Premalignant Lesions of the Anal Canal and Squamous Cell Carcinoma of the Anal Canal

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ABSTRACT

Squamous cell carcinoma of the anus (SCCA) is a rare tumor. However, its incidence has been increasing in men and women over the past 25 years worldwide. Risk factors associated with this cancer are those behaviors that predispose individuals to human papillomavirus (HPV) infection and immunosuppression. Anal cancer is generally preceded by high-grade anal intraepithelial neoplasia (HGAİN), which is most prevalent in human immunodeficiency virus-positive men who have sex with men. High-risk patients may benefit from screening. The most common presentation is rectal bleeding, which is present in nearly 50% of patients. Twenty percent of patients have no symptoms at the time of presentation. Clinical staging of anal cancer requires a digital rectal exam and a positron emission tomography/computed tomography scan of the chest, abdomen, and pelvis. Endorectal/endoanal ultrasound appears to add more-specific staging information when compared with digital rectal examination alone. Treatment of anal cancer prior to the 1970s involved an abdominoperineal resection. However, the current standard of care for localized anal cancer is concurrent chemoradiation therapy, primarily because of its sphincter-saving and colostomy-sparing potential. Studies have addressed alternative chemoradiation regimens to improve the standard protocol of fluorouracil, misogynic, and radiation, but no alternative regimen has proven superior. Surgery is reserved for those patients with residual disease or recurrence.

KEYWORDS: Squamous cell carcinoma, anal margin, neoplasms

Objectives: On completion of this article, the reader should be able to summarize premalignant lesions of the anal canal and anal intraepithelial neoplasia, as well as the epidemiology, etiology, risk factors, clinical features, staging, and treatment of squamous cell carcinoma of the anal canal.

Although squamous cell carcinoma of the anus (SCCA) is a rare disease, its incidence is increasing in men and women worldwide and is particularly high in the human immunodeficiency virus positive (HIV+) population. The most important risks factors are infection with human papillomavirus (HPV), HIV+ patients, anal

intercourse, and immunosuppression. SCCA is generally preceded by anal dysplasia or anal intraepithelial neoplasia (AIN). It is believed that anal dysplasia behaves similarly to cervical dysplasia and it is likely that high-grade AIN is the precursor of SCCA. AIN is closely linked to HPV infection, immunosuppression, HIV, and

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acquired immunodeficiency syndrome (AIDS). Although cytologic screening in cervical cancer is applied to prevent malignant progression, the same rationale is being applied for high-grade AIN (HSIL), whose treatment may prevent malignant transformation to SCCA. However, this approach to screen those patients at high risk for the development of SCCA with the intent to reduce the incidence is still limited by the lack of strong data in support of screening; nevertheless, there is consensus that high-risk individuals may benefit from screening. Different treatment modalities are available for HSIL, depending on clinical expertise, geographic location, and access to new technology such as high-resolution anoscopy (HRA). After excision or destruction of these dysplastic lesions, there is a high rate of local recurrence; hence, patients are placed in surveillance programs. It is critical that patients at risk for the development of SCCA are aware of the symptoms associated with the development of SCCA to allow for an early diagnosis and treatment. When localized SCCA is diagnosed, primary chemoradiation is the gold standard therapy; it is a sphincter-saving and colostomy-sparing modality. Cure can be achieved in the majority of these patients. However, SCCA treatment has been confounded with a higher percentage of HIV + patients developing this disease. In this population of patients, toxicity is greater, which affects therapeutic efficacy and end results. Different chemoradiation protocols with the goal of improving the standard regimen of fluorouracil (5-FU), mitomycin, and radiation have been developed, but no alternative regimens have proven superior. However, important conclusions have been reached in regards to continuity of radiation, the role of induction, and maintenance chemotherapy in this setting, whether chemotherapy can be eliminated for early-stage anal cancer, and the impact of human immunodeficiency virus infection on treatment.

In this article, premalignant anal lesions will be described and a comprehensive review provided on the prevention, epidemiology, etiology, anatomy, histology, pathogenesis, and treatment of squamous cell carcinoma of the anus.

ANAL PREMALIGNANT LESIONS: ANAL INTRAEPITHELIAL NEOPLASIA

Recent terminology used to describe premalignant lesions of the anus, which lead to SCCA, is often confusing. However, the term anal intraepithelial neoplasia (AIN) has emerged as the term most commonly chosen in the literature instead of SCC in situ (CIS), anal dysplasia, squamous intraepithelial lesion (SIL), and Bowen disease, which may all refer to the same histopathology.¹

The anal and cervical canal share embryologic, histologic, and pathologic characteristics. Both are sites

of fusions of endodermal and ectodermal tissue to form a squamocolumnar epithelial junction. They are both subject, if infected with human papillomavirus (HPV), to changes that range from normal metaplastic to abnormal dysplastic. These dysplastic changes in the anal canal are termed AIN and are viewed as analogous to those of cervical dysplasia. AIN is further subdivided into low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). HSIL is considered premalignant and may progress to SCCA, similar to the progression of HSIL lesions to cervical cancer.^{1,2}

Risk factors associated with AIN development are HPV infection, HIV infection, lower CD4 + counts, and receptive anal intercourse.³⁻¹⁰

HPV Infection as a Risk Factor

HPV infection is the most significant risk factor for AIN, and HPV infection of the anal canal and/or the perianal region may be latent, subclinical, or clinically apparent as anal condylomata. In contrast to women with cervical HPV infections where the prevalence declines after the age of 30, in anal HPV in HIV-negative (HIV-) men who have sex with men (MSM), it remains high and constant throughout life.^{11,12} The prevalence of anal HPV infection is greater than cervical HPV infection in women who are HIV +.¹³⁻¹⁵ In immunocompetent heterosexual men, anogenital and anal HPV infections were reported to be present in 65% and 25% of patients, respectively.^{16,17} Predictors of the development of AIN and SCCA are a history of multiple sexual partners in homosexual or heterosexual men or unprotected anal intercourse.¹⁸

HPV is a DNA papovavirus and is the most common, viral sexually transmitted infection. Several subtypes of HPV are linked to anal cancer and its precursor lesions. An estimated 10 to 46% of patients with HPV serotypes 16, 18, 31, 33, and 35 will develop subclinical infections that may harbor malignant potential. HPV 16 has the highest degree of association with anal cancer, detected in ~70% of cases in population-based studies. The prevalence of high-risk HPV is ~85% in patients with SCCA, depending on the sensitivity of the assay and the geographic variations. In one series, high-risk HPV was identified in 90% of SCCA in women and 63% of such cancers in men. HPV- anal cancers were similar to HPV + anal cancers in terms of patient age, adjacent dysplasia, ductal differentiation, and prognosis.¹⁹⁻²¹

HPV infection is associated with a marked increase in the incidence of AIN in HIV + patients. It has been observed that HIV + patients are infected with several HPV serotypes and this has been associated with both prevalent AIN and progression of lesions to a higher grade of dysplasia over a 2-year follow-up,

compared with a single type or no HPV infection. Another factor that may be associated with this higher incidence of AIN lesions in HIV + patients is the greater likelihood of high-risk sexual behavior.^{12,13,22,23}

HIV Infection as a Risk Factor

In patients with HIV, the rate of high-grade AIN is higher than in HIV- patients with an inverse correlation to CD4 counts.^{6,24} Patients with HIV are living longer since the introduction of highly active antiretroviral therapy (HAART) with a resultant increased lifetime risk for the development of anal cancer. In contrast to the reductions in the incidence of Kaposi sarcoma and lymphoma, there has been no significant decrease of anal cancer.²⁵ In a study of 357 HIV + MSM, over 80% had anal dysplasia and 95% had HPV infection.²⁶ Multivariate analysis showed that the use of HAART and detection of more than 6 HPV serotypes were associated with the presence of AIN. HIV infection is also a risk factor for AIN in women. In a study that compared 251 HIV + and 68 HIV- women, the former group had an increased risk of abnormal anal cytology (26% vs 8%) and HSIL (6% vs 2%).²⁷ Risks factors for AIN in this study included a history of receptive anal intercourse, lower CD4 + counts, concurrent abnormal cervical cytology, and a higher lever of plasma HIV RNA.

Sexual Behavior

High-risk sexual behavior is strongly associated with the development of AIN lesions. In a study of 1,262 MSM, AIN was present in 20% of these patients (5% with HSIL and 15% with LSIL).¹² The factors significantly associated with the presence of AIN were high-risk sexual behavior, anal HPV infection, and the number and type of HPV strains identified. Similarly, high-risk sexual behavior was identified as a risk factor for women with a history of repetitive receptive anal intercourse and anal HPV infection.²⁷

Other risk factors that have been associated with the development of AIN in men include a history of anal warts, a history of rectal discharge, intravenous drug abuse, and cigarette smoking. In women, additional risk factors include a history of vulvar and/or cervical cancer, high-grade CSIL or VSIL, and iatrogenic immunosuppression.^{4,7,28} Finally, risks factors associated with the progression from anal LSIL to HSIL include HIV-related immunosuppression and the presence of multiple HPV serotypes.¹³

Pathology of AIN

Both anal and cervical cytology are described using the Bethesda 2001 classification system because they share similar histopathologic features.²⁹ These cytologic

changes are reported, in increasing severity, as atypical squamous cells, LSIL, or HSIL. LSIL corresponds to AIN 1 and is characterized by 20 to 25% of the epithelium being replaced by abnormal basaloid cells (increased nuclear to cytoplasmic ratio), and by the presence of koilocytes, which are indicative of actively replicating HPV infection. HSIL includes AIN 2 and 3 and is diagnosed when abnormal basaloid cells replace more than 50% of the epithelium. Although LSIL lesions may regress or progress to HSIL, HSIL lesions rarely regress regardless of the patient's HIV status.⁸

AIN may be clinically asymptomatic or associated with local symptoms such as pruritus, bleeding, discharge, irritation, tenesmus, and pain. Other key points to include in the medical history are any history of HPV infection or other sexually transmitted disease, HIV status, and CD4 + count if positive, smoking history, previous anal or gastrointestinal (GI) pathology, and a sexual history inquiring about receptive anal intercourse. Physical exam should include anal and perianal skin, digital and anosopic examination of the anal canal, examination of the inguinal lymph nodes. If any cytology is obtained, it should be done before the anal exam and lubricant use.³⁰⁻³²

Screening

Screening programs for high-risk populations have been suggested. However, no randomized control study has documented the value of screening in the high-risk population. The specific populations targeted for screening include MSM and HIV- women with a history of anal intercourse or other HPV-related anogenital malignancies. Screening procedures consist of anal cytology and high-resolution anoscopy (HRA), which is similar to colposcopy for CIN. The rationale for performing screening and research is derived from the success observed in cervical cytology screening in the reduction of cervical cancer incidence.^{33,34}

The United States Public Health Service has adopted no formal guidelines recommending anal Pap smear screening. Although not everyone agrees, some specialists in the area recommend an anal screening program and treatment guidelines for patients at risk for HSIL.³⁵ It is suggested to screen for AIN in the following high-risk groups: women with cervical cancer, high-grade vulvar SIL or vulvar cancer, all MSM, all HIV + patients regardless of sexual orientation, and transplant recipients. The anal screening program relies upon anal cytology as the initial screening test in high-risk patients. The goal of screening is to identify individuals with abnormal cytology (ASC, LSIL, and HSIL) who should then undergo HRA to obtain specimens for histopathologic evaluation.

Anal cytology is performed by inserting an unlubricated, moistened Dacron swab in the anus t ~3 to

4 cm and then slowly removing it in a circular motion to sample the cells from all areas of the anal canal. Samples should be preserved quickly on slides or in a liquid medium to prevent drying. Unfortunately, anal cytology has had variable reported sensitivities, with the probability of AIN in patients with negative cytology 23% for HIV– MSM and 45% for HIV + MSM.^{34–36} In an attempt to reduce the possibility of false-negative reporting, the smear is repeated if the initial cytologic exam is negative. It is recommended that the smear should be repeated yearly in HIV + MSM, and every 2 to 3 years in HIV– MSM. Specific screening strategies have not yet been recommended for other high-risk groups.

Conversely, other studies suggest that anal cytology is an inaccurate predictor of the presence of HSIL, regardless of HIV status. In one series of 153 MSM (100 HIV +) patients who were referred to an anal dysplasia clinic because of abnormal cytology, HSIL on removed anogenital condylomata, or a history of internal or external condylomata, the sensitivity of anal cytology when compared with the histologic findings was only 47% for the detection of AIN 2–3 or invasive SCC.³⁷ These studies suggest that when HSIL is present on anal cytology, there is a high probability of high-grade disease on HRA and biopsy.^{37,38} The finding of LSIL or ASC on cytology, however, does not exclude the presence of HSIL. Hence, patients with any cytology abnormality should be considered for referral for HRA. Although HRA is an excellent and easily performed means of detecting HSIL, resources for HRA are limited. The natural history of untreated SIL is not well known for the HIV– population. For HIV + patients, the disease appears to be more aggressive; with ~50% of LSIL lesions progressing to HSIL within 2 years for HIV + homosexual males. Risk of progression to invasive cancer may be as high as 50% for lesions in HIV + patients.^{39–41}

Following the detection of abnormal anal cytology, the next step is diagnostic evaluation with HRA. HRA uses the application of 3% acetic acid to the anal canal using a large cotton-tip applicator via an anoscope. The acetic acid produces a white appearance in areas of abnormal transitional epithelium and facilitates mucosal examination of anoscopy. Lugol's iodine solution can also be applied to identify normal mucosa. The anoscope should be slowly withdrawn so that all areas of the anal canal may be meticulously examined. Acetic acid is continually applied during the examination to manipulate folds, hemorrhoids, or prolapsing mucosa. Biopsies should be done on any areas that appear abnormal.^{33,36,42}

The cost effectiveness of such an anal screening program to prevent anal cancer has been demonstrated using an economic model in both HIV + patients and HIV– MSM. Studies showed that screening to identify patients with HSIL to be referred for treatment would be cost effective if performed annually for HIV + MSM

and every 2 to 3 years for HIV– MSM, providing benefits in both life expectancy and cost effectiveness.^{1,43}

There are no formal guidelines for the management of anal screening cytology results. This subject remains controversial, especially because there are few data to support the efficacy of treatments for AIN. Several studies are ongoing to answer these questions.

LSIL, including condyloma, do not directly progress to invasive cancer and are believed to have a low malignant potential; therefore, treatment remains optional. Patients with clinical symptoms or psychological distress, however, may benefit from therapy.

Nonetheless, routine follow-up is recommended in patients with LSIL every 6 months because of the high rate of progression to HSIL.

HSIL, on the other hand, carries a more significant risk of malignant transformation and treatment is often recommended, although observation with close surveillance is an acceptable strategy. It has been shown that in HIV + patients, dysplasia returns at high rates despite the most-aggressive attempts at eradication. Because there is no satisfactory treatment with low morbidity that eradicates these lesions with low recurrence postprocedure, it has been suggested that these patients can be followed expectantly with intensive surveillance. In a study of 40 HIV + patients who were followed expectantly, only three patients developed invasive carcinoma over a period of at least a year and they were cured with surgery or chemoradiation.³⁹ If this approach is chosen, patients should be instructed to report on any new anal symptoms such as bleeding, pain, or the appearance of a mass, which may suggest progression to invasive anal cancer. These patients should have surveillance follow-up exams every 4 months so that if cancer is diagnosed at an early stage, the chances for curative intervention are higher.

Topical therapy may be effective for HSIL. For small lesions (<1 cm at the base), local application of trichloroacetic acid (TCA) may be considered. It is generally well tolerated, but can be occasionally painful. Topical 5-fluorouracil (5-FU) has been used for periods of up to 12 weeks with good response. Recurrence, however, may occur with follicular involvement, poorly defined areas of involvement, scar tissue, poor immune response, and recurrent or persistent HPV infection.⁴⁴

Intraanal application of topical immunomodulator 5% imiquimod cream has also shown good response. In one study, 74% of men treated had sustained clearance of AIN, although they remain at risk for new lesions in untreated anal areas. In another study of 49 patients, an 86% complete clinical response was reported at a mean follow-up of 19 months.^{45,46}

Studies on the role of cryotherapy and infrared coagulation have been limited and larger prospective studies are required to confirm benefits. Photodynamic

therapy has also been suggested; however, studies are limited.⁴⁷⁻⁴⁹

First described in 1979, targeted destruction and follow-up is a more aggressive approach to treat lesions. It consists of wide local excision for discrete lesions with the extent of resection based on preoperative mapping, which is done by biopsy of the anal canal at the dentate line, anal verge, and perianal skin at the four major points of the compass. Definitive surgical excision can be performed based on this mapping or by wide local excision based on microscopic clearance by frozen section. Closure can be done by secondary intention, advancement, or split-thickness skin grafts.^{50,51} Anoscopy-directed lesion ablation using HRA is being increasingly used in identifying those areas of involvement for electrocautery ablation.⁵² The use of HRA rather than mapping biopsies may minimize complications and eliminate the morbidity associated with wide local excision. In a retrospective study of 246 patients treated over a period of 10 years, 81% were treated with a single procedure; however, 57% of these patients developed recurrence at an average of 19 months after the initial procedure. Significant complications were observed in only nine patients and included one patient with bleeding, which required reexploration; two anal stenosis; and four anal fissures. However, recurrence rates are nearly 80%, with a mean recurrence time of 12 months in HIV + patients.³⁴ Because of the significant recurrence rate observed with this therapy, careful surveillance following treatment is mandatory. Surveillance in patients with a history of AIN or SIL is recommended at 4- to 6-month intervals while dysplasia is present. Examinations should include anoscopy with or without acetic acid application or HRA. The importance of close follow-up surveillance should be particularly stressed in HIV + patients.⁵³

Finally, therapeutic vaccination has the potential to improve AIN by directing an augmented T-cell-mediated immune response against HPV-infected epithelial cells.

Vaccination of girls against oncogenic HPV is now being recommended for the prevention of cervical cancer. A recent meta-analysis indicated that 80% of anal cancers could be avoided by vaccination against HPV 16 and 18.^{54,55}

There is currently no commercially available licensed vaccine product for the management of AIN in at-risk groups, although this is an active area of research involving both HIV + and HIV- patients.⁵⁶ Prospective studies are needed to further assess the role of prophylactic vaccination in preventing anal cancer.

SQUAMOUS CELL CARCINOMA OF THE ANUS

This section will focus on the epidemiology, histology and anatomy, clinical features, staging, and treatment of SCCA.

Epidemiology

Although it is a rare cancer, which accounts for only 1.5% of cases of GI tract cancer in the United States, the incidence has been increasing in men and women worldwide. In the United States, 5,290 patients in 2009 have been diagnosed with anal cancer with 710 deaths reported. Data from the Surveillance Epidemiology and End Results (SEER) program, reports an annual incidence of 2.04 per 100,000 in men and 2.6 per 100,000 in women between 1994 and 2000, which was twofold higher than between 1973 and 1979 and suggests an increasing incidence. From 1973 to 2000, black men had the sharpest increase in anal cancer incidence rates, followed by white men, white women, and black women in decreasing order.⁵⁷⁻⁵⁹

The median age at diagnosis of anal cancer ranges from 60 to 65 years. The overall 5-year survival rates for anal cancer are 60% in men and 78% in women, based on SEER data analysis for the modern era of therapy, 1994 to 2000.⁶⁰

Of note is that the incidence of anal cancer is much higher in specific populations such as HIV-infected patients and in MSM. The incidence of anal cancer among MSM prior to the HIV epidemic was estimated to be 37 per 100,000. Moreover, in patients with HIV being treated with HAART the incidence of anal cancer has not declined.⁶¹

Anatomy and Histology

A review of the region's anatomy is most important in understanding anal canal cancer and its classification.

The anal canal extends from the perianal skin (anal verge) to the rectal mucosa (Fig. 1). The proximal end of the anal canal corresponds anatomically to the region where the rectum enters the puborectalis sling at the apex of the anal sphincter complex. This is palpable at the anorectal ring on digital rectal exam and is ~1 to 2 cm above the dentate line. It extends distally to the point where the squamous mucosa meets the perianal skin, and corresponds roughly to the intersphincteric groove or the distal end of the internal anal sphincter. The dentate or pectinate line is a macroscopic landmark that divides the anal canal and represents the transition from the nonsquamous mucosa (either transitional or glandular rectal mucosa) to the squamous mucosa. Immediately proximal to the dentate line, a narrow zone of transitional mucosa, which is similar to urothelium, is variably present. Thus, tumors arising in the anal canal can be either keratinizing or nonkeratinizing depending on their location in relation to the dentate line. Importantly, both keratinizing and nonkeratinizing tumors appear to have similar biology and prognosis. Distally, the squamous mucosa (which lacks epidermal appendages) merges with the perianal skin (true epidermis). This mucocutaneous junction has been referred as the

Figure 1 Anatomy of the anus and rectum.

anal margin and it is indistinct on macroscopic examination.^{57,62}

Thus, two categories of tumors arise in the anal region: anal canal cancers and anal margin or perianal cancers. Anal canal cancers are those tumors that arise from any of the three types of mucosa (glandular, transitional, and squamous). The term “anal cancer” refers to squamous cell cancer of the anus (SCCA) arising within the mucosa of the anus. By convention, most series that report outcomes of “anal cancer” refer exclusively to these tumors. A variant of SCCA is the basaloid (also termed junctional or cloacogenic) carcinoma that arises from the epithelial transitional zone. These terms have been abandoned because they are now recognized as nonkeratinizing types of squamous cell carcinoma. An anal margin cancer is a tumor arising distal to the squamous mucocutaneous junction or within the hair-bearing skin—the preferred term is perianal skin cancer, which behaves biologically like skin cancer. Perianal skin cancer is staged, classified, and treated as skin cancer and will not be addressed in this review.^{1,2,62}

Welton and colleagues have proposed a new classification that may prove more useful to all caregivers who diagnose or treat patients with anal cancers. This classification system divides the anus into three easily identifiable regions, intraanal, perianal, and skin. Intraanal lesions cannot be visualized in their entirety or are incompletely visualized while gentle traction is applied to the buttocks. Perianal lesions can be visualized with gentle traction on the buttocks and lie within 5 cm radius of the anus, whereas skin lesions lie outside a 5 cm radius from the anal opening. Lesions that involve the transformation zone are situated in a region of variable height above the dentate line, where squamous metaplasia may be found overlying normal columnar mucosa.¹

Finally, lymphatic drainage of anal cancers depends on the location of the tumor in relation to the dentate line. Lymphatic drainage above the dentate line occurs via the superior rectal lymphatics to the inferior mesenteric lymph nodes and laterally to the internal iliac nodes. Below the dentate line, drainage is primarily to the inguinal nodes, but may also involve the inferior or superior rectal lymph nodes. Patients presenting with anal cancer should undergo both physical and radiographic evaluation of inguinal nodes and any enlarged nodes should be biopsied to further guide therapy.^{1,2}

Risks Factors

Historically, anal cancer was believed to be the result of chronic irritation from benign conditions such as hemorrhoids, fistulas, fissures, and even inflammatory bowel disease. Subsequent studies found little to no impact of these conditions in the development of anal cancer.^{63–67} A Danish population-based cohort study of 6,334 patients with ulcerative colitis and 2,723 patients with Crohn disease who were followed for 10 years showed no increased risk of anal cancer.⁶⁸

Over the last decade, several studies have identified different risks factors for anal cancer, which are a history of persistent high-risk genotype HPV infection, infection with multiple HPV genotypes, cervical dysplasia or cancer, HIV seropositivity, low CD4 count, cigarette smoking, receptive anal intercourse, and immunosuppression following solid organ transplant.⁶⁹

BEHAVIORAL RISK FACTORS

The risk of anal cancer is highest among MSM (odds ratio [OR] = 17.3; 95% confidence interval [CI] = 8.2–36.1). These risks are increased in the population of MSM who are HIV+ (relative risk [RR] = 59.5; it is

mainly due to the increased HPV infection rate rather than isolated HIV infection.⁷⁰⁻⁷³

Several studies have confirmed the relationship between anal cancer and receptive anal intercourse in men.^{6,65,66,70} In a case-control study, the strongest risk factors for anal cancer in women were a history of anal warts (RR = 11.6), genital warts (RR 4.6), 10 or more lifetime sexual partners (RR = 4.5), cervical dysplasia (RR = 2.3), and sexual partners with a history of syphilis or hepatitis (RR = 4.0). Moreover, a history of receptive anal intercourse starting before the age of 30 and at least two anal intercourse partners were also significant risk factors in women.⁷³ Several studies have provided evidence supporting the role of sexual activity in the development of anal cancer and demonstrated a strong relationship between cervical cancer and anal cancer in women.⁷⁴⁻⁷⁶ Data from the SEER program showed that the relative risk of developing anal cancer following the diagnosis of cervical cancer was 4.6.⁷⁶

HUMAN PAPILLOMAVIRUS INFECTION

HPV is the most commonly diagnosed sexually transmitted disease in the United States and high-risk HPV infection has a strong association with the development of premalignant and malignant lesions of the anus, uterine cervix, vagina, and vulva.^{13,23,36,54,73,75,76}

The spectrum of HPV types in the anal canal is similar to that shown in the cervix and associated with the same high-risk serotypes linked to premalignant and malignant lesions. HPV 16 is the one with the highest degree of association, and to a lesser extent, types 18, 31, 33, and 35.^{20,77} The prevalence of high-risk HPV is ~85% in patients with SCC of the anal canal, depending on the sensitivity of the assay and the geographic variations.^{19,20,78} The HPV DNA base has been isolated from 46 to 100% of in situ and invasive anal SCC.^{20,72,77} In one series, high-risk HPV was identified in 90% of anal SCCs in women and 63% of such cancers in men.²⁰ HPV-negative anal cancers were similar to HPV-positive anal cancers in terms of patient age, adjacent dysplasia, ductal differentiation, and prognosis.⁷⁹

The premalignant condition of CIN associated with HPV infection, also happens with HPV infection involving the anus (AIN). As in CIN, AIN can be histologically low grade and high grade (LSIL and HSIL, respectively). AIN, particularly HSIL is considered to be the precursor of anal SCC. Risk factors for AIN and progression to SCC include HIV infection, high-risk HPV serotypes, lower CD4+ counts, and receptive anal intercourse.

The prevalence of anal HPV infection is greater than cervical HPV infection in women who are HIV+ or have a high risk of HIV infection.¹³⁻¹⁵ In a population of healthy Hawaiian women, anal HPV infection was as common as cervical HPV.⁸⁰ In immunocompetent heterosexual men, anogenital and anal

HPV infections were documented in 65.4% and 24.8% of patients, respectively.^{16,17}

IMMUNOSUPPRESSION AND HIV

Immunosuppression probably impairs the body's ability to clear HPV after sexual exposure. The rate of high-grade squamous intraepithelial neoplasia is higher in HIV+ patients than HIV- patients and is inversely related to the CD4 lymphocyte count. However, it is still unclear whether HIV infection and related immunosuppression has a direct effect on the development of anal cancer.^{57,81-84}

Since the introduction of HAART, HIV+ patients are living longer; consequently, they have an increased lifetime risk of developing anal cancer.⁷ Although there have been reductions in the incidence of Kaposi sarcoma and lymphoma, no significant change has been seen in the incidence of anal carcinoma.²⁵ In a study matching a cancer database to AIDS databases, the relative risk of developing anal cancer among HIV+ men with a history of homosexual contact was 59.5, whereas the relative risk for anal cancer was 6.8 in HIV+ women in comparison to the general population.⁸⁵ This and other studies indicate that HIV infection interacts with HPV to predispose to anal cancer.^{13,26}

Immunosuppression not related to HIV infection such as solid-organ transplantation, appears to be associated with the development of HSIL and invasive anal SCC. Patients undergoing organ transplantation have a 10- to 100-fold risk of anal cancer compared with the general population.⁸¹⁻⁸⁴

CIGARETTE SMOKING

Current cigarette smoking appears to be a significant risk factor of anal cancer. In one study, the relative risk for a 50 pack-year history was 5.2.⁶⁶

Clinical Presentation and Staging

Most patients with SCCA present with rectal bleeding; it can be present in up to 45% of patients. Other symptoms include rectal pain and/or mass sensation, which occurs in ~30% of patients. The presentation of anal canal tumors is often nonspecific and 70 to 80% are initially diagnosed as a benign anorectal condition such as hemorrhoids. Twenty percent of patients have no symptoms at the time of diagnosis.^{1,2,86,87}

Physical examination should include a digital rectal exam and evaluation of the inguinal and femoral nodes. Anoscopy or proctoscopy is most important to define location within the anal canal. Biopsy is necessary to confirm diagnosis if not available already.⁵³ Until recently, any suspicious lymph nodes would undergo fine needle biopsy or core biopsy to complete the staging process and guide therapy. However, surgical staging is no longer performed routinely. A radiotherapy boost is

typically added to the affected groin if there is palpable or radiographic evidence of inguinal nodal metastases.⁸⁸

Colonoscopy is required to rule out synchronous colorectal neoplasms.⁵³ A computed tomography (CT) scan of the chest, and a CT or magnetic resonance imaging (MRI) scan of the abdomen and pelvis are also necessary to evaluate lymphadenopathy and to exclude lung and liver metastases.⁸⁹ However, the efficacy of a CT scan/MRI to detect inguinal lymph nodes metastases is suboptimal.⁹⁰ Positron emission tomography (PET) may identify distant metastases that are not detected by these imaging modalities in as many as 25% of cases.⁹¹ Cotter et al⁹² in a study of 41 consecutive patients diagnosed with SCCA showed that prior to therapy, a whole-body PET scan detected more inguinal metastatic disease, with abnormal nodes noted in 29% of all groins in comparison to 16% for a CT scan. In another study of 61 patients with anal cancer in which abnormal lymph nodes were biopsied, the sensitivity of PET for nodal disease was 89% in comparison to 62% for CT and/or MRI.⁹³ These reports suggest that PET might offer better sensitivity in identification of nodal disease. In view of these data, and in agreement with the National Comprehensive Cancer Network (NCCN) guidelines, we recommend a PET scan as an integral part of the pretreatment staging workup.

Endorectal/endoanal ultrasound (ERUS/EAUS) is useful in determining T stage and evaluating perirectal lymph node involvement, with several advantages over physical examination alone.⁹³ ERUS/EAUS has been found to be superior to physical examination in assessing the involvement of internal and external anal sphincter muscle and perirectal lymph nodes. Three-dimensional anal ultrasound has shown improved accuracy in detecting perirectal lymph nodes and some suggestion of improved evaluation of tumor invasion when compared with two-dimensional ultrasound.⁹⁴⁻⁹⁷

The American Joint Committee on Cancer and the International Union Against Cancer had developed a tumor-node-metastasis staging (TNM) system for SCCA. Because few tumors are surgically excised, the system is based on clinical factors with particular emphasis on tumor size because this is known to be an important determinant of prognosis (Table 1.³ Fifty to 60% of patients present with T1-T2 lesions, for which the 5-year survival rate is 80 to 90%. A smaller proportion presents with T4 lesions, which have a 5-year survival rate <50%. The incidence of nodal metastasis is ~10% at diagnosis, but can increase to as high as 20-60% for T4 lesions.⁹⁸ In one study, lymph node metastases were present in 47% of patients with T4 lesions >5 cm in size. Nodal metastases by T stage were as follows: T1 = 0%, T2 = 8.5%, T3 = 29%, T4 = 35%. Lymph node metastases were almost double (58% vs 30%) in those tumors invading beyond the external sphincter compared with invasion of the internal sphinc-

Table 1 TNM Staging for Anal Cancer

PRIMARY TUMOR (T)
TX—Primary tumor cannot be assessed
T0—No evidence of primary tumor
Tis—Carcinoma in situ, high-grade squamous intraepithelial lesions (HSIL), anal intraepithelial neoplasia II-III
T1—Tumor 2 cm or less in greatest dimension
T2—Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3—Tumor more than 5 cm in greatest dimension
T4—Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder; involvement of sphincter muscle, rectal wall, perirectal skin or subcutaneous tissue is not classified at T4
LYMPH NODE (N)
NX—Regional lymph nodes cannot be assessed
N0—No regional lymph node metastasis
N1—Metastasis in perirectal lymph node(s)
N2—Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3—Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
DISTANT METASTASIS (M)
Mx—No distant metastasis
M1—Distant metastasis
STAGE GROUPING
Stage 0—Tis—N0—M0
Stage I—T1—N0—M0
Stage II—T2—N0—M0
T3—N0—M0
Stage IIIA—T1—N1—M0
—T2—N1—M0
—T3—N1—M0
—T4—N0—M0
Stage IIIB—T4—N1—M0
—Any T—N2—M0
—Any T—N3—M0
Stage IV—Any T—Any N—M1

Adapted from Greene FL, Page DL, Fleming ID, et al, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. Material originally published by Springer Science and Business Media LLC, www.springer.com.

ter. Mesenteric lymph nodes are more common in tumors of the proximal anal canal (50%) than the distal anal canal (14%). Moreover, almost half of the positive lymph nodes were <5 mm in size. Distant visceral metastases occur in 10 to 17% of patients at presentation and can be found in the liver, lung, bones, and subcutaneous tissues.⁹⁹ In one study, metastatic disease was the cause of 40% of cancer-specific deaths.¹⁰⁰

Prognosis

In a cohort study of 19,195 patients treated for SSC of the anus that were reported to the National Cancer Database between 1985 and 2000, 5-year survival rates

were 70% for stage I, 59% for stage II, 41% for stage III, and 19% for stage IV. Tumor diameter and nodal status are the main prognostic factors.¹⁰¹

Treatment

Historically, abdominoperineal resection with the formation of a permanent colostomy was the standard of therapy for SCCA and it was associated with 5-year survival rates between 40 to 70% with a perioperative mortality of 3%.^{31,102–105}

However, subsequent work by Nigro and collaborators at Wayne State University showed that the administration of preoperative 5-FU and mitomycin with radiation therapy resulted in a reduced surgical failure rate. The majority of the patients treated with chemoradiation were cured (5-year overall survival rate of 67%) without an APR (5-year colostomy-free survival rate of 59%). Given the high rate of initial complete pathologic response associated with this regimen, chemoradiation therapy became the first line of therapy. The role of abdominoperineal resection (APR) was relegated to those cases where residual tumor remained after chemoradiation. This approach became the standard of care and was supported by several retrospective and prospective studies although no prospective randomized trial has ever been made comparing chemoradiation to surgery. Taken together, these studies have shown that the use of combined chemoradiation therapy results in local failure rates between 14 to 37%, 5-year overall survival rates of 72 to 89% and 5-year colostomy-free survival rates of 70 to 86%.^{99,100,106–111}

CHEMORADIATION WITH 5-FU/MITOMYCIN VERSUS RADIATION THERAPY ALONE

Several studies have been done to evaluate whether radiation therapy alone had similar oncologic results in comparison to chemoradiation therapy with 5-FU and mitomycin.

The first randomized trial was the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) trial, which randomly assigned 585 patients with T1 to T4 SCC of the anal canal or margin to radiation alone (45 Gy in 20 to 25 fractions over 4 to 5 weeks) or radiation combined with chemotherapy (continuous 5-FU, 1,000 mg/m²/d for 4 days or 750 mg/m²/d for 5 days, during the first and final week of radiation treatment, with mitomycin, 12 mg/m² by bolus intravenous infusion on day 1 of chemoradiation). The 3-year local failure rate was 61% in the radiation arm versus 39% in the chemoradiation arm. The incidence of anal cancer-related death was significantly higher in the radiation arm (39%) than in the chemoradiation arm (28%). The 3-year survival rate for the radiation arm was 58% compared with 65% for the chemoradiation arm, which was not a statistically significant difference be-

cause of the excess non-cancer-related mortality on the chemoradiation arm. More acute morbidity and mortality occurred with the combined modality therapy.¹⁰⁰

The European Organization for Research and Treatment of Cancer (EORTC) study randomized 110 patients with T3–4 or N1–3 anal cancer to radiation alone (45 Gy with a 15 or 30 Gy boost) versus chemoradiation therapy. Chemotherapy consisted of 5-FU, 750 mg/m² daily as a continuous infusion on days 1 to 5 and 29 to 33, and mitomycin was given at 15 mg/m² on day 1 of the first course of 5-FU. Complete response was higher in the chemoradiation group (80%) versus the radiation arm (54%). At 5 years, Kaplan-Meier estimates showed 18% more locoregional control ($P = .02$) and a 32% higher colostomy-free interval ($P = .002$) in favor of the chemoradiation arm part 2. In contrast to the UKCCCR trial, morbidity and mortality were not statistically different between the groups.¹¹²

CHEMORADIATION WITH 5-FU/MITOMYCIN VERSUS 5-FU CHEMORADIATION

The role of mitomycin has been questioned due to its inability to sensitize tumor cells to radiation and because of its associated side effects such as pulmonary, renal, and bone marrow toxicities.

These questions were initially addressed in a 1991 meta-analysis of prospective clinical trials using radiation alone, with 5-FU, and with 5-FU/ mitomycin, which reported a significant improvement in local control and 5-year overall survival rate in favor of 5-FU plus mitomycin.¹¹³

Subsequently, a joint trial by the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG)—a phase III randomized clinical trial—confirmed the superiority of 5-FU plus mitomycin (Nigro regimen) over 5-FU plus radiation in the definitive treatment of anal cancer despite a greater associated toxicity.¹¹¹ Three-hundred ten patients with anal cancer of any tumor or nodal stage were randomized to radiation with 5-FU or radiation with the same 5-FU schedule and the addition of mitomycin. Radiation was given at 45 Gy in 5 weeks. Patients with palpable tumor at the end of the 45 Gy dose were given an additional 5.4 Gy. Colostomy rates at 4 years were lower in patients receiving 5-FU plus mitomycin (9%) versus patients receiving 5-FU (23%; $P = .002$). Similarly, the disease-free survival rate was significantly improved in favor of the mitomycin arm (4-year disease-free survival rate was 73% versus 51%; $P = .0003$).

NEOADJUVANT CHEMORADIATION WITH CISPLATIN/5-FU VERSUS MITOMYCIN/5-FU

Cisplatin has been shown to be more active in the treatment of SCCA in general than mitomycin. Several phase II trials have shown promising results of neoadjuvant therapy with 5-FU, cisplatin, and radiation in

the treatment of anal cancer, which prompted the investigation in phase III clinical trials.^{114,115}

The RTOG 98-11 trial, which substituted cisplatin for mitomycin in the treatment of anal cancer, showed no statistically significant overall survival. In this study, 682 patients with T2-T4, M0 anal cancers were randomized to the standard regimen of 5-FU plus mitomycin and radiation versus neoadjuvant chemotherapy followed by 5-FU plus cisplatin with radiation.¹¹⁶ There was no significant difference in 5-year disease-free survival or overall survival. The 3- and 5-year disease-free survival rates in the mitomycin arm were 67% and 60%, respectively. In the cisplatin arm, the 3- and 5-year disease-free survival rates were 61% and 54%, respectively. This mitomycin-favoring trend did not reach statistical significance ($P=.17$). Similarly, a nonsignificant trend ($P=.10$) favored mitomycin therapy for 3-year survival (84% vs 76%) and 5-year survival (75% vs 70%). The 5-year locoregional recurrence rates were 25% and 33% in the mitomycin and cisplatin arms, respectively. Colostomy rates were significantly higher in the cisplatin arm at 3 years (16% vs 10%). Both treatments resulted in a 74% grade 3-4 toxicity rate in each arm. The mitomycin arm showed a significantly increased hematologic toxicity rate.

The addition of neoadjuvant chemotherapy to the cisplatin arm complicated the study design, as it did not allow a direct comparison of radiation with either mitomycin or cisplatin. The second UK Anal Cancer Trial (ACT II), as reported at the American Society of Clinical Oncology 2009 meeting, addressed the issues in the RTOG study design and directly evaluated the role of mitomycin versus cisplatin in the neoadjuvant chemoradiation of anal cancer. In this study, 940 non-HIV-infected patients with anal SCC (T1-4) were randomized to receive 5-FU plus cisplatin with radiation or 5-FU plus mitomycin with radiation. The complete response rate at 6 months (primary endpoint) in the ACT II trial was similar in the mitomycin (94.5%) and cisplatin (95.4%) arms and the 3-year colostomy rate was not significantly different (13.7% vs 11.3%; $P=.26$). Nonhematologic toxicities were seen to the same extent in both arms, whereas hematologic toxicities were significantly higher in the mitomycin arm.¹¹⁷

The ACT II study showed that the outcomes and nonhematologic toxicities with cisplatin were equivalent to mitomycin while resulting in significantly lower hematologic toxicity.¹¹⁷ Taken together, the data suggest that 5-FU plus mitomycin remains the standard of care, but that 5-FU and cisplatin could be considered a reasonable approach as well.

ADDITION OF INDUCTION OR MAINTENANCE CHEMOTHERAPY TO CHEMORADIATION

There appears to be no role for induction chemotherapy or a continuation of chemotherapy beyond concurrent

chemoradiation. The relevance of maintenance (adjuvant) chemotherapy was addressed in the ACT II study. Patients were randomized to an arm receiving two cycles of cisplatin plus 5-FU (maintenance) or to a "no maintenance arm" following completion of chemoradiation. The 3-year disease-free and overall survival rates were 75% and 85% on the maintenance arm versus 75% and 84% on the no maintenance arm.¹¹⁷ The lack of a clinical benefit for induction or maintenance chemotherapy does not support the implementation of these strategies.

CAN CHEMOTHERAPY BE ELIMINATED FOR EARLY-STAGE ANAL CANCER?

While randomized trials have shown that chemoradiation is superior to radiation alone in terms of disease-free survival, colostomy-free survival and local relapse, it remains unclear whether these benefits apply to early-stage anal cancer. Several retrospective series had previously reported excellent outcomes for patients with T1-2, N0, M0 disease with radiotherapy alone.¹¹⁸⁻¹²¹

However, one recent retrospective analysis raised some concerns about the effectiveness of radiation alone. In this study, 146 patients were treated with radiation alone (71 patients) or chemoradiation (75 patients). Locoregional control was improved in the chemoradiation arm (hazard ratio = 2.24), but the difference did not reach statistical significance ($P=.064$).¹²² However, the lack of heterogeneous treatment schedules and radiation dosing limits the conclusions, which may be drawn about radiation alone in early-stage anal disease.

Because a direct comparison between chemoradiation and radiation alone for T1, N0 anal cancer does not exist, mitomycin plus 5-FU and radiation is still recommended for this population. NCCN guidelines correlate with these recommendations.¹²³ However, for the extremely elderly population or for those with significant comorbidities, the elimination of mitomycin and the administration of 5-FU alone or in combination with cisplatin may be a reasonable approach.

ASSESSMENT OF RESPONSE TO PRIMARY CHEMORADIATION: PERSISTENT OR RECURRENT DISEASE

Patients are typically evaluated at 6 to 8 weeks following the completion of therapy. Whether a biopsy is needed at 6 weeks still remains controversial because SCC regresses slowly and continues to do so between 3 to 12 weeks after finalization of therapy. This issue was illustrated in a randomized U.S. intergroup study where 310 patients received either chemoradiotherapy with or without mitomycin. Biopsies were planned at 6 weeks after completion of primary therapy; 25 patients had residual disease following 45 Gy and two courses of 5-FU and mitomycin. Salvage therapy with 9 Gy and cisplatin plus 5-FU achieved a complete response in 55% of these patients 6 weeks later. It remains unclear

whether this high rate of pathologic response was due to the salvage therapy or the additional 6 weeks of tumor regression following initial primary therapy. This is why some researchers recommend no posttreatment biopsy if physical exam is negative, whereas others prefer the routine 6 weeks biopsy following completion of therapy. If there is no residual disease, then patients are reexamined every 6 weeks. If there is persistent or progressive disease at 12 weeks after completion of primary combined modality therapy, then APR is recommended.¹¹¹

TREATMENT OF HIV-POSITIVE PATIENTS WITH ANAL CANCER

Some earlier studies suggested that in HIV+ patients, who had a low CD4 count and were not receiving HAART, survival was worse and toxicities were increased.¹²⁴⁻¹²⁸ In the era of HAART, however, these findings have not been replicated with resultant high median CD4 counts and low levels of detectable viral titers and the use of modern conformal radiation therapy. Most recent data suggest that response to therapy, local control, and survival are as good as in non-HIV-infected patients.¹²⁷⁻¹³⁰ However, there appears to be a higher rate of local relapse. In a series of 87 patients (21 HIV+) treated with mitomycin and radiation, disease recurrence at 6 months was considerably higher in the HIV+ group (29% vs 8%) although both HIV+ and HIV- groups were as likely to achieve a complete response (81% HIV+ and 85% HIV-).¹³¹

In a multiinstitutional retrospective study that compared the outcome of 40 HIV+ (on HAART therapy) and 81 HIV- patients with anal cancer who received primary chemoradiotherapy, complete response was high in both groups (92% vs 96%, respectively). HIV+ patients were more likely to experience grade 3-4 skin and hematologic toxicity. Local recurrence was higher in the HIV+ group in comparison to the HIV- group (61% vs 13%) and HIV+ patients were more likely to die from anal cancer (5-year cancer-free survival of 68% vs 79%; $P = .09$).¹³²

In summary, HIV+ patients in the HAART era should be treated similarly to HIV- patients with standard curative-intent full dose of radiation and mitomycin plus 5-FU. However, these patients and especially those with HIV-/AIDS-related complications need to be monitored more closely, as they may be prone to increased hematologic, GI, and skin toxicity and may require dosage adjustment or treatment without mitomycin. Aggressive follow-up should be conducted after treatment completion, as a higher rate of local relapse with a need for salvage abdominoperineal resection has been described.

SALVAGE THERAPY

Salvage therapy may be indicated for patients with persistent or recurrent disease after completion of pri-

mary chemoradiotherapy. The preferred treatment for persistent or recurrent disease following combined modality therapy is APR.

Complications from salvage APR appear to be greater in patients undergoing this procedure after primary chemoradiotherapy.^{133,134} In a retrospective study of 35 patients who underwent salvage APR for persistent and/or recurrent disease, 13 patients experienced perineal wound infection necessitating reoperation and delayed healing occurred in 23 patients. Fifteen patients, 12 of whom underwent salvage APR for persistent disease, experienced secondary failure. The median survival duration after secondary failure was 19 (range, 1-78) months.¹³⁵ In the UKCCCR trial, there was a relapse rate of 40% in 29 patients who underwent salvage therapy for persistent disease.¹⁰⁰

Recurrent disease is different for patients who undergo sphincter-sparing therapy in comparison to surgery for SCCA. Faynsod et al reported a significantly higher local recurrence rate in patients treated with chemoradiation therapy than those treated surgically (36% vs 17%, respectively). However, 6 of the 7 post chemoradiation therapy recurrences were successfully salvaged by APR. Moreover, 5-year overall survival rates were significantly higher in the chemoradiation therapy group (74%) than the primary surgery group (42%).¹³⁵

SALVAGE CHEMORADIATION THERAPY

Salvage chemoradiation therapy for persistent disease has also been evaluated, but the relative efficacy of this approach remains unclear.

In the Intergroup RTOG/ECOG study evaluating the role of mitomycin, those patients with persistent disease received salvage 5-FU, cisplatin, and 9 Gy electron beam radiation therapy. Of 29 patients treated in this manner, 10 continued to have persistent disease. Nine of these patients went on to salvage APR and at 4 years, three were alive without disease and seven had died—six with recurrent disease.¹⁰⁹

METASTATIC DISEASE

Metastatic disease develops in 10 to 17% of patients treated with primary chemoradiotherapy as reported in the EORTC and UKCCCR trials. The liver is the most common site of distant metastases in SCCA.^{100,112}

There are limited published data on the use of chemotherapy to treat metastatic anal carcinoma. The only widely published active regimen is cisplatin plus 5-FU.^{136,137} Other active agents include doxorubicin, semustine, and cetuximab with or without irinotecan.¹³⁸⁻¹⁴¹

NCCN guidelines recommend cisplatin plus 5-FU as a first-line regimen.¹²³

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