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Key Words. Anal cancer • Chemotherapy • Radiation therapy • Surgery

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the epidemiology of and the risk factors for anal cancer.
2. Outline standard treatment for anal cancer and describe its complications.
3. Understand the issues related to treating HIV-positive patients with anal cancer.

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ABSTRACT

Anal cancer is a rare tumor with an incidence that has been rising over the last 25 years. The disease was once thought to develop as a result of chronic irritation, but it is now known that this is not the case. Multiple risk factors, including human papillomavirus (HPV) infection, anoreceptive intercourse, cigarette smoking, and immunosuppression, have been identified. HIV infection is also associated with anal cancer; there is a higher incidence in HIV-positive patients but the direct relationship between HIV and anal cancer has been difficult to separate from the prevalence of HPV in this population. HIV infection is also associated with anal cancer; there are increasing numbers of HIV-positive patients being diagnosed with the disease. Treatment of anal cancer prior to the 1970s involved abdominoperineal resection, but the standard of care is now concurrent chemoradiation therapy, with surgery reserved for those patients with residual disease. We present a case of anal cancer followed by a general discussion of both risk factors and treatment. *The Oncologist* 2007;12:524–534

Disclosure of potential conflicts of interest is found at the end of this article.

CASE PRESENTATION

A 63-year-old man with a past medical history significant for HIV managed with highly active antiretroviral therapy (HAART) (last CD4 count, 458) and anal squamous cell carcinoma in situ resected in 2000 presented for a routine colonoscopy in July 2006. The examination revealed a 12-mm nodule in the rectum, which was biopsied; pathology revealed invasive squamous cell carcinoma. Subsequent proctoscopy revealed a firm 2-cm mass located just beyond the dentate line. Transrectal ultrasound revealed evidence of invasion. Staging computed tomography (CT) scan revealed numerous low attenuation lesions in the liver concerning for metastasis but no evidence of abdominal or pelvic adenopathy. The patient was referred to gastrointestinal oncology to discuss treatment options.

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Anatomy and Histology

Any discussion of anal canal cancer would be incomplete without a review of the region's anatomy. The anal canal extends from the perianal skin (anal verge) to the rectal mucosa. An important landmark within the canal is the dentate, or pectinate, line, which represents the end of the squamous mucosa and the beginning of a zone of transition from squamous to nonsquamous (either transitional or rectal glandular) mucosa. Thus, tumors arising in the anal canal can be either keratinizing or nonkeratinizing depending on their location in relation to the dentate line. Importantly, both keratinizing and nonkeratinizing tumors appear to have similar biology and prognosis [1]. Adenocarcinomas, on the other hand, behave quite differently and should be treated like rectal cancers.

Lymphatic drainage of anal cancers depends on the location of the tumor in relation to the dentate line. Regional nodes are considered to be the inguinal, internal iliac, and perirectal (anorectal, perirectal, and lateral sacral) nodes. Tumors below the dentate line drain to the inguinal and femoral nodes while tumors above the dentate line drain to the perirectal and paravertebral nodes, a pattern similar to that seen with rectal cancers. Tumors in the most proximal portion of the canal drain to the nodes of the inferior mesenteric system. Patients presenting with anal cancer should undergo both physical and radiographic evaluation of inguinal nodes and any enlarged nodes should be biopsied to further guide therapy.

Radiographic evaluation most commonly includes abdominal and pelvic CT scans, but there has been recent interest in the use of 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) in this setting. Trautmann and Zuger presented a brief report evaluating the use of PET both during staging and after completion of therapy [2]. PET scan identified disease not documented by CT in 5 of 21 (24%) patients, resulting in a change of stage for two (10%) patients. PET scan performed 1 month after completion of therapy did not provide useful information, because there was residual activity noted in 12 of 18 (67%) patients and only three of these 12 (25%) have recurred. Cotter et al. [3] reported a study of 41 consecutive patients with anal carcinoma, including nine HIV-positive patients, who underwent both whole-body FDG-PET scan and abdominal and pelvic CT scan prior to therapy. PET scanning seemed to detect more inguinal disease, with abnormal nodes noted in 29% of all groins as compared with 16% for CT scan. Not surprisingly, HIV-positive patients had a higher incidence of PET-positive inguinal nodes (44% versus 16%). These reports suggest that FDG-PET scanning might offer better sensitivity in identification of nodal disease. This is important because identification of such disease would upstage a patient and influence treatment by introducing the need for a radiotherapy boost to the groins.

Clinical Presentation and Staging

Most patients with squamous cell carcinoma of the anal canal present with rectal bleeding. Diagnosis can be delayed because this bleeding is often ascribed to hemorrhoids. Other symptoms include rectal pain and/or mass sensation, occurring in approximately 30% of patients [4]. Twenty percent of patients have no symptoms at the time of diagnosis [1].

A tumor–node–metastasis (TNM) staging system for anal cancer has been developed by the American Joint Committee on Cancer and the International Union Against Cancer (Table 1). Because few tumors are surgically excised, the system is based on clinical factors with particular emphasis on tumor size, because this is known to be an important determinant of prognosis. Fifty to sixty percent of patients present with T1–T2 lesions, for which the 5-year survival rate is 80%–90%. A smaller proportion presents with T4 lesions, which have a 5-year survival rate $<$50%. The incidence of nodal metastasis is approximately 10% at diagnosis but can increase to as high as 20%–60% for T4 lesions [5].

Epidemiology and Risk Factors

Squamous cell carcinoma of the anus is rare and accounts for only 1.5% of cases of gastrointestinal tract cancer in the U.S. [1]. According to Surveillance Epidemiology and End Results (SEER) data, 4,660 men and women were estimated to have been diagnosed with anal cancer in 2006 and 660 individuals were estimated to have died of the disease [6]. The age-adjusted incidence rate is 1.5 per 100,000; SEER data from 1975–2003 suggest that this incidence is rising [6]. Of note, the incidence of anal cancer is much higher in men who practice anoreceptive intercourse and in those with HIV.

Historically, anal cancer was believed to develop as a result of chronic irritation resulting from benign conditions, including hemorrhoids and fissures, and there was also thought to be an association with inflammatory bowel disease [1]. Several studies over the last decade have found that this is not the case, but have identified other risk factors for anal cancer, including a history of persistent high-risk genotype human papillomavirus (HPV) infection, infection with multiple HPV genotypes, cervical dysplasia or cancer, HIV seropositivity, low CD4 count, cigarette smoking, anoreceptive intercourse, and immunosuppression following solid organ transplant [7].

Table 1. Tumor–node–metastasis (TNM) staging system for anal cancer

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 dimension		
T2	Tumor >2 cm but not ≥5 cm in greatest dimension		
T3	Tumor >5 in greatest dimension		
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder (involvement of the sphincter muscle[s] alone is not classified as T4)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
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		
Stage grouping			
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

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HPV

HPV is a common viral sexually transmitted disease that is rapidly cleared, leaving only 1% of patients to actually develop genital warts [7]. Several population-based epidemiologic studies have evaluated the association between HPV infection and anal cancer. Frisch and colleagues studied 386 anal cancers and detected HPV in 90% of invasive cancers in women and in 63% of invasive cancers in men [8]. In a similar study, Daling and colleagues tested 262 anal cancers. HPV DNA was detected in 87.9% of tumors, though the proportion of tumors positive for HPV was no different between women and men [9].

There are over 80 different HPV subtypes, at least 23 of which have been shown to infect the anogenital mucosa. Each subtype has a different potential for inducing malignant change. Low-risk HPV subtypes are most often identified in lesions with only low-grade dysplasia, whereas those subtypes considered high risk (including 16, 18, 31,

33, 35, 39, 45, 50, 51, 53, 56, 58, 59, and 68) are more often identified in lesions with high-grade dysplasia or invasive carcinoma [10]. HPV subtype 16 appears to be most frequently associated with anal cancer, detected in approximately 70% of cases in population-based studies [9, 11].

Similar to the development of cervical dysplasia and neoplasia, HPV infection is associated with the development of premalignant anal squamous intraepithelial lesions (SILs), which can be low grade (LSIL) or high grade (HSIL). Progression of anal SIL to invasive anal cancer is influenced by HIV seropositivity, low CD4 count, infection with multiple HPV serotypes, serotype of HPV infection, and high levels of DNA of high-risk serotypes.

Immunosuppression

Patients receiving chronic immunosuppressive therapy after solid organ transplant are at a higher risk for squamous cell carcinomas of many sites, including the anal canal. This risk is likely a result of persistent HPV infection [1]. The risk is not insignificant, with at least one study demonstrating a 100-fold higher risk for anal cancer following renal transplantation [12]. The association between immunosuppression and anal cancer has been investigated by Daling and colleagues [9]. The authors noted that the use of corticosteroids was associated with a higher risk for anal cancer (odds ratio [OR], 3.2; 95% confidence interval [CI], 1.4–7.2), particularly in men who were not exclusively heterosexual (OR, 5.6).

Smoking

Several studies have identified cigarette smoking as a risk factor for the development of anal cancer. A population-based case–control study using colon cancer patients as controls noted the relative risk for anal cancer among currently smoking women to be 7.7 (95% CI, 3.5–17.2) and among currently smoking men to be 9.4 (95% CI, 2.3–38.5) [13]. A later study estimated the OR for anal cancer among smokers versus nonsmokers to be 3.0 (95% CI, 1.9–5.0) for women and 5.0 (95% CI, 1.6–16.1) for men [14]. That study also demonstrated that the risk decreased after smoking cessation. A more recent study produced supporting data noting a relationship between smoking and anal cancer among both women (adjusted OR, 3.8; 95% CI, 2.3–6.2) and men (adjusted OR, 3.9; 95% CI, 1.9–8.0). This risk did not vary with age [9].

Sexual Practices

Several epidemiologic studies have linked sexual practices and the risk for anal cancer. An early population-based case–control study conducted by Daling and colleagues reported that men with anal cancer were more likely to never have married, to not have been exclusively heterosexual, and to have practiced anal intercourse [13]. Anal intercourse was also reported more commonly in women with anal cancer (16.9% versus 11.0%). Additionally, women with anal cancer were more likely to be seropositive for *Chlamydia trachomatis* and herpes simplex virus 2. A subsequent study, again by Daling and colleagues, produced similar results [9]. The risk for anal cancer was higher in men who were not exclusively heterosexual (OR, 17.3; 95% CI, 8.2–36.1) and in men who had >15 lifetime sexual partners (heterosexual men: OR, 3.9 versus homosexual men: OR, 6.6). Men who were not exclusively heterosexual and practiced anoreceptive intercourse also had a higher risk (OR, 6.8; 95% CI, 1.4–33.8). Finally, a history of genital warts was strongly related to the risk for anal cancer (OR, 7.4; 95% CI, 3.2–17.1).

HIV

The association between anal cancer and sexual practices, including anoreceptive intercourse and men who have sex with men, is clear, but the association between anal cancer and HIV infection has been difficult to fully separate from confounders. This is likely a result of the fact that HIV-positive patients are more likely to be infected with HPV, often with more than one subtype [15]. Additionally, HIV patients are more likely to have HPV-associated squamous intraepithelial lesions (SILs), particularly those considered high grade [15–17]. Development of these HSILs appears to be inversely related to CD4 count [16–18]. Interestingly, despite the high-prevalence of HSIL in HIV-positive patients, there has not been a dramatic increase in the incidence of invasive cancers. It has been postulated that this may be related to the fact that these individuals may die of other diseases before there is sufficient time for progression [15]. This may change in the era of highly active antiretroviral therapy (HAART).

Numerous population-based studies have attempted to further evaluate the relationship between HIV and anal cancer. These data are difficult to interpret because of the fact that the studies were done at different times, notably before and after the introduction of HAART. Frisch and colleagues addressed this question in a study aimed at clarifying the role of HIV infection in the development of HPV-related malignancies [19]. They observed a higher risk for anal cancer in both men and women with AIDS (relative risk [RR], 6.8; 95% CI, 2.7–14.0 and RR, 37.9; 95% CI, 33.0–43.4, respectively). Interestingly, they failed to find a higher risk among patients with CD4 counts $<200/mm^3$ when compared with those with CD4 counts $>200/mm^3$. The authors concluded that while HPV-related malignancies are present in excess, this may not be related to HIV-

related immunosuppression but rather to unknown cofactors.

Additionally, if HIV was directly associated with anal cancer, one would expect the incidence to decrease in the era after the introduction of HAART. This has been observed for other HIV-related malignancies, including non-Hodgkin's lymphoma and Kaposi's sarcoma, but not for anal cancer. A population-based study demonstrated that the incidence of anal cancer increased when comparing pre-HIV years (incidence, 0.6 per 100,000) with both HIV years (incidence, 0.8 per 100,000) and years after introduction of HAART (incidence, 1.0 per 100,000) [20]. It has been suggested that this lack of decline is a result of the fact that HIV-positive individuals are now living longer and so have a greater period of exposure to HPV, leaving more time for transformation and eventual development of squamous cell carcinoma. In this case, the cancer is not associated with the HIV but rather the persistent HPV infection [15]. Further studies are required if there is interest in establishing the true nature of the relationship between HIV infection and anal carcinoma.

Screening

Given the known high-risk groups for anal cancer, several studies have addressed screening in these populations. Similar to the cervical Papanicolaou (Pap) smear, anal swabs for cytology are a possible screening method for anal SIL and anal cancer. Sensitivity of anal cytology is in the range of 50%–80%, with sensitivity being higher in the HIV-positive population. Studies of the potential cost-effectiveness of screening have found that screening HIV-positive and HIV-negative homosexual and bisexual men every 2–3 years would be cost-effective and have life-expectancy benefits [21, 22]. Other groups in which there is a potential role for screening include all HIV-positive individuals, women with a history of cervical dysplasia or cancer, and transplant recipients.

Treatment

Surgery

Prior to the mid-1980s, the treatment of choice for anal cancer was abdominoperineal resection (APR), a procedure involving removal of the anus and rectum as well as their draining lymph nodes and resulting in a permanent colostomy. The 5-year survival rate after APR for anal carcinoma is in the range of 40%–70%, with worse outcomes for those with larger tumors and nodal metastases [1]. APR is now reserved as salvage therapy for those individuals with persistent disease after combined chemoradiation.

Combination Chemoradiation

The use of chemotherapy in combination with radiotherapy was first evaluated in the early 1970s by a group at Wayne State University. Working on the observation that the use of fluoropyrimidine-based chemotherapy potentiates radiation, Nigro and colleagues administered preoperative 5-fluorouracil (5-FU) (1,000 mg/m^2 continuously on days 1–4 and 29–32) and mitomycin (10–15 mg/m^2 on day 1) in combination with moderate-dose (30 Gy) external beam radiation therapy (EBRT) [23]. The first three patients treated with this regimen had no evidence of residual disease at the time of surgery, raising the question of whether combined chemoradiation therapy obviated the need for APR. This approach was further evaluated in three phase III randomized controlled trials [24–26].

The first of these studies, published in the mid-1990s, compared combined chemoradiation therapy with radiation therapy alone [26]. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) reported results of a trial led by its Anal Cancer Trial Working Party. Five hundred eighty-five patients were randomized to either radiation to 45 Gy over 4–5 weeks or the same radiation dose in combination with 5-FU (1,000 mg/m^2 per day over 4 days or 750 mg/m^2 per day over 5 days) during the first and last weeks of radiation and mitomycin (12 mg/m^2 on day 1 only). The primary endpoint was local failure, as indicated by the need for major surgical intervention, and a secondary endpoint was the 5-year survival rate. The addition of chemotherapy did not increase the number of treatment breaks nor did it increase the time interval between initial radiation therapy and boost. Local failure at 3 years was significantly lower in the chemoradiation arm (39%) than in the radiation alone arm (61%). There was not, however, a statistically significant difference in overall survival at 3 years (radiation alone, 58%; chemoradiation, 65%).

The second randomized phase III trial comparing combined chemoradiation therapy with radiation therapy alone was conducted by the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy and Gastrointestinal Cooperative Groups [25]. That study was also aimed at evaluating the possible late side effects occurring as a result of adding chemotherapy. One hundred ten patients were randomized to radiation therapy (45 Gy over 5 weeks in 1.8-Gy fractions) followed by a boost of 15 Gy (for those patients with complete remission [CR]) or 20 Gy (for those patients with partial remission [PR]) 6 weeks after initial therapy or radiation plus chemotherapy (5-FU, 750 mg/m^2 per day on days 1–5 and 29–33, plus mitomycin, 15 mg/m^2 on day 1 only). The CR rate was higher (80% versus 54%) with the addition of chemotherapy. This difference remained during follow-up, such that the 5-year es-

timates of locoregional control (via the Kaplan-Meier method) showed an 18% advantage for the combined group. Additionally, the colostomy-free survival rate in the combined group was 32% higher at 5 years. When looking at adverse effects, the authors found no difference in acute toxicity, including both skin reaction and diarrhea. Additionally, event-free survival (an endpoint that included the first sign of local tumor progression, colostomy, severe late complications, and death) was better for the chemoradiation group. The authors concluded that combined chemoradiation therapy for anal carcinoma improved locoregional control and reduced the need for colostomy without increasing late complications.

Given the concern over adverse events related to chemotherapy, there was interest in evaluating a combination regimen without mitomycin, because this drug was felt to add significant toxicity. An Intergroup trial was designed to answer this question [24]. Three hundred ten patients were randomized to radiation therapy (45 Gy in 1.8-Gy fractions over 5 weeks) with 5-FU (1,000 mg/m^2 per day on days 1–4 and 28–31) or the identical schedule with the addition of bolus mitomycin (10 mg/m^2 on days 1 and 28, with a maximum of 20 mg per cycle). All participants underwent full-thickness biopsy at 4–6 weeks post-treatment and those with residual disease went on to receive salvage therapy with radiation and chemotherapy. The addition of mitomycin resulted in a nonsignificantly higher CR rate (92.2% versus 86%). Mitomycin also resulted in a significantly higher colostomy-free survival rate at 4 years (71% versus 59%). On subgroup analysis, the impact on the colostomy rate was significant in T3 or T4 tumors but not in T1 or T2 tumors. The disease-free survival (DFS) rate at 4 years was also higher (73% in the mitomycin arm versus 51% in the 5-FU alone arm). These benefits did not come without greater toxicity, as there was more neutropenia and infection in the mitomycin arm. One patient (0.7%) in the 5-FU arm died, compared with four patients (2.7%) in the mitomycin arm. The authors concluded that mitomycin was an important part of combined chemoradiation for anal carcinoma and the regimen has remained the standard of care.

Investigators have continued to evaluate other chemotherapy agents to determine if outcomes for the treatment of anal carcinoma can be further improved. Cisplatin is one such agent that was not available when investigators first began evaluating the combination of chemotherapy and radiation. However, because it has been shown to have activity in numerous other squamous cell cancers, its use in anal carcinoma is being evaluated. The Cancer and Leukemia Group B (CALGB) evaluated the regimen of induction chemotherapy with 5-FU (1,000 mg/m^2 continuous infusion days 1–4 and 29–32) and cisplatin (100 mg/m^2 on days 1 and 29) followed by chemoradiation with 5-FU and mitomycin for patients with locally advanced anal cancer [27]. An initial report of 45 patients treated with this regimen showed a 50% 48-month colostomy- and disease-free survival rate. Because of these impressive data in poorer prognosis patients, the Radiation Therapy Oncology Group (RTOG) 98–11 trial evaluated the use of a cisplatin-based regimen in patients with anal cancer. That trial randomized 682 patients to 5-FU (1,000 mg/m^2 per day on days 1–4 and 29–32) and bolus mitomycin (10 mg/m^2 on days 1 and 29) plus radiation (45–59 Gy) or 5-FU (1,000 mg/m^2 per day on days 1–4, 29–32, 57–60, and 85–88) and cisplatin (75 mg/m^2 on days 1, 29, 57, and 85) plus radiation (45–59 Gy beginning on day 57) [28]. Randomization was stratified on gender, nodal status (positive or negative) and tumor size (2–5 cm or >5 cm). The primary endpoint was DFS and secondary endpoints included overall survival (OS), colostomy-free survival (at 2 years), and rate of locoregional failure. Based on 634 analyzable patients, the hazard ratio (HR) for DFS was 1.15 (95% CI, 0.87–1.50; $p = .33$), indicating no difference between treatment arms. OS was no different and the colostomy rate was higher in the cisplatin-treated patients (HR, 1.6; 95% CI, 1.008–2.63; $p = .04$). Results of this study indicate that cisplatin is not superior to mitomycin and, because the patients in the cisplatin arm had additional chemotherapy with cisplatin and 5-FU, compared with the patients treated in the mitomycin arm, the results suggest that cisplatin may even be inferior to mitomycin. Another study evaluating cisplatin versus mitomycin is the second United Kingdom phase III anal cancer trial of chemoradiation and maintenance therapy (ACT II). Initial toxicity results have been presented but final results are still pending [29]. Therefore, chemoradiation therapy using both 5-FU and mitomycin remains the standard of care for treatment of anal carcinoma. A comparison of the results of the first three phase III randomized controlled trials [24–26] and RTOG 98–11 [28] appears in Table 2.

Treatment Complications

Chemoradiation therapy for anal carcinoma can have both acute and chronic effects. Acute effects include diarrhea, mucositis, skin erythema and desquamation, and myelosuppression. Late complications, some of which necessitate surgery with or without colostomy, include anal ulcers, stricture/stenosis, fistulae, and necrosis. Reported late event rates following chemoradiation therapy for anal cancer are in the range of 3%–16% [12]. The risk for these complications increases as a function of both total radiation dose and fraction size, with complications more frequent when fractions >2.5 Gy are used [30]. As mentioned above, the UKCCCR trial failed to demonstrate a higher in-

Table 2. Results of radiation therapy alone and of combined modality therapy with several different chemotherapy regimens

Study	Years	*n*	Results	XRT alone	CMT (5-FU)	CMT (5-FU/MMC)	CMT (5-FU/Cis)
1987–1999							
Flam et al. [24][F]	1988–1991	291	4-yr DFS		51	73	
			4-yr OS		NA[a]	NA[a]	
			Colostomy rate		23	9	
UKCCCR [26]	1987–1994	585	3-yr DFS	NR		NR	
			3-yr OS	58		65	
			Colostomy rate	39		23	
EORTC [25]	1987–1994	110	3-yr DFS	NA[b]		NA[b]	
			3-yr OS	65		72	
			Colostomy rate	NA[c]		NA[c]	
			2000 to present				
RTOG 98–11 [28]	2006	682	5-yr DFS			56	48
			5-yr OS			69	69
			Colostomy rate			10	20

[a] No statistically significant difference in OS.
[b] Significantly better event-free survival in patients treated with CMT.
[c] CMT improved colostomy rate by 32% at 5 years.
Abbreviations: 5-FU, 5-fluorouracil; Cis, cisplatin; CMT, combined modality therapy; DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; MMC, mitomycin C; NA, not applicable; NR, not reported; OS, overall survival; RTOG, Radiation Therapy Oncology Group; UKCCCR, United Kingdom Coordinating Committee on Cancer Research; XRT, radiotherapy.

cidence of late effects with the use of combined chemoradiation compared with radiation alone.

There is one study in the literature that specifically evaluates quality of life (QOL) after radiation alone or combined chemoradiation [31]. Allal and colleagues evaluated QOL in 41 patients (35 female and 6 male) who were alive at least 3 years after completing therapy for anal cancer. The study has several limitations because it was cross-sectional and compared results on QOL questionnaires with a population-based control group. Nonetheless, the study showed that patients treated with radiation with or without chemotherapy rated their QOL similar to that of the general population, with the exception of noting more frequent diarrhea. Interestingly, while 50% of patients reported suboptimal anal function, 71% reported that they were satisfied with their current function and only 7% would have considered APR as a potential alternative.

Treatment of HIV-Positive Patients

As discussed above, the incidence of squamous cell carcinoma of the anus is greater in patients with HIV. This presents specific challenges in the area of therapy because of a concern as to whether this population can tolerate standard combined modality therapy [32]. There is a suggestion in the literature that HIV-positive patients receive less treatment than HIV-negative patients [33–36]. Several investigators have attempted to further evaluate this issue. Unfortunately, all reports are retrospective. Toxicities and outcomes noted in selected studies appear in Table 3.

Bottomley and colleagues presented data on six HIV-positive patients, four with symptomatic infection and two with asymptomatic infection; five of six patients had CD4 counts $<200/mm^3$ [37]. One patient received radiation therapy alone because he/she refused chemotherapy and the remaining five patients received chemotherapy (5-FU, 1,000 mg/m^2 per day $\times$ 4, and mitomycin, 10 mg/m^2 on day 1 only) plus radiation (dose range, 40–50 Gy). Four patients had CRs (though one eventually relapsed), one patient failed to respond, and one died of AIDS encephalopathy before evaluation for response. The major acute toxicity was mucositis and perineal skin reaction that resulted in treatment delays for four of six patients. Cleator and colleagues reported on 12 patients treated for anal cancer between 1989 and 1999 [38]. All patients received radiation (38–51 Gy) followed by a boost in responders. Chemotherapy consisted of 5-FU (1,000 mg/m^2 per day on days 1–4 or 750 mg/m^2 per day on days 1–5 and 29–33) plus mitomycin (10 mg/m^2 on day 1 only). After a median follow-up of 4.8 years, there were nine CRs, one PR salvaged with APR, and one patient with progressive disease. The 5-year survival

Table 3. Selected retrospective studies evaluating outcomes in patients with HIV/AIDS[a]

Study	*n*		Treatment		Complications	Survival
	HIV	AIDS	XRT only	CMT		
Bottomley et al. [37]	5	1	1	5	Mucositis; skin reaction; treatment break (67%)	Three alive and NED at 7, 43, and 63 months; 1 alive with persistent disease; 1 died at 5 months; one NE
Cleator et al. [38]	5	7		12	Hematologic (50%); dermatologic (92%); diarrhea (83%); no difference in toxicity between CD4 count $<200/mm^3$ and CD4 count $\geq 200/mm^3$	Actuarial 5-yr survival rate, 60% (95% CI, 29%–91%); no significant difference between overall survival and antiretroviral use or CD4 count at diagnosis
Peddada et al. [34]	4	4		8	Moist desquamation (50%); treatment break (62%)	Four alive and NED; 4 died of AIDS (but without evidence of anal cancer)
Holland et al. [39]	3	4		7	Treatment break (100%); hospitalization (43%)	Actuarial 2-yr survival rate, 29%; 4 with AIDS died (mean time to death, 8 months); 3 with HIV alive and NED (mean follow-up, 16.3 months)
Chadha et al. [40]	6	3	2	7	Treatment break >14 days (56%); chemotherapy dose reductions (87%)	Four alive and NED; 4 died of AIDS (but with no evidence of anal cancer)

[a] AIDS is defined either by CD4 count $\leq 200/mm^3$ or AIDS-defining illness.
Abbreviations: CI, confidence interval; CMT, combined modality therapy; NE, not evaluable; NED, no evidence of disease; XRT, radiotherapy.

was 60%, with one patient alive 10 years after therapy. The most common toxicities included grade 1–3 hematologic toxicity (50%), grade 1–3 dermatologic toxicity (92%), and grade 1–5 diarrhea (83%). This toxicity profile is similar to that reported in other series [39, 40]. These statistics were felt to be comparable with toxicities reported in HIV-negative patients in the UKCCCR trial and in the Intergroup trial in which patients received two doses of mitomycin, and were therefore considered acceptable [24, 26].

Given the impact of chemoradiation therapy on the immune system, investigators have wondered if the greater toxicity observed in these patients is related to the impact that HIV infection has on the immune system. Several series have attempted to address this question by evaluating outcomes in the context of CD4 count (Table 4) [32, 41]. Hoffman and colleagues reported on a series of 18 consecutive HIV-positive patients treated at University of California at San Francisco between 1991 and 1997 [32]. Seventeen of these patients were treated with curative intent and were included in the analysis; 16 received combined chemoradiation therapy and one received radiation therapy alone. Patients were analyzed in two groups; group 1 ($n = 8$) included those patients with CD4 counts $<200/mm^3$ and group 2 ($n = 9$) included those patients with CD4 counts $\geq 200/mm^3$. In group 1, seven patients received chemotherapy (either 5-FU alone, $n = 2$; one cycle of 5-FU plus cisplatin, $n = 2$; two cycles of 5-FU with mitomycin on day 1 only, $n = 2$; or 5-FU via protracted venous infusion throughout radiation with mitomycin on day 1, $n = 1$). In group 2, eight of nine patients received two cycles of 5-FU (five with mitomycin on day 1 only and three with mitomycin on days 1 and 29) and the remaining patients received one cycle of 5-FU with mitomycin. Seven of eight patients in group 1 experienced severe toxicity necessitating treatment breaks from 1–4 weeks and four of eight patients required admission. Four of eight patients required colostomy, two for salvage and two for toxicity. In group 2, the disease was controlled in all patients. No patient required admission or colostomy and all nine had intact anal sphincter function. The median time of disease control in group 1 was 13.5 months (range, 6–44 months) and in group 2 it was 24 months (range, 12–74 months). The authors concluded that a pretreatment CD4 count $<200/mm^3$ increased the likelihood of toxicity and that these patients should be treated with caution while patients with CD4 counts $\geq 200/mm^3$ can be expected to tolerate combined modality therapy.

A second series by Place and colleagues reported simi-

Table 4. Selected retrospective studies evaluating the effect of CD4 count on tolerance of therapy

Study	CD4	*n*	Treatment: C alone	Treatment: CMT	Treatment: XRT alone	Complications	Interruptions
Hoffman et al. [32]	<200	8		7	1	Moist desquamation (5); diarrhea (3); ANC <500 (2); thrombocytopenia (1); none (1)	Treatment break (5); stopped early (2); none (1)
	≥200	9		9		Moist desquamation (5); ANC <500 (2); none (3)	Treatment break (4); none (4)
Place et al. [41]	<200	7		5	2	Colitis (1); neutropenic fever (3); urethral stricture (1); none (3)	60% of patients treated prior to 1998 had severe effects requiring treatment breaks; 25% of patients treated after 1998 (since addition of HAART) have required treatment breaks
	≥200	5	1	4		Colitis (1); bone marrow suppression (1); none (3)	
	Unknown	2		2		Hemorrhagic cystitis (1); none (1)	

Abbreviations: ANC, absolute neutrophil count; C, chemotherapy; CMT, combined modality therapy; HAART, highly active antiretroviral therapy; XRT, radiation therapy.

lar findings [41]. Those authors reported on 14 HIV-positive patients treated for squamous cell carcinoma of the anus between 1980 and 1999. Eleven patients received 5-FU plus cisplatin, one received 5-FU plus mitomycin, one patient was offered wide local excision, and one declined therapy. Because of an interest in the impact of HAART on the ability to tolerate treatment, the patients were divided into those treated prior to HAART (designated as prior to 1998) and those treated after the introduction of HAART (designated as 1998). Six of 10 patients treated prior to 1998 suffered significant toxicity while only one of four patients treated after this date required a treatment break. Patients in the pre-HAART era did poorly with 1- and 5-year mortality rates of 40% and 80%, respectively. Those patients treated after the advent of HAART seemed to have better outcomes [32]. While the numbers are small, the authors postulated that the superior outcomes in those patients receiving HAART may be a result of the effects of this therapy on immune function. There are no prospective data available to support the initiation and continued monitoring of HAART during treatment and this question requires further study.

The data regarding the treatment of HIV-positive patients with anal carcinoma with combined modality therapy introduce many interesting questions. There does seem to be greater toxicity when these patients are treated with standard combination chemoradiation therapy. However, removing the chemotherapy is likely not the answer, given that we have randomized data in HIV-negative patients supporting the role of chemotherapy. There are several factors, including CD4 count, use of and compliance with HAART, and performance status, that should be taken into consideration when developing a treatment plan, and decisions should be made on a case-by-case basis. Individuals not on HAART at diagnosis should be referred to an infectious disease provider for consideration of this therapy. If such treatment is deemed appropriate, treatment can be delayed until after initiation of HAART. These individuals should be made aware of the risks associated with treatment and potential modifications to decrease these risks, including eliminating the second cycle of mitomycin, using 5-FU alone, or using radiation alone. Any such discussions should be sure to include notification that these modifications may decrease the chance of a CR.

Persistent or Recurrent Disease

Effects of chemoradiation on anal carcinoma can be present weeks after completion of treatment. Response is best assessed at least 6–8 weeks after completion. There is currently no consensus as to whether response should be assessed by physical examination alone or in combination with biopsy. It is also not clear whether biopsy should play a role in the management of those individuals with a complete clinical response.

There are few data available about predictors of local failure, but one retrospective study was identified [42]. Renehan and colleagues evaluated outcomes of 254 patients with anal cancer treated with either radiotherapy alone ($n = 127$) or combined chemoradiation ($n = 127$) between 1988 and 2000 at a hospital in the United Kingdom. Local failure occurred in 99 (39%) patients and the median time to failure was 20.4 months. Five-year local disease failure rates were significantly different between those patients receiving radiation alone (52.5%) and those patients

receiving combined chemoradiation (35.3%). For patients receiving radiation alone, age, total radiation dose <50 Gy and higher T stage predicted local failure. Conversely, for patients receiving combined chemoradiation, no factor was predictive.

Salvage APR

The preferred treatment for persistent disease following combined modality therapy is APR. This surgery is radical and associated complications appear to be greater in patients undergoing the procedure after combined modality therapy [12]. Nilsson and colleagues retrospectively evaluated the outcomes of 35 Swedish patients (21 with persistent disease and 14 with recurrent disease) undergoing salvage APR following locoregional failure after combined modality therapy for anal carcinoma [43] Thirteen patients developed perineal wound infection necessitating reoperation, and delayed wound healing (defined as healing time >3 months) occurred in 23 patients. Fifteen patients, 12 of whom underwent salvage APR for persistent disease, experienced secondary failure. The median survival duration after secondary failure was 19 (range, 1–78) months. In the UKCCCR trial, there were 29 patients who underwent salvage APR; 40% eventually relapsed [26].

Salvage Chemoradiation Therapy

Salvage chemoradiation therapy for persistent disease has also been evaluated [24]. In the Intergroup study evaluating the role of mitomycin, those patients with persistent disease received salvage 5-FU, cisplatin, and 9 Gy EBRT. Of 29 patients treated in this manner, 10 continued to have persistent disease. Nine of these patients went on to salvage APR and six eventually recurred.

Metastatic Disease

Metastatic disease develops in 10%–17% of patients treated with chemoradiation therapy [25, 26]. The most common site of distant metastasis is the liver. There are limited published data on the use of chemotherapy, particularly newer agents, to treat metastatic anal carcinoma. Active agents include cisplatin plus 5-FU [44, 45], carboplatin [46], doxorubicin [47], and semustine [48]. Participation in a clinical trial should be discussed with all potentially eligible patients.

Conclusions

Anal cancer is a disease whose risk factors correlate with HPV infection. Treatment shifted significantly in the 1970s when chemoradiation was found to cure patients with anal cancer without requiring APR. Since then, however, little progress has been made in modifying or improving treatment regimens. In addition, with the advent of the HIV era, anal cancer and its treatment have been confounded with a higher percentage of HIV-positive patients developing anal cancer. Treatment of HIV-positive patients does need more careful monitoring, because in patients with CD4 counts $<200/mm^3$ the likelihood of toxicity is greater. As in cervical cancer, the use of a screening Pap smear in high-risk patients may lead to an earlier diagnosis of dysplasia, whose treatment may decrease the risk for the development of anal cancer, and anal cancers that do develop may be treated at an earlier stage.

Case Presentation and Follow-Up

The patient was referred for magnetic resonance imaging (MRI) to follow up the hepatic lesions seen on CT scan. The MRI revealed numerous hepatic cysts but no evidence of metastasis. Concurrent chemoradiotherapy was recommended. The patient received continuous infusion 5-FU (225 mg/m^2 daily) and mitomycin (10 mg/m^2 on days 1 and 29) given in combination with radiation therapy (5,580 cGy to gross disease and a 1,000-cGy boost to each groin). He completed all therapy as planned and without treatment delay/complications at the end of September 2006.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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