Epidermoid Carcinoma of the Anal Canal

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ABSTRACT

Anal cancers are rare tumors with only an expected 4000 new diagnoses in 2005. The majority of these are epidermoid or squamous cell cancers. Despite the rarity of this disease, great advances have been made in its understanding and treatment. The human papillomavirus (HPV), immunosuppression for solid organ transplantation, the human immunodeficiency virus (HIV), and sexual practices are changing the demographics of the disease from elderly women to young men who have sex with men and young women infected with HPV and HIV. The treatment of these malignancies was radically changed with Dr. Nigro's description in 1974 of the use of a nonoperative treatment strategy. Today, radiochemotherapy represents first-line therapy and the role of surgery has been largely relegated to that of salvage therapy for treatment failures of nonoperative management.

KEYWORDS: Epidermoid cancer, anal canal, squamous cancer

Objectives: Upon completion of this article, the reader should be able to summarize the management of epidermoid carcinomas of the anal canal.

Anal cancers are rare tumors. With an estimated 4000 new cases and 620 deaths in 2005, these tumors represent less than 2% of all digestive system cancers and less than 0.3% of all cancers (excluding basal and squamous cell skin cancers).¹ Despite the rarity of anal cancers, there has been striking progress in the understanding of their pathobiology and treatment over the last 30 years.² Epidermoid carcinomas of the anal canal and keratinizing squamous and nonkeratinizing squamous carcinomas (basaloid or cloacogenic and mucoepidermoid) are the most common of the anal neoplasms. Evaluation, treatment, and prognosis of these cancers are similar in spite of their histologic differences.³

ANATOMY OF THE ANAL CANAL

Definitions of the anal canal differ among surgeons and anatomists. The surgical anal canal extends from the anorectal ring to the anal verge.^{4,5} This region is lined by

several types of epithelium: columnar epithelium proximal to the dentate line, squamous epithelium distal to the dentate line, and a "cloacogenic" or anal transitional zone in between in which the epithelium might be columnar, cuboidal, transitional (as is found in the urinary bladder), or squamous. This middle zone is often referred to as cloacogenic because of its shared embryologic origin with the urinary bladder. Most authors have adopted the World Health Organization (WHO) classification of the Histologic Typing of Intestinal Tumors; in this system the area proximal to the anal verge is classified as the anal canal and the area distal to the anal verge as the anal margin (Fig. 1).⁴⁻⁶

HISTOLOGIC SUBTYPES

Most carcinomas of the anal canal are squamous cell carcinomas. Although traditionally the terms basaloid, cloacogenic, and mucoepidermoid were utilized and still

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Figure 1 Diagram of anal anatomy.

persist in some of the literature, the American Joint Committee on Cancer (AJCC) and WHO have abandoned their use because these tumors are now recognized as nonkeratinizing types of squamous cell carcinoma.⁴

Squamous Cell Carcinoma

Squamous cell carcinoma of the anal canal arises from the transitional cell epithelium. Most of these are of the nonkeratinizing type.⁷

Basaloid (Cloacogenic) Carcinoma

This represents a variant of the squamous cell type that histologically is similar to basal cell skin cancers. These carcinomas have been labeled “transitional cloacogenic carcinoma” because they appear to arise from the transitional zone.^{7,8}

Mucoepidermoid Carcinoma

In this variant there is a mixture of squamous cells, mucin-secreting cells, and cells of an intermediate type.⁷

CLINICAL PRESENTATION

Historically anal cancer was a disease of elderly women, but this is changing. It was estimated that in 2005, 56% of cases would occur in women.¹ Anal cancer is being seen with increasing frequency in young men who have sex with men and young women with multiple sexual partners.^{9–11}

Rectal bleeding is the most common initial symptom of squamous cell carcinoma of the anus, occurring in

45% of patients. This bleeding is often erroneously attributed to hemorrhoids. Thirty percent of patients have either pain or the sensation of a rectal mass, whereas 20% have no rectal symptoms whatsoever.² Other common presenting symptoms include pruritus ani, mucus seepage, or incidental finding after hemorrhoidectomy or excision of anal condyloma.

EPIDEMIOLOGIC ASSOCIATIONS FOR THE DEVELOPMENT OF ANAL CANCER

Human Papillomavirus

Human papillomaviruses (HPVs) are small DNA viruses with the ability to produce a variety of proliferative epithelial lesions at specific sites throughout the body.¹² HPV DNA has been found in high percentages of patients with anal cancer and anal intraepithelial neoplasia (AIN) but not in control patients with rectal adenocarcinomas.^{13–15} Of the 60 different HPV types, approximately one third infect the epithelium of the anogenital region.¹⁶ As with cervical cancer, HPV types 16 and 18 appear to be the subtypes most frequently associated with anal cancer and high-grade AIN.^{2,17} HPV types 6 and 11 are more often isolated in patients with warts and low-grade AIN^{17,18} (Table 1).

Sexual Activity

Among heterosexual men and women, a history of 10 or more sexual partners, the presence of anal or genital warts, and a history of sexually transmitted diseases are associated with an increased risk of anal cancer.¹⁵ In women, a history of receptive anal intercourse before age

30 is also associated with increased risk of anal cancer.¹⁵ When compared with men who have colon cancer, men with anal cancer are more likely to have engaged in receptive anal intercourse.^{19–21} Finally, women with a history of cervical, vulvar, or vaginal cancers have a higher incidence of anal cancer as these disease entities appear to occur through the same neoplastic pathways.

Human Immunodeficiency Virus

Although human immunodeficiency virus (HIV)-positive patients are more likely to be infected with HPV than HIV-negative patients regardless of sexual practices, it is unclear whether infection with HIV is an independent risk factor for the development of anal cancer.^{22,23} HIV-positive patients who have low-grade AIN are twice as likely as HIV-negative patients to progress to high-grade AIN within 2 years.²⁴ Several epidemiological studies have demonstrated an approximately 60-fold increase in the relative risk of anal cancer in HIV-positive patients compared with HIV-negative patients.^{25,26} The same studies showed 300- to 600-fold increase in the risk of Kaposi's sarcoma and greater than 100-fold increase in the risk of non-Hodgkin's lymphoma. Despite the results of these smaller studies, larger studies looking at more than 300,000 HIV-positive patients were able to identify correlates between the HIV infection and Kaposi's sarcoma and non-Hodgkin's lymphoma but not anal cancers.^{27–29} A report by Bower et al examined the effect of highly active antiretroviral therapy (HAART) on the incidence and survival of patients with HIV infection and anal cancer. Although they showed a markedly increased incidence of anal cancer in HIV-infected individuals (120-fold higher than in age- and gender-matched controls), they showed no differences in overall survival. Interestingly, the incidence of anal cancer was actually increased in the post-HAART era, probably a result of the greater longevity of HIV-infected individuals with their altered immune status.³⁰

Frisch and colleagues studied invasive and in situ anal cancers in 309,365 U.S. patients with HIV infection for a 10-year period. They found, as already mentioned, a markedly increased relative risk of anal malignancy in HIV-infected individuals (relative risk of AIN in men is 60.1 and relative risk of anal cancer in men is 37.9). Over time the relative risk of AIN increases although it does not for anal cancer, leading the authors to conclude that development of AIN may reflect the gradual loss of control over HPV-infected keratinocytes with advancing immunosuppression. Progression to invasive cancer does not seem to be related to immune status.³¹

Immunosuppression

Kidney transplant recipients have a 100-fold increase in the risk of anogenital cancers.³² Chronic immunosup-

Table 1 Risk Factors for Anal Cancer²

Strong Evidence

- Human papillomavirus infection
- History of receptive anal intercourse
- History of sexually transmitted disease
- More than 10 sexual partners
- History of cervical, vulvar, or vaginal cancer
- Immunosuppression after solid organ transplantation

Moderately Strong Evidence

- Human immunodeficiency virus infection
- Long-term use of corticosteroids
- Cigarette smoking

pression has been shown to be a risk factor for other types of squamous cell cancer as well as HPV infection.³³

Smoking

Smoking has been shown to be an independent risk factor for the development of anal cancers in several series, as it is for the development of cervical cancer.^{9,34,35}

Physical Trauma and Inflammation

Anal cancers were formerly thought to be related to chronic local inflammation and trauma.^{36,37} It has subsequently been demonstrated that anal cancers are not caused by benign diseases such as fissure, fistulas, or hemorrhoids even though the diagnosis of benign conditions and anal cancers may be temporally related.^{19,38} Similarly, inflammatory conditions such as Crohn's disease and ulcerative colitis are not associated with an increased incidence of anal cancer.³⁸

DIAGNOSIS

The diagnosis of anal cancers is often delayed because of confusion with or the coexistence of benign perianal disease. A complete anorectal examination including digital rectal examination with attention paid to the size, location, and mobility of the tumor, anoscopy, transrectal ultrasonography, and examination for the presence of inguinal adenopathy should be performed in patients suspected of having anal cancers (Fig. 2). Anesthesia may be necessary to obtain an adequate examination and biopsy of suspicious anal lesions. Palpable inguinal lymph nodes should be assessed by biopsy or fine needle aspiration. When the diagnosis has been made, the patient should be clinically staged with computed tomography of the chest, abdomen, and pelvis. Some surgeons employ a transanal ultrasound scan to evaluate depth of invasion (particularly involvement of the sphincter complex) and perirectal lymph nodes. The role of positron emission tomography for the detection

Figure 2 Epidermoid cancer of the anal canal.

of metastatic disease is unclear, but it is frequently obtained before therapy is started.

STAGING

The tumor, nodes, and metastasis (TNM) classification system is utilized for tumors of the anal canal (Table 2). Staging for anal cancer now most commonly relies on clinical observation, radiographic data, and endoscopic studies because treatment is now most frequently non-surgical.⁴ The classification system is based on historical data from studies performed when surgery was the treatment “gold standard.” Tumor size is the single most important prognostic factor for anal cancers.^{39–42} Interestingly, HPV status is not a prognostic factor in patients with anal cancers.¹⁸

Table 2 TNM Staging for Anal Cancers

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

*Primary tumor (T): TX, primary tumor cannot be assessed; T0, no evidence of primary tumor; Tis, carcinoma in situ; T1, tumor ≤ 2 cm in greatest diameter; T2, tumor 2 to 5 cm; T3, tumor > 5 cm; T4, tumor of any size invades adjacent organ(s) (e.g., vagina, urethra, bladder). Note: Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

†Regional lymph nodes (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, distant metastasis cannot be assessed; M0, no distant metastasis; M1, distant metastasis.

TREATMENT

Abdominoperineal Resection

Prior to Nigro's report in 1974 of the efficacy of combined radiation and chemotherapy, the standard of care for anal cancers was the abdominoperineal resection.^{43,44} The overall cure rate for resectable anal cancers with abdominoperineal resection alone is about 70%.³⁹ Today, surgical therapy for anal cancers has been relegated to salvage therapy in almost all cases. Survival following abdominoperineal resection as salvage therapy for failed medical management is greater than 50%.^{45–49}

Radiation Therapy

Radiation therapy alone is highly effective at obtaining local control with local eradication of tumor and cure in 70 to 90% of patients.^{2,50} The probability of cure is greatly reduced in patients with larger tumors and positive lymph nodes.^{50,51} Optimal tumor eradication is achieved in patients who receive at least 54 Gy of external beam radiation.⁵¹ These high doses are also associated with the greatest adverse effects such as stenosis and ulcers, which may lead to the need for colostomy in up to 12% of patients.⁵⁰

Combined Modality Therapy

The modern gold standard for the treatment of anal cancers is combination therapy similar to that described by Nigro et al in 1974. The Wayne State investigators preoperatively administered fluorouracil and mitomycin in combination with radiation (30 Gy).⁴³ Their initial success led to the policy of treating patients with combination therapy only, reserving surgery for those who had residual tumor identified on post-treatment biopsy.⁵² The utility of this regimen has been prospectively studied in three large trials. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR), which involved 585 patients, and the European Organization for Research and Treatment of Cancer (EORTC), which included 110 patients, compared pelvic radiation therapy alone (total dose of 45 Gy) with the same radiation treatment administered concomitantly with fluorouracil and mitomycin chemotherapy.^{53,54} These studies demonstrated reduction in local failures (18% and 46%, respectively), lower likelihood of recurrence, and a lower likelihood of eventual colostomy in the combination therapy arms. The groups treated with chemotherapy and radiation therapy did experience significantly increased event-free survival over the patients who received radiation therapy alone. However, there was no difference in overall survival. Because of these studies, combined modality treatment is now the standard of care.

The role of mitomycin in the Nigro protocol is unclear because it does not cause sensitization to

radiation, it is not a first-line therapy for other squamous cancers, and it is associated with significant toxicity. To evaluate its role in combination therapy regimens, a prospective trial was undertaken by the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group.⁵⁵ Three hundred and ten patients were randomly assigned to radiation with fluorouracil or radiation with fluorouracil and mitomycin. Patients in the mitomycin arm had fewer local recurrences (22% versus 9%, respectively) and improved 4-year disease-free survival. However, mitomycin did add significant toxicity to the regimen.

COMBINED THERAPY FOR PATIENTS INFECTED WITH HIV

Despite concerns about poor tolerance and greater radio-sensitivity in HIV-positive patients,⁵⁶ there is a growing consensus that chemoradiotherapy in conventional doses is well tolerated and can result in good local control.^{57–59} Although this may be true for patients whose disease is well controlled, patients with CD4-positive lymphocyte counts of less than 200/ μ L and patients who have had a previous acquired immunodeficiency syndrome (AIDS) defining disease do not seem to tolerate chemoradiotherapy as well and the outcome of treatment is worse.^{60,61} Therefore, a different treatment strategy may be required for patients whose HIV is poorly controlled. Strategies such as the one employed by Peddada and colleagues, which used lower doses of radiation, may still be effective therapies. In this small study with four patients whose CD4-positive tells were less than 200/ μ L, the patients received 30 Gy in 15 fractions with mitomycin and fluorouracil. Although all subsequently died of AIDS-related complications, they remained free from recurrence of their anal cancers.⁶²

SALVAGE THERAPY

Although combined modality therapy is highly successful, a subset of patients either do not respond fully or have recurrences. Ten to 15% of patients have persistent disease after definitive chemoradiation therapy, and 10 to 30% of patients develop recurrent disease. Although some have proposed the use of additional chemotherapy or radiation, abdominoperineal resection remains the most common salvage therapy for patients with persistent or recurrent disease. Akbari et al examined 57 patients who underwent salvage abdominoperineal resection after failed chemoradiation therapy. They showed an actuarial 5-year survival of 33% for patients undergoing surgical salvage with a 40% 5-year actuarial survival for patients undergoing "potential curative" resections. Median survival for all patients was 34.1 months. They identified multiple predictors of decreased survival and local recurrence, which included

disease persistence after combined modality therapy, nodal disease at salvage, tumor size greater than 5 cm, and adjacent organ involvement.⁶³ They also reported on five patients who underwent inguinal lymph node dissection. Three patients were alive and disease free at 21.3, 81.7, and 84.3 months. Therefore, they concluded that inguinal node dissection for documented disease may be warranted.

FOLLOW-UP

Follow-up for patients who respond to combined modality is every 3 to 6 months for 5 years with digital rectal examination, anoscopy, biopsy of any suspicious areas, inguinal palpation, and possibly CT scan. Most clinicians have a more heightened level of suspicion and rigorous follow-up regimen for their HIV-infected patients than for their patients with normal immune systems.

SUMMARY

Despite the rarity of squamous anal cancer, there have been extraordinary advances in the understanding of the biology of the disease as well as its treatment. Better understanding of the underlying causes of anal cancer may lead to better prevention of the disease. The greatest potential for this may be the use of HPV vaccination to prevent this viral infection and its subsequent marked increase in the risk of developing anal cancers.

DISCLAIMER

The authors of this article and their spouses have no financial interest in the topics discussed in this article.

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