Management of Anal Cancer in 2010 Part 1: Overview, Screening, and Diagnosis

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Although anal cancer is a rare disease, its incidence is increasing in men and women worldwide. The most important risk factors are behaviors that predispose individuals to human papillomavirus (HPV) infection or immunosuppression. Anal cancer is generally preceded by high-grade anal intraepithelial neoplasia (HGAIN), which is most prevalent in human immunodeficiency virus (HIV)-positive men who have sex with men. There is a general consensus that high-risk individuals may benefit from screening. Meta-analysis suggests that 80% of anal cancers could be avoided by vaccination against HPV 16/18. Nearly half of all patients with anal cancer present with rectal bleeding. Pain or sensation of a rectal mass is experienced in 30% of patients, whereas 20% have no tumor-specific symptoms. According to the Surveillance Epidemiology and End Results (SEER) database, 50% of patients with anal cancer have disease localized to the anus, 29% have regional lymph node involvement or direct spread beyond the primary, and 12% have metastatic disease, while 9% have an unknown stage. Clinical staging of anal carcinoma requires a digital rectal exam and a computed tomography scan of the chest, abdomen, and pelvis. Suspicious inguinal lymph nodes should be subject to pathologic confirmation by fine-needle aspiration. The 5-year relative survival rates are 80.1% for localized anal cancer, 60.7% for regional disease, and 29.4% for metastatic disease. Part 2 of this two-part review will address the treatment of anal cancer, highlighting studies of chemoradiation.

The treatment of anal squamous cell cancer with definitive chemoradiation is cemented as the gold-standard therapy for localized anal cancer, mainly due to its sphincter-saving and colostomy-sparing potential. Over the course of the past 2 decades, several studies have addressed different chemoradiation regimens in hopes of improving on the standard Nigro protocol of fluorouracil, mitomycin, and radiation. While these studies failed to reveal any superiority of alternative regimens to the Nigro protocol, important conclusions were derived regarding the continuity of radiation as well as the role of induction (pre-chemoradiation) and maintenance chemotherapy (post-chemoradiation) in patients with anal cancer.

Before we continue with a consideration of treatment, some background on anal cancer is in order. Part 1 of this review will provide an overview of anal cancer epidemiology, risk factors, screening, prevention, and diagnosis. Part 2, which will appear in the next issue of ONCOLOGY, will focus on treatment, highlighting the current status of chemoradiation for anal cancer and potential areas for future improvement.

Epidemiology

Anal cancer affected an estimated 5,290 patients (2,100 men and 3,190 women), and led to approximately 710 deaths in 2009.[1] Although it is a rare disease, the incidence of anal cancer is increasing in men and women worldwide.[2-6] The incidence rates according to the Surveillance Epidemiology and End Results (SEER) database are 1.4 per 100,000 in men and 1.7 per 100,000 in women.[1] Women have a higher incidence rate than men for age groups over 50 years, whereas men dominate for the ages of 20 to 49 years. Over the period 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. 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. During the same period, the 5-year overall survival of black men decreased to 28%, presumably due to complicating human immunodeficiency virus (HIV) infection.[2]

Risk Factors for Anal Cancer
TABLE 1

<table>
<thead>
<tr>
<th>Risk Factors for Anal Carcinoma</th>
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<tr>
<td>HPV infection</td>
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<tr>
<td>Receptive anal intercourse</td>
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<tr>
<td>Lifetime number of sexual partners</td>
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<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Cigarette smoking</td>
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<tr>
<td>Genital warts</td>
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<td>Immunosuppression post-organ transplant</td>
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The risk factors associated with anal cancer are summarized in Table 1.[1-30] The most important risks are behavioral factors that predispose individuals to human papillomavirus (HPV) infection or immunosuppression.

**Behavioral Risk Factors**

Specific sexual practices have been associated with an increased risk of anal cancer. The risk of anal cancer appears to be the highest among men having sex with men[7-10] (odds ratio [OR] = 17.3; 95% confidence interval [CI] = 8.2-36.1).[9] These risks are increased in the setting of men having sex with men who are HIV-positive (relative risk [RR] = 59.5). It is now recognized that the increased risk of anal cancer in this population is due to the increased HPV infection rate rather than isolated HIV infection.

Risk factors common to both men and women are receptive anal intercourse, lifetime number of sexual partners, cigarette smoking, and a history of genital warts.[9] For women, additional risk factors include history of high-grade vulvar intraepithelial neoplasia, and vulvar cancer or cervical cancer.[7,9,11-14]

**HPV**

Squamous cell cancer of the anal region is similar to that of the uterine cervix, vagina, and vulva,[15] and shares the common association with high-risk HPV infection.[10,12,16-21] While the prevalence of cervical HPV infection in women declines after age 30 years, anal HPV in HIV-negative men who have sex with men (MSM) remains high and constant throughout life.[22,23]

The prevalence of anal HPV infection is greater than cervical HPV infection in women who are HIV-positive or have a high risk of HIV infection.[24-26] In a population of healthy Hawaiian women, anal HPV infection was as common as cervical HPV.[27] In immunocompetent heterosexual men, anogenital and anal HPV infections were documented in 65.4% and 24.8% of patients, respectively.[28,29] History of multiple sexual partners in homosexual or heterosexual individuals or of unprotected anal intercourse were predictive of greater risk of developing anal intraepithelial neoplasia (AIN) and invasive anal cancer.[30]

Several subtypes of HPV are linked to anal cancer and its precursor lesions. HPV 16 has the highest degree of association and, to a lesser extent, types 18, 31, 33, 35 and others have been connected. The prevalence of high-risk HPV is about 85% in patients with squamous cell cancer of the anal canal, depending on the sensitivity of the assay[15,31,32] and the geographic variations.[33] In one series, high-risk HPV was identified in 90% of anal squamous cell carcinomas in women and 63% of such cancers in men.[31] HPV-negative anal cancers were similar to HPV-positive anal cancers in terms of patient age, adjacent dysplasia, ductal differentiation, and prognosis.[34]

**Immunosuppression and HIV**

Immunosuppression probably impairs the body’s ability to clear HPV after sexual exposure.[35-38] Patients undergoing organ transplantation have a 10- to 100-fold risk of anal cancer compared to the general population.[39-44] The rate of high-grade squamous intraepithelial neoplasia is higher in HIV-positive patients than HIV-negative patients and is inversely related to the CD4 lymphocyte count.[45,46] However, HIV-related immunosuppression has not been clearly established as an independent risk factor for anal cancer.
Since the introduction of highly active antiretroviral therapy (HAART), HIV patients are living longer and consequently, have an increased lifetime risk of developing anal cancer.[47] Although there have been reductions in the incidence of Kaposi’s sarcoma and lymphoma, no significant change has been seen in the incidence of anal carcinoma.[48] In a study matching a cancer database to AIDS databases, the relative risk of developing anal cancer among HIV-positive men with a history of homosexual contact was 59.5, while the relative risk for anal cancer was 6.8 in HIV-positive women in comparison to the general population.[49]

Benign Lesions and Anal Cancer

Benign lesions in the anal canal such as fistulas or fissures do not appear to predispose to cancer.[30] Similarly, inflammatory bowel disease does not appear to predispose to anal squamous cell cancer.[50,51] A Danish population-based cohort study of 6,334 patients with ulcerative colitis and 2,723 patients with Crohn’s disease who were followed for 10 years showed no increased risk of anal cancer.[52]

Screening and Prevention

Screening of High-Risk Individuals

Anal cancer is generally preceded by high-grade anal intraepithelial neoplasia (HGAIN), a precursor lesion analogous to cervical intraepithelial neoplasia (CIN) in carcinoma of the cervix.[53-56] HGAIN progresses to anal cancer at a rate of about 1% per year.[56,57] The prevalence of HGAIN is highest in HIV-positive MSM (52%-44%), followed by HIV-negative MSM (24%) and HIV-positive women (9%). By contrast, HIV-negative women have an estimated incidence of 1%.[58-64] No randomized trials or ecologic studies (ie, epidemiologic investigations in which the unit of analysis is a population rather than an individual) have shown any improved outcome with screening for anal cancer.[65] However, there is a general consensus that high-risk individuals may benefit from screening.

In 2007, the New York State Department of Health AIDS Institute issued guidelines recommending targeted anal cancer screening for HIV-infected patients, MSM, women with abnormal vulvar or cervical cytology, and patients with a history of anogenital warts. Screening involves a digital rectal exam, anal pap smear (cytology), and high-resolution anoscopy (HRA)-directed biopsy. One study reported a sensitivity of 95% and a specificity of 64% for physican-performed anal cytology, whereas patient-collected cytology had a sensitivity 75% and a specificity of 50%.[66] This suggests that cytology alone may not be enough to screen for high-risk patients in view of its low negative-predictive value. HRA-directed biopsy, first described by Jay et al, is now the gold standard for diagnosis of HGAIN.[59,67]

Treatment of HGAIN involves local administration of an agent such as trichloroacetic acid, which can be applied by either the patient or the physician.[68] Other physician-applied ablative techniques include electrocautery, photodynamic therapy, and surgery.[69-73] HGAIN can recur in up to 25% of patients who are HIV-negative and up to 80% of patients who are HIV-positive, indicating the need for close follow-up and repeated ablations.[69] It should be noted that HRA screening is limited to select centers and may not be available for population-based screening. Furthermore, the impact of HRA screening on overall outcome is yet to be determined. In centers where HRA is not available, screening should focus on digital anal examination and screening anal Pap smears.

HPV Vaccination

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 16/18.[74] Vaccination of boys along with girls has been recommended by some.[75] Prospective studies are needed to further assess the role of prophylactic vaccination in preventing anal cancer.

Symptoms and Stage at Presentation

Almost half of all patients with anal cancer will present with rectal bleeding. Pain or sensation of a rectal mass is experienced in 30% of patients, while 20% have no tumor-specific symptoms.[76-78] Cancer extends beyond the anal canal into the rectum and/or perineal skin in about half of all cases. Anovaginal septum invasion occurs in about 10% of female cases.[79] Anal cancer metastasizes via the lymphatic system and less often by hematogenous spread. The distal anal canal below the dentate line drains into the inguinal and femoral lymph nodes, whereas
the proximal anal canal drains into the perirectal lymph node. The staging of anal cancer is summarized in Table 2.

### Table 2

**Anal Cancer Staging**

The SEER database shows that 50% of patients with anal cancer have disease localized to the anus, 29% have regional lymph node involvement or direct spread beyond the primary, and 12% have metastatic disease, while 9% have an unknown stage.[see http://www.seer.cancer.gov/statfacts/html/anus.html]

### Diagnostic Tests

Clinical staging of anal carcinoma requires a digital rectal exam and a CT scan of the chest, abdomen, and pelvis. Any suspicious inguinal lymph node should be subject to pathologic confirmation by fine-needle aspiration (FNA). The role of PET scanning in anal cancer has not been adequately studied.[80,81] PET is superior to CT in visualizing the primary tumor, with a detection rate of 91% to 98% compared to CT rates of only 58% to 76%. [80-82] Surgical series have shown that up to 44% of metastases occur in lymph nodes smaller than 5 mm that are not considered to be involved by CT imaging criteria.[83] PET assessment relies more on metabolic activity than on simple size and may have an advantage in addressing smaller lymph nodes. Several reports suggest that 17% to 20% of patients will be found to have previously undetected lymph node involvement on baseline PET. However, these metabolically positive cases of lymph node involvement on PET scan were not confirmed by FNA, and therefore, false-positivity cannot be ruled out. Thus, PET is not routinely indicated in the staging of anal cancer. MRI may be useful in distinguishing tumors from normal pelvic structures, especially in the setting of disease recurrence.

Along with anal examination and staging, a gynecologic exam including cervical cancer screening is recommended for women with anal cancer. HIV testing is recommended in the setting of associated risk factors or a history of multiple sexual partners. CD4 levels should be measured in HIV-positive patients for prognostic evaluation.

Endoanal ultrasound, although not routinely done, helps in evaluating the depth of invasion of the primary tumor and the involvement of adjacent nodes.[84-87]

### Prognosis

The 5-year relative survival rates are 80.1% for localized anal cancer, 60.7% for regional disease, and 29.4% for metastatic disease.[see http://www.seer.cancer.gov/statfacts/html/anus.html] Extra-pelvic metastases are associated with the worst prognosis.[2,88] Nodal involvement, T stage, and male gender predict for a higher risk of local and distant relapse, a higher colostomy rate, and a worse overall survival following treatment with chemoradiation.[89,90-92] In HIV-positive patients, high viral load, low CD4+ counts, and AIDS are poor prognostic factors in terms of local tumor control, survival, and impaired tolerance of radiation and chemotherapy.[93,94]

This article will conclude in the April 30th issue of ONCOLOGY. Part 2 will address the treatment of anal cancer, including questions about chemoradiation and neoadjuvant chemotherapy, how duration of therapy affects tumor control, and the management of HIV-positive patients.

Commentaries by Drs. Derek R. McHaffie and Kevin R. Kozak; and Drs. Clifford D. Fuller and Charles R. Thomas, Jr, will accompany part 2.

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**References:**

References


a Tx = primary tumor cannot be assessed; T0 = no evidence of primary tumor; T1 = tumor size 2 cm or less in greatest dimension; T2 = tumor > 2 cm but < 5 cm; T3 = tumor > 5 cm; T4 = tumor of any size invading adjacent organs.
b Nx = regional lymph nodes cannot be assessed; N0 = no regional lymph node metastasis; N1 = metastasis in perirectal lymph node; N2 = metastasis in unilateral internal iliac or unilateral inguinal lymph node; N3 = metastasis in perirectal and inguinal lymph node and/or bilateral inguinal lymph node and/or bilateral internal iliac lymph nodes.
c Mx = distant metastasis cannot be assessed; M0 = no distant metastasis; M1 = distant metastasis.

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