

ARTICLE TITLE: Anal Cancer: Current Standards in Care and Recent Changes in Practice

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After reading the article "Anal Cancer: Current Standards in Care and Recent Changes in Practice" the learner should be able to:

1. Discuss/review the risk factors for anal cancer.
2. Review recommendations for staging and evaluation of patients with anal cancer.
3. Summarize current recommendations for treatment and follow-up for patients with anal cancer.

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Anal Cancer: Current Standards in Care and Recent Changes in Practice

Ravi Shridhar, MD, PhD^{1*}; David Shibata, MD, FACS, FASCRS^{2,3}; Emily Chan, MD, PhD⁴; Charles R. Thomas, Jr., MD⁵

The management of squamous cell carcinomas of the anal canal has evolved from surgery as first-line treatment to curative chemoradiation, with surgery reserved for salvage. Significant progress has been made in understanding how to most effectively deliver chemotherapy and reduce toxicity through advancements in radiation delivery. The purpose of this article is to review the multimodality approach to the diagnosis and management of anal cancer based on a review of the published data and in light of available guidelines. *CA Cancer J Clin* 2015;000:000-000. © 2015 American Cancer Society.

Keywords: anal cancer, squamous cell carcinoma, intensity modulated radiation therapy, chemoradiation, abdominoperineal resection, brachytherapy, quality of life, sentinel lymph node biopsy, chemotherapy, salvage therapy



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Introduction

Incidence and Mortality

It is predicted that 7210 new cases of anal cancer will be diagnosed in the United States in 2014 and that the disease will account for approximately 950 deaths.¹ Of these estimated cases, 2660 will occur among men, whereas 4550 will occur among women. While it is an uncommon cancer, accounting for 0.43% of all malignancies, the incidence rates in the United States have increased from 0.8 to 1.7 cases per 100,000 persons per year from 1975 to 2011, respectively. Although multiple tumor types can arise in the anal canal, squamous cell carcinoma (SCCA) is the most common histologic diagnosis (85%) followed by adenocarcinoma (10%).² Other rare histologic subtypes include melanoma, neuroendocrine tumor, carcinoid, sarcoma, gastrointestinal (GI) stromal tumor, and lymphoma, all of which account for <3% of anal cancers.³

Anatomy

It is important to differentiate anal canal cancer from anal margin malignancies, as treatments may differ between these sites. The anal canal is defined as the terminal part of the large intestine extending from the anorectal junction of the upper part of the pelvic floor to the anal verge (hair-bearing skin around the anus). This area includes the dentate line at the mucosa level and the anorectal ring at the muscle level. The anorectal ring is a palpable ring that defines the level of the puborectalis muscle of the pelvic floor.

The mucosa of the proximal anal canal is of endodermal origin and has lymphatic and venous drainage to the hypogastric (internal iliac) vessels. The mucosa of the distal anal canal is of ectodermal origin and has lymphatic and venous drainage to the inferior hemorrhoidal vessels. The latter area has sensory innervation from the somatic nervous system via the pudendal nerve branches. The anal canal is divided by the dentate line, a visible landmark that overlies the transition from glandular to squamous mucosa; immediately proximal to the dentate line, a narrow zone of transitional mucosa is present. The proximal region of the anus encompasses glandular, transitional, and nonkeratinizing squamous mucosa from proximal to distal. Distally, the squamous mucosa (which is devoid of epidermal appendages, such as hair follicles, apocrine glands, and sweat

¹Associate Professor, Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL; ²Professor, Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, FL; ³Professor, Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL; ⁴Associate Professor, Department Medical Oncology, Vanderbilt University, Nashville, TN; ⁵Professor and Chair, Department of Radiation Medicine, Oregon Health and Sciences University, Portland, OR

Corresponding author: Ravi Shridhar, MD, PhD, Department of Radiation Oncology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612; ravi.shridhar@moffitt.org

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glands) merges with the perianal skin (true epidermis). This mucocutaneous junction has been referred to as the anal verge or margin and is a key landmark in differentiating between anal canal and anal margin (perianal skin) cancers.

Anal margin tumors are tumors of the perianal skin (defined as the skin starting at the anal verge to a 5-cm margin) and have high cure rates with wide local excision alone, particularly when they are small (<3 cm in greatest dimension) and well differentiated.⁴ This is likely because these tumors are more readily detectable and present at a much earlier stage.

Terminology

Historically, human papillomavirus (HPV)-associated cancers and precancerous lesions of the vulva, vagina, cervix, anus, and penis had disparate nomenclatures and histopathological classifications. In 2012, the College of American Pathologists-American Society for Colposcopy and Cervical Pathology Lower Anogenital Squamous Terminology Standardization (LAST) project proposed a unified nomenclature across groups that serves as the most current terminology for HPV-associated squamous proliferations, including anal neoplasia. A 2-tiered nomenclature consisting of high-grade squamous intraepithelial lesion (HSIL) and low-grade squamous intraepithelial lesion (LSIL) is recommended. For anal lesions, these entities may be further subclassified into corresponding levels of anal intraepithelial neoplasia (AIN). AIN I would correspond to anal LSIL, and AIN II/AIN III would correspond to anal HSIL.⁵

Minimally invasive squamous carcinoma of the anus is termed *superficially invasive squamous cell carcinoma* (SISCCA) and is described as microinvasive disease. It is amenable to conservative or excisional treatment and has a low risk for metastasis. In the anal canal, the suggested definition of SISCCA includes a completely excised lesion with invasion less than 3 mm from the basement membrane and with less than 7 mm in horizontal spread. Invasive cancers with greater dimensions than SISCCA generally require more aggressive treatment.⁶

Risk Factors

Age, Gender, and Race

The median age at anal cancer diagnosis (including all histologic types) is 60 years. In the United States, incidence rates are 1.5 and 2.0 cases per 100,000 persons per year among men and women, respectively. Among men, incidence rates are highest for blacks (2.0 cases per 100,000 persons per year) and whites (1.5 cases per 100,000 persons per year) and are lowest for Asians/Pacific Islanders (0.5 cases per 100,000 persons per year). In women, the highest incidence is among whites (2.2 cases per 100,000 persons per year) and blacks (1.6 cases per 100,000 persons per year), and the lowest incidence is among Asians/Pacific

Islanders (0.6 cases per 100,000 persons per year). Several well known risk factors have been identified, including HPV; receptive anal intercourse; a history of cervical, vulvar, or vaginal cancer; immunosuppression; and smoking.^{7,8}

Sexual Activity

A population-based case-control study compared 148 anal cancer patients and 166 controls with colon cancer diagnosed between 1978 and 1985. It was found that a history of receptive anal intercourse was strongly associated with the occurrence of anal cancer among men (relative risk, 33.1; 95% confidence interval [CI], 4.0-272.1), but this association was weak and was not statistically significant among women (relative risk, 1.8; 95% CI, 0.7-4.2).⁹ In a population-based case-control study of 306 anal cancer patients diagnosed between 1986 and 1998 and 1700 control patients in the Seattle area, a history of receptive anal intercourse and a higher number of lifetime sexual partners (≥ 15) were associated with increasing incidence of anal cancer.¹⁰

HPV

The effect of behavioral factors noted in the preceding section is mediated by a higher prevalence of anal infection with carcinogenic HPV types. HPV is the most common sexually transmitted virus that affects the genital tract of males and females. Although the virus is cleared in most people, about 1% develops genital warts. HPV is a small DNA tumor virus with over 100 different genotypes identified, of which at least 30 HPV genotypes are sexually transmitted and infect the anogenital tract.¹¹ HPV-16 is the type most commonly associated with cancer, including anal cancer.^{9,10,12} Only a small minority of anal cancers are HPV-negative.¹⁰ AIN, which is a precursor of anal cancer, is strongly associated with high-risk HPV types. HPV-16 was detected in 84% of anal cancer cases compared with 0% of rectal cancer cases.¹² In fact, 98% of tumors from nonexclusively heterosexual men were positive for HPV, with 73% harboring HPV-16.¹⁰ Although the majority of anal cancers associated with HPV are caused by type 16, HPV types 6, 11, and 31 account for 1.4% to 4.1%, whereas HPV-18 accounts for 3.4% to 7%.^{13,14}

Immunosuppression

Chronic immunosuppression caused either by organ transplantation or by long-term steroid use for the treatment of autoimmune diseases leads to increased incidence of genital warts, AIN, and anal cancer, likely because of persistent HPV infection.^{15,16} Progression of AIN to anal cancer is more likely associated with immunosuppression.^{17,18} The prevalence of anal HPV-16, HPV-18, HPV-6, or HPV-11 in liver transplant patients 3 weeks after transplantation has been reported at 18%,¹⁹ which is similar to the overall HPV prevalence in liver and kidney transplant patients within 24 hours of transplantation (29% and 21%, respectively).²⁰

Although there is a strong association between sexual practices like receptive anal intercourse and anal cancer, the relationship between human immunodeficiency (HIV) infection and anal cancer is less clear. In addition, HIV-positive patients are more likely to have HPV infection, which suggests a more indirect effect of immunosuppression rather than a direct effect of the virus. A meta-analysis of 53 studies revealed that the presence of both low-risk and high-risk HPV types, anal cytologic abnormalities, and anal cancer was significantly higher in HIV-positive men who have sex with men (MSM) compared with HIV-negative MSM.²¹ It concluded that high-risk HPV is the causative agent in anal cancer and that the higher incidence of anal cancer in HIV-positive MSM is because of higher rates of HPV infection.

Data from the HIV/Acquired Immunodeficiency Syndrome (AIDS) Cancer Match Study revealed that the increase in anal cancer incidence between 1980 and 2005 was because of the epidemic of HIV infection among males.²² In a study of 34,189 HIV-infected individuals and 114,260 HIV-uninfected individuals from 13 North American cohorts with follow-up between 1996 and 2007, the unadjusted anal cancer incidence rates per 100,000 person-years were 30 for HIV-infected women, 0 for HIV-uninfected women, 131 for HIV-infected MSM, 46 for other HIV-infected men, and 2 for HIV-uninfected men.²³

Several studies agree that low CD4 counts are a risk factor for HIV-positive individuals developing AIN and invasive anal cancer. Palefsky et al showed that, for HIV-positive men, having CD4 cell counts below 200/mm³ was associated with a >3-fold increased incidence of progression (based on cytology and/or biopsy) of normal or atypical epithelium to AIN, or from low-grade AIN to a higher grade lesion.¹⁷ Having a CD4 cell count nadir below 200/mm³ and having a long duration of low CD4 cell counts both were strongly associated with anal cancer incidence.^{24,25} Conversely, longer periods of undetectable HIV viral loads were associated with a decreased risk of developing anal cancer.²⁶

However, several studies have not found an association of antiretroviral therapy use or the absence thereof (based on medical records, or on treatment before or after availability of antiretroviral drugs) and any difference in anal cancer incidence.^{24,25,27} Nonetheless, widespread use of antiretroviral therapy to avoid a low and/or prolonged CD4 cell count nadir might be effective in reducing anal cancer incidence.²⁵ However, there is concern about an association between the long-term use of protease inhibitor therapy and an increased risk of anal cancer.²⁸

Smoking

Smoking is a well established risk factor for the development of anal cancer. In an early population-based case-control study from the Washington state and British Columbia area, there was a

significant difference in the prevalence of current smoking between controls (25%) and anal cancer cases (60%). The risk of anal cancer was significantly less for former smokers compared with current smokers and continued to diminish with increasing time from cessation of smoking.²⁹ In a more recent study, Daling and colleagues performed a population-based case-control study and concluded that current smokers among men and women were at a substantially higher risk for anal cancer independent of age and other risk factors (men: odds ratio, 3.9 [95% CI, 1.9-8.0]; women: odds ratio, 3.8 [95% CI, 2.4-6.2]).¹⁰

Screening and Prevention

Although it is not routine for the general population, and although formal national standards have yet to be established, anal cancer screening has been advocated for high-risk populations, such as HIV-positive individuals. The components of anal cancer screening have been adopted from strategies for cervical cancer and include anal canal swabs for cytological evaluation (eg, anal Papanicolaou [Pap] test) and visualization of the anal canal using high-resolution anoscopy, an adaptation of cervical colposcopy. A 2014 review summarized screening recommendations from 7 international, national, and state-based agencies. Although that review noted that, “no formal national or international guidelines exist for routine screening of anal cancer for HIV-infected individuals” and that “to date, no randomized control trial provides strong evidence supporting efficaciousness and effectiveness of an anal cancer screening program,” it concluded that, “...anal cancer screening, albeit unproven, may be beneficial at decreasing the incidence of anal cancer.” To the best of our knowledge, the New York State Department of Health is the only state-level organization³⁰ to establish formal anal cytology screening recommendations for HIV-positive individuals.³¹

High-resolution anoscopy can be performed with or without sedation in an office setting. After the application of acetic acid to the perianal region and anal canal, a magnifying colposcope is used to carefully observe the squamous mucosa. Dysplastic areas demonstrate acetowhite staining, and these areas are further examined for vascular changes characteristic of HSIL, such as punctuation, mosaicism, and epithelial patterns like honeycombing and hyperpigmentation. Lugol's iodine solution can be used on nonkeratinized anal mucosa to further enhance contrast of acetowhite areas. With the application of Lugol's, HSIL will turn yellow because of the absence of glycogen, whereas normal mucosa will turn dark brown.³² High-resolution anoscopy also allows for excisional or destructive treatment of involved areas with more accuracy when compared with traditional anoscopy.³³

Education about how high-risk sexual practices like receptive anal intercourse have been linked to increases in homosexual men would have to be part of any preventive

initiatives along with education on how condoms can have a protective effect on HPV infection, with an associated reduction of neoplasia.³⁴ In a randomized trial of 4065 males ages 16 to 26 years, a quadrivalent (HPV-6, HPV-11, HPV-16, HPV-18) HPV vaccine showed a significant reduction in external genital lesions compared with placebo.³⁵ In a planned subset analysis of that trial, the incidence of AIN decreased by 50% with the quadrivalent vaccine.³⁶ This has led to approval by the US Food and Drug Administration for the use of a quadrivalent vaccine (Gardasil; Merck, Readington Township, NJ) to prevent anal cancer. HPV vaccinations are now routinely recommended for boys and girls.

Clinical Presentation

Precancerous Lesions

Patients harboring AIN are usually asymptomatic, and these lesions are often found incidentally in minor anorectal surgical specimens. AIN is not always visibly apparent on routine examination but may be associated with plaques, erythema, and/or pigmentation. In such patients, these lesions may be associated with anorectal bleeding, irritation, and pruritis.^{37,38}

Anal Cancer

The clinical manifestations of anal cancer are frequently late and nonspecific and generally relate to the size of the tumor and the extent of infiltration. Anorectal bleeding is the most common presenting sign of anal cancer, occurring in 45% of patients. Anorectal pain and fullness are present in 30% of patients. The diagnosis of anal cancer is often delayed, because anorectal bleeding is initially thought to be caused by hemorrhoids, and 20% of patients present with no symptoms. Other symptoms include thin-caliber stools and changes in bowel movements, including the sensation of incomplete evacuation.^{39,40}

Pathology

Cytology

The cytologic classification of squamous intraepithelial lesion (SIL) of the anus is reported with increasing severity of changes in cellular morphology as atypical squamous cells (ASC) of undetermined significance (ASCUS), LSIL, ASC suggestive of HSIL (ASCH), and HSIL.⁴¹

Histology: SIL

SIL is generally characterized in tissue sections by a loss of epithelial stratification and nuclear polarity as well as nuclear polymorphism, hyperchromatism, and increased mitotic activity. SIL may be associated with the presence of koilocytes, which are enlarged cells with a cytoplasmic halo surrounding the nucleus and suggestive of HPV infection.

LSIL is defined as the replacement of 20% to 30% of the epithelium by abnormal cells, whereas, in HSIL, abnormal cells replace greater than 50% of the epithelium.^{37,42}

Anal Cancer

Anal canal cancers have previously been characterized as keratinizing, nonkeratinizing, and basaloid (also termed junctional or cloacogenic) subtypes,³⁷ but the value of these distinctions has been questioned. Given significant interobserver variability, the small size of diagnostic biopsies, and the lack of proven prognostic impact of different histologic features, it is generally recommended that the generic term “squamous carcinoma” be used for these tumors with the inclusion of a comment describing any distinct histopathologic features (eg, size of predominant neoplastic cell, basaloid features, degree of keratinization, and adjacent AIN).

Staging

Because radical surgery is no longer the first option in the primary treatment of anal cancers, tumors are staged clinically by physical examination and radiographic imaging. Anal cancers are currently staged according the tumor, lymph node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC), seventh edition (Tables 1, 2). The tumor category (T) is determined by the size and invasion of adjacent structures, like the vagina and prostate. Lymph node staging is based on the location of involved perirectal, pelvic, or inguinal lymph nodes. Tumors of the perianal skin (excluding melanoma) are staged as nonmelanoma skin cancers, as the 2 share similar biology. However, it should be noted that the seventh edition of the *AJCC Cancer Staging Manual* made substantial changes to the staging of cutaneous SCCA, making it much less appropriate for the staging of cancer of the anal margin. Furthermore, many patients with anal margin cancers have involvement of the anal canal or have high-grade precancerous lesions in the anal canal. It is important to look for such anal canal involvement, particularly if conservative management (eg, simple excision) is being considered. Otherwise, many patients, particularly those who are HIV-positive, could be significantly undertreated. It should be noted that, because of these issues, the National Comprehensive Cancer Network (NCCN) guidelines use the anal cancer staging system for tumors of the anal canal and the anal margin.⁷ Most patients present with early stage disease. A national survey revealed that, at the time of diagnosis, 25% of anal cancers are stage I, 52% are stage II, 17% are stage III, and 6% are stage IV.⁴³

Prognosis and Patterns of Spread

Anal cancer can spread through direct extension and invasion of adjacent structures; lymphatic dissemination

TABLE 1. TNM Classification of Anal Carcinoma According to the American Joint Committee on Cancer, 7th Edition (Excluding Melanoma, Carcinoid, and Sarcoma)

CATEGORY	DEFINITION
T category	
Tx	Primary tumor cannot be assessed
T0	No evidence of tumor
Tis	Carcinoma in situ (Bowen's diseases, high-grade squamous intraepithelial lesion, anal intraepithelial neoplasia II-III)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organs (vagina, urethra, bladder, prostate)
N category	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph nodes
N2	Metastasis in unilateral internal iliac and/or inguinal lymph nodes
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastases

through perirectal, pelvic, and inguinal lymph nodes; and hematogenously to distant organs like liver and lung. Tumors arising above the dentate line tend to spread to perirectal (N1) lymph nodes, whereas tumors at or below the dentate line spread to inguinofemoral (N2) lymph nodes. Lymph node positivity is directly related to the size and extent of invasion of the primary tumor. Lymph node metastases are seen in 0% to 10% of T1 and T2 tumors and in 40% to 50% of T3 and T4 tumors.^{44,45} Gerard et al reported on 270 patients, of whom 10% presented with inguinal adenopathy (16% among patients with T3/T4 tumors).⁴⁶ Of those with uninvolved inguinal lymph nodes who received no inguinal radiation, 7.8% developed metachronous inguinal metastasis. Similarly, Papillon and Montbarbon demonstrated a 7.4% metachronous inguinal metastases rate in clinically inguinal lymph node-negative patients.⁴⁷ In a series of 208 anal cancer patients, 27 (13%) presented with macroscopic inguinal lymph node metastasis.⁴⁸ In a group of patients with uninvolved inguinal lymph nodes who were not treated with prophylactic inguinal radiation, the 5-year cumulative rate of inguinal recurrence was 12% for those with T1 and T2 tumors and 30% for those with T3 and T4 tumors ($P = .02$).⁴⁸

A retrospective analysis of the Radiation Therapy Oncology Group (RTOG) study 98-11 (RTOG 98-11) data set sought to determine the impact of 6 TN categories (T2 and lymph node-negative [T2N0], T3N0, T4N0, T2N1-N3, T3N1-N3, and T4N1-N3) on survival, local failure requiring abdominoperineal resection (APR), and colostomy and relapse rates in this patient group.⁴⁹ The worst outcomes were observed in patients with T3/T4 lymph node-positive (N+) anal cancer. Colostomy failure was lowest for the T2N0 and T2N+ categories (11% for both) and worst for the T4N0, T3N+, and T4N+ categories (26%, 27%, and 24%, respectively). That analysis suggested that TN category of disease has a statistically significant impact on outcome in patients treated with chemoradiotherapy and may be a useful prognosticator of outcome in patients with anal carcinoma. On multivariate analysis, prognostic factors relating to worse colostomy-free survival derived from the second United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Anal Cancer Trial (ACT II) were male gender, tumor size >5 cm, T3 and T4 tumors, and lower baseline hemoglobin.⁵⁰

The most well established prognostic factors predicting for worse overall survival (OS) and disease-free survival (DFS) that were derived from the RTOG 98-11 and European Organization for Research and Treatment of Cancer (EORTC) 22861 (EORTC-22861) trials were male gender, tumor diameter, and positive lymph nodes.^{51,52} In a University of Washington retrospective study, cigarette smoking had a negative impact on survival, whereas HIV and a CD4 count below 200/mm³ had no impact.⁵³

Evaluation

Patients who have findings suspicious for anal cancer require a detailed history to assess for known risk factors, such as homosexuality and bisexuality in men (ie, MSM), receptive anal intercourse, HIV positivity, AIDS, intravenous drug

TABLE 2. Staging and TNM Classification of Anal Carcinoma According to the American Joint Committee on Cancer, 7th Edition (Excluding Melanoma, Carcinoid, and Sarcoma)

STAGE	T CATEGORY	N CATEGORY	M CATEGORY
0	Tis	N0	M0
I	T1	N0	M0
II	T2-T3	N0	M0
IIIA	T1-T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2-N3	M0
IV	Any T	Any N	M1

use, and smoking, as well as risk factors associated with non-HIV-related immunosuppression, such as chronic steroid use and organ transplantation.

The degree of rectal bleeding and sphincter incontinence should be ascertained. A complete physical examination is critical, including careful inspection of the perianal skin and anal verge. This should be followed by digital anorectal examination. Sphincter function, size and location of the tumor, as well as contiguous involvement of adjacent structures, such as the vagina in women and the prostate in men, should be documented. In addition, inguinal lymphadenopathy should be evaluated.

The anal canal and distal rectum should then be evaluated by anoscopic/proctoscopic examination to identify any abnormalities, such as masses, nodules, ulcerations, and/or areas of discoloration. Women should be evaluated for cervical dysplasia/neoplasia by Pap test, and men should receive a penile examination. Colonoscopy may be used to determine the extent of anorectal involvement and to assess for other colonic lesions; however, colonoscopy is not as accurate as high-resolution anoscopy nor is it mandated by national or international guidelines.^{7,54} Laboratory studies should include a complete blood count, renal and hepatic function, and HIV status. Although it has been suggested that transrectal ultrasound may provide improved accuracy of pretreatment staging, high-level evidence to support its utility is lacking and is not mandated by national or international guidelines.^{7,54,55}

Radiographic imaging should include computed tomography (CT) scans of the chest, abdomen, and pelvis to assess for metastatic disease to the lungs and liver and to retroperitoneal, pelvic, and inguinal lymph nodes. Compared with CT, magnetic resonance imaging of the pelvis can provide better anatomic detail with respect to the invasion of local structures, especially the sphincter-related musculature, and also for the evaluation of mesorectal lymph node involvement,⁵⁶ and it is the preferred imaging modality.⁵⁴ A CT scan is inferior to physical examination for detecting the primary tumor. Positron emission tomography (PET) has provided utility in identifying the primary tumor and spread to inguinal lymph nodes and in assessing response to therapy. A retrospective study in 41 patients with anal cancer showed that PET detected the primary tumor in 91% of patients, whereas CT was able to detect tumor in only 59% of patients.⁵⁷ PET was able to detect the involvement of inguinal lymph nodes that were deemed negative on CT in 17% to 23% of patients.^{57,58} HIV-positive patients had a higher incidence of PET-positive inguinal lymphadenopathy. Because these lymph nodes may also be reactive and show hypermetabolic activity on PET, all suspicious inguinal adenopathy should be biopsied to allow for lower prophylactic radiation dosing of inguinal lymphatics if biopsies are negative.

Sentinel Lymph Node Biopsy

Patients with clinically uninvolved inguinal lymph nodes have very low rates of inguinal recurrence in T1 and T2 tumors.^{46,48} This would suggest that the majority of patients who are prophylactically treated with inguinal radiation are over treated. However, even early stage lymph node-negative patients recur in the groin. Properly identifying patients who have microscopic groin disease and will likely benefit from groin radiation could improve outcomes. Many groups have investigated sentinel lymph node biopsy (SLNB) to identify patients who will absolutely require groin radiation.^{59,60} The accuracy of SLNB was 90% to 100%, with metastatic inguinal lymph nodes detected in 0% to 33%; however, those studies were very heterogeneous in tumor stage.⁵⁹ Mistrangelo et al compared inguinal metastasis detection between PET-CT and SLNB in 27 patients.⁶¹ PET-CT detected inguinal lymph nodes in 7 patients; however, SLNB confirmed metastasis in 3 of those 7 patients. PET-CT had a sensitivity of 100%, a negative predictive value of 100%, specificity of 83%, and a positive predictive value of 43%, all of which were inferior to SLNB. In a published 2013 series, inguinal metastases were detected in 13 of 63 patients (20.6%) with no false-negatives observed.⁶⁰ The sensitivity, specificity, negative predictive value, and positive predictive value was 100%, 83%, 100%, and 43%, respectively. However, in a prospective study of 50 patients with anal cancer who underwent SLNB for clinical staging, de Jong et al found that nearly 10% of patients with a negative sentinel lymph node went on to develop inguinal metastasis at 1-year follow-up.⁶² Moreover, the complication rate from this procedure was 24%. Although it may be a useful tool, current data do not yet support the routine use of SLNB for clinical staging to determine the need for radiation treatment to the inguinal basin. The current standard of care to evaluate lymph nodes is either CT-guided or ultrasound-guided fine-needle aspiration.

Treatment

Precancerous Lesions

Condyloma and low-grade dysplasia can be treated by either topical therapy or surgical destruction. Most commonly used topical therapies include 3.75% imiquimod cream and 5% fluorouracil.

Transanal excision is only indicated for patients with AIN when there is an absence of invasion. Microinvasive disease, including SISCCA, presents a challenge and, if incompletely excised, reexcision is required once the surgical site is fully healed. Imiquimod, a nucleoside analog of the imidazoquinolone family, has local proinflammatory and antiviral properties and has been shown to have significant results in the eradication of AIN III disease.⁶³ Imiquimod can be used in

both immunocompetent and immunosuppressed patients with similar efficacy.^{64,65} Fluorouracil has been shown to have high efficacy but causes significant side effects, such as burning, irritation, and pain, in up to 85% of patients.⁶⁶ In a randomized study, HIV-positive MSM with known AIN were treated with imiquimod, fluorouracil, or surgical fulguration with electrocautery. Although electrocautery improved initial success with decreased side effects compared with the other treatment modalities, the recurrence rate was equally high in all treatment groups (67% at 72 weeks).⁶⁷ Other options for surgical treatment included infrared coagulation, cryotherapy, CO₂ laser ablation, and 5-aminolaevulinic acid/photodynamic therapy; however, 3-year recurrence rates were high (77%), regardless of the treatment modality.⁶⁸

High-grade dysplasia and SISCCA can be treated with surgical excision to negative margins or ablation with high-resolution anoscopy. Recurrence rates after initial treatment remain high, with 59% of HIV-positive patients experiencing a recurrence within the first year.⁶⁸ After treatment, patients should be carefully monitored with repeat anoscopy to detect recurrence. There is currently no established consensus to support the optimal interval for surveillance, although a range of every 3 to 6 months has been recommended.⁶⁹

Anal Margin Cancer

For patients with T1N0, well differentiated anal margin cancer, treatment should consist of wide local excision where one-cm margins can be obtained. In the event of a positive margin, reexcision should be attempted. If reexcision is not feasible, radiotherapy (RT) with or without 5FU-based chemotherapy to a dose of 60 Gray (Gy) is recommended. For T2 or greater lesions, chemoradiation similar to the treatment for anal canal cancers should be performed. Local excision is only indicated for anal margin squamous tumors, and not for anal canal squamous cancers.

Anal Canal Cancer

Surgery

APR was the standard of care for the primary treatment of anal carcinoma before the development of effective nonsurgical, sphincter-preserving chemoradiation therapy. The average 5-year OS rates with APR alone reportedly were 50% (range, 25%-75%).⁷⁰⁻⁷² Locoregional relapse and distant relapse occurred in up to 35% and 10% of patients, respectively, with higher rates of relapse for patients who had positive pelvic or inguinal lymph nodes. Because of the high morbidity and high rates of recurrence after APR as initial stand-alone therapy, this procedure is now reserved for salvage therapy.

Chemoradiation

In a small series of anal cancer patients treated with low-dose RT (30 Gy) concurrent with 5-fluorouracil (5FU) and

mitomycin C (MMC), Nigro et al established that a complete response was possible.⁷³ In a larger phase 2 study of 45 patients treated preoperatively with the same chemoradiation regimen, 38 patients (84%) were rendered free of cancer. No recurrence of tumor was noted in those patients who achieved a complete response. Seven patients (15%) with residual cancer after preoperative therapy have had recurrences, all in distant sites, and all have died of disease.⁷⁴ Several randomized trials have addressed the role of concurrent chemotherapy, induction chemotherapy, maintenance chemotherapy, and biologic therapy (Table 3).

Chemoradiation Versus RT

Although chemoradiation had been shown to be efficacious in anal cancer, the question arose whether chemotherapy was necessary, as some early studies had evaluated high-dose RT alone and shown efficacy as well. Furthermore, there was a concern about late toxicities with the radiation potentiating effects of chemotherapy.

The first UKCCCR Anal Cancer Trial (ACT I) sought to answer this question by randomizing 585 patients to either radiation monotherapy (45 Gy of radiation over 4-5 weeks) or the same radiation regimen combined with 5FU and MMC chemotherapy.⁷⁵ Patients who had a good response 6 weeks after treatment received a RT boost, whereas poor responders went on to salvage surgery. After a median follow-up of 42 months, the chemoradiation arm had an improved local failure rate compared with the RT alone arm (36% vs 59%; $P < .0001$). Chemoradiation did result in more early morbidity (48% vs 39%; $P = .03$), but the late morbidity rates (42% vs 38%; $P = .39$) were similar in both groups. Although the updated results after 13 years of follow-up showed a survival advantage for the chemoradiation arm that was not statistically significant, there was a statistically significant reduction in the risk of dying from anal cancer.⁷⁶ The median OS was 7.6 years for the chemoradiation arm and 5.4 years for the RT alone arm ($P = .12$). There was a 33% decrease in deaths from anal cancer ($P = .004$). The EORTC also conducted a phase 3 randomized trial of RT versus chemoradiation in 110 patients with anal cancer.⁵² The radiation dose was 45 Gy over 5 weeks, followed by a 6-week rest, and then a boost of 20 or 15 Gy in partial or complete responders, respectively. Surgical resection was performed if patients had not responded 6 weeks after 45 Gy or for those who had palpable residual disease after therapy completion. Patients in the chemoradiation arm received 5FU and MMC with radiation. The chemoradiation arm had a higher complete response rate (80% vs 54%). This improved local control also translated to lower locoregional recurrences and higher colostomy-free rates ($P = .002$). Acute toxicities were not significantly different in the 2 groups. Late toxicities also were similar in the 2 groups with the exception of an

TABLE 3. Randomized Trials of Chemoradiation for Anal Cancer

TRIAL	NO.	TREATMENT ARMS	MEDIAN F/U, mo	TIME POINT, y	LC, %	CFS, %	COLOSTOMY RATE, %	PFS, %	DFS, %	OS, %
UKCCCR ACT I (Arnott 1996, ⁷⁵ Northover 2010 ⁷⁶)	585	RT +/- 5FU/MMC	157	10	66 ^a	36 ^a			36 ^b	42 ^b
		RT alone			43	26		24	36	
EORTC (Bartelink 1997 ⁵²)	110	RT + 5FU/MMC	42	5	69 ^a					69 ^b
		RT alone			55				64	
RTOG 87-04 (Flam 1996 ⁷⁷)	310	RT + 5FU	36	4		59 ^a	22 ^a		51 ^a	
		RT + 5FU/MMC				71	9		73	
RTOG 98-11 (Ajani 2008, ⁷⁸ Gunderson 2012 ⁷⁹)	644	RT + 5FU/MMC	156	5	80 ^b	72 ^a	12 ^b		68 ^a	78 ^a
		Induction CDDP → RT + 5FU/CDDP			74	65	17		58	71
ACT II (James 2013 ⁸⁰)	940	RT + 5FU/MMC	1	3	89 ^b		CDDP vs MMC	73 ^b		
		RT + 5FU/CDDP			87		72			
		RT + 5FU/MMC → adjuvant 5FU/CDDP			88	11 ^b	73			
		RT + 5FU/CDDP → adjuvant 5FU/CDDP			88	14	74			
ACCORD-03 (Peiffert 2012 ⁸¹)	307	Induction 5FU/CDDP → RT (standard boost) + 5FU/MMC	50	5		70 ^b				
		Induction 5FU/CDDP → RT (high-dose boost) + 5FU/MMC				82				
		RT (standard boost) + 5FU/CDDP				77				
		RT (high-dose boost) + 5FU/CDDP				73				

5FU, 5-fluorouracil; ACT, Anal Cancer Trial; CDDP, cis-diamminedichloroplatinum(II) (cisplatin); CFS, colostomy-free survival; DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; F/U, follow-up; LC, local control; MMC, mitomycin C; OS, overall survival; PFS; progression-free survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; UKCCCR, United Kingdom Coordinating Committee on Cancer Research. ^aThe difference between treatment arms was statistically significant. ^bThe difference between treatment arms was not statistically significant.

increased incidence of anal canal ulcers in the combined modality group. The chemoradiation arm had an improved progression-free survival (PFS) ($P = .05$). There was no difference in OS between the 2 groups, although it should be noted that the median survival time had not been reached at the time of the study report.

ACT I and the EORTC trial confirmed the superiority of chemoradiation over RT alone in the treatment of anal cancer. Both trials showed improvements in locoregional control and PFS with the addition of chemotherapy. The ACT I trial further showed that the addition of chemotherapy resulted in a nonsignificant improvement in OS, but this improvement was evident only after long-term follow-up and possibly was caused by the increase in non-anal cancer deaths in the chemoradiation arm during the first 10 years.

Role of Mitomycin

Although ACT I and the EORTC studies established the role of chemotherapy in combination with RT for the treatment of anal cancer, they did not answer the question of

whether or not mitomycin was necessary to the regimen, because both studies used 5FU and mitomycin.

RTOG 87-04/Eastern Cooperative Oncology Group (ECOG)1289 was a phase 3 intergroup study designed to answer whether mitomycin was necessary in the treatment of anal cancer.⁷⁷ Patients ($n = 310$) with anal cancer were randomized to chemoradiation with either 5FU or 5FU/MMC. Both arms received the same radiation dose. The MMC arm had a lower colostomy rate at 4 years (9% vs 23%; $P = .002$). The impact on colostomy rate reduction with the addition of mitomycin appeared to be confined to T3 and T4 primary tumors ($P = .019$). The addition of mitomycin also resulted in improved 4-year PFS (73% vs 51%; $P = .0003$). However, there was no statistically significant difference in 4-year OS ($P = .31$). The addition of mitomycin did result in more acute toxicities, primarily neutropenia and thrombocytopenia ($P < .001$). One toxic death (0.7%) occurred in the 5FU arm, and 4 toxic deaths (2.7%) occurred in the mitomycin arm, all from neutropenic sepsis. Rates of late toxicities were similar in the 2 groups ($P = .26$). That trial confirmed the benefit of

adding mitomycin to 5FU and RT for anal cancer, but it also suggested that careful consideration be given to immunosuppressed individuals given the neutropenia rate and toxic deaths seen in the mitomycin arm. Currently, our practice is to use full-dose MMC in patients with normal white blood cell and platelet counts or in HIV-positive patients who are on antiretroviral therapy with CD4 counts below 200/mm³ and to use reduced-dose MMC (5 mg/m²) in patients with abnormally low blood counts. Other institutions may substitute cisplatin in place of MMC.

Role of Cisplatin

Given the encouraging results of these phase 2 studies incorporating cisplatin compared with historical results of chemoradiation with 5FU and mitomycin, further evaluation of cisplatin was warranted in anal cancer.^{82,83}

Induction or Maintenance Chemotherapy

RTOG 98-11 was an intergroup phase 3 trial that evaluated whether cisplatin was superior to mitomycin in the treatment of anal cancer.⁷⁸ Patients (n = 682) were randomized to chemoradiation with 5FU/MMC and RT (range, 45-59 Gy) or induction cisplatin and 5FU followed by chemoradiation with cisplatin and 5FU. In the long-term update of this study, chemoradiation with 5FU/MMC resulted in superior 5-year DFS (67.8% vs 57.8%; $P = .006$) and 5-year OS (78.3% vs 70.7%; $P = .026$), with a trend toward improved colostomy-free survival (71.8% vs 64.9%; $P = .053$) compared with chemoradiation with 5FU and cisplatin.⁷⁹ Hence, chemoradiation with 5FU and mitomycin remained the standard of care.

Patients in the cisplatin experimental arm of RTOG 98-11 had 2 cycles of induction chemotherapy before chemoradiation was initiated. The hypothesis was that the induction chemotherapy could reduce the burden of disease and make the chemoradiation more effective, resulting in improved DFS. Unfortunately, as noted above, results for the cisplatin and 5FU arm were inferior, suggesting no benefit for the induction chemotherapy or for the use of cisplatin when mitomycin is an option. Several hypotheses were proposed for the negative results. One was that induction chemotherapy delayed the start of definitive chemoradiation, resulting in poorer outcomes, and thus was not a fair comparison of the chemoradiation effectiveness of each regimen. Another hypothesis was that giving induction 5FU and cisplatin may have caused platinum-induced radioresistance or may have accelerated repopulation.

The UNICANCER ACCORD 03 phase 3 trial sought to improve on the results of chemoradiation in anal cancer by adding either induction chemotherapy with 5FU and cisplatin or dose escalation of the radiation boost.⁸¹

Patients (n = 307) with anal cancer were randomized to one of the following 4 treatment arms: Arm A, 2 cycles of induction chemotherapy with 5FU and cisplatin, chemoradiation with 45 Gy concurrent with 5FU and cisplatin, followed by a standard-dose boost (15 Gy); Arm B, 2 cycles of induction chemotherapy with 5FU and cisplatin, chemoradiation with 45 Gy concurrent with 5FU and cisplatin, followed a high-dose boost (20-25 Gy); Arm C, chemoradiation with 45 Gy concurrent with 5FU and cisplatin followed by a standard-dose boost (15 Gy); and Arm D, chemoradiation with 45 Gy concurrent with 5FU and cisplatin followed by a high-dose boost (20-25 Gy). Arm C was the reference arm in this 2 × 2 factorial design, and the primary endpoint was colostomy-free survival. There was no statistically significant benefit in 5-year colostomy-free survival to either induction chemotherapy ($P = .37$) or high-dose radiation boost ($P = .067$). Secondary endpoints examined included 5-year local control, 5-year disease-specific survival, and 5-year tumor-free survival, and none of these endpoints showed a statistically significant benefit with the addition of either induction chemotherapy or high-dose radiation boost. ACT II also evaluated the role of cisplatin in the treatment of anal cancer.⁸⁰ This 2 × 2 factorial trial randomly assigned patients (n = 940) to one of 4 groups to receive RT (50.4 Gy) and 5FU with either MMC or cisplatin with or without 2 cycles of maintenance chemotherapy (5FU and cisplatin). With regard to cisplatin, there was no significant difference in the complete response rate at 26 weeks (90.5% for mitomycin and 89.6% for cisplatin; $P = .64$) or in toxicity (71% for mitomycin and 72% for cisplatin). There was also no difference in 3-year PFS with regard to maintenance or no maintenance (74% vs 73%, respectively; $P = .70$). Given these results, chemoradiation with 5FU and mitomycin remains the standard of care for the treatment of anal cancer.

Biologic Therapy (Cetuximab)

The *EGFR-1* (epidermal growth factor receptor 1) signaling pathway is thought to play a pivotal role in tumor growth and progression of various human neoplasms, including colorectal cancer. *EGFR-1* belongs to the human epidermal growth factor receptor (*HER*) family of receptors and can bind several ligands that induce receptor homodimerization or heterodimerization with another *EGFR-1* receptor or with other *HER* family members. Various studies have demonstrated that *EGFR-1* signaling is dysregulated in colorectal cancer and other tumor types and that the overexpression of *EGFR-1* correlates with disease progression, a poor prognosis, and reduced sensitivity to chemotherapy.⁸⁴ Therefore, *EGFR-1* is considered a molecular target, and several strategies have been developed to target *EGFR-1*, including small-molecule tyrosine kinase inhibitors (ie, erlotinib) and anti-*EGFR-1* monoclonal

antibodies (ie, cetuximab and panitumumab). Cetuximab exerts its antitumor effects through ligand-independent processes, which stimulate receptor internalization, and it has been noted that combination therapy with cetuximab and chemotherapeutic agents leads to a synergistic antitumor effect.⁸⁵ Van Damme et al evaluated 30 patients with SCCA of the anal canal to determine the significance of *EGFR* gene amplification and the presence of a *KRAS* (Kirsten rat sarcoma viral oncogene homolog) mutation.⁸⁶

A phase 1 study was conducted of chemoradiation with 5FU, cisplatin, and cetuximab.⁸⁷ All patients received from 55 to 59 Gy over 6.0 to 6.5 weeks. In total, 23 individuals were enrolled in this phase 1 study. Despite a response rate of 95%, the study was closed early because of toxicity concerns, including 6 (26%) episodes of thrombosis/embolism, 52% grade 3 or 4 radiation dermatitis, and 44% grade 3 or 4 diarrhea. Similarly, the ACCORD 16 phase 2 trial evaluating cetuximab concurrently with chemoradiation for anal cancer was closed because of excessive toxicity.⁸⁸ Phase 2 trials from ECOG (3205) and the AIDS Malignancy Consortium failed to provide sufficient evidence to recommend the use of cetuximab in anal cancer.

Protracted, Continuous-Infusion 5FU

EORTC 22953 was a phase 2 study that tested the feasibility of reducing the gap between sequences to 2 weeks to deliver MMC in each RT sequence and 5FU continuously during the treatment.⁸⁹ The first sequence consisted of 36 Gy over 4 weeks, 5FU 200 mg/m² on days 1 through 26, MMC 10 mg/m² on day 1 and a gap of 16 days. Then, a second sequence of 23.4 Gy over 17 days, 5FU 200 mg/m² on days 1 through 17, and MMC 10 mg/m² on day 1 was given. Forty-three patients with T2-T4, N0-N3 tumors were enrolled. The complete response rate was 90.7%. Grade 3 skin toxicity, diarrhea, and hematologic toxicity were documented in 28%, 12%, and 2% of patients, respectively. The 3-year rates for local control, colostomy-free interval, the severe late toxicity-free interval, and OS were 88%, 81%, 84%, and 81%, respectively. This is now considered the new standard scheme by the EORTC.

Capecitabine

Capecitabine is oral fluoropyrimidine-based chemotherapy. A multicenter phase 2 trial evaluated a capecitabine/MMC-based chemoradiation regimen in anal cancer.⁵⁴ RT comprised the schedule of the UK ACT II trial (50.4 Gy in 28 fractions of 1.8 Gy), with MMC (12 mg/m²) on day 1 and capecitabine on each RT treatment day divided into 2 doses (825 mg/m² twice daily). Thirty-one patients were enrolled. Compliance with chemotherapy was 68% with no dose interruptions or delays, and compliance with RT was 81%. Grade 3 diarrhea was seen in 1 patient.

Three patients experienced grade 3 neutropenia. There were no treatment-related deaths. Four weeks after the completion of chemoradiation, 24 patients (77%) had a complete clinical response, and 4 (16%) had a partial response. With a median follow-up of 14 months, 3 locoregional relapses occurred.

A phase 2 study from The University of Texas MD Anderson Cancer Center (Houston, Tex) (MD Anderson) enrolled patients with histologically proven carcinoma of the anal canal, AJCC stage II through IIIB, and no prior therapy for capecitabine/oxaliplatin (XELOX)-based chemoradiotherapy.⁹⁰ Chemotherapy initially consisted of capecitabine (825 mg/m²) twice daily on Monday through Friday and weekly oxaliplatin (50 mg/m²; group 1) with subsequent modification to the omission of chemotherapy during weeks 3 and 6 (group 2). RT was provided in the following manner: for T1 tumors, 45 Gy in 25 fractions; for T2 tumors, 55 Gy in 30 fractions; and, for T3 and T4 tumors, 59 Gy in 32 fractions. Intensity-modulated RT (IMRT) was allowed. Twenty patients were evaluable for toxicity, and 17 were evaluable for response. Five of 11 (45%) patients developed grade 3 treatment-related diarrhea (group 1). Therefore, the chemotherapy schedule was modified, and only one of 9 patients in group 2 developed grade 3 diarrhea. The complete response rates were 90% in group 1 and 100% in group 2. One patient in group 1 developed distant failure. After a median follow-up of 19 months, no patient has developed local recurrence or required salvage resection with colostomy, for a colostomy-free rate of 100%.

Mitomycin and Cisplatin

A follow-up to the EORTC 22953 trial was a randomized phase 2 study (EORTC 22011-40014) to assess the feasibility and activity of chemoradiation with MMC and cisplatin in locally advanced anal cancer compared with chemoradiation with MMC and 5FU.⁹¹ Patients who had tumors greater than 4 cm or who were lymph node-positive received radiation (36 Gy with a 2-week gap then 23.4 Gy) with either MMC/cisplatin or MMC/5FU (MMC 10 mg/m² on day 1 of each sequence, 5FU 200 mg/m² daily, cisplatin 25 mg/m² weekly). Forty-four patients were enrolled in each arm. The objective response rate was 79.5% with MMC/5FU versus 91.9% with MMC/cisplatin. In the MMC/5FU group, 2 patients (5.1%) discontinued treatment because of toxicity versus 11 patients (29.7%) in the MMC/cisplatin group. Nine grade 3 hematological events occurred with MMC/cisplatin versus none with 5FU/MMC. The rate of other toxicities did not differ. There were no treatment-related deaths. Thirty-one patients in the MMC/5FU arm (79.5%) and 18 in the MMC/cisplatin arm (48.6%) were fully compliant with the protocol treatment ($P = .005$).

HIV

The presence of HIV is not a contraindication to combined modality treatment. Although acute treatment-related toxicity and relapse rates may be higher, chemoradiotherapy has been successfully implemented in patients with HIV-AIDS; and local control, response to therapy, and survival in these patients are comparable to those in HIV-negative patients.⁹²⁻⁹⁵ CD4 counts greater than 200/mm³ have been correlated with toxicity and disease control. An analysis of 17 HIV-positive patients who were treated for anal cancer with chemoradiation, 9 patients with CD4 counts above 200/mm³ were able to complete treatment and had disease controlled. Four patients required a 2-week break because of toxicity but did not require hospitalization. In the remaining 8 patients who had CD4 counts below 200/mm³, significant toxicity was documented, including moist desquamation and intractable diarrhea requiring hospitalization. Half of these patients required colostomy for treatment-related complications; however, only one patient failed, requiring salvage colostomy.⁹⁶ A multicentric cohort comparison of 40 HIV-positive patients and 81 HIV-negative patients with anal cancer who were treated with chemoradiation suggested equivalent complete response rates and 5-year OS. However, local control and acute dermatologic and hematologic toxicity were worse in HIV-positive patients.⁹⁴ In a comparison of 19 immunocompetent and 17 immunodeficient (14 HIV-positive) patients with anal cancer who were treated with chemoradiotherapy, there was no difference in acute and late toxicity, OS, or colostomy-free survival.⁹³ Finally, an analysis of 21 HIV-positive patients receiving antiretroviral therapy who were treated with chemoradiation for anal cancer revealed that, despite drops in CD4 counts and increases in viral load, these parameters returned to baseline, and no dose reductions in chemotherapy were required.⁹⁷ Patients with HIV-related complications like opportunistic infections may require dosage reduction of MMC.⁷

Tumor Regression

The response to chemoradiotherapy may be immediate or may evolve slowly over several months. Cummings et al demonstrated that the rate of regression over time was not a good measure of the effectiveness of treatment. They found that the median time to complete response was 3 months and that some cancers could take up to 12 months to disappear.⁹⁸ In a French study, patients who achieved a response rate >80% versus <80% after the initial phase of RT had a 5-year colostomy-free survival rate of 65% versus 25%, respectively ($P = .002$). Finally, the ACT II trial showed that, in the 29% of patients who did not achieve a complete response at 11 weeks, a complete response occurred at 26 weeks. These results suggest that it may be

appropriate to follow patients who have persistent disease as long as there is no evidence of disease progression.⁹⁹

IMRT

IMRT allows for safe tumor dose escalation while reducing the dose to surrounding normal tissues like skin, small bowel, bladder, femoral heads, external genitalia, and bone marrow. IMRT has been evaluated in several dosimetric studies and was superior to 3-dimensional (3D) conformal therapy planning.⁷ Dermatologic and small bowel toxicity can necessitate treatment breaks, which potentially can negatively affect outcomes. By reducing the dose to surrounding normal tissues, acute toxicity will be minimized, resulting in fewer treatment breaks and shorter overall treatment time.¹⁰⁰⁻¹⁰³ Several small retrospective series with patient numbers ranging from 17 to 78 and median follow-up ranging from 16 months to 24 months have demonstrated the safety and feasibility of IMRT chemoradiation (Table 4).^{101,104-112} The rates of 2-year to 3-year locoregional control, colostomy-free survival, and OS ranged from 77% to 95%, from 81% to 93%, and from 87% to 100%, respectively. Acute grade 3 or greater GI toxicity was reported in a range from 0% to 28%, and acute grade 3 or greater dermatologic toxicity was reported in a range from 0% to 38%. In RTOG 98-11, in which all patients were treated with conventional RT, the acute grade 3 or greater GI and dermatologic toxicity rates were 36% and 49%, respectively.^{78,79} RTOG 0529 is a completed, prospective phase 2 trial to determine whether dose-painted IMRT could reduce toxicity compared with RTOG 98-11.¹⁰¹ The primary endpoint was a 15% reduction in combined grade 2 or greater genitourinary and GI toxicity. Of 63 patients enrolled, 52 were evaluable. Although the trial failed to meet its primary endpoint, there were significant reductions in acute grade 2 or greater hematologic toxicity and grade 3 or greater dermatologic and GI toxicities. As such, IMRT has evolved as a de-facto standard of care in the administration of RT for anal cancer patients undergoing combined modality therapy.¹¹³

Several retrospective studies comparing the toxicity and outcomes of 3D conformal RT (3DCRT) with the outcomes of IMRT^{100,102,103,114,115} are presented in Table 5. Of 4 studies^{100,102,103,115} that reported on toxicity, 3 studies showed a significant reduction in acute grade 3 or greater GI and dermatologic toxicity,^{100,102,115} and one study by Chuong et al showed a reduction in late grade 3 or greater GI toxicity in favor of IMRT (24.3% vs 5.8%; $P = .012$).¹⁰⁰ All but one study¹⁰² reported equivalent outcomes with regard to locoregional control, colostomy-free survival, and OS. Bazan et al showed that IMRT confers survival and local control benefits over conventional RT; however, the outcomes

TABLE 4. Summary of Studies Evaluating Intensity-Modulated Radiotherapy-Based Chemoradiation for Anal Cancer

STUDY	NO.	MEDIAN TUMOR DOSE (RANGE), Gy	MEDIAN F/U, mo	TIME POINT, y	LRC, %	CFS, %	OS, %	ACUTE G3+ GI TOXICITY, %	ACUTE G3+ SKIN TOXICITY, %
Retrospective studies									
Milano 2005 ¹⁰⁴	17	54 (45-59.4)	20.3	2	82	82	91	0	0
Salama 2007 ¹⁰⁵	53	51.5 (32-60.9)	14.5	1.5	84	84	93.4	15.1	37.7
Peppek 2010 ¹⁰⁶	29	54 (37.8-64)	19	2	95	91	100	9	0
Call 2011 ¹⁰⁷	34	50.4 (48.6-57.6)	22	3	88	NR	87	NA	NA
Chuong 2012 ¹⁰⁸	52	56 (50-62.5)	21	3	94	93	100	9.6	11.5
Kachnic 2012 ¹⁰⁹	43	54	24	2	95	90	94	7	10
DeFoe 2012 ¹¹⁰	78	55.8	16	2	84	81	87	28	29
Viellot 2012 ¹¹¹	39	63 (40-65)	24	2	77	85	89	10	0
Mitchell 2014 ¹¹²	65	54 (50-58.8)	19	2	93	NR	96	9	17
Prospective studies (RTOG 98-11 3DCRT included for comparison)									
RTOG 0529 Ph 2 (Kachnic 2013 ¹⁰¹)	52	T2, 50.4; T3-T4, 54	27	2	NA ^a	NA ^a	86	21	23
RTOG 98-11 Ph 3 (Ajani 2008, ⁷⁸ Gunderson 2012 ⁷⁹)	649	(45-59)	NR	5	80 ^b	72 ^b	78.3 ^b	36 ^c	49 ^c

3DCRT, 3-dimensional conformal radiation therapy; CFS, colostomy-free survival; F/U, follow-up; G3+, grade 3 or greater; GI, gastrointestinal; Gy, grays; LRC, locoregional control; OS, overall survival; NA, not available; Ph, phase; RTOG, Radiation Therapy Oncology Group. ^aThe 2-year outcomes were similar to those reported in RTOG 98-11. ^bThese values are for patients in the mitomycin C arm. ^cThese values are for all patients.

of their 3D conformal group were inferior to those reported in RTOG 98-11 and in the other comparative studies.

Brachytherapy

Brachytherapy is a technique for delivering very high and sometimes ablative doses directly to the tumor while allowing maximal sparing of surrounding normal tissues that cannot be achieved with other techniques. Brachytherapy can be delivered in several ways, including interstitial tumor application of radioactive implants delivering doses of from 10 to 25 Gy over a period of 3 or 4 days while the patient is immobilized in the hospital. This represents a low-dose-rate application. The other, more attractive alternatives are remote afterloading of an iridium-192 source either intraluminally, through a rectal applicator that has direct contact with the tumor, or through interstitially placed catheters, which traverse the tumor and represent high-dose-rate applications. Catheters are placed through an external template under CT or rectal ultrasound guidance. The advantage of this technique is that there is no hospitalization required, and 2 or 3 treatments can be delivered on an outpatient basis. Brachytherapy for the treatment of anorectal malignancies typically has been performed as a boost after external radiation^{75,116-119} or as salvage treatment for isolated local failures after external beam RT.¹²⁰

Brachytherapy for the treatment of anal cancers has been performed for nearly a century.^{121,122} Studies have been conducted to compare external beam boost versus brachytherapy boost.^{115,123,124} However, despite improved local control and proctitis, data are conflicting. Given the lack of prospective data, it is difficult to support the use of brachytherapy given the recent advancements in radiographic imaging and radiation delivery that have led to improved toxicity profiles. The benefit of brachytherapy may be limited to patients who have a poor response to initial chemoradiotherapy. The very high dose per fraction delivered by brachytherapy may overcome the radiotolerance in this population of patients.

Management of Inguinal Lymphatics

Synchronous inguinal metastases are present in about 10% of patients, and the incidence is higher in patients with T3 and T4 tumors.⁴⁶ The inguinal recurrence rate of clinically lymph node-negative patients who are not prophylactically treated with inguinal radiation ranges from 7.5% to 16%, with rates as high as 30% for those with T3 and T4 tumors.^{46,48} Patients with clinically uninvolved lymph nodes who received prophylactic inguinal radiation had inguinal recurrence rates as low as 2%.⁴⁸ The role of inguinal radiation in T1 and T2 tumors is still controversial. A phase 2 study by Matthews et al revealed that the overall

TABLE 5. Retrospective Studies Comparing 3-Dimensional Conformal Radiotherapy Versus Intensity-Modulated Radiotherapy for Anal Cancer

STUDY	TECHNIQUE	NO.	MEDIAN DOSE (RANGE), Gy	MEDIAN F/U, mo	MEDIAN RT, d	TIME POINT, y	LRC, %	CFS, %	OS, %	ACUTE G3+ GI TOXICITY, %	ACUTE G3+ SKIN TOXICITY, %
Saarilathi 2008 ¹¹⁵	3DCRT	39	NR	81	NR	NR	92.3	NR	NR	12	32
	IMRT	20	NR	19	NR	NR	85	NR	NR	0	16
	<i>P</i>						.54			.004	NS
Bazan 2011 ¹⁰²	3DCRT	17	54 (45-62.4)	26	57	3	57	NR	52	29	41
	IMRT	29	54 (45-59.4)	32	40	3	92	91	88	7	21
	<i>P</i>				<.0001		<.01		<.01	.003	.003
Dewas 2012 ¹⁰³	3DCRT	27	59.4 (30.6-66.6)	60	59	2	76.5	81.1	81.1	3.7	33.3
	IMRT	24	59.4 (30.6-66.6)	23	47	2	63	60.3	88.5	4.2	37.5
	<i>P</i>				.0007		.12	.12	.58	1.0	.756
Dasgupta 2013 ¹¹⁴	3DCRT	178	45 (45-50.4)	73.2	39	2	82	91	90	NR	NR
	IMRT	45	54 (50-56)	27.6	40	2	87	97	93	NR	NR
	<i>P</i>		< .01		.62		.2	.1	.91		
Chuong 2013 ¹⁰⁰	3DCRT	37	59.4 (45-63)	62	49	3	92	94	86	30 ^a	65
	IMRT	52	56 (50-62.5)	20	39	3	91	91.3	91	9.6 ^a	11.5
	<i>P</i>		.038		<.0001		>.1	>.1	>.1	.061	<.0001

3DCRT, 3-dimensional conformal radiation therapy; CFS, colostomy-free survival; F/U, follow-up; G3+, grade 3 or greater; GI, gastrointestinal; Gy, grays; IMRT, intensity-modulated radiation therapy; LRC, locoregional control; NR, not reported; NS, not significant; OS, overall survival; RT, radiotherapy. ^aThe rate of chronic G3+ GI toxicity for 3DCRT versus IMRT was 24.3% versus 5.8%, respectively ($P = .012$).

inguinal recurrence rate in 44 patients with T1/T2N0 tumors who did not receive inguinal radiation was 22.5%.¹²⁵ In a group of 201 patients with uninvolved inguinal lymph nodes who did not receive prophylactic inguinal radiation, the 5-year cumulative rate of inguinal recurrence was 12% for patients with T1 and T2 tumors and 30% for patients with T3 and T4 tumors ($P = .02$).⁴⁸ In a retrospective study from Zilli et al, those authors reported the outcomes of 116 patients with T2N0 disease who received chemoradiotherapy versus RT with or without inguinal radiation.¹²⁶ The overall 5-year inguinal relapse-free survival rate was 92.3%, and inguinal recurrences developed in 2 patients (4.7%) who were treated without inguinal radiation. There were no groin relapses in the patients who received groin radiation. The 5-year locoregional control rates for patients who did and did not receive groin radiation and received RT alone versus chemoradiotherapy were 80.1% versus 77.8% ($P = .967$) and 71% versus 85.4% ($P = .147$), respectively. A trend toward a higher rate of grade 3 or greater acute toxicity was observed in the patients who received groin radiation (53% vs 31%; $P = .076$). Determination of who should receive groin radiation prophylactically will depend on the increasing reliance of SLNB and PET-CT. Groin radiation is usually associated with the increased toxicity that is observed.¹²⁶ However, lower doses of 36 to 42 Gy in 1.5-Gy to 1.8-Gy

fractions with IMRT to clinically uninvolved lymph node regions has resulted in equivalent outcomes with an associated decrease in dermal toxicity.^{100,102,107-109}

Recurrences

The locoregional recurrence rate after chemoradiation reportedly has ranged from 10% to 30%.^{127,128} Studies support the finding that patients with recurrence after chemoradiation who undergo salvage APR surgery have a 5-year survival rate of 40% to 60% compared with a 3-year OS rate of 5% for patients who are unsuitable for surgery.¹²⁹ A study from MD Anderson¹²⁷ reported a 5-year survival rate of 64% in a cohort of 31 patients with a median follow-up of 29 months. The most significant prognostic factor after salvage APR was a negative resection margin (R0), with increased DFS and OS rates ($P < .001$ and $P = .03$, respectively).¹³⁰ The median survival for patients with negative and positive margins after salvage surgery was 33 months versus 14.3 months, respectively. Therefore, an R0 salvage APR can improve survival significantly. Salvage APR for anal cancer (also known as radical APR) is different from that performed for low rectal cancer. The salvage APR involves wider lateral margins to the ischial tuberosity. If the lesion is large (eg, close to the vaginal wall), then an en-bloc resection is required because of the risk of fistulae caused by prior RT. As a result of the larger perineal

wound, a variety of reconstructive tissue flap approaches have been applied, with the vertical rectus abdominis myocutaneous flaps most commonly used.^{131,132}

Patients with inguinal recurrence who did not receive radiation to the groin can be salvaged with chemoradiation. However, if there is inguinal recurrence after groin radiation, an inguinal lymph node dissection should be performed, and an APR can be avoided if there is no recurrence in the anus.

Reirradiation

In patients with biopsy-proven, persistent disease after chemoradiotherapy in the intergroup trial that evaluated the role MMC, an external beam boost was attempted as a salvage treatment.⁷⁷ Twenty-five patients with persistent disease were treated with 5FU, cisplatin (100 mg/m²), and 9 Gy of external beam RT. Of those 25 patients, 22 underwent posttreatment biopsies, and 12 (55%) were negative. Of these 12 patients, 4 remained disease free for 4 years, 4 underwent APR and remained free of disease, and 4 died. In the 10 patients who had residual disease after salvage treatment, 9 underwent APR, 7 died (6 of progressive disease), and 3 remained free of disease. Overall, 50% of salvage patients were alive without disease at 4 years.

Metastases

Chemotherapy

Other than the standard doublet radiation regimens used for locally advanced disease, there are no uniformly accepted chemotherapy regimens for the treatment of anal cancer in the metastatic setting. Many patients present with localized disease, which is often curable through definitive chemoradiation therapy, usually consisting of MMC and infusional 5FU. This regimen is now largely considered the standard of care, and APR is reserved for salvage therapy. A minority of patients (12%) will present with metastatic disease, and 10% to 20% of those treated with curative intent will later develop metastatic disease.^{75,133,134} The most common site of metastasis is the liver; however, other sites often affected are the lungs, lymph nodes, peritoneum, and bones.¹³⁵ Similar to lung carcinoma, this cancer has also been noted to metastasize to the brain.

Most of the literature available regarding treatment is based on case studies or series. In the metastatic setting, when treating patients whose primary tumors remain intact, a multidisciplinary approach is preferred and includes medical, surgical, and RT if appropriate. Discussing these possible options early on is of utmost importance to help ensure ideal quality of life (QoL), especially when dealing with locally advanced disease. Potential complications of locally advanced, recurrent disease include ulceration and necrosis of the inguinal lymph nodes, which can be debilitating.

Given the rarity of SCCA, the treatment regimens used today are extrapolated from those for more common SCCAs, such as lung and cervical cancers. There is no standard systemic chemotherapy regimen that is recommended for treating patients with unresectable disease. In this review, we hope to provide insight into the aspects of treating this disease, and we highlight treatment options.

The Standard: 5FU and Cisplatin

The most commonly reported regimen is 5FU plus cisplatin, which, in a case series of 18 patients, demonstrated a partial response rate of up to 50% and a complete response rate of 15%.^{136,137} The regimen consisted of a continuous infusion of 5FU (1 g/m² daily for 5 days) plus an infusion of cisplatin (100 mg/m²) on day 2 every 4 weeks. All patients received a median of 4 cycles, and all had acceptable toxicities. The most common toxicities included mucositis, nausea, vomiting, diarrhea, neutropenia, electrolyte imbalances, peripheral neuropathy, and tinnitus. On occasion, delayed sensitivity reactions were noted in some patients.¹³⁸ In addition, another case series on 3 patients with hepatic metastasis who were treated with cisplatin demonstrated a significant response to the cisplatin-fluoropyrimidine chemotherapy combination, which was given for 3 consecutive days. A PFS greater than 17 months was reported in 2 of the 3 patients.¹³⁹ Although effective in demonstrating some degree of response, this therapy has not been previously proven to provide long-term control or cure. A recent retrospective experience at MD Anderson described 53 patients with metastatic disease. Twenty-three treatment-naïve patients were identified who had received platinum-based therapy.¹⁴⁰ Patients had received a median of 3 subsequent lines of systemic chemotherapy. After a median follow-up of 18 months, the median PFS was 19 weeks, and the median OS was 38 months.

Carboplatin/Paclitaxel

Combined carboplatin and paclitaxel is commonly used in squamous cancer of the lung, but its efficacy in anal cancer is unclear. Researchers at the Moffitt Cancer Center (Tampa, Fla) retrospectively determined the tolerability and outcome of patients with metastatic SCCA of the anal canal who were treated with carboplatin/paclitaxel (every 3 weeks). Thirteen patients who were treated between 2007 and 2012 were included in the analysis. The median number of cycles delivered was 4. The response rate was high at 62%, with 2 patients achieving a complete response and 6 patients achieving a partial response. Grade 3 toxicities included peripheral neuropathy in 3 patients, diarrhea in one patient, and infection in 3 patients. Four patients had grade 3 neutropenia, and one patient had grade 4 anemia. The median PFS was 4.6 months, and the median OS was 10.5 months.¹⁴¹

Carboplatin/Paclitaxel/Continuous-Infusion 5FU

Hainsworth and colleagues conducted a phase 2 study of 60 patients with metastatic SCCA of any malignancy, excluding the lungs, that included 4 patients with SCCA of the anal canal. The chemotherapy regimen consisted of paclitaxel 200 mg/m² by 1-hour intravenous infusion on days 1 and 22, carboplatin (area under the curve = 6) on days 1 and 22, and 5FU 225 mg/m² daily by 24-hour continuous intravenous infusion on days 1 through 36, to be repeated every 6 weeks. In that study, all patients received a maximum of 4 cycles of therapy. This schedule caused a high incidence of grade 3 and 4 toxicities, including myelosuppression (48%), diarrhea (17%), and mucositis (28%). An impressive overall response rate of 65% and a complete response rate of 25% were reported; 2 patients with a complete response had a primary anal squamous carcinoma. The median duration of response for the anal carcinoma patients was 26 months.¹⁴²

Resection of Hepatic Metastases

Hepatic resection has proven to be effective, with 5-year OS rates from 20% to 65% in metastatic colorectal cancer.¹⁴³ However, in metastatic anal cancer, the data in the literature are less robust, with the majority being small studies. In a multicenter analysis, 52 patients at 8 major cancer centers with hepatic metastases from multiple squamous cell carcinomas of various primary tumor types, including the anal canal (N = 27), were evaluated. The majority of patients (70%) with primary SCCA of the anal canal received chemotherapy with or without RT, and the remaining patients received chemotherapy with or without RT plus surgery or surgery alone. The authors reported a postresection OS of 22.3 months. In addition, synchronous disease, hepatic tumor size greater than 5 cm, and positive surgical resection margins were associated with worse OS.¹⁴⁴ In summary, there are minimal data regarding prognosis and outcome after hepatic resection in patients with SCCA of the anal canal. However, as in other malignancies, for lung or liver metastases, the consideration of metastatic surgical resection is not unreasonable if it can be potentially provided with curative intent. The definitive role of neoadjuvant and adjuvant chemotherapy after surgical resection is unknown.

In summary, several challenges remain in the treatment of metastatic anal cancer. There is a dearth of published studies on the treatment of metastatic SCCA of the anal canal, with the majority of published studies comprising small case series or individual studies. The majority of chemotherapeutic regimens, mainly 5FU and platinum-based therapy, have been adopted from other squamous cell carcinomas. The optimal duration of chemotherapy remains unestablished. On the basis of preliminary findings, systemic

chemotherapy should be considered in any patients who demonstrate a good performance status, and therapy may be continued indefinitely for maximal outcome if it is well tolerated. Similar to the uncertainty regarding the type and duration of systemic chemotherapy, the role of neoadjuvant and/or adjuvant chemotherapy in the setting of surgically resectable metastatic disease remains unclear. However, when the primary tumor is in place, multidisciplinary management is imperative to optimize the care and QoL of the patient. In the future, clinical trials should be created to shed more light on the role of biologic agents and specific chemotherapeutic regimens for unresectable disease in both HIV-positive and HIV-negative patient populations.

Radiation Techniques

Target Volume and Radiation Field Design

With the increased use of multifield techniques for 3DCRT and IMRT, proper delineation of tumor and lymph node volumes is required. The gross tumor volume (GTV) is representative of the tumor and grossly involved lymph nodes. The extent of GTV can be determined by information from physical examination and endoscopic findings. In addition, the GTV can be more accurately delineated by fusion of the treatment-planning CT scan with a treatment-planning magnetic resonance imaging or PET-CT scan obtained at the time of simulation. The clinical target volume (CTV) includes microscopic extension of the GTV in addition to the high-risk lymph node areas, including perirectal and mesorectal lymph nodes, pelvic lymph nodes (including the bilateral internal and external iliac chains), bilateral inguinal lymphatics, and presacral lymph nodes. The superior extent of the CTV is at the level of the sacral promontory or the iliac bifurcation. The inferior extent of the CTV is 3 cm below the GTV of the anal canal.

A retrospective study from MD Anderson of 167 patients treated with chemoradiation revealed that all pelvic failures occurred in patients whose superior field border was placed at the bottom of the sacroiliac joints. It was concluded that the superior border should be placed at the L5-S1 interface.¹⁴⁵ In addition, an analysis of 173 patients treated at Memorial Sloan Kettering Cancer Center (New York, NY) revealed that, of the 20 patients who developed regional recurrences, 4 were in the common iliac region, and 3 were presacral, suggesting that common the iliacs should be included in advanced-stage patients.¹⁴⁶

The NCCN recommends following the multifield technique according to RTOG 98-11,⁷⁸ although IMRT-based treatment is also commonly used.¹¹³ PET-CT should be performed for treatment-planning purposes to accurately delineate the GTV and involved lymphatics. For lymph node-negative patients, field reduction off the superior border and groins is recommended after 30.6 Gy and 36 Gy, respectively.

Attempts should be made to reduce dose to the femoral heads. In patients treated with an anteroposterior-posteroanterior approach, lateral inguinal lymphatics should be brought to a minimum dose of 36 Gy using an anterior en-face electron boost matched to the posteroanterior field exit dose. IMRT can be used in place of 3DCRT but requires precise contouring of normal tissues, GTV, and CTV to reduce marginal miss. In RTOG 0529, 81% of patients required IMRT replanning, with 3 cases of major deviations of normal tissues.¹⁰¹ Atlases for the precise contouring of anal cancer targets and normal tissues are provided by the RTOG (available at: atc.wustl.edu/protocols/rtog-closed/0529/ANAL_Ca_CTVs_5-21-07_Final.pdf, accessed on December 10, 2014) and from the Australasian GI Trials Group.¹⁴⁷

Radiation Dose and Fractionation

This section will discuss generally recommended radiation doses. The established dosing from RTOG 98-11 is to treat the initial field to 30.6 Gy in 1.8-Gy fractions followed by a field reduction of the superior border to below the sacroiliac joints. For N0 patients, a second field reduction off the groins after 36 Gy is suggested. For lymph node-positive patients, an additional 14.4 Gy are delivered in 1.8-Gy fractions. For patients with T3 tumors, T4 tumors, lymph node-positive disease, or residual disease after a T2 tumor, a boost to gross disease is given with an additional 10 to 14 Gy in 2-Gy fractions to a total dose of 55 to 59 Gy. RTOG 0529 established the feasibility of dose-painting IMRT. The advantage of dose-painting IMRT is that only one plan is required rather than the several sequential plans required with 3DCRT. In RTOG 0529, T2N0 patients were treated with a dosing schema of 1.8 Gy per fraction to 50.4 Gy to the GTV and 1.5 Gy per fraction to 42 Gy (in 28 fractions) to regional lymphatics. For T3N0 and T4N0 patients, the dosing schema was 1.8 Gy per fraction to 54 Gy to the GTV and 1.5 Gy per fraction to 45 Gy (in 30 fractions) to regional lymphatics. For patients with positive lymph nodes, the dosing schema was 1.68 Gy per fraction to 50.4 Gy (in 30 fractions) for lymph nodes ≤ 3 cm and 1.8 Gy per fraction to 54 Gy for lymph nodes > 3 cm. Other small retrospective studies of IMRT have established other dose-painting IMRT schema with lower doses of 36 to 42 Gy at 1.5 to 1.8 Gy per fraction with IMRT to clinically uninvolved lymph node regions.^{100,102,107-109} Chuong et al reported on a dose-painting IMRT technique using 1.8 Gy per fraction to a dose of 36 Gy to uninvolved lymphatics, 45 to 50.4 Gy for involved lymphatics, and 2 Gy per fraction to 56 Gy for gross disease.^{100,108} In general, doses > 54 Gy result in improved local control, while doses > 60 Gy do not result in added benefit.^{81,148-151} Higher doses per fraction above 2 Gy have resulted in increased toxicity without added benefit. In a Princess Margaret Hospital study, patients who received

50 Gy in 2.5-Gy fractions had unacceptably high acute and late toxicity compared with patients who received 48 Gy in 2-Gy fractions with a treatment break.⁹⁸ However, in the UKCCCR trial (now ACT I), patients deemed to be good responders after the initial 45 Gy in 1.8-Gy fractions were treated with a boost of either 25 Gy with brachytherapy or 15 Gy in 2.5-Gy fractions with external beam RT.^{75,76}

In conclusion, total tumor doses ranging from 50.4 to 54 Gy are recommended for very good responders ($> 80\%$ response) or complete responders after 45 Gy, and doses from 56 to 60 Gy are recommended for patients with residual disease ($< 80\%$ response) after 45 Gy. For patients with significant residual disease after 45 Gy, either a brachytherapy boost or a hypofractionated boost (≥ 2.5 Gy per fraction) to a total dose of 60 Gy is recommended.

Treatment Breaks

ECOG 4292, a phase 2 trial of chemoradiation with 5FU and cisplatin in anal cancer, enrolled 33 patients.⁸² This trial prescribed a radiation dose of 59.4 Gy in 33 fractions over 60 days. There were 2 cohorts. Cohort 1 ($n = 19$) had a planned 2-week break in RT after receiving 36 Gy, and cohort 2 ($n = 13$) had no planned break in RT. The 5-year OS rate for all 32 patients was 69% (cohort 1, 58%; cohort 2, 84%). The PFS rate was 53% for cohort 1 and 85% in cohort 2. A comparison of outcomes in patients treated on RTOG 87-04 (50.4 Gy) versus RTOG 92-08 (59.4 Gy, split course) revealed that OS, DFS, and colostomy-free survival were inferior in patients who received split-course RT.¹⁵² In a recent analysis of pooled data from RTOG 98-11 and RTOG 87-04, total treatment time, but not total RT duration, was significantly associated with colostomy failure and local failure in univariate analysis.¹⁵³ It was suggested that induction chemotherapy may contribute to local failure by increasing total treatment time. Finally, the results of the ACT II randomized trial showed high complete response and 3-year relapse-free survival rate of 74% with 50.4 Gy chemoradiation.⁸⁰ The good results were attributed to the lack of a treatment break. Treatment breaks in general should be avoided whenever possible. However, this may be unavoidable because of treatment-related toxicity like skin desquamation and diarrhea.¹⁵⁴ IMRT has been shown to reduce toxicity and RT duration compared with 3DCRT; however, no differences in locoregional control, OS, or colostomy-free survival were noted (Table 5).

Follow-Up

Because most anal carcinomas regress slowly, they regress even after completion of chemoradiation treatment. It is estimated that, by 12 weeks after the completion of treatment, the majority of patients should manifest the maximum treatment response. It is thought that this initial response is an independent prognosticator for survival.¹⁵⁵ NCCN guidelines

TABLE 6. Surveillance Recommendations After Completion of Treatment

PARAMETER	NCCN (2012)	ASCRS (2008)	UK ACT II Trial (2009)	ESMO (2010)
History and physical examination; digital rectal examination (anoscopy, proctoscopy, inguinal lymph node examination) ^a	After completion of treatment within 8-12 wk, then every 3-6 mo for 5 y	After completion of treatment within 6-12 wk, then every 3-6 mo	Year 1, every 2 mo; Year 2, every 3 mo; Years 3-5, every 6 mo	Years 1-2, every 3-6 mo; Years 3-5, every 6-12 mo for high-risk patients ^b
CT chest, abdomen, and pelvis	For high-risk patients every 6 mo, 9 mo, and 1 y up to 3 y ^b	For advanced disease only ^c	Year 1, every 6 mo; Years 2-3, every y	Not recommended
MRI	Not recommended	Not recommended	Every 6 mo in high-risk patients or those with residual disease ^b	Not discussed
Examination under anesthesia with biopsy	Not recommended	Controversial	Not discussed	Not discussed

ACT, Anal Cancer Trial; ASCRS, American Society of Colorectal Surgeons; CT, computed tomography; ESMO, European Society for Medical Oncology; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network. ^aProctoscopy is indicated if the lesion is high. ^bHigh-risk patients are defined as those with T3/T4, lymph node-positive (N+) cancers or those with residual disease. ^cAdvanced disease is defined as T3/T4 and N+ disease.

recommend that patients be evaluated at an 8-week to 12-week interval after the completion of treatment. At that stage, patients are classified as complete responders versus nonresponders; nonresponders are further categorized with either stable but persistent disease or progressive disease.¹⁵⁶ Routine biopsy is controversial in monitoring response to treatment, with some clinicians supporting random biopsies at a 3-month interval and others supporting biopsies only when there is the question of a suspicious lesion.¹⁵⁷ According to NCCN guidelines, patients with persistent disease and nonprogressive disease can be followed in 4 weeks.¹⁵⁶ Because most recurrences occur within the first 3 years, it is important to survey these patients closely for detection of recurrence to offer salvage surgical therapy. The recommended guidelines by various societies are summarized in Table 6.

QoL of Patients Treated for Anal Cancer

The majority of patients treated with chemotherapy and RT after the diagnosis of anal cancer have excellent outcomes.⁷⁸ However, special problems in psychological adjustment are posed as a result of both immediate side effects as well as late toxicities that also may adversely affect the QoL. While treatment approaches are more effective, they may result in unavoidable late effects. Among the effects are sexual dysfunction, urological/GI complaints, financial difficulties, fatigue, and a reduction in emotional and social well being.^{158,159}

Cancers of the colon and rectum produce psychological problems that relate primarily to concerns about the cancer itself and the impact of treatment on bowel or urinary function in relation to social and sexual activity. Acute effects of chemoradiation for anal carcinomas include diarrhea, mucositis, skin erythema, and myelosuppression. Late complications include anal ulcers, stricture, stenosis, fistulae, and necrosis.⁸

Allal and colleagues evaluated the QoL of patients after RT alone or combined with chemoradiation. While small

in numbers (41 patients; 35 women and 6 men), the study showed that patients treated with RT with or without chemotherapy rated their QoL similar to that of the general population with the exception of noting more frequent diarrhea. In that study, while 50% of patients reported sub-optimal anal function, 71% reported that they were satisfied with their current function. However, we note that the sexual functioning score in that study was dramatically low, with only 35% of patients reporting some sexual activity. Moreover, the extent of this activity varied greatly among patients and never reached the maximum level of functioning in any patient. Because genital organs are in close proximity to the high-dose treatment volume, the high degree of sexual dysfunction is in keeping with the earlier results observed in women with gynecologic cancers¹⁶⁰ and men with prostate cancers,¹⁶¹ in whom loss of sexual desire and/or orgasm, dyspareunia, and loss of potency are frequent.

Das and colleagues also evaluated long-term QoL in patients treated with RT or chemoradiation for anal cancer. They evaluated 32 patients using the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument and the Medical Outcomes Study (MOS) Sexual Problems Scale. The results of that study indicated that patients treated with RT or chemoradiation had acceptable overall QoL scores but poor sexual functioning scores, whereas younger patients had lower QoL and sexual functioning scores.¹⁶²

Bowel Function

The primary side effects of RT or chemoradiation for anal cancer include diarrhea, nausea, fecal incontinence, buttock pain, rectal urgency, and flatulence. These symptoms vary in nature and severity. However, Bentzen et al observed that the social and role functions were clearly reduced in long-term survivors, in part because the symptoms were perceived as private and embarrassing and had an impact on self-confidence and daily life.¹⁶³

Urinary Function

Urinary function can also be affected as a result of pelvic RT and chemoradiation for anal cancers. The most notable side effects are urinary frequency, urinary incontinence, and dysuria.¹⁶³ A comparison of conformal RT and IMRT techniques by Ferrigno et al¹⁶⁴ found that patients treated with whole pelvic IMRT showed less GI toxicity, but the same acute genitourinary toxicity was reported in both groups.

Sexual Side Effects

As noted by Allal et al,¹⁶⁵ sexual functioning is affected by treatments of anal cancer in both men and women. Considerable reductions in sexual interest and sexual dysfunction are reported among anal cancer survivors.¹⁶⁶ The majority of male anal cancer survivors report inability to achieve or sustain an erection, difficulty climaxing, weaker and less-satisfying orgasms, lack of interest in sex, less energy, and/or feeling less attractive. A large proportion of women report dyspareunia, fatigue, loss of sexual desire, loss of attractiveness, and/or emotional changes that affect sexual functioning. These findings are consistent with results of late-effects and QoL findings after RT for other pelvic malignancies.^{166,167}

Psychological Adjustment

There are very few studies that identify a specific link between depression and anal cancers. However, an estimated 25% of cancer patients of all types experience major depression at some point during their illness. In addition, approximately 30% of all cancer patients experience anxiety, and 30% experience “distress” related to cancer.^{168,169} Despite the relatively significant number of patients experiencing psychological problems along a continuum, they often go undiagnosed and/or untreated. The reasons for this include the finding that signs of depression may be confused with symptoms of cancer or its treatment, health care providers may not inquire, and patients may not report psychological symptoms. Screening tools, such as the Brief Symptom Inventory, the Distress Thermometer developed by the NCCN, and the Patient Health Questionnaire 9-point depression scale, can be helpful in determining which patients may benefit from further psychosocial support. Treatment for depression is optimized through a combination of therapy and medication; treatment for anxiety and distress is optimized through support, cognitive behavioral therapies, and stress-reduction techniques.

Proactive Approaches

Sexual Side Effects

For patients who experience immediate and long-term effects of treatment for anal cancers, earlier and proactive

interventions are appropriate. For women receiving pelvic radiation, the early and ongoing use of dilators, moisturizers, and lubricants should be encouraged, with clear information given about their importance. Vaginal foreshortening because of pelvic radiation-induced fibrosis is a significant subacute and late side effect of treatment. Cullen et al suggest 8 care recommendations that address the concerns of women treated with pelvic radiation.¹⁷⁰ They include: 1) introduce the dilator in a light and straightforward manner, 2) enhance dilator accessibility, 3) introduce the dilator early in treatment, 4) emphasize health maintenance over intercourse as a benefit of dilator use, 5) explore and acknowledge women’s values and views on sexuality, 6) increase awareness and sensitivity to emotional reactions, 7) enhance psychoeducational resources for supporting vaginal dilator use, and 8) ensure consistent institutional practice when introducing the dilator. Early involvement of support services, including physical therapists, pelvic rehabilitation specialists, dieticians, and psychosocial support, can be very helpful. Also, topical estrogen, vaginal moisturizers, lubricants, and vaginal dilators can help improve sexual function in women. In addition, minimizing the RT dose to a portion of the anterior wall of the vaginal vault may be helpful.

Phosphodiesterase inhibitors, such as sildenafil, can help improve sexual function in men. For both groups, it is important to consider the impact of depression and/or emotional distress on sexual functioning, and referral to pelvic rehabilitation specialists or a certified sex therapist may be helpful.

Fertility Issues

In recent years, increasing attention has been given to fertility issues and fertility sparing for young cancer patients of reproductive age. Recent estimates suggest that 450,000 cancer survivors are of reproductive age.¹⁷¹ QoL for young cancer survivors includes fertility issues. It is essential that oncologists discuss fertility preservation and refer patients of child-bearing age to a reproductive endocrinologist.¹⁷²

GI Side Effects

Recent articles have reviewed the appropriate management of GI and sexual dysfunction after pelvic RT.¹⁷³⁻¹⁷⁵ Opiate agonists like loperamide, bulking agents, and a low-fiber diet can help decrease GI symptoms.

Sacral Nerve Stimulation

Some studies suggest that the use of short-term sacral nerve stimulation can notably decrease episodes of fecal incontinence.¹⁷⁶ It also may be a possible treatment option for some patients with urinary retention, urinary incontinence, anal incontinence, and constipation.¹⁷⁷ Malouf et al found that, in patients with sphincter degeneration and weakness, and possibly in those with sphincter disruption, sacral nerve

stimulation markedly improved fecal incontinence.¹⁷⁸ Traditionally, these patients are managed with conservative therapies such as antidiarrheal agents and dietary manipulation.

Hyperbaric Oxygen Therapy

Some research has shown that hyperbaric oxygen therapy can help reduce inflammation in bones and adjacent soft tissue injury caused by radiation. There is need for more randomized clinical studies to determine the overall value and efficacy of hyperbaric oxygen therapy in reducing the side effects of RT.^{179,180}

Conclusions

Although more research needs to be done, the results of recent studies suggest that more emphasis needs to be placed on identifying and addressing treatment-related symptoms during and after chemoradiation for anal cancer. Long-term follow-up of these patients is necessary to identify and treat the consequences of successful cancer therapy, and it is important to note that a disconnect often exists between provider-related toxicity scores and patient-reported QoL scores.¹⁶² An interdisciplinary approach to identify and intervene with the issues affecting the QoL of patients treated for anal cancer is optimal. ■

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