate the entire circumference and length of the anal canal, beginning in the rectum. Palpate the mucosa over the internal sphincter and the walls of the distal anal canal. Palpate for warts, masses, and areas of induration, discomfort, or pain. Once completed, also examine the prostate in men. Finally, palpate the perianal region in its entirety. Areas that are hard, firm, indurated or immobile are suspicious for cancer. Warts are typically soft, mobile, and nodular or gritty to palpation. Document the location and size of any palpated abnormalities and correlate these with the visual exam.

17.4.5 High-Resolution Anoscopy

To begin the HRA, lubricate the anoscope with additional lubricant/lidocaine gel mixture and insert it into the anus. Either disposable or nondisposable anoscopes can be used. Remove the anoscope’s obturator and insert a cotton-tipped swab wrapped in gauze previously soaked in 3% to 5% acetic acid (Figure 17.20). Medical grade acetic acid (not glacial acetic acid) can be used, but commercially available white table vinegar is 5% acetic acid, and it can be used or diluted to 3%. Remove the anoscope, leaving the gauze-wrapped cotton-tipped swab in place (Figure 17.21). Allow the vinegar to saturate the epithelium of the anal canal for 1 to 2 minutes. Remove the cotton-tipped swab and gauze, and reinsert the anoscope with the obturator in place; remove the obturator again for the exam itself.

Begin using a colposcope on low magnification; a larger area in the field of vision aids in establishing anatomic landmarks. With the anoscope fully inserted, the first area visualized is the distal rectum. Observing through the colposcope,
slowly withdraw the anoscope until the anal SCJ and/or AnTZ come into focus. Refocus the colposcope continually while the anoscope is repositioned and withdrawn. The anal canal varies from 2 to 5 cm in length. In some patients, the SCJ, the most proximal aspect of the AnTZ, is viewed immediately with the anoscope completely inserted. In other patients, the SCJ is not seen until the anoscope is withdrawn nearly to the anal verge. The first landmark to identify is the anal SCJ. The SCJ, the junction between the rectal columnar epithelium and anal squamous epithelium, is located where the darker red colonic epithelium abuts the lighter pink anal squamous epithelium (Figure 17.22). Once the SCJ is identified, additional vinegar is applied, using a cotton-tipped swab, to examine the entire circumference of the transformation zone. The AnTZ is distal to the SCJ; it is the region of squamous metaplasia. As with the cervix, its appearance varies: it may appear as a thin-white line of metaplasia (Figure 17.22), a wider zone with gland openings, islands of columnar epithelium within the mature squamous epithelium, or a more diffuse region of faint acetowhite epithelium (AWE) (Figure 17.23A,B).

After locating the SCJ and AnTZ, continue to reapply vinegar throughout the exam. Use higher magnification (e.g., 16×)

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**FIGURE 17.22.** Rectal columnar epithelium and anal squamous epithelium abut at the SCJ. Note that the rectal mucosa is dark red compared to the lighter pink color of the anal epithelium. The AnTZ here is seen as a thin, white line of metaplasia.

**FIGURE 17.23.** Appearance of anal squamous metaplasia. Arrows in (A) point to acetowhite-ringed gland openings and an island of mature squamous epithelium surrounded by columnar epithelium. B: Diffuse acetowhiteness in early metaplasia; between arrows, Mid metaplasia is shown in (C) with acetowhite ringed glands noted between the arrows. D: Islands of columnar epithelium and coalesced glands indicative of early metaplasia.
to 25×) for better visualization of specific regions. To view all aspects of the SCJ and AnTZ, manipulate the anoscope or use cotton-tipped swabs to visualize areas hidden by folds, hemorrhoids, normal anal papillae, or prolapsed mucosa. An adequate HRA requires that the entire SCJ and AnTZ are visualized. With proper manipulation of the mucosa, it is rare for an exam to be inadequate.

After completely examining the SCJ and AnTZ, begin withdrawing the anoscope to examine the distal anal canal. Continue to move the colposcope to maintain focus as the anoscope is withdrawn. Although most HGAIN arises in the AnTZ, it can also be found in the distal canal, especially in patients who have had prior treatment. Low-grade lesions may be found anywhere in the anal canal.

Application of Lugol’s iodine solution helps to distinguish lesions more likely to be high-grade from those that are low-grade. Most high-grade lesions will be negative staining. Low-grade AIN may be Lugol’s negative, show partial Lugol’s uptake, or occasionally be Lugol’s positive. Complete the entire entire exam prior to applying Lugol’s stain. Lugol’s stain can obscure the margins of a lesion previously identified with acetic acid. Columnar epithelium, scar tissue from prior treatments, and keratinized epithelium will not stain. These nonstaining areas need to be distinguished from true Lugol’s-negative lesions.

Continue withdrawing the anoscope until the anal verge comes into view. The anal verge is where the epithelium of the distal anal canal transitions to the epidermal epithelium of the perianus. The anal margin begins at the anal verge, proximally, and extends onto the perianal skin. The anal verge is viewed through the anoscope or visualized directly, by gentle retraction of the buttocks. Visualize the remainder of the perianus using the colposcope; the anoscope is not needed. The perianus (anal margin) extends out to approximately 5 cm from the anal verge (see Figure 17.24). The 10× magnification typically allows adequate viewing of the perianus. Switch to higher magnification for better viewing of specific lesions or other abnormal findings.

A complete HRA includes evaluation of the entire anal canal including the SCJ, AnTZ, distal anal canal, anal verge, and perianus. An adequate HRA indicates that these areas are seen in their entirety. Documentation should include whether or not the HRA was adequate and, if not, the reasons noted. Reasons for inadequate exams include mucosal swelling, obscuring stool, condyloma, large hemorrhoids, or the patient’s inability to tolerate the procedure. Whenever possible, repeat an inadequate exam at another visit.

17.4.6 Differences between HRA and Cervical Colposcopy

The principles of cervical colposcopy have been instrumental in the development of HRA. While there are many similarities, compared with cervical colposcopy, HRA can be more challenging. In many ways, HRA is more similar to vaginal and vulvar colposcopy. Clinicians familiar with cervical colposcopy may be surprised by the difficult transition. During HRA, one hand continually holds and manipulates the anoscope; only the alternate hand is available for adjusting the colposcope and other tasks. HRA is physically more challenging for the colposcopist; the hand holding the anoscope is extended for long periods, often applying significant pressure to keep the anoscope in place. Ergonomically, angled lenses on the colposcope are preferred; few tables can be raised high enough to comfortably use a colposcope with straight-on lenses for HRA. As noted earlier, colposcopes with only low magnification settings will be inadequate for evaluating anal lesions. Colposcopes with zoom lenses can be used but may be more difficult to keep in focus with the frequent repositioning during HRA, although a zoom controlled by a foot pedal can be helpful.

With HRA, once the anoscope is in place, it is more difficult to locate the SCJ and AnTZ. The mucosa needs to be manipulated to view the entire SCJ to have an adequate exam. Vinegar needs to be regularly reapplied. In general, more vinegar is needed than with the cervical exam to adequately visualize lesions. Locating lesions and distinguishing HGAIN from LGAIN are all more challenging. The similarities and differences in terminology and lesion characteristics were noted previously.

Clean technique is more difficult to maintain with HRA than with cervical colposcopy. Using disposable covers on parts of the colposcope touched during the exam (e.g., the magnification dials, fine focus knobs, or stand) will help keep the instrument clean. Use disinfectant wipes or other nonabrasive cleansers to disinfect the colposcope between patients. Another difference between cervical colposcopy and HRA is the length of the learning curve. Expertise develops in both fields with time and experience. However, becoming an expert HRA provider takes more time, even for those experienced in cervical colposcopy. As it is a young field with a paucity of providers, novice learners will rarely have the benefit of an expert to proctor or provide observation experience. Maintaining logbooks, correlating with cytology and histology results, exam adequacy, and clinical impression, will provide feedback on the adequacy of the cytology specimens as well as a record of discordant cytology/histology results. A discordant result is considered one in which the histology result indicates a lower grade disease than the cytology. In these cases, it is assumed that the higher-grade disease was missed, as a false-positive HSIL on anal cytology is rare in our experience. As expertise with HRA develops, there should be fewer discordant results. Logbooks will help document and determine improvement over time.

A complete HRA is one in which all anatomic landmarks are seen and all lesions identified, using adequate amounts of vinegar and Lugol’s solution. Documentation should indicate the adequacy of the exam, or if inadequate, the reasons for this. Rarely, patients may require a mild sedative prior to examination. Novice HRA providers may take longer than those with more experience to perform the exam; the anal mucosa can swell and obscure parts of the anal canal with prolonged examination. A reasonable balance between the time needed to visualize the entire canal and the exam’s length is needed.

Dedicating a sufficient amount of clinic time is necessary for clinicians wanting to develop expertise in HRA. Minimally, a
half-day or 4 to 6 exams weekly is recommended. This should ensure an adequate number and frequency of exams to develop the skill set used for HRA. A consistent clinical practice will enable the novice provider, with patience, to become an expert HRA provider.

### 17.4.7 Anal and Perianal Biopsies

Histology results are the gold standard for determining the patient’s diagnosis. All lesions with significant colposcopic abnormalities should be biopsied. For anal canal biopsies, use small biopsy forceps to reduce risk of bleeding and infection. Anal biopsies taken from above the dentate line do not require anesthesia. Distal canal and perianal biopsies require local anesthesia. Perianal biopsies require topical lidocaine gel or spray followed by injection of 1% to 2% lidocaine. For the anal canal, biopsy the lower or more dependent lesions first as bleeding may obscure the field of vision for subsequent biopsies. Once all biopsies are complete, use Monsel’s solution or silver nitrate for hemostasis; however, the pressure of the anal walls, which are apposed at rest, is usually sufficient to stop bleeding once the anoscope is removed.

Generally, patients can expect to feel a sensation of pressure, but not pain, after intra-anal biopsies. Mild bleeding with bowel movements is common and may persist for several days. Complications such as infection or severe bleeding are extremely rare. Patients should also be advised to avoid receptive anal intercourse for at least 1 week and then only if bleeding has ceased.

### 17.4.8 HRA Terminology

The terminology for HRA is adapted from cervical colposcopy. The SCJ in the anus is the area where anal squamous epithelium abuts colonic-type rectal glandular epithelium. The original SCJ is located near the dentate line. The current SCJ is the proximal edge of the AnTZ adjacent to the glandular epithelium of the distal rectum. The AnTZ is the region of squamous metaplasia that extends from the current SCJ to the original SCJ (Figure 17.25). The AnTZ has similar features to the cervical transformation zone. These features, although not as common in the anus, include acetowhite ringed gland openings (Figure 17.23A, C), islands of columnar epithelium (Figure 17.23D), and acetowhite accentuation of the current SCJ (Figure 17.23A).

![FIGURE 17.25. A partial view of the AnTZ indicating the transformation zone between the original and current anal SCJ.](Image)

On HRA, lesions are described using terms similar to cervical colposcopy: color, contour, margins, vascular patterns, and Lugol’s staining. Exceptions, unique to HRA, are termed epithelial honeycombing (EH) and a vascular pattern termed striated vessels.

- **Color:** Acetowhite changes occur after the application of vinegar. The acetowhiteness may be barely visible or distinct. AWE can be snowy white or have a gray hue. The sheen can be flat or shiny (Figures 17.26 and 17.27).
- **Contour:** Lesions can be flat or raised. Slightly raised lesions reflect thickening of the epithelium. Papillae and micropapillations can be seen (Figures 17.28 and 17.29).
- **Margins:** Determine the size and borders of the lesions. The borders may be distinct or indistinct. Identify lesions within lesions or internal margins; they may indicate HGAIN. The border of a lesion adjacent to the rectum at the SCJ is often indistinct and can be difficult to distinguish from the rectal mucosa (Figures 17.30 and 17.31A, B).
- **Vascular patterns:** These are similar to cervical patterns with some exceptions. Punctuation and mosaic patterns are usually coarse; fine mosaic and punctate patterns are rarely seen in the anus. Mosaic patterns are infrequent in LGAIN. Looped warty vessels are typical in raised LGAIN and are associated with warty papillae. Atypical or abnormal vessels can be seen with both HGAIN and cancer. They include nonbranching, thickened, and dilated vessels with bizarre shapes. Striated patterns or linear vessels are often seen in patients who have had prior ablative procedures, but can also be seen associated with AIN (Figures 17.32 to 17.37).
- **Lugol’s staining:** Also similar to cervical staining patterns; normal squamous epithelium picks up the stain completely, turning a dark mahogany brown color. Warts and other LGAIN may partially or completely stain with iodine. Negative or nonstaining epithelium is yellow in color. Normal rectal mucosa is also nonstaining and is typically pale yellow. Lugol’s can be especially helpful at demarcating the squamous-squamous borders of a lesion. Lugol’s negative lesions at the SCJ may be difficult to distinguish from the normal rectal mucosa. Partial staining patterns show varying uptake of the stain or a mottled appearance. It is important to continue looking through the colposcope while applying the Lugol’s so that the lesion can still be located. (Figure 17.38). Lugol’s can also obscure vessel detail, so biopsy of lesions with atypical vessels may need to be performed prior to its application.

(Text continuous on page 503)
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

**FIGURE 17.27.** The acetowhite coloring has a grey hue and flat sheen in this HGAIN lesion.

**FIGURE 17.28.** Example of flat contour in HGAIN lesion. Faint acetowhite with coarse punctation and mosaic pattern.

**FIGURE 17.29.** Example of a raised contour in HGAIN lesion. Acetowhite with coarse punctation and mosaic pattern.

**FIGURE 17.30.** Example of a distinct margin in an acetowhite HGAIN lesion with coarse punctation and striated vessels. Single arrow points to lower border of lesion; double arrows, near upper edge.

**FIGURE 17.31.** A: Example of an indistinct margin in an acetowhite HGAIN lesion at arrow. B: The lesion margins are better defined with application of Lugol’s seen in this lower powered view.
FIGURE 17.32. Warty looped capillary vessels typical of a condyloma (LGAIN).

FIGURE 17.33. An example of coarse punctation in a HGAIN lesion. Note the mosaic pattern at arrow.

FIGURE 17.34. An example of mosaic pattern in a HGAIN lesion. There is also diffuse coarse punctation in this lesion.

FIGURE 17.35. Atypical/abnormal vascular patterns that have bizarre patterns and irregular dilations. This lesion was HGAIN and is adjacent to a typical-appearing condyloma (arrow).

FIGURE 17.36. Striated vascular pattern can be considered a variation of punctation. It can frequently be seen following treatment, such as IRC, but can be found in AIN. It should be biopsied regardless of treatment history.

FIGURE 17.37. Striated vessels; biopsy showed HGAIN.
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

503

Ephelium, termed early, mid, and late (Figure 17.23A). In early or immature metaplasia, coalescence and clustering of the columnar epithelium is just beginning; it is barely acetowhite. The grapelike clustering of the coalesced columnar epithelium, seen in the cervical transformation zone, is not as pronounced in the AnTZ (Figure 17.23B). In mid metaplasia, coalescence is more advanced, and acetowhite changes are more prominent (Figure 17.23C). Late or mature metaplastic changes are more pronounced with nearly complete coalescence of the columnar epithelium that can mimic the appearance of a true lesion. In the AnTZ, gland openings and islands of columnar epithelium within fully mature squamous epithelium can be seen (Figure 17.23D). They help identify the region of the original SCJ. The zone between them and the current SCJ constitute the active AnTZ.

17.4.10 Abnormal Anal Transformation Zone

Typical patterns encountered on HRA are summarized in Table 17.2. As with cervical colposcopy, the features associated with the abnormal AnTZ overlap with benign changes of squamous metaplasia, AIN, and sometimes, even cancer. Biopsy remains the mainstay for grading of lesions.

Low- and high-grade lesions in the immature AnTZ can be subtle; it is often difficult to distinguish between normal and abnormal changes. Areas of AWE in the AnTZ (Figure 17.40), even with the absence of vascular changes, are often high-grade lesions. EH is nonspecific and can be associated with either squamous metaplasia or AIN in the AnTZ (Figures 17.39, 17.41 to 17.43). Isolated ringed gland openings are normal and indicate mature squamous metaplasia surrounding the opening to a gland in the mucosa. In the AnTZ, a preponderance of ringed glands clustered in an acetowhite lesion may, however, indicate HGAIN (see Figure 17.44).

17.4.10.1 HRA: Low-Grade Anal Intraepithelial Neoplasia

Typical low-grade lesions are acetowhite. Condylomas often have contour changes such as micropapillae or delicate papillae with central looped capillary vessels (Figures 17.32, 17.45 and 17.46). They frequently have a cauliflower-like profile...
TABLE 17.2 TYPICAL SQUAMOUS PATTERNS ON HRA

<table>
<thead>
<tr>
<th>TYPICAL SQUAMOUS PATTERNS ON HRA</th>
<th>COLOR (AWE)</th>
<th>SURFACE ARCHITECTURE (CONTOUR)</th>
<th>MARGINS (BORDERS)</th>
<th>VASCULAR CHANGES</th>
<th>LUGOL'S STAINING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign AnTZ</td>
<td>+ translucent</td>
<td>Flat</td>
<td>AWE edge or line at SCJ</td>
<td>None</td>
<td>Mature AnTZ = positive</td>
</tr>
<tr>
<td>Posttreatment changes</td>
<td>+</td>
<td>Flat</td>
<td>Indistinct</td>
<td>Striated vessels</td>
<td>Immature AnTZ = negative</td>
</tr>
<tr>
<td>Low-grade lesions</td>
<td>++ to +++</td>
<td>Variable flat or raised</td>
<td>Distinct or indistinct</td>
<td>Punctuation, looped capillaries</td>
<td>Negative, partial, positive</td>
</tr>
<tr>
<td>High-grade lesions</td>
<td>+ to +++</td>
<td>Flat, slightly raised or thickened</td>
<td>Distinct or indistinct</td>
<td>Coarse punctuation and mosaic, atypical vessels, or none</td>
<td>Negative</td>
</tr>
<tr>
<td>Cancer</td>
<td>Variable</td>
<td>Irregular, raised or ulcerated</td>
<td>Poorly defined, peeling edges</td>
<td>Atypical vessels, often friable</td>
<td>Negative</td>
</tr>
</tbody>
</table>

AWE, acetowhite epithelium; AnTZ, anal transformation zone; SCJ, squamocolumnar junction; + to +++: faint to distinct.

(Figure 17.46). Condyloma with cerebriform contour can mimic high-grade vascular changes and particularly when also Lugol's negative should be biopsied to exclude high-grade disease (Figure 17.49). The Lugol's staining pattern is variable with LGAIN; it may be positive, show partial staining, or be Lugol's negative. Lugol's staining is particularly helpful in defining the squamous-squamous border of the lesion (Figure 17.50).

Flat low-grade lesions can be subtle, with minor acetowhitening and Lugol's-negative staining (Figures 17.51 and 17.52). Biopsy is essential to confirm the colposcopic impression of lesion grade and truly distinguish these lesions from benign squamous metaplasia of the AnTZ.

17.4.10.2 HRA: High-Grade Anal Intraepithelial Neoplasia

Similar to cervical colposcopy, the classic appearance of HGAIN on HRA is a flat or thickened area of AWE associated with vascular changes including punctation and a mosaic pattern (Figure 17.53). High-grade lesions are frequently located in the AnTZ near the SCJ (Figures 17.54 and 17.55). In high-risk populations, high- and low-grade lesions often coexist; examining around the base of condyloma will often yield HGAIN on biopsy (Figures 17.56 and 17.57). Vinegar must be regularly reapplied to the entire SCJ and AnTZ and distal canal during the exam for adequate visualization of lesions.

Acetowhitening, particularly in the AnTZ, is an important clue for identifying high-grade lesions (Figures 17.54 and 17.55). HGAIN can have a variety of appearances and be quite subtle with only faint AWE (Figure 17.58). Although HGAIN is frequently flat or plaque-like, high-grade lesions with other surface contours can be seen (Figure 17.59); biopsy is needed for confirmation. Reapplying vinegar to the entire AnTZ is crucial during HRA in order to visualize lesions.

Since vinegar causes vasoconstriction, vessels will appear more prominent prior to the application of vinegar and after the vinegar effect diminishes. Vessel changes associated with high-grade lesions include punctuation and mosaic pattern; these are most commonly coarse in appearance on HRA. Examples of punctuation are seen in Figures 17.59 and 17.60. A more subtle presentation of punctuation, unique to HRA, is termed striated vessels and although this finding is nonspecific, it is frequently associated with HGAIN (Figure 17.61). Mosaic patterns are similar to those seen with cervical colposcopy (Figures 17.62 and 17.63). Whenever atypical vessels are seen or focal areas of atypical vessels are seen within an acetowhite lesion, these areas should be targeted for biopsy to evaluate for possible occult invasion (Figure. 17.64 to 17.66).

Most HGAIN will be negative staining with Lugol's solution. It can be helpful during HRA to help identify lesions (Figures 17.52, 17.59 and 17.67). Care must be taken to correlate with the appearance on vinegar exam; lesions at the SCJ may be difficult to differentiate from rectal mucosa after Lugol's is applied.

17.4.10.3 HRA: Invasive Squamous Cell Carcinoma

DARE is an essential part of the examination of the anal canal. Palpable hard masses or thickening is pathognomonic for invasive cancer (Figures 17.68 to 17.70). On HRA, cancers are often friable or ulcerated lesions with atypical vessels

(Text continuous on page 511)
FIGURE 17.41. Epithelial honeycombing; biopsy (arrow) showed HGAIN.

FIGURE 17.42. Biopsy of another area of honeycombing (arrow), in same patient as Figure 17.41, showed immature and reactive squamous metaplasia.

FIGURE 17.43. Epithelial honeycombing. Both images are from the same patient. Arrows indicate biopsy sites. A: Biopsy showed HGAIN. B: Biopsy showed immature and reactive squamous metaplasia.

FIGURE 17.44. Atypical metaplasia with ringed glands; biopsy (designated by circle) showed HGAIN.

FIGURE 17.45. Micropapillae seen in typical LGAIN.
FIGURE 17.46. Extensive condyloma; patient required surgical treatment. A: At SCJ, B: mid-canal near dentate line, C: distal canal near verge, and D: perianal condyloma.

FIGURE 17.47. Intraoperative HRA. Arrow points to Hill-Ferguson anal retractor. Black line outlines SCJ. (A, Normal rectal glandular openings. B, Condyloma.)

FIGURE 17.48. Atypical-appearing condyloma, biopsy showed LGAIN.
FIGURE 17.49. A: A WE with cerebriform appearance and mosaic pattern, low-power view. B: Lugol's negative staining; biopsy (arrow) showed LGAIN. C: Magnified view prior to application of Lugol's to lesion.

FIGURE 17.50. A: Micropapillae. B: Lugol's negative staining; biopsy showed LGAIN.
FIGURE 17.52. A: Biopsy of the more granular lesion with Lugol’s partial staining showed LGAIN (see arrow). B: Biopsy of flat AWE that was Lugol’s negative showed HGAIN (see arrow).

FIGURE 17.51. A: Faint AWE. B: Lugol’s negative staining; biopsy at arrow showed LGAIN.

FIGURE 17.53. AWE with punctuation and mosaic pattern. Biopsy at arrow showed HGAIN. Additional biopsies (e.g., toward the top of the image) are also appropriate.

FIGURE 17.54. Biopsy of this dense acetowhite lesion with abnormal ringed glands, at arrow, showed HGAIN.
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

**FIGURE 17.55.** Thickened, dense acetowhite lesion. Biopsy at arrow showed HGAIN.

**FIGURE 17.56.** Punctuation off the SCJ and adjacent to a condyloma; biopsy at arrow showed HGAIN.

**FIGURE 17.57.** Punctuation and mosaic pattern at base of condyloma (arrow); biopsy showed HGAIN.

**FIGURE 17.58.** AWE extends over the rectal mucosa and is outlined in black line; biopsy showed HGAIN. (Arrows: A, AWE of immature AnTZ adjacent to lesion. B, Translucent normal squamous mucosa. C, Normal rectal mucosa.)

**FIGURE 17.59.** The lower lesion is cerebriform and Lugol's negative (arrow in [A]). The other two areas show punctuation (arrows in [B]). Arrows also indicate biopsy sites; all showed HGAIN.
FIGURE 17.60. A: Coarse punctation. B: Effect of vinegar has waned. Coarse punctation is more apparent, higher power view; biopsy at arrow showed HGAIN.

FIGURE 17.61. AWE with striated vessels, outlined in black line; biopsy showed HGAIN.

FIGURE 17.62. Reapplying acetic acid is essential to visualize lesions. A: Area prior to reapplication of vinegar. B: Coarse mosaic pattern demonstrated after reapplying vinegar. C: Higher magnification after vinegar. Biopsy showed HGAIN.
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

FIGURE 17.63. Mosaic pattern and punctation and in the distal canal; biopsy designated by arrow showed HGAIN.

FIGURE 17.64. Coarse punctation and atypical vessels causing concern for occult invasion; biopsy designated by arrow showed HGAIN. Lesion was successfully ablated using IRC.

FIGURE 17.65. Thickened, friable, dilated, abnormal vessels clinically suspicious for occult invasion denoted between arrows; biopsy multiple areas to rule out invasion; here, however, biopsy showed HGAIN, and lesion was ultimately treated in-office with good results.

FIGURE 17.66. A: Coarse mosaic pattern; biopsy (arrow) showed HGAIN. B: Adjacent area with atypical vessels; biopsy (arrow) read as suspicious for superficial invasion. The lesion in (B) was subsequently excised in the OR and because of the complex growth pattern; superficial invasion was still suspected but not confirmed.

(Figures 17.71 and 17.72). The diagnosis of anal cancer can sometimes be technically challenging. The patient in Figure 17.68 had a 3-cm palpable mass, but a biopsy in the office was superficial and only showed HGAIN. She was referred for additional surgical biopsies under anesthesia which confirmed invasive cancer. The patient depicted in Figure 17.73 had a similar presentation and required an examination under anesthesia (EUA) to definitely diagnose invasive cancer.

With advanced anal cancer, patients may present with a mass or symptoms of pain or unexplained bleeding. At presentation, the patient in Figure 17.74 had an obvious advanced cancer that extended from the SCJ through the entire anal canal to the verge. The patient in Figure 17.75 had previously been treated with radiation and chemotherapy for anal cancer, but never returned for surveillance until he developed pain, bleeding, and an obvious mass.

Often cancer is obvious, but in its earliest stages, there may be only subtle changes on DARE and it can be detected only after careful HRA. When patients have lesions that are clinically or colposcopically concerning for invasion and a
diagnosis of invasive cancer cannot be made in the office, then EUA, with larger or multiple biopsies, is indicated.

17.4.11 Perianal Examination

The perianal exam begins at the anal verge, the distal end of the anal canal, which is just visible with gentle retraction of the buttocks. The anal verge is where the squamous mucosal epithelium transitions to true skin of the perianus. The exam includes all aspects of the perianus. By convention, the perianus extends distally approximately 5 cm from the anal verge (Figure 17.76).

HRA of the perianus is similar to colposcopy of the vulva. Perianal disease often presents in diffuse or circumferential patterns and may be hard to distinguish from perianal excoriation. Visually, differentiation of abnormal from benign changes or LGAIN from HGAIN may be difficult. HPV-associated changes present in patterns similar to the vulva and are often contiguous with vulvar disease. Compared with intra-anal disease, there are fewer lesion characteristics to help distinguish between high-grade and low-grade lesions. Biopsy of all abnormal areas determines the extent and grade of disease.

Examine the perianus prior to applying vinegar. Look for fissures, ulcerations, and generalized excoriation, which may result from excessive wiping after bowel movements. Fissures and other skin breaks can be sensitive when vinegar is applied; however, the lidocaine-lubricant mixture used at the beginning of the HRA generally provides adequate anesthesia even if skin breaks are present. Make note of areas of leukoplakia. This is

![Figure 17.67](image_url)

**FIGURE 17.67.** A: Faint AWE within a fold at arrow. B: High magnification. C: Lugol’s negative staining. D: Fold opened up better displaying the entire lesion. Arrow in (A) indicates biopsy site: HGAIN.

![Figure 17.68](image_url)

**FIGURE 17.68.** Patient had a 3-cm palpable mass. HRA showed friable papillary lesion; EUA with biopsy (arrow) revealed invasive cancer.
**FIGURE 17.69.** A, B: Patient had palpable thickening on DARE. HRA showed a mass with atypical vessels. *Arrows* indicate biopsy sites taken in office; biopsies showed invasive SCC.

**FIGURE 17.70.** Patient had palpable thickening on DARE. HRA showed the mass with atypical vessels consistent with cancer. A: At SCJ. B: In distal canal, at dentate line. *Arrows* indicate biopsy sites performed in the office; biopsies showed invasive SCC.

**FIGURE 17.71.** A: Ulcerated, friable lesion with atypical vessels; office biopsy (*arrow*) was suggestive of superficial invasion. B: Ulcerated, friable lesion with atypical vessels; biopsy of this site (*arrow*) showed superficially invasive SCC.
FIGURE 17.72.  A–D: Obvious cancer extending from the SCJ to the distal canal with thickened area palpated in the anterior midline. Biopsy showed superficially invasive SCC. The lesion was adherent to the sphincter clinically; he was referred for CMT. E,F: 15 months after completion of CMT showing a complete response.
FIGURE 17.73. Patient with palpable mass that was initially difficult to visualize during HRA until correlated with the DARE. In-office biopsy showed HGAIN; due to the clinical concern for invasive cancer, the patient was referred for EUA that confirmed the diagnosis of invasive SCC. A: Low magnification. B: Same lesion, higher magnification.

FIGURE 17.74. A–D: Advanced cancer with friable mass that extended throughout the anal canal to the verge denoted by arrows.
A typical high-grade lesion is acetowhite or grey, with or without hyperpigmentation. Perianal HGAIN may be flat, slightly raised, or raised. On the perianus, vascular changes are less common than on nonkeratinized squamous epithelium, but if present, the lesion is often high-grade. The findings may also be subtle; an ulcer in the center of a granular warty-type lesion may indicate high-grade changes or cancer. Ulcerations can present as shallow, denuded epithelium or can be deep. Perianal HGAIN can also present as discrete or clustered lesions. Bowen’s disease and bowenoid papulosis, respectively, are clinical terms sometimes used to describe these patterns of perianal HGAIN (Figures 17.87 to 17.97).

A painful, hard, friable mass is likely to be a cancer. Large warts may be painful and may bleed, but are not typically hard to palpation. Early cancers may present as subtle areas of focal discomfort with fissures, ulcerations, or small abnormal growths within a lesion that looks otherwise like LGAIN (Figures 17.98 to 17.101).

To help distinguish a true lesion from benign excoriations caused by pruritus, vigorous wiping, or frequent stools, patients should be advised to use moist wipes, apply a cream such as hydrocerin gel, Califlora gel or aloe vera gel daily, and return for a repeat exam in 1 month. If there is no improvement in

17.4.11.1 Features of Perianal Disease

There is a range of perianal disease patterns. A typical low-grade lesion is acetowhite, granular, raised, or slightly raised. Raised lesions often have warty papillae or a verrucous contour. Similar to the vulva, perianal LGAIN may present as clusters of lesions with similar patterns or discrete lesions (Figures 17.83 to 17.86).
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

**FIGURE 17.79.** Redundant perianal tissue or skin tag.

**FIGURE 17.80.** Perianal hemorrhoid (arrow).

**FIGURE 17.81.** Perianal hyperkeratosis occurs with excessive wiping or as fissures heal. It is difficult to distinguish from AIN (see Figure 17.83).

**FIGURE 17.82.** Perianal hyperpigmentation in a field of AWE in a woman with a history of treated HGAIN. The pigmented area shown by *arrow* was LGAIN.

**FIGURE 17.83.** Perianal LGAIN: cluster of three granular, flat acetowhite lesions.

**FIGURE 17.84.** Perianal LGAIN: cluster of verrucous condyloma with papillae.
FIGURE 17.85. Perianal LGAIN: circumferential raised granular lesions with areas of hyperpigmentation.

FIGURE 17.86. Perianal LGAIN: flat, with pigmentation, acetowhitening, and an area of coarse punctation at the base of the lesion (arrow).

FIGURE 17.87. Perianal HGAIN: discrete, flat, acetowhite lesion with jagged edges. Viewed at low power denoted by arrow (A) and high power (B).

FIGURE 17.88. Perianal HGAIN: faint, barely visible lesion with granularity, small fissure, and indistinct margins.

FIGURE 17.89. Perianal HGAIN: acetowhite, slightly raised, and granular with a shallow ulceration at the base where the epithelium is peeling.
FIGURE 17.90. Perianal HGAIN: acetowhite, flat, granular, and thickened.

FIGURE 17.91. Perianal HGAIN: thickened and raised lesion with ulcerations. Adjacent to benign perianal tags.

FIGURE 17.92. Perianal HGAIN: erythematous barely acetowhite lesion with a discrete margin, slightly raised or thickened, course punctation, and several fissured areas.

FIGURE 17.93. Perianal HGAIN: extensive lesion with flat and slightly raised areas at the base and center, and a raised thickened area with defined margins at the superior aspect of the lesion.

FIGURE 17.94. A: Perianal HGAIN: thickened, acetowhite and hyperpigmented lesion with shallow ulcerations. B: Mosaic patterns can be seen adjacent to the ulcerations in the high-power image.
FIGURE 17.95. Perianal HGAIN: diffuse but well-demarcated denuded epithelium. Thickening is seen at the base of the lesion.

FIGURE 17.96. Perianal HGAIN adjacent to high-grade VIN. The perianal mass is thickened and hyperpigmented.

FIGURE 17.97. Perianal HGAIN, suspicious for invasion. A: The lesion before vinegar has thickening and punctation that is barely visible. B: After soaking the perianus with vinegar, the thick acetowhiten-ing, punctation, and fissuring are more apparent. C: Three months later, the lesion has progressed; abnormal vascular changes are more prominent. It showed SCC on excision.
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

**FIGURE 17.98.** Perianal superficially invasive SCC at low power (A) and high power (B). The epithelium is diffusely ulcerated with small protruding polyploid growths.

**FIGURE 17.99.** Perianal SCC with polyploid growths emanating from ulcerated areas in the mass. These growths are a hallmark of perianal cancer.

**FIGURE 17.100.** Perianal cancer associated with a fistula tract. A: The mass before treatment. B: The normal epithelial changes after radiation therapy.

1 month, biopsy the abnormal-appearing areas. A gentle scraping of the perianal skin for a wet mount smear can be done if a fungal infection is suspected; if positive, the patient can be directed to use an over-the-counter antifungal agent. There are various dermatologic conditions that can cause pruritus; refer patients to a dermatologist for perianal pruritus that is long-standing and unresponsive to treatment.

Because perianal lesions are harder to grade clinically, it is important to biopsy representative areas to ascertain the extent and grade(s) of disease. Once the region is anesthetized, these biopsies are generally well tolerated. There is little bleeding from perianal biopsies and hemostasis can easily be managed by applying a silver nitrate stick to the biopsy site.

**17.5 MANAGEMENT AND TREATMENT OF ANAL CANAL AND PERIANAL LESIONS**

Once AIN is biopsy-confirmed, a management strategy is individually designed to reduce the potential risk for progression of HGAIN to cancer, to relieve symptoms if present, and by factoring in underlying health conditions, such as immune
status and medical conditions that predispose to bleeding and/or infection.

17.5.1 Rationale for Treating HGAIN or Condyloma

Since HGAIN is considered precancerous, it is treated to prevent progression to anal cancer, analogous to treatment of high-grade CIN (CIN 3). To date, no prospective, randomized studies comparing treatment of HGAIN to observation have been conducted demonstrating that treatment prevents the development of anal cancer. However, several published studies indirectly suggest that treatment of HGAIN may prevent progression to cancer. In a retrospective review of 246 patients treated surgically at UCSF using HRA to guide therapy, 3 patients progressed to cancer for a progression rate of 1.2%. This compares to a rate of 7.5% (3 of 40) in patients with HGAIN progressing to cancer who were managed expectantly by physical exam every 6 months with biopsy of any new masses or ulcerations. In a German study following 156 HIV-positive men with HGAIN, five subjects (3.2%) who refused ablative therapy progressed to cancer. None of the remaining subjects who had HGAIN treated progressed to cancer. Warts are not thought to progress directly to cancer.

17.5.3 Office-Based Treatment of AIN

Several options exist for office-based treatment of AIN, and office-based treatment is preferred whenever possible. Each of the options will be briefly discussed along with the best application for treatment of AIN. See Table 17.3 for an overview of treatment options.

17.5.3.1 Provider-Applied Therapy: Cryotherapy and 85% Trichloroacetic Acid

Cryotherapy is generally not useful for the treatment of intranal lesions; however, it is very useful for small to moderate-sized perianal lesions, including condyloma and HGAIN in the clinical experience of the author (JMB). It is difficult to use intra-anally because the vapors produced obscure visualization, making it difficult to determine if a lesion has been adequately frozen. It can be used on multiple perianal lesions measuring up to 2 cm. Cryotherapy can be easily applied by soaking a cotton-tipped wooden swab in liquid nitrogen and directly applying it to the lesion until an ice ball develops or using a probe to spray the liquid nitrogen directly on the lesion. It is common to do three freeze-thaw cycles. Some providers will apply 85% trichloroacetic acid (TCA) after freezing without problems reported; however, there are no published data...
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

### TABLE 17.3
**AN OVERVIEW OF TREATMENT OPTIONS FOR CONDYLOMA AND HGIN**

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>PERIANAL CONDYLOMA</th>
<th>PERIANAL HGAIN</th>
<th>INTRA-ANAL CONDYLOMA</th>
<th>INTRA-ANAL HGAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5% Podoflox gel</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5% Imiquimod</td>
<td>Yes</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
<tr>
<td>5% Fluorouracil</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
<tr>
<td>15% Sinecatechins</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Trichloroacetic acid†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ablation‡</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Excision</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Only FDA-approved indications are designated as “yes” in the table; otherwise use is non–FDA-approved or “off-label.”

†Best for smaller nonbulky lesions.
‡IRC, hycrcation, electrocautery, laser ablation, and argon beam coagulation.

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using this approach. Cryotherapy is somewhat uncomfortable, but anesthesia is usually not required. Erythema and blistering may occur fairly quickly and there may be burning for several days. The area usually heals in 7 to 14 days. The process can be repeated every 2 to 3 weeks until clearance of lesions. If the lesions do not resolve, then other topical therapies or ablative methods can be used (see Section 17.5.3.3). If lesions progress or there is hyperpigmentation or ulceration unrelated to the treatment, then lesions should be biopsied.

Eighty-five percent TCA is most useful for small perianal or intra-anal lesions or in combination with cryotherapy. Two or fewer thin, flat areas of HGAIN comprising <25% of the perianal circumference tend to respond well to TCA treatment. Thicker lesions and bulky warts do not respond as well. The wooden end of a cotton-tipped swab is placed in a small amount of TCA, the excess is shaken off to prevent dripping, and the stick is directly applied to the lesions (Figure 17.102). Treatments are repeated at 3- to 4-week intervals for up to four treatments. In a retrospective analysis of patients treated in the UCSF Anal Neoplasia Clinic, complete clearance of HGAIN was found in 9 of 28 patients (32%); however, the response rate per HGAIN lesion was 64%. Recurrence of AIN was common and occurred in 15 of 21 patients (72%). Clearance rates were higher in HIV-negative compared with HIV-positive men, but the difference was not statistically significant.

17.5.3.2 Patient-Applied Topical Treatments: 0.5% Podoflox Gel, 5% Imiquimod Cream, 5% Fluorouracil Cream, 15% Sinecatechins

Given appropriate instructions, most patients can self-apply podoflox gel (Condylox®), to perianal condyloma. The gel is applied in a thin film twice daily for 3 consecutive days followed by 4 days off; this cycle can be repeated for up to four courses. Patients often experience transient erythema, burning, or shallow erosions, which resolve in about a week. Clearance rates have been reported between 37% and 83%. Unpurified podophyllin is no longer used based on its theoretical potential toxicity and mutagenicity.

Imiquimod cream (Aldara®) is rubbed into the affected cutaneous areas thoroughly at bedtime and then rinsed off in the morning. It is applied on alternating days three times a week, until the lesion disappears. Frequency of application can be reduced if perianal inflammation, erosion, and pain secondary to the treatment impede compliance. Imiquimod is dispensed in a box of 12 packets and prescribed for up to 16 weeks of treatment. It is an immune modulator and induces production
FIGURE 17.102. (Continued) C: After application of TCA. D: First follow-up after TCA, 1 month later. E: Second application of TCA. F: Follow-up after TCA, 3 weeks later. G: Third application of TCA and, (H) no lesions are seen 4 months later.

of cytokines and stimulates dendritic cells locally. In immunocompetent patients evaluated in placebo-controlled studies, complete response rates of 40% to 70% were seen; these differences were statistically significant from placebo response rates of 0% to 34%.77 Better efficacy has been reported against genital warts in HIV-negative compared with HIV-positive patients, with 62% of HIV-negative patients having complete clearance compared with 31% of HIV-positive patients. In another study, podofilox and imiquimod were directly compared in 45 nonimmunocompromised patients with anogenital
warts; there were no statistical differences between associated side effects or response rates at 72% and 75%, respectively.76

There are limited reports of efficacy using imiquimod for treatment of intra-anal HGAIN in cohort studies and case reports.77 In one study, 14 of 19 (74%) HIV-positive MSM had complete regression of either intra-anal or perianal AIN after treatment with imiquimod and 5 developed recurrent HGAIN. A decrease in the number of HPV types and HPV viral load was also seen following treatment.78 The results from a randomized, double-blind placebo-controlled study of imiquimod for anal canal HGAIN were reported in 33 patients. In the treatment arm, 4 resolved and 8 were downgraded to AIN 1 versus only 1 of 25 in the placebo arm who spontaneously regressed. Patients from both arms were treated with open-label imiquimod after completing the study; 29 of 47 (61%) had sustained regression of HGAIN with imiquimod. Interestingly, patients were instructed to use only half a packet per application three times per week, applied no more than 2 cm into the canal; they were treated for 4 months, and the dosage was reduced if significant symptoms developed.80

There are limited data evaluating 5% fluorouracil (5FU, Efudex®) for genital warts; however, a Cochrane review suggests that despite the paucity and heterogeneity of the literature, there is evidence for a therapeutic effect against genital warts.81 A randomized study evaluated 5FU as maintenance therapy to decrease recurrence of high-grade CIN following loop electro-surgical excision procedure (LEEP) in HIV-positive women. Recurrence of CIN was 47% in the observation arm compared with 28% in the 5FU group. In addition, time without recurrence was significantly prolonged, and the likelihood of high-grade CIN recurrence was decreased from 31% to 8%.82

Published literature describing the specific use of 5FU for anal lesions is also limited. In one study, evaluating treatment of patients with perianal HGAIN, 7 of 8 patients treated with 5% fluorouracil cream, applied twice a week for 16 weeks, had no evidence of Bowen’s disease on follow-up biopsies 1 year later.83 An open-label study has been reported in 46 patients with intra-anal lesions; multifocal lesions were seen in 76%, and 74% had HGAIN. All were HIV positive. In this study, 1 g of 5FU cream was inserted into the anus using an applicator two nights a week for 16 weeks. Complete responses were seen in 12 of 34 patients and partial responses, with a decrease in HGAIN to LGAIN, were seen in an additional 8 subjects. Moderate to severe side effects of redness, swelling, pain, irritation, erosion, and ulceration were reported in 48%.84 Results were recently reported in 11 patients using a slightly different dosing schedule inserting approximately 0.25 g of 5FU intra-anally each night, as tolerated, for a median treatment time of 20 weeks. One patient discontinued therapy due to side effects, and 73% of patients experienced some amount of irritation. Six patients had improvement in their disease including one with extensive condyloma who had no lesions on follow-up HRA.85

Sinecatechins 15% (Veregen®) ointment is FDA approved for the treatment of genital warts and is an extract of green tea leaves. The pooled results of two randomized, placebo-controlled trials demonstrate complete clearance of all warts defined at baseline and new warts in 54.9% of subjects compared with 35.4% treated with placebo.86 The ointment is self-applied three times daily for a total of 16 weeks. Subjects had normal immune function and either genital or perianal warts, but not vaginal or “rectal” warts that required treatment. Erosion, ulceration, or erythema was associated with response and often occurred with greatest intensity between weeks 2 and 4. Subjects treated with active ointment were more likely to have a local skin reaction than those treated with vehicle alone, 85.9% versus 60.4% respectively. Overall, sinecatechins 15% ointment is an effective and well-tolerated treatment for external genital warts. It has not been evaluated for treatment of HGAIN, for treatment of intra-anal lesions, or in immunocompromised patients.

17.5.3.3 Surgical Excision and Ablative Techniques

Surgical excision is the preferred treatment method when additional histopathologic analysis is required to rule out cancer. There are multiple techniques for physically ablating HGAIN and condyloma, including infrared coagulation (IRC), hyfrecation, electrocautery, laser ablation, and argon beam coagulation. To date, there are no published studies comparing effectiveness or morbidity of each of the various methods. See Table 17.4 for a comparison of equipment costs and feasibility for office-based treatment associated with various methods of ablation. In the absence of comparative effectiveness, the choice of ablation primarily relates to availability of equipment and to the provider’s training, experience, and comfort in using a particular method. All ablative methods, except for IRC, require a smoke evacuator. For more extensive perianal lesions, IRC may be more difficult because the unit tends to overheat in this situation. Judging depth of ablation using laser and electrocautery is required; significant problems can occur if providers are not properly trained.

There is a paucity of literature describing treatment of HGAIN and very few articles in which HRA was used to guide treatment. At UCSF, HRA is used in the operating room to guide surgical treatment of HGAIN. We performed over 530 HRA-guided operations for treatment of anal lesions between 2001 and 2010, and published two reports describing our experience.18,87 The first, published in 2002, described outcomes and morbidity for HRA-guided surgical ablation of HGAIN in 29 HIV-positive and 8 HIV-negative patients.18 In this report, among HIV-negative patients, no recurrence of HGAIN was seen, but in 79% (23 of 29) of HIV-positive patients recurrence of HGAIN was seen within 12 months. Uncontrolled pain was reported in 16 of 29 patients lasting a mean of 2.9 weeks. No stenosis, incontinence, infection, or significant bleeding occurred postoperatively.

### TABLE 17.4 COMPARISON OF OFFICE-BASED ABLATION METHODS INCLUDING APPROXIMATE EQUIPMENT COSTS

<table>
<thead>
<tr>
<th>Method</th>
<th>Published Results</th>
<th>Smoke Evacuator</th>
<th>Office-Based</th>
<th>Equipment Expense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrared coagulation</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>$8,395</td>
</tr>
<tr>
<td>Hyfrecation</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>$825*</td>
</tr>
<tr>
<td>Electrocautery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>$2,600*</td>
</tr>
<tr>
<td>Laser ablation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>$75,000</td>
</tr>
<tr>
<td>Argon plasma coagulation</td>
<td>Abstract</td>
<td>Yes</td>
<td>Yes</td>
<td>$38,000</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>$25,000*</td>
</tr>
</tbody>
</table>

*Smoke evacuator separate ~$2600.

*Operating Microscope.
Two factors mitigate the apparently poor results seen in the HIV-positive patients. First, some patients had lesions too extensive to be treated in a single operation. For purposes of this analysis, they were scored as recurrences, when in fact they had not completed their planned treatment. Second, this study was completed prior to the introduction of IRC as an office-based treatment. The only option for treatment of recurrences was to return to the operating room. These results indicate that, particularly in HIV-positive patients, surgical treatment alone is insufficient to control HGAIN. If surgical ablation is not guided by HRA, less favorable results will likely occur since many lesions will potentially be missed. The lack of efficacy of ablative therapy has often been cited based on the results of this paper.

In October 2002, we began using IRC in the office at UCSF to treat patients with HGAIN. Collectively, our group performed over 2500 IRC procedures. Based on our clinical experience, IRC demonstrates good efficacy and mild to moderate morbidity that is well tolerated. Retrospective studies, initially published by Goldstone and subsequently by Cranston, confirm the efficacy and minimal morbidity of IRC. Combining results from these studies, the individual lesion eradication rate was 64% to 81% with 35% to 47% having a per-subject complete response.

As with other modalities, 60% developed metachronous lesions; however, with successive treatments, the likelihood of recurrence decreased. Results from a prospective multicenter pilot study conducted by the AIDS Malignancy Consortium showed a complete response at 1 year in 10 of 16 (63%) HIV-positive persons with an eradication rate of 66% per lesion. Treatment efficacy is better in HIV-negative patients than in HIV-positive patients. In all of these studies, HRA was used to guide treatment.

Nathan et al. published their results using HRA-guided office-based laser ablation of both high-grade and low-grade AIN in 181 patients. No evidence of disease at 12 months was seen in 114 of 181 (63%) patients, and they experienced minimal morbidity. Kreuter et al. in Germany prospectively followed a cohort of 446 HIV-positive men. HGAIN was diagnosed in 156 (35%), LGAIN in 163 (36.5%), and 11 (2.5%) were diagnosed with anal cancer. Subjects were followed with HRA, and lesions were treated with electrocautery. Progression to invasive cancer was seen only in the five subjects who refused treatment of their lesions.

Our 10-year results treating 246 patients with HGAIN using HRA-guided surgical ablation combined with office-based treatment of recurrences using IRC demonstrates the feasibility of treating HGAIN (Figure 17.103). In this study, 192 of 246 (78%) had no evidence of HGAIN at their last follow-up.

FIGURE 17.103. Fifty-four-year-old HIV-negative woman with a remote history of vaginal warts developed an external perianal lump and bleeding with bowel movements. A: Friable atypical condyloma in anal canal. B: Arrow indicates biopsy site somewhat more distal to image (A); histology was HGAIN. C: Palpable firm, ulcerated but not indurated perianal lesion; histology showed HGAIN. She was successfully treated with HRA-guided ablation. D: She had a small recurrence of intra-anal HGAIN detected at her 4-month postoperative visit that was easily treated with IRC in the office. Image is after infiltration of lidocaine prior to IRC. One year later she remains disease free.
Only nine patients developed complications of note: one had bleeding requiring reoperation, two developed anal stenosis, four developed anal fissures, one had a myocardial infarction on post-op day 3, and one developed cellulitis at the local anesthetic injection site. Overall, three patients progressed to invasive cancer despite treatment: two were lost to follow-up after treatment until they presented 14 and 19 months later with symptomatic masses; the third patient had preexisting anal stenosis that complicated treatment and had multiple recurrences of HGAIN prior to progressing to invasive cancer.

Guidelines for treatment of HGAIN were published by Chin-Hong and Palefsky, what conclusions can be drawn based on our clinical experience and these published studies regarding treatment of HGAIN? The majority of patients, who present to the UCSF Anal Neoplasia Clinic and are diagnosed with HGAIN, are treated in the office. Whenever clinically appropriate, we treat patients in the office because recovery is quicker, postprocedure pain associated with office-based treatment is less, and it is a more pragmatic and economical way to treat HGAIN, particularly if lesions are likely to recur and additional treatments are needed. It is also similar to the rationale for office-based management of CIN. Not surprisingly, most patients prefer office-based treatment to surgical treatment. However, when lesions are too extensive or there is a clinical suspicion that cancer may be present, patients are referred for surgical consultation.

Currently, for patients with circumferential intra-anal or perianal lesions and who have relatively intact immune function (here defined as a CD4+ lymphocyte count >200/mm3), and are otherwise healthy, we routinely offer staged surgery followed by office-based treatment with good results. In staged surgery, approximately 60% of the lesions are ablated at the first operation. Patients are then evaluated 8 to 10 weeks after surgery and scheduled for their second procedure 2 to 4 weeks later. In addition to surgical ablation, almost all require additional in-office ablation. Ultimately, the majority of these patients have no HGAIN identified on subsequent follow-up. HGAIN can be successfully eradicated in almost all patients who are medically fit and motivated. However, patients with significant comorbidities or severely compromised immune function are usually observed carefully with regular DARE with the goal of early detection of cancer should it develop.

Successful eradication of HGAIN requires close patient follow-up using HRA and treatment of persistent or recurrent HGAIN. Recurrence and persistence of HGAIN are common, particularly in HIV-positive persons, and some of these lesions may progress to cancer. We have seen progression to superficially invasive cancer in as little as 3 months postoperatively. However, based on the experience in the UCSF Anal Neoplasia Clinic, in the absence of HRA, regular follow-up every 4 to 6 months with anal cytology, DARE, and simple anoscopy should be performed. Close follow-up facilitates the early detection of cancer. Additionally, early recognition and treatment of persistent or recurrent HGAIN maximizes the likelihood of eliminating HGAIN. Whether treatment of HGAIN ultimately succeeds in preventing progression to invasive cancer is still unknown.

17.5.3.3.1 Office-Based Infrared Coagulation

Prior to IRC, patients have HRA with biopsy to confirm HGAIN, rule out occult invasion, and identify areas of metaplasia that do not require treatment. Immediately prior to IRC, 5% anorectal lidocaine cream is applied topically for 10 to 15 minutes; it does not affect the appearance of the lesions. HRA is repeated to visualize all areas that need to be treated; these areas are then infiltrated with local anesthetic, such as 1% lidocaine with epinephrine buffered with sodium bicarbonate (1 mL bicarbonate added to 5 mL lidocaine). Injections are usually performed via the anoscope using a 25-gauge spinal needle attached to a 10-mL control syringe. Small volumes are infiltrated beginning proximally, at the SCJ, and working out distally towards the dentate line. Papillae that extend proximally from the dentate line and the portion of the canal distal to it are cutaneously innervated and highly sensitive. A 1-inch 30-gauge needle is used for injection in these areas and for the verge and perianal region. Once all areas in the canal are anesthetized, the anoscope is removed to allow bleeding secondary to the injections to stop.

For the IRC, the anoscope is replaced and lesions reidentified with the application of vinegar. The light guide of the IRC machine is placed in contact with the lesional mucosa and the trigger fired. The IRC machine is set for 1.5 seconds; this corresponds to approximately 1.5-mm depth of burn, which is sufficient for most lesions. Immediate blanching of the mucosa is observed. The ablated tissue can easily be debrided down to the level of the submucosal vessels. Following debridement, the base of the lesion is usually retreated both for hemostasis and for control of disease. Figures 17.104 to 17.106 show examples of in-office IRC from identification of lesions using HRA to final debridement. Patients are instructed to maintain

![Image A](image1.png)

![Image B](image2.png)

**FIGURE 17.104.** Large lesion occupying the anterior midline. Multiple deep biopsies of the raised friable area were taken, indicated by *arrows* in (A); biopsies showed HGAIN. The patient had a medical contraindication to surgery, so was offered treatment in the office using IRC. B: Higher power view.
FIGURE 17.104. (Continued) C,D: Distal margins of lesion.

FIGURE 17.105. Panels (A–D) show progressive ablation of lesion, followed by debridement down to the level of the submucosal vessels. In (D), the lesion extends into the distal canal, so this area was anesthetized and ablated.
Chapter 17: The Anal Canal and Perianus: HPV-Related Disease

17.5.4 Approach to Patients in the Operating Room: UCSF Experience

Patients are placed in the prone jackknife position, buttocks taped apart, and prepped with antiseptic solution. Some providers prefer to treat patients in the dorsal lithotomy position. Usually patients are heavily sedated, but not given general or a spinal anesthetic. Once the patient is sedated, a perianal block is placed using a combination of a short- and long-acting anesthetic such as lidocaine and bupivacaine. DARE is repeated by the surgeon to palpate for masses and areas of induration. The anus is saturated with 5% acetic acid, and HRA is repeated by the surgeon, if trained in this technique. Alternatively, the surgeon exposes or everts the anal mucosa so that it can be examined using the operating microscope. Areas clinically suspicious for cancer are excised; the remaining lesions are ablated using electrocautery. Treatment of circumferential lesions that extend from the distal canal to the verge and perianal area are staged to avoid anal stenosis.

17.5.5 Specific Management Scenarios If Cancer Is Identified or Suspected

1. If an intra-anal or perianal mass or indurated area is felt that is associated with obvious high-grade vascular changes, the most worrisome-appearing areas should be biopsied. If invasive cancer is found, then refer for combined modality therapy (CMT). If cancer is not diagnosed or the biopsy is only suspicious, or has features suggestive of cancer, then patients should be referred for an EUA and surgical biopsy (Figure 17.107).

2. If superficially invasive cancer in found in perianal or anal margin lesions, patients may be candidates for

FIGURE 17.106. Three months following IRC, a small persistent area of AIN 2 was biopsied (arrow) and ablated with IRC seen in (A) and (B). In (C) and (D), 4 months later, he had no evidence of HGAIN.
local excision. To determine who is a suitable candidate, patients should be carefully evaluated by an expert in anal neoplasia to rule out simultaneous intra-anal HGAIN or cancer. Please see discussion below regarding treatment of superficially invasive cancer (Figure 17.108).

3. If a submucosal mass without a mucosal component is palpated, it is best to refer the patient for an incisional biopsy in the operating room; these are difficult to biopsy in the office. DARE is an essential part of the anal exam; when a mass is palpated and there is no clear underlying cause, patients should be referred for a surgical evaluation. Refer again to Figure 17.108.

4. If a patient has known HGAIN, extensive perianal lesions, or areas that are focally tender, or if ulcerated areas with atypical vessels are seen during HRA, and HRA-guided biopsies do not show cancer, then EUA with biopsy should be considered. If the clinical suspicion of cancer is high and the patient is not able to easily be examined in the office, refer for EUA and biopsy, particularly since multiple areas need to be sampled to determine whether or not cancer is present (Figures 17.109 to 17.111).

5. If a large firm papillary lesion, not typical for condyloma, is identified and biopsy reveals HGAIN, refer for EUA and additional biopsies; these patients are at high risk of occult cancer and must have adequately sized biopsies or excision under anesthesia (Figure 17.112).

6. If a biopsy in the office is interpreted as having features suggestive of invasion, the patient should be referred for EUA and HRA-guided surgical biopsies.

### 17.5.6 Specific Recommendations for Management and Treatment of HGAIN and Condyloma

#### 17.5.6.1 Extensive Circumferential Lesions

1. If a patient is in good medical condition and has circumferential perianal and intra-anal HGAIN with lesions that extend through the distal canal, or >25% involvement of distal canal, he or she is best managed with surgery as described above. An alternative is to use local excision. To determine who is a suitable candidate, patients should be carefully evaluated by an expert in anal neoplasia to rule out simultaneous intra-anal HGAIN or cancer. Please see discussion below regarding treatment of superficially invasive cancer (Figure 17.108).

A: Forty-six-year-old HIV-positive MSM with obvious mass at anal verge and absence of perianal mucosal changes. B: HRA-guided biopsy (arrow) of very coarse punctation in anal canal showed AIN 3. C: Histology of this area of abnormal vessels distally (arrow) also was AIN 3; however, biopsy was superficial, and invasion could not be excluded. D: Histology of this area of mosaic pattern and abnormal vessels (arrow) was superficially invasive SCC (<1 mm depth of invasion). Clinically, there was invasion of the sphincter and therefore, the mass was not resectable, and the patient was referred for radiation and chemotherapy.

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10/6/2011   6:26:57 PM
FIGURE 17.108. A: Sixty-two-year-old HIV-positive man presented for screening. On DARE, firm nodularity was palpated. A: During HRA, there appeared to be a submucosal bulge with mass effect. Biopsy adjacent to it as indicated by the arrow was AIN 3. B: Biopsy of this friable lesion (arrow) with blunted papillae and abnormal vessels showed superficially invasive SCC. Because there appeared to be a deeper submucosal component, the patient was not considered a candidate for conservative management and was successfully treated with CMT.

FIGURE 17.109. A: This is a 44-year-old woman, s/p liver transplant 20 years ago for autoimmune hepatitis. In November 2009, she had excision of two anal masses, thought to be hemorrhoids, which showed superficially invasive carcinoma. She was referred for further evaluation to the UCSF Anal Neoplasia Clinic. Subsequent cervical evaluation showed high-grade CIN. A: On initial HRA, biopsy at arrow showed HGAIN with foci suspicious for invasion. However, a larger surgical excisional biopsy of this area showed only HGAIN. B: Patient returned for follow-up 5 months later, and exam had worsened clinically, and anal cytology was HSIL with features suspicious for invasion. The arrow indicates the area of primary concern corresponding to previous suspicious biopsy. C: Subsequent intraoperative excision showed superficially invasive SCC.
This is a 57-year-old HIV-positive man who presented with a year of anal irritation. He was seen by a local surgeon and biopsy of an anal verge ulcer showed HGAIN. Clinically, the lesion was highly suspicious for cancer. A: On his initial evaluation, multiple biopsies were taken of this area (one site designated by arrow); histology was HGAIN. B: Note coarse mosaic pattern and punctation; histology again HGAIN. C: Because of the concern for occult invasion, the patient was taken to the operating room. Arrows indicate margin of excision. Histology was focally invasive SCC associated with HGAIN. D: Additional intraoperative image showing fulguration of additional adjacent areas of HGAIN.

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FIGURE 17.111. Fifty-four-year-old HIV-positive man, with suspicious perianal lesion. Excision showed a superficially invasive well-differentiated SCC (arrow) arising in condyloma acuminatum.

FIGURE 17.112. Fifty-one-year-old HIV-positive man who presented with a 5-cm distal rectal mass and bleeding. Colonoscopic biopsy was highly suspicious for invasion. He was taken to the operating room for biopsy, which showed superficial stromal invasion. Perirectal nodes were present on endoanal ultrasound and on CT scan; therefore, he was staged as a T3N1M0 and referred for CMT. He had an initial complete response, but developed a local recurrence and pulmonary metastases within 10 months after completing therapy.
located within the anal canal (71% to 87%), while only 13% not readily apply to perianal cancers. Most anal cancers are related to skin cancers of the head and neck region and does

17.16). Tumors beyond the verge and continuing for 5 cm to the mucocutaneous junction at the anal verge. The palpable intersphincteric groove, at the distal border of

mucosal epithelium is keratinized but devoid of hair follicles nonkeratinized squamous epithelium that continues distally to the puborectalis sling; this can be palpated as the anorectal

Invasive anal cancer is curable in many patients, particularly those with early stages and small tumors. A distinction is made with regard to stage and treatment between cancers of the anal canal and perianal or anal margin cancers. The anal canal begins at the anorectal junction where the rectum enters the puborectalis sling; this can be palpated as the anorectal ring and is where the AnTZ is located. Histologically, this is nonkeratinized squamous epithelium that continues distally to the dentate line. Distal to the dentate line, the squamous mucosal epithelium is keratinized but devoid of hair follicles and apocrine and sweat glands; it lines the distal anal canal continuing to the mucocutaneous junction at the anal verge. The palpable intersphincteric groove, at the distal border of the internal sphincter muscle, is located in this portion of the canal. The anal canal is usually about 4 cm long (Figure 17.16). Tumors beyond the verge and continuing for 5 cm radially are classified as perianal or anal margin cancers.

Anal canal cancer is clinically staged according to the T, N, and M (TNM) (Table 17.5). In the current American Joint Committee on Cancer (AJCC) Staging Manual, perianal cancers are staged using the same criteria as cutaneous squamous cell cancers. Specific adaptation for perianal cancers will likely need to be created, since much of the staging is related to skin cancers of the head and neck region and does not readily apply to perianal cancers. Most anal cancers are located within the anal canal (71% to 87%), while only 13% to 29% are described as anal margin cancers. However, in one study comparing outcomes in HIV-positive versus HIV-negative patients, anal margin cancers comprised 63% of the cancers in HIV-positive patients.

Once a diagnosis of anal cancer is made, consultation with a cancer specialist is recommended. Appropriate staging studies are performed to determine whether it is localized or has metastasized either to nearby lymph nodes or to distant organs. The recommended staging workup for patients diagnosed with anal cancer is DARE to evaluate tumor size and location, HRA or standard anoscopy with biopsy to confirm diagnosis, palpation of inguinal nodes with biopsy or fine needle aspiration if clinically suspicious, chest x-ray or chest CT scan, abdominal and pelvic CT scan or MRI. A PET-CT can be considered, but its routine use has not been validated. HIV testing is indicated with CD4 lymphocyte count. Women should have a gynecologic exam including screening for cervical cancer.

Prior to the 1970s, the standard treatment for anal cancer was an abdominoperineal resection (APR) with colostomy. Currently, the standard of care for treatment of anal cancer is CMF: mitomycin and 5-fluorouracil combined with radiation. The exception may be a small T1 (<2 cm) intra-anal tumor that is not deeply invasive, if it can be excised without compromising sphincter function. This is based on review of older surgical literature prior to the advent of CMT as the standard of care for treatment of anal cancer and represents a very small proportion of patients.

Local excision for anal margin cancers was an abdominoperineal resection (APR) with colostomy. The two patients who did not achieve a complete response when treated with radiation alone. The two patients who did not achieve a complete response had AIDS. One additional patient who did not receive inguinal node irradiation subsequently died of recurrent anal cancer. This study also provides an excellent review of the available literature with guidelines for treatment that mirror the National Comprehensive Cancer Network (NCCN) treatment guidelines.

A series from Germany, however, reported inferior results among those with only anal margin involvement; overall survival was 54% compared to 75% in anal canal cancers. A series from Germany, however, reported inferior results among those with only anal margin involvement; overall survival was 54% compared to 75% in anal canal cancers. One speculation for this imbalance was an excess of patients with larger tumors and nodal involvement. Many perianal cancers are noticed at less advanced stages because they are more likely to be symptomatic earlier. According to NCCN Guidelines, surgical resection is recommended for well-differentiated T1, N0 tumors if adequate margins can be achieved without compromising sphincter function. All other perianal cancers are treated in the same fashion as anal canal cancer, with CMT.

17.5.6.2 Medium and Small-Volume Disease

1. HGAIN occupying 25% to 50% of circumference, some lesions relatively thick. Thicker lesions covering a greater extent are probably better managed with IRC than TCA.

2. A thin HGAIN lesion occupying <25% of circumference can be treated easily with TCA.

3. LGAIN occupying 25% to 50% of intra-anal circumference. Treat using IRC or observe with repeat HRA every 6 months and treat if HGAIN develops.

4. Several small condyloma occupying <25% of circumference can be treated easily with TCA or observation.

17.5.7 Management of Anal Cancer

17.5.7.1 Staging and Management of Invasive Anal Cancer

Invasive anal cancer is curable in many patients, particularly when diagnosed early while tumors are small. A distinction is made with regard to staging and treatment between cancers of the anal canal and perianal or anal margin cancers. The anal canal begins at the anorectal junction where the rectum enters the puborectalis sling; this can be palpated as the anorectal ring and is where the AnTZ is located. Histologically, this is nonkeratinized squamous epithelium that continues distally to the dentate line. Distal to the dentate line, the squamous mucosal epithelium is keratinized but devoid of hair follicles and apocrine and sweat glands; it lines the distal anal canal continuing to the mucocutaneous junction at the anal verge. The palpable intersphincteric groove, at the distal border of the internal sphincter muscle, is located in this portion of the canal. The anal canal is usually about 4 cm long (Figure 17.16). Tumors beyond the verge and continuing for 5 cm radially are classified as perianal or anal margin cancers.

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### TABLE 17.5 STAGING OF ANAL CANAL CANCER

<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>N0</th>
<th>M0</th>
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<tbody>
<tr>
<td>Stage 0: Tis</td>
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<td></td>
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<tr>
<td>Stage I: T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II: T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA: T1</td>
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<td>M0</td>
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<tr>
<td></td>
<td>T2</td>
<td>N0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
</tr>
<tr>
<td>Stage IIIB: T4</td>
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<td>M0</td>
</tr>
<tr>
<td></td>
<td>any T</td>
<td>N2</td>
</tr>
<tr>
<td></td>
<td>any T</td>
<td>N3</td>
</tr>
</tbody>
</table>


#### 17.5.7.2 Conservative Management of Superficially Invasive Squamous Cell Carcinoma of the Anus

According to NCCN guidelines, well-differentiated T1 (<2 cm) SCCs of the anal margin can be excised if clear margins can be achieved (Figure 17.110).\(^1\) If, with re-excision, margins remain positive, patients should be referred for standard CMT. Outside of this specific recommendation for anal margin cancers, CMT is the standard of care for all other invasive anal cancers regardless of depth of invasion. The pathologic equivalent to microinvasive cervical carcinoma, which is treated with cold knife cone excision and has a low incidence of nodal metastases, has not been validated in the anus. As high-risk patients are more frequently being screened and followed, an increasing number of patients with asymptomatic, superficially invasive squamous cell carcinomas of the anus (SISCCA) are being identified. Although not part of the formal recommendation, based on our clinical experience, patients with SISCCA of the anal margin need careful evaluation by providers experienced in managing anal neoplasia, preferably who perform HRA. In patients referred for conservative management, other areas of invasion were occasionally found intra-anally that had been unrecognized; these patients are not good candidates for simple excision. The histologic diagnosis of superficially invasive cancer must be put in clinical context. Often it is challenging to get representative biopsy samples of suspected anal cancers that are large enough for diagnosis, so if a patient has a mass or mass effect and a diagnosis of SISCCA, these patients should be referred for CMT (Figures 17.107, 17.108, and 17.112). Therefore, anal margin cancers that are superficially invasive can be managed with local excision, which is consistent with NCCN guidelines. With the exception of clinical trials, all other superficially invasive cancers should be managed with CMT.

### TABLE 17.6 PREVALENCE AND OUTCOME OF ANAL CANCER ACCORDING TO STAGE IN 19,199 PATIENTS FROM THE NATIONAL CANCER DATA BASE

<table>
<thead>
<tr>
<th>STAGE</th>
<th>PERCENTAGE OF PATIENTS AT DIAGNOSIS</th>
<th>FIVE-YEAR OVERALL SURVIVAL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>25.3</td>
<td>69.5</td>
</tr>
<tr>
<td>Stage II</td>
<td>51.8</td>
<td>59.0</td>
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<td>Stage III</td>
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<tr>
<td>Stage IV</td>
<td>5.7</td>
<td>18.7</td>
</tr>
</tbody>
</table>

HPV 6 or 11. The Advisory Committee on Immunization Practice (ACIP) subsequently issued a permissive recommendation for the quadrivalent vaccine, indicating that it may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. Although it does not carry the same “routine recommendation” as in similarly aged girls and women, the ACIP did recommend that the vaccine be covered for boys under the Vaccines for Children program; thus the vaccine is also provided free of charge to eligible boys between 9 and 18 years of age.

The FDA’s approval of the quadrivalent vaccine was based on data recently published from the Merck 020 protocol. The Merck 020 protocol was a double-blinded, placebo-controlled randomized clinical trial of the quadrivalent vaccine. The study included 3463 heterosexual men and 602 MSM. The data from this study showed that the vaccine was well tolerated and immunogenic in boys aged 16 to 26 years old with no more than five reported lifetime partners. The data also showed that it was effective in preventing persistent penile/scrotal/perianal infection with each of HPV 6 (84%), 11 (91%), 16 (100%) and 18 (100%) in vaccine recipients naïve to these four vaccine HPV types throughout the vaccination period (the per-protocol [PP] population). In the intent to treat (ITT) population of all trial participants, whether or not naïve to the four vaccine HPV types, the

**FIGURE 17.113.** A: Fifty-one-year-old HIV-positive man presented with locally advanced perianal cancer measuring 8 to 9 cm. B: After application of acetic acid. C: Arrow indicates site with grossly abnormal vessels; biopsy showed invasive SCC. D: 1 year after completing CMT with no evidence of disease.

### 17.6 SUMMARY AND CONCLUSIONS

The treatment of anal cancer is one of the success stories of modern cancer care, and many patients will be cured with surgery or CMT. However, the side effects of therapy can be substantial, and not all patients respond well to treatment. Early diagnosis will help improve outcome, and small tumors can be treated more effectively and with fewer side effects. There is little doubt that the best way to treat anal cancer is to prevent it from occurring. Patients with an increased risk of anal cancer may benefit from screening with anal cytology and DARE followed by eradication of identified HGAIN, the precursor of anal cancer. It is our hope that with screening, rates of anal cancer will decline similar to the success seen with cervical cancer screening.

#### 17.6.1 Primary Prevention: Hope for the Future

In 2009, the U.S. Food and Drug Administration approved the quadrivalent HPV vaccine for use in boys aged 9 to 26 years for the prevention of external genital warts associated with HPV 6 or 11. The Advisory Committee on Immunization Practice (ACIP) subsequently issued a permissive recommendation for the quadrivalent vaccine, indicating that it may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. Although it does not carry the same “routine recommendation” as in similarly aged girls and women, the ACIP did recommend that the vaccine be covered for boys under the Vaccines for Children program; thus the vaccine is also provided free of charge to eligible boys between 9 and 18 years of age.

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vaccine was less effective, with lower, but statistically significant efficacies for HPV 6 (45%), 11 (59%), 16 (47%), and 18 (56%). In this age group, most of the incident external genital lesions would be expected to be condyloma acuminatum, and thus almost all of the lesions that were prevented compared with the placebo group were condyloa acuminatum, with an 89% efficacy in the PP population and 67% in the ITT population. A study in the Merck 020 protocol evaluated 602 MSM for prevention of intra-anal HPV infection and AIN. The data showed prevention of 95% of intra-anal infection with HPV 6/11/16/18 in the PP population and 59% in the ITT population. The data also showed prevention of 75% of HGAIN related to vaccine types. These results may not be generalizable to older individuals and those with more than five lifetime partners, as they have a higher risk of prior exposure to vaccine-targeted HPV types. Based on these and other data, in December 2010, the FDA added prevention of AIN and anal and cervical precursors of HPV infection to the list of approved indications of the quadrivalent HPV vaccine. The ACIP is reviewing these data and is expected to decide whether to retain the current permissive recommendation for boys and men, or recommend that the vaccine be given on a routine basis as it is for girls. Since this is a prophylactic vaccine, optimal efficacy will be achieved with the lowest number of prevaccination sexual partners, hence the recommendation that boys (and girls) be vaccinated prior to initiation of sexual activity, if possible. The bivalent vaccine has not yet been studied in males and is not currently approved for use in this population. However, the demonstration that the quadrivalent HPV vaccine prevents most cases of HGAIN related to the most important HPV types causing anal cancer means that HPV vaccination should be an important tool for primary prevention of anal cancer in the long term. This is especially important given the absence of routine screening for AIN and challenges in treating HGAIN when diagnosed.

References


538 Chapter 17: The Anal Canal and Perianus: HPV-Related Disease


