cancernetwork
home of the journal ONCOLOGY

ONCOLOGY. Vol. 24 No. 4

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

By Ali Abbas, MBBS[1], Gary Yang, MD[2], Marwan Fakih, MD[3] | April 12, 2010
[1] Medical Resident, School of Medicine and Biomedical Sciences, State University of New York at Buffalo [2] Director, Gastrointestinal, Radiation Medicine, Roswell Park Cancer Institute [3] Associate Professor of Oncology, Roswell Park Cancer Institute, Buffalo, New York

ABSTRACT: 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 (Drug information on fluorouracil), mitomycin(Drug information on 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 1

Risk Factors for Anal Carcinoma

- HPV infection
- Receptive anal intercourse
- Lifetime number of sexual partners
- Female gender
- Cigarette smoking
- Genital warts
- Immunosuppression post–organ transplant

Risk Factors for Anal Carcinoma

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.

Financial Disclosure: *The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.*

References

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2009. *CA Cancer J Clin* 59:225-249, 2009.

2. Johnson LG, Madeleine MM, Newcomer LM, et al: Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer* 101:281-288, 2004.

3. Chiao EY, Krown SE, Stier EA, et al: A population-based analysis of temporal trends in the incidence of squamous anal canal cancer in relation to the HIV epidemic. *J Acquir Immune Defic Syndr* 40:451-455, 2005.

4. Frisch M, Melbye M, Moller H: Trends in incidence of anal cancer in Denmark. *BMJ* 306:419-422, 1993.

5. Brewster DH, Bhatti LA: Increasing incidence of squamous cell carcinoma of the anus in Scotland, 1975-2002. *Br J Cancer* 95:87-90, 2006.

6. Goldman S, Glimelius B, Nilsson B, et al: Incidence of anal epidermoid carcinoma in Sweden 1970-1984. *Acta Chir Scand* 155:191-197, 1989.

7. Daling JR, Weiss NS, Hislop TG, et al: Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med* 317:973-977, 1987.

8. Daling JR, Sherman KJ, Hislop TG, et al: Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol* 135:180-189, 1992.

9. Daling JR, Madeleine MM, Johnson LG, et al: Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 101:270-280, 2004.

10. Frisch M, Glimelius B, van den Brule AJ, et al: Sexually transmitted infection as a cause of anal cancer. *N Engl J Med* 337:1350-1358, 1997.

11. Ogunbiyi OA, Scholefield JH, Robertson G, et al: Anal human papillomavirus infection and squamous neoplasia in patients with invasive vulvar cancer. *Obstet Gynecol* 83:212-216, 1994.

12. Melbye M, Sprogel P: Aetiological parallel between anal cancer and cervical cancer. *Lancet* 338:657-659, 1991.

13. Jiménez W, Paszat L, Kupets R, et al: Presumed previous human papillomavirus (HPV) related gynecological cancer in women diagnosed with anal cancer in the province of Ontario. *Gynecol Oncol* 114:395-398, 2009.

14. Rabkin CS, Biggar RJ, Melbye M, et al: Second primary cancers following anal and cervical carcinoma: Evidence of shared etiologic factors. *Am J Epidemiol* 136:54-58, 1992.

15. Zbar AP, Fenger C, Efron J, et al: The pathology and molecular biology of anal intraepithelial neoplasia: Comparisons with cervical and vulvar intraepithelial carcinoma. *Int J Colorectal Dis* 17:203-215, 2002.

16. Palefsky JM: Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women. *J Natl Cancer Inst Monogr* (23):15-20, 1998.

17. Chin-Hong PV, Palefsky JM: Human papillomavirus anogenital disease in HIV-infected individuals. *Dermatol Ther* 18:67-76, 2005.

18. Panther LA, Schlecht HP, Dezube BJ: Spectrum of human papillomavirus-related dysplasia and carcinoma of the anus in HIV-infected patients. *AIDS Read* 15:79-82, 85-76, 88, 91, 2005.

19. Tilston P: Anal human papillomavirus and anal cancer. *J Clin Pathol* 50:625-634, 1997.

20. Duggan MA, Boras VF, Inoue M, et al: Human papillomavirus DNA determination of anal condylomata, dysplasias, and squamous carcinomas with in situ hybridization. *Am J Clin Pathol* 92:16-21, 1989.

21. Palefsky JM, Holly EA, Gonzales J, et al: Detection of human papillomavirus DNA in anal intraepithelial neoplasia and anal cancer. *Cancer Res* 51:1014-1019, 1991.

22. Schiffman MH: Recent progress in defining the epidemiology of human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst* 84:394-398, 1992.

23. Chin-Hong PV, Vittinghoff E, Cranston RD, et al: Age-related prevalence of anal cancer precursors in homosexual men: The EXPLORE study. *J Natl Cancer Inst* 97:896-905, 2005.

24. Palefsky JM, Holly EA, Ralston ML, et al: Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. *J Infect Dis* 183:383-391, 2001.

25. Melbye M, Smith E, Wohlfahrt J, et al: Anal and cervical abnormality in women--prediction by human papillomavirus tests. *Int J Cancer* 68:559-564, 1996.

26. Williams AB, Darragh TM, Vranizan K, et al: Anal and cervical human papillomavirus infection and risk of anal and cervical epithelial abnormalities in human immunodeficiency virus-infected women. *Obstet Gynecol* 83:205-211, 1994.

27. Hernandez BY, McDuffie K, Zhu X, et al: Anal human papillomavirus infection in women and its relationship with cervical infection. *Cancer Epidemiol Biomarkers Prev* 14:2550-2556, 2005.

28. Nielson CM, Harris RB, Dunne EF, et al: Risk factors for anogenital human papillomavirus infection in men. *J Infect Dis* 196:1137-1145, 2007.

29. Nyitray A, Nielson CM, Harris RB, et al: Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. *J Infect Dis* 197:1676-1684, 2008.

30. Frisch M: On the etiology of anal squamous carcinoma. *Dan Med Bull* 49:194-209, 2002.

31. Frisch M, Fenger C, van den Brule AJ, et al: Variants of squamous cell carcinoma of the anal canal and perianal skin and their relation to human papillomaviruses. *Cancer Res* 59:753-757, 1999.

32. Bjorge T, Engeland A, Luostarinen T, et al: Human papillomavirus infection as a risk factor for anal and perianal skin cancer in a prospective study. *Br J Cancer* 87:61-64, 2002.

33. Scholefield JH, Kerr IB, Shepherd NA, et al: Human papillomavirus type 16 DNA in anal cancers from six different countries. *Gut* 32:674-676, 1991.

34. Williams GR, Lu QL, Love SB, et al: Properties of HPV-positive and HPV-negative anal carcinomas. J Pathol 180:378-382, 1996.

35. Ryan DP, Compton CC, Mayer RJ: Carcinoma of the anal canal. *N Engl J Med* 342:792-800, 2000.

36. Sillman F, Stanek A, Sedlis A, et al: The relationship between human papillomavirus and lower genital intraepithelial neoplasia in immunosuppressed women. *Am J Obstet Gynecol* 150:300-308, 1984.

37. Sillman FH, Fruchter RG, Chen YS, et al: Vaginal intraepithelial neoplasia: Risk factors for persistence, recurrence, and invasion and its management. *Am J Obstet Gynecol* 176:93-99, 1997.

38. Goncalves MA, Donadi EA: Immune cellular response to HPV: Current concepts. *Braz J Infect Dis* 8:1-9, 2004.

39. Sillman FH, Sentovich S, Shaffer D: Ano-genital neoplasia in renal transplant patients. *Ann Transplant* 2:59-66, 1997.

40. Adami J, Gabel H, Lindelof B, et al: Cancer risk following organ transplantation: A nationwide cohort study in Sweden. *Br J Cancer* 89:1221-1227, 2003.

41. Penn I: Cancers of the anogenital region in renal transplant recipients. Analysis of 65 cases. *Cancer* 58:611-616, 1986.

42. Arends MJ, Benton EC, McLaren KM, et al: Renal allograft recipients with high susceptibility to cutaneous malignancy have an increased prevalence of human papillomavirus DNA in skin tumours and a greater risk of anogenital malignancy. *Br J Cancer* 75:722-728, 1997.

43. Albright JB, Bonatti H, Stauffer J, et al: Colorectal and anal neoplasms following liver transplantation. *Colorectal Dis* Mar 26 2009 (epub ahead of print).

44. Patel HS, Silver AR, Northover JM: Anal cancer in renal transplant patients. *Int J Colorectal Dis* 22:1-5, 2007.

45. Critchlow CW, Surawicz CM, Holmes KK, et al: Prospective study of high grade anal squamous intraepithelial neoplasia in a cohort of homosexual men: Influence of HIV infection, immunosuppression and human papillomavirus infection. *AIDS* 9:1255-1262, 1995.

46. Palefsky JM, Holly EA, Hogeboom CJ, et al: Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual men. *J Acquir Immune Defic Syndr Hum Retrovirol* 17:314-319, 1998.

47. Palefsky JM: Anal squamous intraepithelial lesions: relation to HIV and human papillomavirus infection. *J Acquir Immune Defic Syndr* 21(suppl 1):S42-S48, 1999.

48. Hessol NA, Pipkin S, Schwarcz S, et al: The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol* 165:1143-1153, 2007.

49. Patel P, Hanson DL, Sullivan PS, et al: Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med* 148:728-736, 2008.

50. Preston DM, Fowler EF, Lennard-Jones JE, et al: Carcinoma of the anus in Crohns disease. *Br J Surg* 70:346-347, 1983.

51. Slater G, Greenstein A, Aufses AH Jr: Anal carcinoma in patients with Crohns disease. Ann Surg 199:348-350, 1984.

52. Frisch M, Johansen C: Anal carcinoma in inflammatory bowel disease. *Br J Cancer* 83:89-90, 2000.

53. Watson AJ, Smith BB, Whitehead MR, et al: Malignant progression of anal intra-epithelial neoplasia. *ANZ J Surg* 76:715-717, 2006.

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

55. Abbasakoor F, Boulos PB: Anal intraepithelial neoplasia. Br J Surg 92:277-290, 2005.

56. Fenger C: Anal neoplasia and its precursors: Facts and controversies. *Semin Diagn Pathol* 8:190-201, 1991.

57. Klencke BJ, Palefsky JM: Anal cancer: An HIV-associated cancer. *Hematol Oncol Clin North Am* 17:859-872, 2003.

58. Palefsky JM, Holly EA, Efirdc JT, et al: Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS* 19:1407-1414, 2005.

59. Berry JM, Palefsky JM, Jay N, et al: Performance characteristics of anal cytology and human papillomavirus testing in patients with high-resolution anoscopy-guided biopsy of high-grade anal intraepithelial neoplasia. *Dis Colon Rectum* 52:239-247, 2009.

60. Hessol NA, Holly EA, Efird JT, et al: Anal intraepithelial neoplasia in a multisite study of HIV-infected and high-risk HIV-uninfected women. *AIDS* 23:59-70, 2009.

61. Goldstone SE, Winkler B, Ufford LJ, et al: High prevalence of anal squamous intraepithelial lesions and squamous-cell carcinoma in men who have sex with men as seen in a surgical practice. *Dis Colon Rectum* 44:690-698, 2001.

62. Panther LA, Wagner K, Proper J, et al: High resolution anoscopy findings for men who have sex with men: Inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. *Clin Infect Dis* 38:1490-1492, 2004.

63. Fox PA, Seet JE, Stebbing J, et al: The value of anal cytology and human papillomavirus typing in the detection of anal intraepithelial neoplasia: A review of cases from an anoscopy clinic. *Sex Transm Infect* 81:142-146, 2005.

64. Cranston RD, Hart SD, Gornbein JA, et al: The prevalence, and predictive value, of abnormal anal cytology to diagnose anal dysplasia in a population of HIV-positive men who have sex with men. *Int J STD AIDS* 18:77-80, 2007.

65. Chiao EY, Giordano TP, Palefsky JM, et al: Screening HIV-infected individuals for anal cancer precursor lesions: A systematic review. *Clin Infect Dis* 43:223-233, 2006.

66. Chin-Hong PV, Berry JM, Cheng SC, et al: Comparison of patient- and clinician-collected anal cytology samples to screen for human papillomavirus-associated anal intraepithelial neoplasia in men who have sex with men. *Ann Intern Med* 149:300-306, 2008.

67. Jay N, Berry JM, Hogeboom CJ, et al: Colposcopic appearance of anal squamous intraepithelial lesions: Relationship to histopathology. *Dis Colon Rectum* 40:919-928, 1997.

68. Wieland U, Brockmeyer NH, Weissenborn SJ, et al: Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. Arch Dermatol 142:1438-1444, 2006.

69. Chang GJ, Berry JM, Jay N, et al: Surgical treatment of high-grade anal squamous intraepithelial lesions: A prospective study. *Dis Colon Rectum* 45:453-458, 2002.

70. Runfola MA, Weber TK, Rodriguez-Bigas MA, et al: Photodynamic therapy for residual neoplasms of the perianal skin. *Dis Colon Rectum* 43:499-502, 2000.

71. Pineda CE, Berry JM, Jay N, et al: High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: A ten-year experience. *Dis Colon Rectum* 51:829-837 (incl discussion), 2008.

72. Goldstone SE, Hundert JS, Huyett JW: Infrared coagulator ablation of high-grade anal squamous intraepithelial lesions in HIV-negative males who have sex with males. Dis Colon Rectum 50:565-575, 2007.

73. Cranston RD, Hirschowitz SL, Cortina G, et al: A retrospective clinical study of the treatment of high-grade anal dysplasia by infrared coagulation in a population of HIV-positive men who have sex with men. Int J STD AIDS 19:118-120, 2008.

74. De Vuyst H, Clifford GM, Nascimento MC, et al: Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: A meta-analysis. *Int J Cancer* 124:1626-1636, 2009.

75. Gillison ML, Chaturvedi AK, Lowy DR: HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. *Cancer* 113(10 suppl):3036-3046, 2008.

76. Singh R, Nime F, Mittelman A: Malignant epithelial tumors of the anal canal. *Cancer* 48:411-415, 1981.

77. Schneider TC, Schulte WJ: Management of carcinoma of anal canal. *Surgery* 90:729-734, 1981.

78. Schraut WH, Wang CH, Dawson PJ, et al: Depth of invasion, location, and size of cancer of the anus dictate operative treatment. *Cancer* 51:1291-1296, 1983.

79. DeVita VTL, Theodore S, Rosenberg SA (eds): *Devita, Hellman and Rosenbergs Cancer: Principles & Practice of Oncology,* 8th ed, vol 1. Philadelphia, Lippincott Williams & Wilkins, 2008.

80. Cotter SE, Grigsby PW, Siegel BA, et al: FDG-PET/CT in the evaluation of anal carcinoma. *Int J Radiat Oncol Biol Phys* 65:720-725, 2006.

81. Nguyen BT, Joon DL, Khoo V, et al: Assessing the impact of FDG-PET in the management of anal cancer. *Radiother Oncol* 87:376-382, 2008.

82. Scherrer A, Reboul F, Martin D, et al: CT of malignant anal canal tumors. *Radiographics* 10:433-453, 1990.

83. Wade DS, Herrera L, Castillo NB, et al: Metastases to the lymph nodes in epidermoid carcinoma of the anal canal studied by a clearing technique. *Surg Gynecol Obstet* 169:238-242, 1989.

84. Giovannini M, Bardou VJ, Barclay R, et al: Anal carcinoma: Prognostic value of endorectal ultrasound (ERUS). Results of a prospective multicenter study. *Endoscopy* 33:231-236, 2001.

85. Tarantino D, Bernstein MA: Endoanal ultrasound in the staging and management of squamous-cell carcinoma of the anal canal: Potential implications of a new ultrasound staging system. *Dis Colon Rectum* 45:16-22, 2002.

86. Goldman S, Norming U, Svensson C, et al: Transanorectal ultrasonography in the staging of anal epidermoid carcinoma. *Int J Colorectal Dis* 6:152-157, 1991.

87. Roseau G, Palazzo L, Colardelle P, et al: Endoscopic ultrasonography in the staging and follow-up of epidermoid carcinoma of the anal canal. *Gastrointest Endosc* 40:447-450, 1994.

88. Tanum G, Tveit K, Karlsen KO, et al: Chemotherapy and radiation therapy for anal carcinoma. Survival and late morbidity. *Cancer* 67:2462-2466, 1991.

89. Ajani JA, Winter KA, Gunderson LL, et al: US intergroup anal carcinoma trial: Tumor diameter predicts for colostomy. *J Clin Oncol* 27:1116-1121, 2009.

90. Goldman S, Auer G, Erhardt K, et al: Prognostic significance of clinical stage, histologic grade, and nuclear DNA content in squamous-cell carcinoma of the anus. *Dis Colon Rectum* 30:444-448, 1987.

91. Bartelink H, Roelofsen F, Eschwege F, et al: Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 15:2040-2049, 1997.

92. Newman G, Calverley DC, Acker BD, et al: The management of carcinoma of the anal canal by external beam radiotherapy, experience in Vancouver 1971-1988. *Radiother Oncol* 25:196-202, 1992.

93. Hoffman R, Welton ML, Klencke B, et al: The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. *Int J Radiat Oncol Biol Phys* 44:127-131, 1999.

94. Place RJ, Gregorcyk SG, Huber PJ, et al: Outcome analysis of HIV-positive patients with anal squamous cell carcinoma. *Dis Colon Rectum* 44:506-512, 2001.

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 metastastsis; 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.