Epidermoid Cancer of the Anal Canal

Shawn P. Webb, M.D.¹ and Chong S. Lee, M.D.¹

ABSTRACT

Anal canal cancer is a rare cancer with incidence that continues to rise. This has been in large part due to increased prevalence of immunosuppressed conditions such as organ transplantation and human immunodeficiency virus along with transmission of the human papillomavirus. Identification of high-risk groups and close monitoring of these groups can help to detect earlier stages of cancer. Chemoradiation therapy remains the mainstay of treatment with excellent outcomes. Surgery for anal canal carcinoma remains as a salvage technique for failed chemoradiation or recurrent disease.

KEYWORDS: Epidermoid carcinoma, squamous carcinoma, anal canal

Objectives: Upon completion of this article, the reader should be able to summarize the risk factors, workup, and treatment for epidermoid carcinoma of the anal canal.

INCIDENCE

Anal cancer represents only 1.5 to 2% of all gastrointestinal (GI) malignancies. That being so, the incidence has continued to rise in the United States from 0.6 per 100,000 with the increased spread of human immunodeficiency virus (HIV) to 0.8 in 100,000 and even further with the increased survival of HIV with highly active antiretroviral treatment (HAART) therapy to 1.0 in 100,000.^{1,2} There were an estimated 5260 new cases of anal cancer and 720 deaths in the United States in 2010.³ Epidermoid carcinomas have remained the most common anal cancer in the United States, averaging 80% of anal cancers.

ANATOMY

The anatomy of the anal canal is very important to delineate in regards to treatment therapy. The most important discussion in anatomy is that between the anal canal and the anal margin. The anal canal, which consists of 85% of anal cancers, cannot be visualized with

gentle traction on the buttocks. The surgical landmarks of the anal canal extend from the anorectal ring to the anal verge. This area contains the distal columnar mucosa of the rectum, an area of transition extending ~0 to 1.2 cm that contains both transitional cell epithelium and squamous epithelium without skin appendages distal to the dentate line. Epithelium above the dentate line is nonkeratinizing. Epithelium below the dentate line is keratinizing.⁴ The transformation zone that was proposed in the last edition of the American Society of Colon and Rectal Surgery (ASCRS) textbook,⁵ accounts for the 6 to 10 cm projection of squamous cells that can undergo metaplasia under the influence of HPV in the anorectum. This transformation zone includes the anal canal and the distal rectum. The second anatomic consideration is the anal margin, which has been extensively debated in the literature. The definition has ranged from “the area of hair-bearing epithelium to the mucocutaneous junction” to “the area between the dentate line and 5 cm outside of the anal verge.”⁶ Despite the debate about the anatomic

¹Division of Colon and Rectal Surgery, Henry Ford Hospital, Detroit, Michigan.

Address for correspondence and reprint requests: Chong S. Lee, M.D., Division of Colon and Rectal Surgery, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, MI 48202 (e-mail: clee1@hfhs.org).

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definitions, this area is treated similarly to other areas of skin with cancer, but undergoes the particular risks associated with this part of the body, particularly the close association with sexually transmitted diseases and the environmental location of the anus.

TERMINOLOGY

In the United States, the vast majority of anal canal carcinomas are squamous, either keratinizing or non-keratinizing. The nonkeratinizing squamous cancers cover the out of date terminology of basaloid, mucoepidermoid, and cloacogenic carcinomas. The terminology associated with carcinoma in situ, originally described in 1912 by Bowen, has carried many names. Anal intraepithelial neoplasm (AIN) was adapted from the cervical naming for the similar disease process including the association with HPV. The grading of AIN-1 (dysplasia in lower third of epithelium), AIN-2 (lower two thirds), and AIN-3 (full-thickness epithelium) for degree of dysplasia has shown too much interobserver variability. Some have proposed another grading system utilizing low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL; which covers AIN II, AIN III, carcinoma in situ, and high-grade dysplasia) (Fig. 1) and invasive cancer (Fig. 2). Although anal cancer arises from these high-grade precursor lesions, only 1% of intraepithelial lesions progress to squamous cancer each year.⁷

EPIDEMIOLOGY

The median age of diagnosis of anal canal cancer in the United States is 60 to 65 years old. This being so, almost 50% of these patients are between the ages of 45 and 65.⁸ There is a recent trend from older women to younger patients of both sexes as sexually transmitted diseases, such as HIV and HPV, have become more common.⁹ The majority of cancers of the anal canal are squamous, with adenocarcinoma and melanoma making up the rest.

Figure 1 High grade dysplasia.

Figure 2 Invasive squamous cancer.

Regional discrepancies exist. Although 80% of anal cancers in the United States are squamous, only 20% in Japan are squamous. The etiology of this difference has not been identified. Some specific risk factors for anal cancer that have been shown in the literature are female gender (1.5 to 4 times more likely),^{7,9} HPV infection, history of sexually transmitted diseases, number of sexual partners greater than 10, genital warts, cigarette smoking, anal receptive intercourse of either gender, and HIV infection.^{9,10}

Studies have shown that immunosuppression can play a significant role in the development of squamous carcinoma. The prevalence of HSIL in HIV-positive men is 40 to 50%,^{4,11} in HIV-negative men is 10 to 20%,¹² and solid organ transplant recipients is 5 to 10%.¹³ Several studies have demonstrated an increased incidence of anal cancer in HIV + patients from 2- to 120-fold. This increased incidence has not shown a disease-specific survival difference.^{2,14}

HPV is necessary to develop SILs.⁹ The association between HPV and cancer was first observed in patients with epidermodysplasia verruciformis, which can progress to SCC in sun-exposed areas. Since then several serotypes of HPV have been shown to have oncogenic potential (16,18,31,33,35,39,45,51,52,56,58, 59,68,73, and 82) in cervical and possibly anal cancer.¹⁵ The most well-established serotypes that produce HSIL are 16 and 18. By PCR analysis of 955 squamous cell cancers of the anal canal, >90% of AIN have HPV, >85% of squamous cell cancers of the anal canal have HPV, and 78.9% of these are HPV 16 and 18.¹⁶ HPV is sexually transmitted through both vaginal and anal intercourse. HPV can infect the anal region without having to have direct anal intercourse contact.

SCREENING AND DIAGNOSIS

In certain patients that are at higher risk, such as HIV-positive, the presence of genital warts, women with cervical dysplasia, solid organ transplant recipients, or

recipients of anoreceptive intercourse, it has been advocated to perform anal cytology by Pap smear. Any abnormal cytology should be followed by high-resolution anoscopy (HRA) (anal colposcopy) to identify early lesions for monitoring. The efficacy of screening utilizing HRA is variable and user dependant with an accuracy ranging from 67 to 97% in some studies.^{17,18} Palefsky followed 277 HIV + men who have had intercourse with men over 4 years. He found an incidence of 49% of HSIL. Because the HSIL progresses to invasive cancer in only 1% of these patients and this occurs very insidiously, the purpose of screening is to identify and eradicate early lesions.¹⁹ Although HSIL can be eradicated in immunocompetent patients, HIV + status has shown recidivism with 80% recurrence over a 2-year period and almost 100% over 4 years after eradication.²⁰

Patients with invasive carcinoma most commonly present with bleeding. The second most common symptom is pain. Patients with these complaints warrant further evaluation by direct visualization with bedside anoscopy and biopsy. If they cannot tolerate this, exam under anesthesia is warranted. A tissue sample should be obtained. Examination should also focus on location of tumor, fixation, and palpation for inguinal adenopathy. Once diagnosed, metastatic workup has traditionally been by computed tomography (CT) of the chest, abdomen, and pelvis. Extrapelvic metastatic disease has been found in 5% of people at the time of initial presentation.²¹ Studies focusing on fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT versus CT alone have shown improved detection of primary tumors (91% as opposed to 59%) and both pelvic and inguinal nodal involvement (20% not detected by CT alone).^{22,23} Magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis has shown similar efficacy as CT in diagnosis of metastatic workup. This could be utilized for those patients with contraindications to CT.

STAGING

The American Joint Committee on Cancer first proposed the TNM classification for anal carcinoma in 1989 (Table 1). The staging system has not changed since then. Bilimoria and colleagues evaluated the AJCC staging system for prediction of survival utilizing the National Cancer Database, which keeps data on ~70% of all cancers diagnosed in the country. Survival by stage was as follows: stage I = 70%, stage II = 59%, stage III = 40%, and stage IV = 19%.

Although tumor size has been shown to be the most important predictor of survival in the past, other predictors of survival include age (worse > 65), tumor size (T4 hazard ratio of 2.42), tumor grade, nodal involvement, metastasis, gender (male worse than female), race (Black worse than White and Hispanic, all worse than Asian) and socioeconomic status.²⁴

Table 1 TNM Staging System for Anal Cancer

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2 or T3	N0	M0
Stage IIIA	T1, T2, or T3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N2 or N3	M0
Stage IV	Any T	Any N	M1

Adapted from the American Joint Committee on Cancer (AJCC), 6th Ed. Available at: <http://cancerstaging.org/products/>. Accessed October 30, 2010.

Primary Tumors: Tis, carcinoma in situ; T1, tumor 2 cm or less; T2, tumor between 2–5 cm; T3, tumor >5 cm; T4, any size tumor that invades nearby organs (i.e., vagina, urethra, bladder).

Lymph Nodes: N0, no regional lymph node metastasis; N1, metastasis to perirectal lymph nodes; 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: M0, no distant metastasis; M1, distant metastasis.

TREATMENT

High-Grade Squamous Intraepithelial Lesion

In patients diagnosed with HSIL, surveillance and topical therapy are both appropriate therapies. As mentioned above, only 1% of HSIL progress to invasive cancer. These lesions can be treated with surveillance and biopsy. Some groups have advocated topical treatments such as imiquimod or topical 5-FU. A 61% HPV eradication and 77% resolution of AIN has been demonstrated in one study utilizing imiquimod.²⁵ A follow-up study to this revealed 26% recurrence of treated AIN in HIV + patients and 55% new areas not previously treated of AIN in these same patients.²⁶ Pain with application of topical imiquimod has limited its utilization. Topical 5-FU has been investigated to treat AIN. In one study of 46 HIV-positive patients, 39% of patients had clearance of AIN with 50% recurrence at 6 months of these patients. Side effects were significant enough to stop therapy in only 4%.²⁷

Invasive Carcinoma

Once the HSIL progress to invasive lesions, chemotherapy has become the mainstay of therapy, with surgery reserved for salvage treatment. In 1974, Nigro described chemoradiation therapy as definitive treatment for anal canal cancer. He demonstrated an 86% clinical response with an 80% disease-free survival rate.²⁸ Compared with surgical therapy, which had shown survival rates of 40 to 70%^{29–31} and the need for permanent ostomy, this revolutionized treatment. This survival benefit has been shown several times over since this first description.^{21,32–35} Although Nigro had proposed radiation, 5-FU and mitomycin C, several studies have been published to evaluate other options. The superiority of

chemotherapy with radiation therapy over radiation therapy alone for locoregional control was established by the United Kingdom Coordinating Committee on Cancer Research and the European Organization for Research and Treatment of Cancer.^{21,32} They showed a reduction of the local failure rate of 50 to 60% failure with radiation alone to a 32 to 39% failure rate with combined therapy along with a decreased chance for need for colostomy. Neither study showed a significant difference in survival between the groups. The toxicity of mitomycin-C has shown a difficulty in patient completion of therapy. The Radiation Therapy Oncology Group (RTOG) 87-04 and The Eastern Cooperative Oncology Group (ECOG) conducted a randomized trial comparing RT with 5-FU alone or with mitomycin-C. They found a reduction in the need for colostomy from 22% down to 9% demonstrating improved sphincter preservation along with a reduced disease-free survival rate (51% vs 73%).^{33,34} They did demonstrate a reduced hematologic toxicity with the omission of mitomycin (3% vs 18%).

Cisplatin as an alternative to mitomycin was demonstrated showing a 94% response rate in the late 1990s.^{36,37} More recent investigations have been performed evaluating cisplatin in place of mitomycin revealed no difference in survival or disease-free survival, but an increased rate of need for colostomy from 10% with mitomycin to 19% with cisplatin^{33,34} along with a reduced rate of grade 3 and 4 hematologic toxicity with cisplatin (12% vs 25%)³⁸ The ACT II trial also did not show any survival benefit of maintenance chemotherapy over induction chemotherapy.

Radiation

The optimal dose of radiation therapy for anal canal carcinoma has not been well established. Nigro originally utilized 30 Gy in his study. Escalating doses have been trialed and have shown improved locoregional control. Doses of 55 Gy have shown good local control and survival in T1 and T2 tumors.³⁹ Recently, research has shown that escalating doses of radiation up to 50 Gy (70% control at 5 years)⁴⁰ and even 60 Gy (90% locoregional control at 5 years)³⁹ can have improved survival in T3 and T4 tumors. Toxicity at levels of >65 Gy have shown necrosis of the anal canal.⁴¹ Inguinal lymph node basins should be included in the radiation field with additional boosts given for clinically positive nodes. Radiotherapy should be given over 6 weeks. Breaks in this therapy or prolongation of the therapy have shown worse rates of local control.⁴²

HIV PATIENTS

HIV + patients were excluded from the major randomized trials. This leads to the question as to how to treat this particular population. The studies that have focused on HIV + patients with anal squamous neoplasms have

been mostly small. The most striking finding reported in the literature on HIV + patients is the intolerance of toxicity leading to the need to delay or interrupt therapy.⁴³⁻⁴⁶ The reported hematologic toxicity ranged from 52 to 80%. This break in treatment did not correlate with a reduction in disease-specific survival. The overall patient survival correlated with CD4 count <200 cells/mL. Mortality was mainly due to infectious complications rather than the malignancy. One study was performed⁴⁷ that showed a correlation of low CD4 counts and toxicity intolerance. They advocated treatment with HAART therapy prior to treatment with chemoradiation therapy.

ELDERLY

Elderly patients often cannot tolerate full-dose chemoradiation therapy side effects. This should not preclude their treatment for this disease process. Charnley and colleagues performed a study on 16 patients age 77 to 91 with anal squamous cancer. They tolerated 30 Gy with short-course 5-FU therapy. No one experienced hematologic toxicity. All had some mild skin irritation, with only one patient having grade 3 skin toxicity. The disease-specific survival rate was 86% with overall survival of 69% over the 16-month follow-up.⁴⁸

COMPLICATIONS OF RADIATION THERAPY

Long-term complications of radiation therapy include fibrosis of the rectum and anal canal, skin dryness and irritation, vaginal shrinkage, and erectile dysfunction. Complications of radiation have significant implications on quality of life. The primary complications that carry the most impact to patients' quality of life are skin toxicity and poor sexual function.^{35,49} Younger patients showed worse impact on quality of life than elderly.

Salvage

Although the response rates to chemoradiation therapy have been 80%, failure to respond occurs in 10 to 15% of patients and recurrence occurs in 10 to 30%.³⁴ Salvage chemoradiation therapy has been shown to have 19⁵⁰ to 50%⁵¹ survival rates. Surgical abdominoperineal resection is the mainstay of salvage therapy with 5-year survival rates ranging from 30 to 60%.⁵²⁻⁵⁶ Surgery is also advocated in response to complications of radiation therapy, including stenosis and incontinence. Although surgery is an option after failed chemoradiation therapy or recurrent disease, the perineal wound complications have been reported from 66 to 80% of patients.⁵⁶⁻⁵⁹ These wound complications have only slightly improved with reconstruction with tissue flaps.^{60,61}

Metastatic Treatment Options

Metastasis is present in 5% of patients upon initial presentation and despite treatment with chemoradiation,

distant metastasis develop in 10 to 17% of patients.^{21,32} Given the rarity of the disease process, there is a paucity of literature to support a standard of therapy for treatment of metastatic anal squamous carcinoma. Chemotherapeutic treatment for extrapelvic metastasis should be addressed with cisplatin-based drugs and the patient should be enrolled in a clinical trial.⁶²

Follow-Up

Follow-up should begin 6 to 12 weeks after completion of treatment. Examinations should be done every 3 to 6 months with physical exam, and anoscopy with biopsy of any questionable lesions. Different surveillance methodologies have been utilized for surveillance. Endoanal ultrasound (EUS) has been advocated by some to objectively follow local recurrence,⁶³ whereas EUS has not shown any predictive benefit for recurrence in other studies.^{64,65} MRI has shown promise in small case reports to evaluate local response rates of anal squamous carcinoma response to therapy.⁶⁶ FDG-PET/CT has been shown to be more sensitive, 90 to 100%, than CT alone in detecting lymph node recurrence. This comes with a price of decreased specificity of 83% and a PPV of 43%.⁶⁷ Any positive findings of distant disease should be evaluated by tissue sampling.

CONCLUSION

Squamous cell carcinoma of the anal canal is still a rare malignancy. The treatment has remained primarily non-surgical with good tolerance of chemoradiation by the patient population. Earlier detection with close monitoring of high-risk patients offers an even greater chance of survival in a population in which the incidence is getting younger. Close follow-up after therapy is important for identification of early recurrence. The key to making an impact on disease occurrence may lie in prevention. Given the high association of HPV 16 and 18 with HSIL and progression to invasive carcinoma, perhaps vaccination and education prior to sexual activity of any kind would further reduce the incidence of this disease process.

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