

Practice Parameters for Anal Squamous Neoplasms

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It should be recognized that these guidelines should not be deemed inclusive of all proper methods of care or exclusive of methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of all of the circumstances presented by the individual patient.

METHODOLOGY

A MEDLINE search of English language references from 1965 through December 2006 was performed by using the following key words: “anal cancer”; “anal carcinoma”;

“anal intraepithelial neoplasia”; and “squamous-cell cancer.” The Cochrane Database of Collected Reviews and selected embedded references also were reviewed.

INTRODUCTION

Squamous-cell cancer (SCC) of the anus is an uncommon malignancy, affecting approximately 4,600 patients per year in the United States.¹ The relatively low incidence of anal cancer limits the power of studies to make high-grade, evidence-based recommendations for diagnosis and treatment. Anal intraepithelial neoplasia (AIN) is the putative precursor lesion of anal cancer. The incidence of both anal SCC and AIN is increasing, particularly in patients infected with the human immunodeficiency virus (HIV). Although a wide array of rare tumors can present in the anal canal, this practice parameter will focus on squamous neoplasms.

ANAL CANAL SQUAMOUS-CELL CARCINOMA

Pretreatment Evaluation

A. A disease-specific history should be taken, emphasizing symptoms and predisposing factors. Level of Evidence: IV; Grade of Recommendation: B.

Most patients with anal SCC have anal bleeding (which frequently can be mistaken for hemorrhoidal bleeding), pain, or the sensation of a mass; however, 20 percent of patients are asymptomatic.²⁻⁴ Groin pain may indicate inguinal lymph node involvement. Risk factors that have been associated with carcinoma of the anus include infection with the human papilloma virus (HPV) or HIV, a history of cervical cancer, cervical intraepithelial neoplasia, other sexually acquired diseases, cigarette smoking, anoreceptive intercourse, multiple sexual partners, and immunosuppression.²⁻⁶ A history of medical comorbidities that might limit the patients ability to undergo chemoradiation or radical surgery also should be sought.

No reprints available.

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Dis Colon Rectum 2008; 51: 2-9
DOI: 10.1007/s10350-007-9093-3
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B. A disease-specific physical examination should be performed to determine tumor size and possible lymph node involvement. Level of Evidence: IV; Grade of Recommendation: B.

Because the staging and prognosis of anal cancer is related to tumor size and lymph node involvement, physical examination has a critical role.⁷ According to American Joint Commission on Cancer/International Union against Cancer (AJCC/UICC) criteria, an anal cancer is classified as T1 if the tumor is < 2 cm in size, T2 if it is 2 to 5 cm, T3 if it is > 5 cm, and T4 regardless of the size if it invades adjacent organs, such as the bladder, vagina, or urethra. Invasion of the anal sphincter or perianal skin does not constitute a T4 lesion. Fixation and location of the tumor within the anal canal also should be determined to aid in subsequent treatment and evaluation.⁸ Perirectal lymph nodes may sometimes be palpated on digital rectal examination. The presence or absence of inguinal adenopathy should be ascertained by palpation. A fine-needle aspiration or core biopsy of an enlarged inguinal lymph node with or without ultrasound guidance may supplement the physical examination and confirm malignant involvement.

C. Endoscopic and radiologic evaluation should be performed. Level of Evidence: IV; Grade of Recommendation: B.

Biopsy via anoscopy or sigmoidoscopy allows histologic confirmation that a suspicious mass within the anal canal is a primary anal epidermoid cancer (squamous-cell) and not a primary rectal cancer (adenocarcinoma) or anal glandular adenocarcinoma. Patients older than aged 50 years or those with risk factors for concomitant colorectal cancer, such as hematochezia, alterations in their bowel habits, or predisposing family history, should undergo colonoscopy to rule out a synchronous colorectal neoplasm.

Endoanal ultrasound (ERUS) may be useful and has been reported to be superior to physical examination in assessing tumor involvement of the anal sphincter and perirectal lymph nodes.⁹ CT scans should usually be performed in the pretreatment evaluation of anal cancer to exclude metastatic disease. Positron emission tomography (PET) scanning may have a role as an adjunct to CT of the pelvis, abdomen, and chest, identifying sites of metastasis not observed on CT in 25 percent of cases. Almost 20 percent of patients with inguinal nodes that are negative by both physical examination and CT scan are positive on PET.¹⁰ This has prognostic significance and may influence the radiation treatment plan.¹¹

Treatment

A. Primary Treatment

1. Combined modality chemoradiation therapy should usually be first-line therapy: Level of Evidence: I; Grade of Recommendation: A.

Since the first description by Nigro of complete pathologic responses to concurrent 5-fluorouracil (5-FU), mitomycin C, and radiation therapy in patients with anal cancer, further study has established primary chemoradiation (CRT) therapy as the first-line treatment for squamous-cell carcinoma of the anal canal. Several multi-institutional prospective, randomized trials have shown that the addition of chemotherapy to radiation therapy results in lower rates of local failure, tumor recurrence, and need for colostomy compared with patients treated with radiation therapy (RT) alone.¹²⁻¹⁵ Although there seems to be no significant change in overall survival, a higher disease-free survival has been demonstrated with CRT. These improved results, however, are accompanied by an increased incidence of

LEVELS OF EVIDENCE AND GRADE RECOMMENDATION

Level	Source of Evidence
I	Meta-analysis of multiple well-designed, controlled studies, randomized trials with low false-positive and low false-negative errors (high power)
II	At least one well-designed experimental study; randomized trials with high false-positive or high false-negative errors or both (low power)
III	Well-designed, quasi-experimental studies, such as nonrandomized, controlled, single-group, preoperative–postoperative comparison, cohort, time, or matched case-control series
IV	Well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Case reports and clinical examples
Grade	Grade of Recommendation
A	Evidence of Type I or consistent findings from multiple studies of Type II, III, or IV
B	Evidence of Type II, III, or IV and generally consistent findings
C	Evidence of Type II, III, or IV but inconsistent findings
D	Little or no systematic empirical evidence

Adapted from Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1992;102(4 Suppl):305S–311S. Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989;92(2 Suppl):2S–4S.

hematologic toxicity.¹²⁻¹⁵ RT alone may be considered in patients who cannot tolerate the additional toxicity of chemotherapy. Local excision is an appropriate consideration for small, superficial lesions.¹⁶

2. Multidrug chemotherapy with radiation is usually preferable to single drug chemotherapy with radiation: Level of Evidence: I; Grade of Recommendation: A.

Two controlled studies have established that the addition of mitomycin C (MMC) to RT and 5-fluorouracil (5-FU) achieves superior local control, colostomy-free survival, and disease-free survival compared with 5-FU alone plus RT. These improved results are accompanied by an increased incidence of acute hematologic toxicity.^{12,14} A regimen of cisplatin instead of MMC with 5-FU chemotherapy is currently being studied with interest in large intergroup trials in the United States and Europe.¹⁷ Although there was no difference in disease-free or overall survival between the treatment arms, the cisplatin arm was associated with a higher colostomy rate at five years (19 vs. 10 percent) but a lower incidence of severe hematologic toxicity.

3. Higher doses of radiation therapy without prolonged breaks in treatment is preferable when tolerated: Level of Evidence: III; Grade of Recommendation: B.

The usual dose of radiation given in CRT for anal SCC varies between 45 to 59 Gy. Total radiation dose (>54 Gy) was seen to be a significant factor in increasing local control and survival.¹⁸ However, the incidence of late complications, including the need for colostomy, is directly related to the total RT dose.^{12,19} RT is usually given over six weeks, because inferior local control rates have been demonstrated with unplanned treatment prolongation compared with radiation therapy without treatment breaks.^{20,21}

B. Treatment of Recurrent or Persistent Disease

Despite excellent results of CRT in the primary treatment of these cancers, locoregional failure occurs in up to 30 percent of patients. Of these patients, approximately one-half can be classified as persistent disease and the other half as recurrent disease.^{3,12,22,23} Several recent studies have suggested improved overall survival after abdominoperineal resection (APR) in patients with recurrent disease compared with patients with persistent disease.²⁴⁻²⁶ Although some have reported on the use of an additional boost of CRT to treat persistent or recurrent disease, the efficacy of this approach is questionable.¹⁴

1. Abdominoperineal resection is effective salvage therapy for persistent or recurrent disease: Level of Evidence: III; Grade of Recommendation: B.

Abdominoperineal resection is primarily reserved for salvage therapy when CRT has failed to achieve a complete response or when a local recurrence is diagnosed. APR also may be considered in patients with severe RT-induced

complications, including stenosis, nonhealing ulceration, or incontinence. Salvage APR is associated with five-year overall survival rates ranging from approximately 24 to 58 percent.²⁶ There is appreciable perineal wound morbidity after salvage APR, leading some to advocate immediate plastic surgery reconstruction using rotation or advancement flaps to promote healing.

2. Systemic chemotherapy should be considered in patients with extrapelvic metastasis or recurrence after surgical salvage: Level of Evidence: III; Grade of Recommendation: B.

There is no uniformly agreed upon regimen for extrapelvic metastatic disease. Combination therapy using cisplatin with 5-FU, however, has shown promise in these patients.^{27,28} Other agents active for primary squamous-cell carcinomas in other locations may have utility.

C. Management of Inguinal Lymph Node Disease

1. Chemoradiation is the treatment of choice for inguinal lymph node disease: Level of Evidence: III. Grade of Recommendation: B.

CRT is the treatment of choice for synchronous nodal involvement, with cure rates approaching 90 percent.^{12,29} Both inguinal nodal basins should be incorporated into the radiation fields with the addition of a boost technique for clinically positive lymph nodes. Metachronous lymph nodes are seen in 10 to 20 percent of patients, usually appearing within six months after treatment of the primary lesion.³⁰ These lymph node deposits also respond well to CRT.¹⁶ Lymph node dissection may be considered in patients who have persistent nodal disease after CRT.

Prophylactic lymph node dissection is not indicated because of the potential for serious long-term wound and lower extremity complications.³¹ Sentinel lymph node dissection is an appealing concept for detecting occult metastasis to the inguinal nodes.³² Nevertheless, the clinical impact of this procedure on the therapeutic approach is unclear as long as the inguinal nodes are included in the radiation field.

D. Anal Cancer in HIV-Positive Patients

1. CD4 counts may be used to predict the outcome and tolerance of CRT in HIV-positive patients: Level of Evidence: III. Grade of Recommendation: B.

The incidence of anal carcinoma is higher in individuals who are HIV-positive.³³ Pretreatment CD4 counts may determine the response of HIV-positive patients to chemoradiation for anal cancer³⁴ and their ability to tolerate the potential toxicity of therapy. Patients with CD4 counts > 200 cells/ml should usually be treated with combined chemoradiation as with non-HIV infected individuals.³⁵ Patients with CD4 < 200 cells/ml tend to experience more toxicity from CRT,³⁴ and therapy must be individualized in this setting.

Highly active antiretroviral therapy (HAART) allows patients to better tolerate CRT and may improve local tumor control.^{36,37}

Posttreatment Surveillance

1. Follow-up should usually include digital rectal examination, anoscopy, and inguinal palpation. Level of Evidence: IV. Grade of Recommendation: B.

Anal cancers usually regress slowly after CRT,³⁸ and follow-up may begin 6 to 12 weeks after completion of treatment.^{3,39} Patients should be followed since recurrences often may be retreated for cure. Examinations may be performed every three to six months with digital rectal examination, anoscopy with biopsy of any suspicious lesion, inguinal palpation, and perhaps CT scan for more advanced disease. Digital examination alone is unreliable in confirming residual malignancy in lesions that persist after CRT.³⁸ Controversy exists about the need for multiple random biopsies vs. biopsy of suspicious lesions only.

ERUS may help in the early detection of recurrence.^{40,41} A recent study indicated that three dimensional ERUS in conjunction with digital rectal examination and anoscopy can improve detection rates compared with two dimensional ERUS and three dimensional ERUS alone.⁴¹

ANAL MARGIN SQUAMOUS-CELL CARCINOMA

A. A disease-specific physical examination should be performed, emphasizing tumor size and anatomic location. Level of Evidence: IV; Grade of Recommendation: C.

Significant differences in treatment and survival distinguish anal margin cancers from anal canal tumors; the location of these tumors must be accurately assessed. Anal margin lesions refer to tumors starting at the distal end of the anal canal to a 5-cm margin surrounding the anal verge.⁷

The staging of anal margin cancers by the American Joint Committee on Cancer follows that of skin cancer. T1-3 are staged the same as carcinoma of the anal canal but T4 signifies invasion of deep extradermal structures, such as bone, nerve, striated muscle, or cartilage. N0 and N1 refer to no regional and regional lymph node spread respectively.⁷

Wide local excision alone is appropriate for T1 and early T2 lesions that can be excised with a 1-cm margin.⁴² However, larger cancers usually should be treated with the addition of prophylactic radiation to the inguinal lymph nodes along with radiation or excision of the primary tumor. For T3 and T4 lesions, radiation to both inguinal regions and the pelvis, along with chemotherapy, such as 5-FU and mitomycin C or

Cisplatin, usually should be added. Abdominoperineal resection is most appropriate for patients who are already incontinent with large, bulky tumors extending into the sphincter muscle or in patients who have failed CRT.⁴³

ANAL INTRAEPITHELIAL NEOPLASIA

Anal intraepithelial neoplasia (AIN) has many disease characteristics in common with cervical intraepithelial neoplasia (CIN) and is thought to be a precursor to anal SCC. The term anal squamous intraepithelial lesion also is used to describe AIN and is classified into low-grade anal squamous intraepithelial lesion (LSIL), equivalent to AIN Grade 1, and high-grade anal squamous intraepithelial lesion (HSIL), equivalent to AIN Grades 2 or 3. AIN lesions are classified by using criteria for the evaluation of cervical cytology.⁴⁴ In LSIL, koilocytes and superficial and high intermediate cells are seen. Binucleation is frequently observed. The nuclear membrane often is angulated and irregular. Atypical parakeratotic cells may be numerous. In HSIL, the abnormal squamous cells are of low intermediate or immature squamous metaplastic type. Nuclei typically have coarse chromatin and wrinkling or irregularity of the nuclear membrane. The terms anal carcinoma *in situ* and Bowens disease of the anus are sometimes used to denote HSIL, but they are best avoided because they create confusion among clinicians.

Pretreatment Evaluation

A. A disease-specific history should be taken, emphasizing symptoms and predisposing factors. Level of Evidence: IV; Grade of Recommendation: B.

AIN is being detected with increasing frequency in both males and females with impaired immune function. HIV seropositivity is not only an established risk factor for AIN but it also is associated with progression to HSIL, particularly in patients with a low CD4 cell count.⁴⁵ AIN also is associated with immunosuppression for organ transplantation.⁴⁶

The association between HPV infection and AIN has been demonstrated in both males and females.^{47,48} These findings parallel observations in the cervix in which HPV infection causes the development of CIN, the precursor lesion to invasive cervical cancer.⁴⁹ Although limited data exist on the natural history of anal HPV infection, the association between the presence of HPV infection among patients with anal SCC has been firmly established and seems to mimic the relationship observed with cervical cancer.^{50,51}

There are limited data regarding the natural history of untreated AIN in the HIV-negative population. Once

established in the anal epithelium, it seems that HSIL rarely regresses, even in HIV-negative individuals.⁵² The natural history of AIN in the HIV-positive population is more ominous. LSIL has been reported to progress to HSIL in more than 50 percent of HIV-positive homosexual males within two years.⁴⁵ The risk for progression to invasive cancer ranges from 10 to 50 percent among HIV-positive patients.⁵³⁻⁵⁵

B. Anal Papanicolaou smear cytological examination may be useful in the detection and follow-up of AIN. Level of Evidence III; Grade of Recommendation: C.

Based on numerous similarities between AIN and CIN, anal Papanicolaou (Pap) smear cytology has been proposed for both screening of high-risk individuals and surveillance after treatment of AIN. The sensitivity of anal Pap smear evaluation compared with high-resolution anoscopy-directed biopsies ranges from 69 to 93 percent and specificity ranges from 32 to 59 percent.⁵⁶⁻⁵⁸ Although some economic modeling studies have suggested that frequent anal cytology may be a cost-effective method to prevent anal cancer,^{59,60} there have not been any randomized or cohort studies to demonstrate improved survival or outcomes.

Treatment

A. Observation alone with close clinical follow-up is an appropriate management option for AIN. Level of Evidence: IV; Grade of Recommendation: C.

The high risk for recurrent AIN after targeted destruction, particularly among HIV-positive patients, has led some to advocate an approach of expectant management.⁵³ Excision is reserved for clinically definable lesions. Unlike perianal Pagets disease, there is no association of AIN with other tumors.⁶¹ Accordingly, there is no need for an aggressive search for visceral malignancy.

B. Topical 5 percent imiquimod cream is appropriate therapy for AIN. Level of Evidence: IV; Grade of Recommendation: C.

Imiquimod is an immunomodulatory amid with both anti-HPV and anti-tumor effects. It has been used to treat AIN with significant rates of response (>50 percent), a decline in HPV load, and a reduction in the number of HPV subtypes.⁶² These findings are similar to those reported for imiquimod treatment of intraepithelial neoplasia of the vulva.^{63,64} Although preliminary results demonstrating high response rates make this an attractive approach, its use has been limited by local side effects, including irritation, burning, and erosions, which adversely affect patient compliance.^{63,65} However, a recent systematic review of imiquimod in the treatment of anogenital warts identified a treatment

withdrawal rate of < 5 percent.⁶⁶ Although adverse effects are not uncommon, treatment often can be reinitiated after a brief break in therapy.

C. Topical 5 percent 5-fluorouracil cream is an appropriate treatment option for AIN. Level of Evidence: IV; Grade of Recommendation: C.

Since topical 5-FU has been reported to be an effective initial therapy for extramammary Bowen's disease,^{67,68} it also has been used for HPV-related anogenital neoplasia.⁶⁹ Initial response rates have been reported to be as high as 90 percent, and recurrence risk may be minimized with protracted application.⁶⁷ The primary limitation to its use is local irritation.

D. Photodynamic therapy is an appropriate treatment option for AIN. Level of Evidence: V; Grade of Recommendation: D.

Photodynamic therapy with photosensitizing agents, such as 5-aminolevulinic acid, is used as standard therapy to treat a variety of skin cancers, including SCC *in situ* and has been considered for use in AIN.⁷⁰⁻⁷² In one study of five HIV-positive patients with biopsy-proven HSIL, three patients had improvement in dysplasia and two patients had no recurrence of dysplasia identified on anal Pap smear.⁷³ Despite its established role in preinvasive squamous-cell lesions at other sites, evidence for its use in AIN is from case reports only.

E. Targeted destruction and close clinical follow-up is appropriate therapy for AIN. Level of Evidence: III; Grade of Recommendation: C.

The strategy of destroying AIN comes from treatment considerations in CIN in which surgical ablation is performed to prevent progression to invasive cervical cancer. A variety of approaches to destruction of AIN have been described, including wide local excision and targeted therapy using high-resolution anoscopy.^{51,74,75} Wide local excision is guided by frozen sections of the affected areas. One-centimeter margins are used, with large skin and mucosal defects closed with local flaps. Wide excisional therapy is associated with high rates of disease recurrence and anal incontinence or stenosis.^{76,77} Targeted destruction guided by high-resolution anoscopic examination is effective to identify, biopsy, and destroy high-grade AIN without the morbidity associated with wide local excision,⁷⁸ but there is a high risk for persistent or recurrent disease among HIV-positive patients. Surgical complications, such as incontinence and stenosis, are not generally reported.⁷⁹ Infrared coagulation (IRC) also has been used as an effective ablative device and may be associated with less pain; nevertheless, IRC also has been associated with a high risk of recurrence among HIV-positive

males.⁸⁰ Effectiveness in preventing progression to invasive cancer has been demonstrated with either approach.^{79,80}

F. Patients with AIN should be offered follow-up. Level of Evidence: III; Grade of Recommendation: B.

Patients with AIN should usually be monitored for the development of anal cancer. Surveillance examinations may be performed at six-month intervals as long as dysplasia is present.^{48,51,53} This approach allows for retreatment of recurrent or persistent dysplasia or for the detection of invasive SCC. Follow-up generally includes anoscopic examination, with or without the aid of magnification or the application of acetic acid and Lugol's solution.⁸¹ The importance of close follow-up should be particularly emphasized among HIV-positive patients who have been shown to have a high risk of persistence or recurrence of high-grade dysplasia, regardless of primary treatment modality.^{79,80,82}

ACKNOWLEDGMENTS

Contributing Members of the ASCRS Standards Committee: Amir Bastawrous, M.D., Elin Sigurdson, M.D., Ravin Kumar, M.D., Scott Steele, M.D., Raham Newstead, M.D., Scott Strong, M.D., Terry Phang, M.D., Joe Tjandra, M.D., Paul Shellito, M.D.

REFERENCES

- Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
- Ryan DP, Mayer RJ. Anal carcinoma: histology, staging, epidemiology, treatment. *Curr Opin Oncol* 2000;12:345–52.
- Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. *N Engl J Med* 2000;342:792–800.
- Robb BW, Mutch MG. Epidermoid carcinoma of the anal canal. *Clin Colon Rectal Surg* 2006;19:54–60.
- Welton LM, Sharkey FE, Kahlenberg MS. The etiology and epidemiology of anal cancer. *Surg Oncol Clin N Am* 2004;13:263–75.
- Fuchshuber PR, Rodriguez-Bigas M, Weber T, Petrelli NJ. Anal canal and perianal epidermoid cancers. *J Am Coll Surg* 1997;185:495–505.
- Anal canal. In: Greene FL, Page DL, Fleming ID, eds, *et al.* *AJCC cancer staging manual*. 6th ed. New York: Springer, 2002:125–30.
- Nguyen W, Beck DE. Epidermoid carcinoma of the anal canal. *Clin Colon Rectal Surg* 2002;15:263–70.
- Giovanni M, Bardou VJ, Barclay R, *et al.* Anal carcinoma: prognostic value of endorectal ultrasound (ERUS). Results of a prospective, multicenter study. *Endoscopy* 2001;33:231–6.
- Trautmann TG, Zuger JH. Positron emission tomography for pretreatment staging and posttreatment evaluation in cancer of the anal canal. *Mol Imaging Biol* 2005 7:309–13.
- Cotter SE, Grigsby PW, Siegel BA, *et al.* FDG-PT/CT in the evaluation of anal carcinoma. *Int J Rad Oncol Biol Phys* 2006;65:720–5.
- Cummings BJ, Keane TJ, OSullivan B, Wong CS, Catton CN. Epidermoid anal cancer: treatment by radiation alone or by radiation and 5-fluorouracil with and without mitomycin C. *Int J Rad Oncol Biol Phys* 1991;21:1115–25.
- Arnott SJ, Cunningham JD, Gallagher J, *et al.* UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomized trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet* 1996;348:1049–54.
- Flam M, John M, Pajak TF, *et al.* Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase 3 randomized intergroup study. *J Clin Oncol* 1996;14:2527–39.
- 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 Phase 3 randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997;15:2040–9.
- Fuchshuber PR, Rodriguez-Bigas M, Weber T, Petrelli NJ. Anal canal and perianal epidermoid cancers. *J Am Coll Surg* 1997;185:494–505.
- Ajani JA, Winter KA, Gunderson LL, *et al.* Intergroup RTOG 98-11: a phase III randomized study of 5-fluorouracil (5-FU), mitomycin, and radiotherapy versus 5-fluorouracil, cisplatin and radiotherapy in carcinoma of the anal canal. *J Clin Oncol* 2006;24:4009.
- Constantinou EC, Daly W, Fung CY, *et al.* Time-dose considerations in the treatment of anal cancer. *Int J Radiat Oncol Biol Phys* 1997;39:651–7.
- Touboul E, Schlienger M, Buffat L, *et al.* Epidermoid carcinoma of the anal canal. Results of curative-intent radiation therapy in a series of 270 patients. *Cancer* 1994; 73:1569–79.
- Graf R, Wust P, Hildebrandt B, *et al.* Impact of overall treatment time on local control of anal cancer treated with radiochemotherapy. *Oncology* 2003;65:14–22.
- Deniaud-Alexandre E, Touboul E, Tiret E, *et al.* Epidermoid carcinomas of the anal canal treated with definitive radiation therapy in a series of 305 patients. *Cancer Radiotherapie* 2003;7:237–53.
- Rehnan AG, Saunders MP, Schofield PF, ODwyer ST. Patterns of local disease failure and outcome after salvage surgery in patients with anal cancer. *Br J Surg* 2005;92:605–14.
- Das P, Bhatia S, Eng C, *et al.* Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. *Int J Rad Oncol Biol Phys* 2007;68:794–800.

24. Nilsson PJ, Svensson C, Goldman S, Glimelius B. Salvage abdominoperineal resection in anal epidermoid cancer. *Br J Surg* 2002;89:1425–9.
25. Akbari RP, Paty PB, Guillem JG, *et al.* Oncologic outcomes of salvage surgery for epidermoid carcinoma of the anus initially managed with combined modality therapy. *Dis Colon Rectum* 2004;47:1136–44.
26. Papaconstantinou HT, Bullard KM, Rothenberger DA, Madoff RD. Salvage abdominoperineal resection after failed Nigro protocol: modest success, major morbidity. *Colorectal Dis* 2006;8:124–9.
27. Carey RW. Regression of pulmonary metastases from cloacogenic carcinoma after cis-platinum/5-fluorouracil treatment. *J Clin Gastroenterol* 1984;6:257–9.
28. Ajani JA, Carrasco CH, Jackson DE, Wallace S. Combination of cisplatin plus fluoropyrimidine chemotherapy effective against liver metastases from carcinoma of the anal canal. *Am J Med* 1989;87:221–4.
29. Sischy B. The use of radiation therapy combined with chemotherapy in the management of squamous cell carcinoma of the anus and marginally respectable adenocarcinoma of the rectum. *Int J Rad Oncol Biol Phys* 1985;11:1587–93.
30. Golden GT, Horseley JS. Surgical management of epidermoid carcinoma of the anus. *Am J Surg* 1976;131:275–80.
31. Quan SH. Anal and perianal tumors. *Surg Clin N Am* 1978;58:549–603.
32. Perera D, Pathman-Nathan N, Rabbitt P, Hewett P, Rieger N. Sentinel node biopsy for squamous cell carcinoma of the anus and anal margin. *Dis Colon Rectum* 2003;46:1027–31.
33. Melbye M, Cote T, Kessler L, *et al.* High incidence of anal cancer among AIDS patients. The AIDS/Cancer Working Group. *Lancet* 1994;343:636–9.
34. Hoffman R, Welton M, Klencke B, Weinberg V, Krieg R. The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. *Int J Rad Oncol Biol Phys* 1999;44:127–31.
35. Berry JM, Palefsky JM, Welton ML. Anal cancer and its precursors in HIV-positive patients: perspectives and management. *Surg Oncol Clin N Am* 2004;13:355–73.
36. Cleator S, Fife K, Nelson M, Gazzard B, Phillips R, Bower M. Treatment of HIV-associated invasive anal cancer with combined chemoradiation. *Eur J Cancer* 2000;36:754–8.
37. Place RJ, Gregorcyk SG, Huber PJ, Simmang CL. Outcome analysis of HIV-positive patients with anal squamous cell carcinoma. *Dis Colon Rectum* 2001;44:506–12.
38. Papillon J, Mayer M, Montbarbon JF, Gerard JP, Chassard JL, Bailly C. A new approach to the management of epidermoid carcinoma of the anal canal. *Cancer* 1983;51:1830–7.
39. Longo WE, Vernava AM, Wade TP, *et al.* Recurrent squamous cell carcinoma of the anal canal. Predictors of initial treatment failure and results of salvage therapy. *Ann Surg* 1994;220:40–9.
40. Herzog U, Boss M, Spichtin H. Endoanal ultrasonography in the follow-up of anal carcinoma. *Surg Endosc* 1998;8:1186–9.
41. Christensen AF, Nielsen MB, Svendsen LB, Engelholm SA. Three-dimensional anal endosonography may improve detection of recurrent anal cancer. *Dis Colon Rectum* 2006;49:1527–32.
42. Behrs OH, Wilson SM. Carcinoma of the anus. *Ann Surg* 1976;184:422–8.
43. Zelnick RS, Haas PA, Ajloun M, *et al.* Results of abdominoperineal resections for failure after combination chemotherapy and radiation therapy for anal canal cancers. *Dis Colon Rectum* 1992;35:574–8.
44. Darragh TM, Winkler B. The ABCs of anal-rectal cytology. College of American Pathologists. Available at: <http://www.cap.org/apps/cap.portal>. Accessed June 20, 2007.
45. Palefsky J, 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* 1998;17:314–9.
46. Ogunbiyi OA, Scholefield JH, Raftery AT, *et al.* Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. *Br J Surg* 1994;81:365–7.
47. Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *J Natl Cancer Inst* 2001;93:843–9.
48. 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* 2005;97:896–905.
49. Schiffman MH, Castle P. Epidemiologic studies of a necessary causal risk factor: human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst* 2003;95:E2.
50. Frisch M, Glimelius B, van den Brule AJ, *et al.* Sexually transmitted infection as a cause of anal cancer. *N Engl J Med* 1997;337:1350–8.
51. Chang GJ, Welton ML. Anal neoplasia. *Sem Colon Rectal Surg* 2003;14:111–8.
52. Palefsky J, Holly E, Ralston M, *et al.* Anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual and bisexual men: prevalence and risk factors. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:320–6.
53. Devaraj B, Cosman BC. Expectant management of anal squamous dysplasia in patients with HIV. *Dis Colon Rectum* 2006;49:36–40.
54. Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. *ANZ J Surg* 2006;76:715–7.
55. Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. *Br J Surg* 2005;92:1133–6.

56. Arain S, Walts AE, Thomas P, Bose S. The anal Pap smear: cytomorphology of squamous intraepithelial lesions. *CytoJournal* 2005;2:4.
57. Palefsky JM, Holly EA, Hogeboom CJ, Berry JM, Jay N, Darragh TM. Anal cytology as a screening tool for anal squamous intraepithelial lesions. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;14:415–22.
58. 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* 2005;81:142–6.
59. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA* 1999;281:1822–9.
60. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *Am J Med* 2000;108:634–41.
61. Arbesman H, Ransohoff DF. Is Bowens disease a predictor for the development of internal malignancy? A methodological critique of the literature. *JAMA* 1987;257:516–8.
62. Wieland U, Brockmeyer NH, Weissenborn SJ, *et al.* Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006;142:1438–44.
63. Wendling J, Saiag P, Berville-Levy S, Bourgault-Villada I, Clerici T, Moyal-Barracco M. Treatment of undifferentiated vulvar intraepithelial neoplasia with 5% imiquimod cream: a prospective study of 12 cases. *Arch Dermatol* 2004;140:1220–4.
64. Diakomanolis E, Haidopoulos D, Stefanidis K. Treatment of high-grade vaginal intraepithelial neoplasia with imiquimod cream. *N Engl J Med* 2002;347:374.
65. Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM Jr. Treatment of genital warts with an immune-response modifier (imiquimod). *J Am Acad Dermatol* 1998;38:230–9.
66. Moore RA, Edwards JE, Hopwood J, Hicks D. Imiquimod for the treatment of genital warts: a quantitative systematic review. *BMC Infect Dis* 2001;1:3.
67. Bargman H, Hochman J. Topical treatment of Bowens disease with 5-fluorouracil. *J Cutan Med Surg* 2003;7:101–5.
68. Cox NH, Eedy DJ, Morton CA. Guidelines for management of Bowens disease: 2006 update. *Br J Dermatol* 2007;156:11–21.
69. Gonzalez Sanchez JL, Flores Murrieta G, Chavez Brambila J, Deolarte Manzano JM, Andrade Manzano AF. Topical 5-fluorouracil for treatment of vaginal intraepithelial neoplasms. *Ginecol Obstet Mex* 2002;70:244–7.
70. Braathen LR, Szeimies RM, Basset-Seguin N, *et al.* Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. *J Am Acad Dermatol* 2007;56:125–43.
71. Hamdan KA, Tait IS, Nadeau V, Padgett M, Carey F, Steele RJ. Treatment of grade III anal intraepithelial neoplasia with photodynamic therapy: report of a case. *Dis Colon Rectum* 2003;46:1555–9.
72. Runfola MA, Weber TK, Rodriguez-Bigas MA, Dougherty TJ, Petrelli NJ. Photodynamic therapy for residual neoplasms of the perianal skin. *Dis Colon Rectum* 2000;43:499–502.
73. Webber J, Fromm D. Photodynamic therapy for carcinoma in situ of the anus. *Arch Surg* 2004;139:259–61.
74. Abbasakoob F, Boulos PB. Anal intraepithelial neoplasia. *Br J Surg* 2005;92:277–90.
75. Scholefield JH, Ogunbiyi OA, Smith JH, Rogers K, Sharp F. Treatment of anal intraepithelial neoplasia. *Br J Surg* 1994;81:1238–40.
76. Marchesa P, Fazio VW, Oliart S, Goldblum JR, Lavery IC. Perianal Bowens disease: a clinicopathologic study of 47 patients. *Dis Colon Rectum* 1997;40:1286–93.
77. Brown SR, Skinner P, Tidy J, Snith JH, Sharp F, Hoise KB. Outcome after surgical resection for high-grade anal intraepithelial neoplasia (Bowens disease). *Br J Surg* 1999;86:1063–6.
78. Pineda CE, Berry JM, Welton ML. High-resolution anoscopy and targeted treatment of high-grade squamous intraepithelial lesions. *Dis Colon Rectum* 2006;49:126.
79. Chang GJ, Berry JM, Jay N, Palefsky JM, Welton ML. Surgical treatment of high-grade anal squamous intraepithelial lesions: a prospective study. *Dis Colon Rectum* 2002;45:453–8.
80. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum* 2005;48:1042–54.
81. Jay N, Berry JM, Hogeboom CJ, Holly EA, Darragh TM, Palefsky JM. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. *Dis Colon Rectum* 1997;40:919–28.
82. Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *Clin Infect Dis* 2002;35:1127–34.