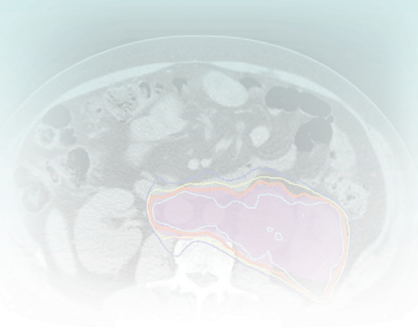
CHAPTER

# 52 Anal Carcinoma



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## INCIDENCE

In 2015, there were an estimated 7270 new cases and 1010 deaths attributable to anal squamous cell carcinoma,[1] representing approximately 2% of gastrointestinal malignancies in the United States.[2]

## BIOLOGIC CHARACTERISTICS

Prognostic factors predictive for local control and survival are size, extent of the primary tumor, and regional lymph node involvement.

## STAGING EVALUATION

Staging should generally include a complete history and physical examination, anoscopy with biopsy, complete blood cell count, liver function tests, serum creatinine levels, chest radiograph, and computed tomography (CT) scanning of the abdomen and pelvis. Positron emission tomography (PET) imaging should be considered.

Endoscopic ultrasound may be used to evaluate the depth of invasion.

## PRIMARY THERAPY

Definitive radiotherapy and concomitant 5-fluorouracil (5-FU) and mitomycin-C are appropriate treatment for most patients with anal cancer. Five-year survival rates range from 40% to 80%.

Local control with anal preservation is achieved in more than 95% of patients with tumors less than 2 cm in size and in 60% to 75% of those with larger tumors.

## ADJUVANT THERAPY

Adjuvant radiotherapy and concurrent chemotherapy are indicated for those rare patients who are managed initially with abdominoperineal resection but have primary tumor extension beyond the anal sphincter or metastases to regional lymph nodes.

Approximately 60% of patients with persistent or recurrent local disease after radiotherapy plus chemotherapy may still be cured with abdominoperineal resection.

## LOCALLY ADVANCED DISEASE

Radiotherapy and concurrent chemotherapy are effective in patients with large primary cancers with or without invasion of adjacent organs. Two thirds of patients with locally advanced primary tumors maintain sphincter function.

Patients with positive nodes have a 5-year survival of 40% to 60%.

## PALLIATION

Palliative chemotherapy with 5-FU and mitomycin C in patients with metastatic disease is associated with a 50% response rate.

Brain and osseous metastases may be effectively palliated with hypofractionated radiotherapy.

Carcinoma of the anal canal accounts for about 1.9% of all malignant tumors of the digestive system in patients in the United States.[1] Despite the rarity of anal cancer, it is a model for successful oncology research, both in the laboratory and in the clinic. Epidemiologic observations about the increased incidence of anal cancer in some populations, along with advances in molecular biology that have allowed the identification of human papillomavirus (HPV) DNA in most anal tumors, have provided the initial clues to the mechanism of anal carcinogenesis. Retrospective studies have provided important information about the natural history and patterns of spread of anal cancer, as well as hypotheses to test in prospective trials. Prospective randomized trials have been completed successfully and have led to the adoption of a combination of radiotherapy and chemotherapy as the standard of care for patients with anal cancer. Questions remain, however, about the most effective and least toxic regimens of radiotherapy and chemotherapy.

This chapter focuses on the biologic characteristics of anal cancer, the rationale for patient evaluation, treatment recommendations, and results of treatment. Radiotherapy techniques for patients with anal cancer will also be discussed.

## ETIOLOGY AND EPIDEMIOLOGY

Anal cancer occurs much less frequently than other types of cancer of the digestive tract. In 2015, there were an estimated 7270 new cases and 1010 deaths attributable to anal cancer,[1] representing approximately 2% of gastrointestinal malignancies in the United States.[2] In the United States, the annual incidence is 0.47 per 100,000 white men and 0.69 per 100,000 white women.[3] The annual incidence among African Americans is higher: 0.57 per 100,000 men and 0.78 per 100,000 women.[3] Overall, 87% of patients diagnosed with anal cancer are non-Hispanic whites, 5% are African American, and 3% are Hispanic.[4] The median age at diagnosis is 62 years.[4] Thus, the typical American patient with anal cancer is a white woman in her seventh decade of life.

Epidemiologic studies from the United States, Europe, and Australia have reported an increased incidence of anal cancer in the past 30 to 40 years.[5-7] Within the United States, the incidence of anal cancer in the general population has increased over the last 30 years, from 10 to about 20 per million.[5] In a review of the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2000, the incidence of anal

cancer in men and women was found to have risen from 1.06 and 1.39 per 100,000 persons to 2.04 and 2.06 per 100,000 persons.[5] In particular, the incidence of squamous cell anal carcinoma has increased dramatically after 1997 for men and women, consistent with the impact HIV has had on the acquisition and persistence of HPV.[8] In England, between 1990 and 2010, there has been a 69% increase in squamous cell anal carcinoma from 0.43 per 100,000 population in 1990–1994 to 0.73 in 2006 to 2010, with effect more marked in women than men.[9] Similarly, the number of new cases of anal cancer in Denmark has doubled in men and tripled in women.[10]

The incidence of anal cancer is higher in urban than in rural populations, and increases in the incidence of anal cancer have been greater in urban than in rural populations.[3,10] In the United States, the increased incidence of anal cancer has been predominantly limited to densely populated regions. Young men account for a substantial proportion of this increase.[8] In Denmark, the median age at diagnosis in men has decreased from 68 to 63 years, whereas in women, it has remained constant at 66 to 67 years.[10]

## Association with HIV Infection

At least part of the increased incidence in young men can be explained by the observation that men who have sex with men (MSM) are at increased risk for the development of both anal intraepithelial neoplasia (AIN) and anal cancer, particularly among patients with HIV.[11-15] The population at highest risk for anal cancer appears to be MSM (odds ratio [OR], 17.3),[16] and in particular in the subset of these men who are HIV-positive. A meta-analysis of 53 studies found that prevalence of anal cancer (45.9 versus 5.1 per 100,000 men) was significantly higher among MSM who were HIV-positive as compared to HIV-negative.[11]

With the introduction of highly active antiretroviral therapy (HAART), although the incidence of some AIDS-associated cancers, including Kaposi's sarcoma and non-Hodgkin's lymphoma, have decreased in incidence, the incidence of anal cancer has not declined.[21-24] Two large cohort studies from England and France recently demonstrated no significant difference in the standardized incidence ratio (SIR) for development of invasive anal cancer with the introduction of HAART.[23,24]

The incidence of anal cancer is markedly increased in both men and women who have AIDS. The relative risk (RR) estimated from a linkage analysis of cancer registries and AIDS registries is 63, and it is higher for homosexual men (RR, 84) than for heterosexual men (RR, 38). The increased risk is also apparent during the 5-year period before an AIDS diagnosis. The absolute risk of anal cancer in patients with AIDS is 1 per 1000.[25]

## Risk Factors

The pathogenesis of anal cancer is multifactorial. A diagnosis of anal cancer represents the result of an interplay of multiple environmental and host factors. Patients with epidermoid anal cancer are more likely than control patients to have had a previous diagnosis of malignant disease, including cancers of the vulva, vagina, or cervix and lymphoma or leukemia. Patients with anal cancer who are diagnosed before age 60 years are at higher risk of subsequent development of malignant diseases of the respiratory system, bladder, vulva, vagina, and breast, but they are not at increased risk for subsequent development of colon or rectal cancers.[26] Overexpression of the c-*myc* oncogene has been implicated in the pathogenesis of both anal squamous cell neoplasia and breast cancer.[27,28] This finding, along with an observed pattern of second malignant diseases and prior malignant diseases in patients with anal cancer, suggests a multifactorial pathogenesis and common oncogenetic risk factors. These factors may include sexually transmitted viruses, environmental carcinogens such as cigarette smoke, immunosuppression, and genetic susceptibility.[26]

Anal cancer and cancers of the female genital tract share a common pathogenesis.[29] In the embryo, the anal and cervical canals are both derived from closely related anlagen.[30] Women patients with anal cancer are more likely than women with colon or stomach cancer to have had a prior diagnosis of cervical intraepithelial neoplasia.[29] An association between anal cancer and the number of lifetime sexual partners has been reported in women.[31] Case-control studies have also found an association between anal cancer and some sexually transmitted diseases.[17,31-33] This association, along with the increased incidence in young homosexual men, strongly suggests an etiologic factor for anal cancer associated with increased sexual activity.[3]

Among sexually transmittable infectious agents, HPV has been the most thoroughly studied potential causative agent. Although there are more than 60 types of HPV, those most commonly associated with benign genital condylomata acuminata are HPVs 6 and 11, whereas HPVs 16, 18, 31, 33, and 35 are associated with malignancy or high-grade dysplasia.[34] Several investigators have also reported an association between genital warts and anal cancer in men and women.[32-36] The development of anal warts in both sexes has been linked with the practice of anal intercourse.[32]

The likelihood of finding HPV DNA in specimens of anal cancer varies according to patient demographics and laboratory technique. Patients with HPV-associated anal cancer are 10 years younger on average than patients with reportedly HPV-negative cancers.[37] In addition, HPV-associated anal cancer has been reported more frequently in Europe and South America than in South Africa and India.[38] When in situ hybridization techniques are used to analyze biopsy specimens of anal cancer, the rate of HPV DNA detection ranges from 17% to 73%.[34,37]

Exposure to HPV may be a risk factor even for patients in whom HPV DNA is not detected in the carcinoma specimen. Serum IgA antibodies to a peptide antigen from the E2 region of HPV 16 have been found in 89% of patients with anal cancer compared with only 24% of controls.[37] In another study, antibodies to HPV 16 capsids were elevated in 55% of patients with anal cancer compared with 3% of controls. Antibodies to HPV-capsid antigen were detected in an equal number of cancer specimens from patients whose HPV DNA was negative or positive (as assessed by in situ hybridization), which suggests that some patients presumed to be HPV-negative had been exposed to HPV.[40]

HPV infection and anal cytologic abnormalities are common in patients with HIV infection.[12] Patients who are HIV-positive with HPV DNA found in anal biopsy specimens seem to have a high rate of cytologic abnormalities. In one study of 12 patients who are positive with HIV without AIDS, 11 patients (92%) with normal cytologic findings but with HPV DNA found in anal mucosa later had cytologic abnormalities at 17-month follow-up.[41]

Although the true influence of HPV in anal carcinogenesis is uncertain, some laboratory findings point to the involvement of the HPV E6 and E7 proteins. These findings include the observation that the *E6* and *E7* oncogenes are consistently expressed in tumor cells but that normal E6 and E7 regulatory mechanisms are absent.[43] In addition, the E7 protein of HPV 16, in cooperation with the E6 protein, is able to transform mammalian cells in vitro while blocking *E6* and *E7* gene function, which results in reversal of the malignant

HPV DNA is more likely to be detected with polymerase chain reaction analysis. Studies comparing both techniques have found that polymerase chain reaction techniques detect HPV DNA in 78% to 85% of patients, whereas in situ hybridization techniques find HPV DNA in only 17% to 50% of the same patients.[34,39]

Additionally, recently published data of 34,189 individuals infected with HIV and 114,260 individuals not infected with HIV in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from 1996 to 2007, the unadjusted anal cancer incidence rates were 131 for MSM who were infected with HIV, 46 for other men who were infected with HIV, and 2 for men who were uninfected with HIV per 100,000 person-years.[15] Although in most areas of the world, anal cancer is more common in women than in men of all age groups,[17,18] in areas with a relatively high proportion of MSM, however, anal cancer may be more common in men. For example, in San Francisco, the incidence of anal cancer in white men more than doubled from 0.53 per 100,000 in 1975 to 1.2 per 100,000 in 1989,[3] and in Los Angeles, anal cancer has become more common in men than in women younger than age 35.[19] A study of Danish MSM living in registered "marriage-like partnerships" identified an incidence of cancer double what was expected, which could be accounted for by HIV-related cancers, including Kaposi's sarcoma, non-Hodgkin's lymphoma, and anal cancer. The relative risk ([RR] of anal cancer in this population was 31, and anal cancer appeared to be associated with a positive HIV status.[20]

Many patients with AIDS most likely die of opportunistic infections before anal cancer is manifested. Although the impact of effective antiretroviral therapy on the incidence of anal cancer is not yet clear,[42] further increases in the incidence of anal cancer may be observed in patients with AIDS as survival time is prolonged.[41]

phenotype.[43,44] Interactions of HPV oncoproteins with known tumor suppressor gene products have been reported. The E6 protein of HPV 16 and HPV 18 forms stable complexes with the p53 protein product of the *P53* tumor suppressor gene.[45-47] The cellular p53-E6 protein complex results in a lack of appropriate G1 arrest and subsequent genomic instability. The E7 protein also forms complexes with the retinoblastoma gene product and with p107, p130, p33, cdk2, and cyclin A. E7 also activates the cyclin-A promoter and overrides two inhibitory functions that restrict the expression of cyclin A and cyclin E.[44]

Some evidence suggests that infectious agents other than HPV may contribute to anal carcinogenesis. Associations have been found between the development of anal cancer and a history of syphilis or gonorrhea in men[33,48] and between anal cancer and *Chlamydia* and herpes simplex virus type 2 in both sexes.[31,32] In a study of patients in and around San Francisco, herpes simplex virus DNA was detected in 3 of 15 patients with invasive anal cancer and in 3 of 4 patients with high-grade intraepithelial neoplasia.[39] No Epstein-Barr virus or cytomegalovirus DNA was found in the tumor specimens of the 15 patients with anal cancer. Further studies are needed to determine whether these and other sexually transmitted agents are involved in anal oncogenesis or are merely surrogate markers for probable HPV infection.

Chronic immunosuppression is associated with an increased risk for anal malignant disease. Renal transplant recipients have an increased incidence (as high as 100-fold) of carcinoma of the vulva or anus.[49,50] These cancers occur at an earlier age than they do in the general population.[49] Renal transplant patients also have an increased incidence of cutaneous neoplasia and viral warts. Those with a high susceptibility to cutaneous malignant disease (four or more skin cancers) are more likely to have HPV DNA-associated skin cancer and are more likely to have an anogenital malignant tumor.[51] The increased incidence of anal malignant disease in patients who are HIV-positive is most likely caused in part by chronic immunosuppression.

A number of authors have reported an association between anal cancer and cigarette smoking.[31,32,35,52] When compared with a control group of patients with colon cancer, both men and women smokers were found to have an increased risk of anal cancer.[32]

Although in the past, chronic inflammation or irritation from benign anal conditions (e.g., hemorrhoids, anal fissure, fistula, or inflammatory bowel disease) had been associated with anal cancer,[18,53-55] recently published case controlled series have failed to demonstrate an association between benign anal conditions and anal cancer.[35,56] A Danish population-based study found that patients with anal fissure, fistula, perianal abscess, or hemorrhoids were at increased risk for anal cancer; however, the RR for invasive anal cancer was highest in the year immediately after a diagnosis of benign anal pathology, and it declined from a high of 12 the first year to 1.8 after 5 or more years. Thus, despite a temporal association between the diagnosis of benign anal lesions and the diagnosis of anal cancer, this suggests that a so-called benign anal condition is often a symptom or misdiagnosis rather than a cause of anal cancer.[56]

## PREVENTION AND EARLY DETECTION

Prevention of anal cancer should include educational efforts about the causal link of sexually transmitted HPV infection with malignant diseases of the anogenital tract. Recommendations of the 1996 National Institutes of Health Consensus Panel on cervical cancer prevention are also applicable to anal cancer and include encouragement to delay onset of sexual intercourse.[58] Barrier methods, such as condoms, do not prevent HPV transmission.[59] The panel also recommended development of an effective vaccine to prevent transmission of HPV, and a subsequent Phase III clinical trial provided encouraging results in this regard.[60-62]

In a randomized trial of 4065 healthy males 16 to 26 years of age, a quadrivalent vaccine was effective in preventing infection with HPV types 6, 11, 16, and 18 and prevented the development of external genital lesions. In the per-protocol population, efficacy against lesions related to HPV types 6, 11, 16, or 18 was 90.4%.[63] A planned substudy of that trial analyzed the impact of HPV vaccine on the development of anal squamous intraepithelial lesion (SIL) in 602 MSM who had a history of five or fewer lifetime sexual partners. Participants with a history or evidence of anal lesions were excluded, as were participants who were HIV positive at enrollment on the protocol. The primary endpoint of the trial was the development of anal SIL associated with HPV types 6, 11, 16, or 18. In the per-protocol population, which included 402 of the 598 men (67%) who received all three doses of vaccine, the incidence of anal SIL associated with HPV 6, 11, 16, or 18 was decreased by 78 percent in those receiving vaccine compared with placebo (1.3 versus 5.8 events per 100 person years at risk). Additionally, there was a 75% decrease in the incidence of high-grade squamous intraepithelial lesion (HSIL) with vaccine (0.8 versus 3.1 events per 100 person-years at risk).[64] As a result of these promising results, in October 2011, the Advisory Committee on Immunization Practices (ACIP) recommended the routine use of quadrivalent vaccine in males aged 11 or 12 years.[65]

Additional preventive efforts should be focused on the treatment of HPV infection, including the development of antiviral agents, targeting of E6 and E7 to block transforming activities, and vaccines to prevent progression of HPV infection.[51,58] Education is also required about the causal role of cigarette smoking in anal and other cancers.

Because of the rarity of anal cancer, efforts at early detection through widespread screening are not feasible. However, screening may be feasible in certain high-risk subsets. Anal intraepithelial neoplasia is a common finding in people who are infected with HPV.[12,41] Analogous to the situation with cervical cancer, where cervical SILs may progress to cervical carcinoma, HSIL may be a precursor to invasive anal cancer.[66-68] Anal cytologic smears have been used to diagnose HSIL in high-risk patients. Because the specificity of anal cytology for the detection of HSIL is low, anoscopy with biopsy is required to differentiate anal condylomata acuminata from HSIL.[66] However, the colposcopic criteria to distinguish low-grade squamous intraepithelial lesions (LSIL) from cervical HSIL have been used to distinguish LSIL from HSIL of the anus in homosexual and bisexual men.[69] This information may allow for a targeted biopsy of suspected HSIL, resulting in increased sensitivity for detection. One study of anal cytology in homosexual and bisexual men reported the sensitivity and specificity for detection of HSIL to be 69% and 59%, respectively, in men who are HIV-positive and 47% and 92%, respectively, in men who are HIV-negative.[68]

## BIOLOGIC CHARACTERISTICS

Unlike most gastrointestinal tract malignant diseases, anal cancer is predominantly a locoregional disease, and distant metastasis is relatively rare. Most relapses after curative therapy are located in the pelvis, perineum, or inguinal regions.[70] Only 5% to 10% of patients will have cancer that has spread beyond the pelvis at diagnosis,[53,59,71] and 10% to 30% of patients will have disease relapse at distant sites after curative local therapy.[60,70,72,73] Although chemotherapy is considered a

In a population-based case-control study of patients with anogenital cancers in the Pacific Northwest, 60% of patients with newly diagnosed anal cancer were current smokers compared with 25% of the controls. The risk of anal cancer was positively correlated with both the number of cigarettes smoked per day and the number of years the patient had been a smoker.[52]

Supporting evidence for this view is found in a study of patients treated for benign anal conditions at U.S. Veterans Affairs hospitals. The elevated RR for anal cancer in these patients was most pronounced in the first year after the benign pathologic condition was diagnosed, and it decreased rapidly thereafter until there was no increased risk of anal cancer between year 5 and year 22.[57]

component of standard therapy for anal cancer, its addition has not decreased the number of patients with distant metastases.[71,74,75] As the number of metastatically involved regional nodes increases, so does the risk of distant metastasis.[76] The most common site of distant metastasis is the liver, followed, in variable order, by the lungs, extrapelvic lymph nodes, skin, or bones.[71,75,77-80]

Characteristics of anal cancer that have consistently been correlated with local control and survival are the size and extent of the primary tumor and the status of the inguinal and pelvic lymph nodes.[81-83] The 5-year survival for patients with tumors 2 cm or less in diameter that are treated surgically is about 80% but declines to 55% to 65% when the tumor is 2 cm to 5 cm or to 40% to 55% when the tumor is more than 5 cm.[76,84] The depth of invasion and the size and extent of the primary tumor are prognostic for response to treatment, local control, and survival when patients are treated nonsurgrically with radiotherapy and chemotherapy.[70,75,80,85-88]

The survival for patients with regional lymph node metastases who are treated primarily with surgical procedures with or without adjuvant therapy is about half that observed in similar patients without nodal metastases.[84,89] Similarly, 5-year survival after radiotherapy alone in patients with inguinal lymph node metastases range from 0% to 36% compared with 5-year survival of more than 50% in patients without lymph node involvement.[89-91]

There is relatively little information in the medical literature about the prognostic significance of regional nodal metastases in patients who receive combined radiotherapy and chemotherapy. In a retrospective, recursive, partitioning analysis of patients treated at Princess Margaret Hospital (PMH), patients who are node-positive at 5-year follow-up were found to have a trend toward lower cause-specific survival (CSS) (57% versus 81%; $p = 0.07$).[74] In the European Organization for Research and Treatment of Cancer (EORTC) randomized trial of radiotherapy alone versus concurrent chemoradiation, regional nodal metastases were associated with significantly worse local control ($p = 0.004$) and survival ($p < 0.001$).[82] However, in node-positive patients, the number of involved nodes (≥1), their size (<2 cm or >2 cm), and the extent of involvement (N1, N2, or N3 category) added no further prognostic information.[82] Similarly, in a secondary analysis evaluating the impact of TN category on outcomes for RTOG 98-11, the best outcomes were found among patients with T2-3N0 disease, and the worse outcomes were in patients with T4N0, T3N+, and T4N+ disease. Outcomes for T2N+ patients were intermediate between T3N0 and T4N0.[73]

Patient-related variables that have been evaluated as potential prognostic factors for local control and survival in patients with anal cancer include age, gender, race, performance status, hemoglobin levels, and white blood cell counts. Age probably does not have independent prognostic significance for any endpoint. A retrospective Canadian study found that older patients were treated with less aggressive chemotherapy and were less likely to be offered salvage surgery for recurrence; therefore patients older than 65 years of age were found to be at higher risk for death from anal cancer.[92] An Australian study reported that although requirement for treatment break was higher in elderly patients, chemoradiation was safe and tolerable in elderly patients and provides equivalent disease control rates compared to the younger age group.[93] Conflicting data exist about the impact of gender on prognosis. Several studies have reported no difference in outcome by gender in patients treated with radiotherapy or combined radiotherapy and surgery.[74,91,92,94] However, a trend toward higher survival in women has been reported in some surgical series,[76,84] and in the EORTC randomized trial, female sex was associated with better survival ($p = 0.12$) and local control ($p = 0.05$).[82] Similarly, in recently published analyses of the Radiation Therapy Oncology Group (RTOG) 98-11 and United Kingdom Coordinating Committee on Cancer Research (UKCCCR) study respectively, male sex was significantly associated with poorer locoregional control,[83] disease-free survival (DFS),[81] disease-specific survival,[83] and overall survival (OS).[81,83] Lower survival has been reported in patients with a lower performance status, in nonwhite patients, and patients with higher white blood cell count with anal cancer who received combined-modality therapy.[83,95] A lower hemoglobin level has also been suggested to have an adverse effect on disease-specific survival.[83]

Several histopathologic variables have been evaluated as potential prognostic factors in patients with anal cancer. The histologic subtype (squamous cell cancer versus cloacogenic subtype), tumor cell morphology, extent of differentiation or keratinization, cell size, architecture, and pleomorphism are of no prognostic significance.[74,91,92,94,96] The extent of differentiation may be associated with tumor stage because patients with advanced-stage cancer tend to have tumors that are less differentiated.[76] The depth of invasion of the primary tumor has been reported to have prognostic significance in patients treated primarily with surgical resection.[96] DNA ploidy has also been associated with prognosis in surgically treated patients with DNA aneuploid tumors predictive of an inferior outcome.[96] In a Mayo Clinic study of surgically treated patients, those with aneuploid tumors had inferior survival compared with patients with DNA diploid or tetraploid tumors on univariate analysis. On multivariate analysis, however, DNA ploidy was not a significant predictive variable.[97]

There are currently no clinically useful tumor markers. Despite negative liver imaging, patients with elevated alkaline phosphatase or lactate dehydrogenase are at increased risk for subsequent liver metastases.[98] In one study, reduced expression of $p21^{waf1}$, a cyclin-dependent kinase inhibitor, was associated with shorter OS.[99] Preliminary information suggests that serum antibodies to HPV proteins may eventually be useful as prognostic markers. Elevated serum IgA antibodies to HPV 16 E2:9 peptide have been associated with lower survival rates independent of tumor size.[37] In another study, patients who died of anal cancer were found to have higher levels of IgG against HPV E7:5 peptide than did patients with anal cancer in complete remission or patients who died of other causes.[40]

## PATHOLOGY AND PATHWAYS OF SPREAD

The World Health Organization (WHO) classification of malignant epithelial tumors of the anal canal includes squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and undifferentiated carcinoma. Most cases of adenocarcinoma of the anus are actually distal rectal adenocarcinomas with extension into the anal canal. True primary anal canal adenocarcinoma is rare, as is small cell carcinoma of presumed neuroendocrine origin.[18,76] Subsets of squamous cell carcinoma in the WHO system include large-cell keratinizing carcinoma, large-cell nonkeratinizing or transitional carcinoma, and basaloid carcinoma.[100] Although basaloid carcinomas have historically been considered to be nonkeratinizing tumors, most basaloid carcinomas exhibit keratinization and should be considered squamous cell carcinomas.[67]

Although most anal canal malignant tumors are squamous cell carcinomas or squamous cell variants, marked morphologic heterogeneity is characteristic.[67] Classification of epidermoid anal cancers on the basis of morphologic appearance has led to the use of several potentially confusing terms. These include transitional cell carcinoma, basaloid carcinoma, and mucoepidermoid carcinoma. These tumors all arise from the

anal transition zone and are often grouped together as *cloacogenic carcinoma. Mucoepidermoid carcinomas* contain mucous microcysts and are histologically dissimilar to mucoepidermoid carcinomas of the salivary glands. The natural history is identical to that of squamous cell carcinoma of the anus without microcysts. Although sometimes considered to be distinct lesions in the medical literature, cloacogenic carcinoma, transitional cell carcinoma, basaloid carcinoma, and mucoepidermoid carcinoma are all subtypes of squamous cell carcinoma because patients with these various tumor subtypes have similar clinical characteristics and the tumor subgroups do not differ in natural history or response to therapy[18,53,70,101]

Primary anal melanoma is a rare tumor that accounts for only 1% of all anal cancers. Anal melanoma is similar to melanoma of the skin in that it rarely affects African Americans and is characterized by the distant spread of disease.[102] Outcome is poor after wide local excision or abdominoperineal resection, with just a 10% survival in most series at 5-year follow-up.[103]

## Pathways of Tumor Spread

Anal cancer tumors spread by direct extension to surrounding tissues, lymphatic dissemination to pelvic and inguinal lymph nodes, or hematogenous spread to distant viscera.[104] At diagnosis, about half of all anal cancers have been found to invade the anal sphincter or surrounding soft tissue. Although Denonvilliers fascia is usually an effective barrier to prostatic invasion in men, direct extension to the rectovaginal septum is a common occurrence in women.[105]

The anal canal has several potential lymphatic drainage pathways. The superficial inguinal nodes are the primary drainage basin for that part of the anal canal distal to the dentate line.[106,107] Lymphatic drainage around the dentate line occurs to perirectal lymph nodes and along the pathway of the inferior and middle hemorrhoidal vessels to obturator and hypogastric lymph nodes. Lymphatic connections also join the anus to presacral, external iliac, and deep inguinal nodes.[108]

Metastatic involvement of pelvic lymph nodes has been reported in 25% to 35% of patients treated primarily with abdominoperineal resection.[53,76] Inguinal node metastases are found in about 10% of patients at diagnosis; the risk depends on the size and extent of the primary tumor.[71,77] The incidence of inguinal node metastases may be as high as 20% for tumors more than 4 cm in diameter and as high as 60% when there is direct invasion of adjacent pelvic organs.[77] Relapse in undissected inguinal nodes has been reported in 13% of surgically managed patients with clinically negative inguinal lymph nodes.[76] Cumulative rates of inguinal relapse among patients treated with definitive chemoradiation without prophylactic inguinal irradiation has been reported in 30% of T3-T4 patients[109] and 7% to 12% of T1-T2N0 patients.[109,110] Prophylactic irradiation may significantly reduce the rate of inguinal recurrence.[109]

# CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Rectal bleeding is the most common symptom of anal malignant disease. Perineal pain, mass sensation at the anus, and a change in bowel habits are also frequently reported.[18,53,108,111-113] Many patients with symptoms of early anal cancer are diagnosed initially with a benign anal condition, such as hemorrhoids, anal fissures, or fistulae.[18,53]

Most patients with anal cancer are diagnosed at an early stage. A national survey of such patients found that 73% were diagnosed with stage 0 to II cancer, whereas only 8% were diagnosed with stage IV cancer.[4] The interval from the onset of symptoms to diagnosis may be quite prolonged, however, exceeding 1 month in 80% of patients and 6 months in 33%. A study of Norwegian patients with anal cancer found that nearly one third of them had a delay of more than 6 months from onset of symptoms to diagnosis.[91,113] This finding emphasizes the importance of a thorough digital rectal examination in patients with anal symptoms.[56,57,113]

## Patient Evaluation

Evaluation of the patient with known or suspected anal cancer should begin with a thorough history and physical examination. The patient should be questioned about anal sphincter function and any history of risk factors (sexual or drug abuse) for HIV infection.

In addition to a complete general physical examination, a detailed examination should be conducted of the abdomen, inguinal region, anus, and rectum. The extent of circumferential involvement of the anal canal should be noted, and documentation should be made of the size, extent, and location of the primary tumor. The size, location, and mobility of palpable inguinal lymph nodes should be noted. Perirectal lymph nodes may be involved metastatically, but these are rarely palpable by digital rectal examination.[91]

Laboratory studies should include a complete blood cell count, measurement of serum creatinine levels, and liver function studies of bilirubin, alkaline phosphatase, lactate dehydrogenase, and glutamic-oxaloacetic transaminase. For patients with HIV risk factors, a determination of HIV status should be made before the initiation of therapy. Although concentrations of serum carcinoembryonic antigen (CEA) are elevated in 20% of patients with anal cancer, posttreatment CEA values have not been found to correlate with clinical outcomes and have not proven useful in patient management.[114] There are no other clinically useful tumor markers for anal cancer.

Radiographic evaluation should include chest radiographs and CT scanning of the abdomen and pelvis. The CT scan is generally inferior to the physical examination for the characterization of primary tumors, but it is useful for the evaluation of the liver and the perirectal, inguinal, pelvic, and paraaortic lymph nodes. Magnetic resonance imaging (MRI) has not yet been proven to be more clinically useful than CT scanning. The depth of invasion of the primary tumor may be evaluated with ultrasonography.[115]

PET imaging is useful in further evaluating the extent of the primary tumor and the presence of regional lymph node metastases and distant metastases, as well as in evaluating the response to therapy.[116-121] A retrospective evaluation of the sensitivity of PET/CT imaging compared with physical examination and CT scanning alone among 41 patients with anal cancer showed that PET/CT imaging detected the primary tumor in 91% of patients compared with only 59% by CT scanning alone.[122] In addition, PET/CT identified positive inguinal nodes in 17% of patients who were found to be clinically negative by CT and physical examination. Another series reports that use of PET during initial staging led to a change in stage in 23% of patients and radiotherapy field changes in 13% of patients.[123] Furthermore, a posttherapy PET scan showing resolution of metabolic activity was reported to be highly associated with improved progression-free survival (PFS) (95% at 2 years versus 22%; $p < 0.0001$).[124] Posttreatment PET/CT demonstrating resolution of metabolic activity performed 3 months compared to 1 month after completion of treatment may yield higher sensitivity (100% versus 66%) and specificity (97.4% versus 92.5%) with respect to predicting outcomes.[120]

## Staging

Anal cancer should be staged according to the TNM staging system of the American Joint Committee on Cancer (AJCC)[125] (Table 52-1). Tumors are classified according to their maximum diameter and their invasion of adjacent structures, as determined by the physical examination and any imaging studies.

The AJCC staging system for anal canal cancer is applicable to all carcinomas that arise from the anal canal. Cancers of the anal margin (distal to the anal verge) are staged as skin cancers, but melanoma of the anal canal is excluded. For staging purposes, the regional lymph nodes in the AJCC system are the anorectal, perirectal, lateral sacral, internal iliac (hypogastric), and superficial and deep inguinal lymph nodes.[126]

**TABLE 52-1** TNM 7th Edition Staging System of the American Joint Committee on Cancer, 2010

| Stage | T* | N† | M |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| II | T2 | N0 | M0 |
| | T3 | N0 | M0 |
| IIIA | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| | T4 | N0 | M0 |
| IIIB | T4 | N1 | M0 |
| | Any | N2 | M0 |
| | Any | N3 | M0 |
| IV | Any | Any | M1 |

**Tumor category:* Tis, *carcinoma in situ;* T1, *tumor 2 cm or less in greatest dimension;* T2, *tumor more than 2 cm but 5 cm or less in greatest dimension;* T3, *tumor more than 5 cm in greatest dimension;* T4, *tumor of any size invades adjacent organs, for example, vagina, urethra, bladder (Note: direct invasion of the rectal wall, perirectal skin, subcutaneous tissue or the sphincter muscle is not classified as T4).*

*†Nodal category:* N0, *no regional lymph node metastases;* N1, *metastasis in perirectal lymph node(s);* N2, *metastasis in unilateral internal iliac or unilateral inguinal lymph node(s);* N3, *metastasis in perirectal and inguinal or bilateral internal iliac or bilateral inguinal lymph node(s).*

# PRIMARY THERAPY

## Surgery Alone

Before the establishment in the 1980s of sphincter-sparing therapy as the standard of care for epidermoid anal cancer, most patients with anal cancer in North America were treated surgically with abdominoperineal resection. Reported 5-year OS after abdominoperineal resection for anal cancer ranged from 25% to 70% (average, 50%).[76,84,127] Locoregional recurrence developed in 25% to 35% of patients and distant metastasis in 10%.[76,84,127] Patients at highest risk for local recurrence (range, 36% to 48%) after abdominoperineal resection are those with extension of the primary tumor beyond the anal sphincter or metastases to inguinal or pelvic lymph nodes.[76] A component of locoregional disease is present in as many as 84% of patients with relapse after abdominoperineal resection.[76] When the inguinal lymph nodes are metastatically involved, 5-year OS after primary surgical therapy is only 10% to 20%.[127] Although abdominoperineal resection is now rarely used initially, it is still useful for treatment of patients with local recurrence after conservative therapy and for management of complications after conservative therapy.[127]

## Irradiation Alone or Plus Chemotherapy

High-dose radiotherapy without surgical resection or other adjuvant therapy is an effective treatment for small stage T1 tumors without inguinal adenopathy. Table 52-2 summarizes the local control and survival results from retrospective series of radiotherapy alone for small anal cancers. For patients with anal cancers of 2 cm or less in diameter, 100% local control 5 years after radiotherapy without chemotherapy has been reported in several small series of less than 10 patients each.[74,75,128] In a larger French retrospective series, however, among 66 patients treated with T1 tumors ≤1 cm, 6 developed local recurrence at a median interval of 50 months.[129] Local control rates at 5 years are lower (57% to 76%) in patients with 2- to 5-cm tumors.[74,75,130]

**TABLE 52-2** 5-Year Disease Control and Survival after Radiotherapy Alone for Early-Stage Anal Cancer

| First Author/ Reference | No. Pts. | Total RT Dose (Gy) | Tumor Size | Local Control (%) | Overall Survival (%) |
|---|---|---|---|---|---|
| Allal[75] | 5 | 60-65[a] | ≤2 cm | 100 | 100 |
| | 37 | 60-65[a] | 2-5 cm | 76 | 63 |
| Cummings[74] | 6 | 45-55[b] | ≤2 cm | 100 | NR |
| | 23 | 45-55[b] | 2-5 cm | 57 | NR |
| Martenson[128] | 18 | 55-67 | ≤5 cm[c] | 100 | 94 |
| Schlienger[91] | 63 | 60-65 | T1-T2, UICC[d] | 71 | 85 |
| Doggett[77] | 35 | 45-76 | ≤5 cm | 77 | 92 |
| Papillon[130] | 63 | 45-50[d] | ≤4 cm | 87 | 76 |
| Eschwege[90] | 27 | 60-65 | T1-T2, UICC[e] | 90 | 72 |
| Ortholan[129] | 69 | 35-70 | Tis, T1 | 91 | 89 |

No. pts, *number of patients;* NR, *not reported;* UICC, *Union Internationale Contre le Cancer.*

[a]*Usually, 40 Gy of external beam radiation therapy (EBRT) plus 20 Gy to 25 Gy with interstitial implant.*

[b]*Overall 4-week treatment period.*

[c]*One patient with tumor >5 cm.*

[d]*Equivalent to 30 Gy in 10 fractions, followed by 15 Gy to 20 Gy with interstitial implant.*

[e]*1979 UICC staging: T1, less than one third length and circumference of anal canal; T2, more than one third length or circumference of anal canal or infiltration of external sphincter.*

In previous editions of the staging system of the Union Internationale Contre le Cancer (International Union Against Cancer [UICC]),[91] primary tumors were classified not by size but rather according to the length and extent of their circumferential involvement with the anal canal. Tumors involving less than one third of the length and circumference of the anal canal were classified as T1 category of disease, whereas those that involved more than one third of the length or circumference or that invaded the external sphincter were classified as T2. T3 tumors involved the rectum or perianal skin, and T4 tumors invaded adjacent structures.

### *Radiation Alone or Plus 5-FU and Mitomycin C*

The only prospective randomized trial to compare radiotherapy alone with the combination of radiotherapy and chemotherapy in patients with node-negative anal cancers 5 cm or less in diameter (T1 to T2, N0) was carried out by the UKCCCR Anal Cancer Trial Working Party.[131] In this trial, 223 of 585 patients had T1 or T2, N0 anal cancer and were randomized to receive 40 Gy to 45 Gy of external beam radiotherapy (EBRT) to the pelvis, followed by a 15-Gy to 25-Gy boost with a perineal field or interstitial implant with or without two 4- or 5-day infusions of 5-FU and a single bolus injection of mitomycin C. Using local control as the endpoint, subset analysis showed a statistically significant advantage for combined-modality therapy for patients with T1N0 or T2N0 anal cancer.[132]

Combined-modality therapy with radiotherapy and chemotherapy is appropriate for most patients with anal cancer and has become the standard of care. Statistics from the U.S. National Cancer Data Base for 1988 and 1993 show that the use of chemotherapy has increased and the use of resection as the primary treatment has declined.[4]

The initial studies that led to the adoption of combined-modality therapy with nonsurgical treatment were conducted at Wayne State University. Before scheduled surgical resection, 30 Gy of radiation in 15 fractions was delivered to the true pelvis, medial inguinal nodes, and anal canal in conjunction with concomitant 5-FU 1000 mg/m$^2$ every 24 hours for 4 days as a continuous infusion and mitomycin C (MMC) in a single bolus injection of 15 mg/m$^2$. After five of the first six patients were found to have no residual tumor in the abdominoperineal resection (APR) specimen 4 to 6 weeks after the completion of radiotherapy, surgical resection was subsequently reserved for locally persistent or recurrent disease after radiotherapy and concurrent chemotherapy.[80] Overall, 86% of patients (24 of 28) had a clinical complete response to chemoradiation, and 7 of the 12 patients (58%) who had an APR had a complete pathologic response.[133]

Table 52-3 summarizes the disease control and survival results with concomitant chemoradiation from several series. Local failure after radiation doses of 45 Gy to 60 Gy with concomitant chemotherapy occurred in 11% to 40% of patients, and 5-year OS was 65% to 80%.

Two randomized studies comparing radiotherapy alone with concomitant radiotherapy plus 5-FU and MMC have been performed by the EORTC[82] and the UKCCCR Anal Cancer Trial Working Party.[131] For patient eligibility, the EORTC trial required a locally advanced primary tumor (T3 or T4 category) or involvement of regional lymph nodes, whereas the UKCCCR trial enrolled patients with any stage of disease, including distant metastases. Initial radiotherapy was similar in both trials and consisted of 45 Gy to the pelvis over 4 to 5 weeks. In the EORTC trial, partial responders at 6 weeks after induction therapy were boosted with an additional 20 Gy and complete responders received 15 Gy. In the UKCCCR trial, a 15-Gy to 25-Gy boost was administered to patients with more than a 50% tumor response; patients with less than a 50% response had radical surgery. Concurrent chemotherapy in the EORTC trial consisted of 5-FU 750 mg/m$^2$ every 24 hours on days 1 to 5 and days 29 to 33 with a single 15-mg/m$^2$ dose of MMC on day 1. Chemotherapy in the UKCCCR trial consisted of 5-FU 1000 mg/m$^2$ every 24 hours on days 1 to 4 and days 29 to 32 or 750 mg/m$^2$ every 24 hours on days 1 to 5 and days 29 to 33, with a single MMC dose of 12 mg/m$^2$ given on the first day of radiotherapy.

Results of the EORTC[82] and UKCCCR[131] trials are summarized in Table 52-4. The complete response rate 6 weeks after boost radiotherapy was significantly improved with the addition of chemotherapy to radiotherapy (80% versus 54%; $p$ = 0.02) in the EORTC trial. A nonstatistically significant trend toward a higher complete response rate was also reported in

**TABLE 52-3** Disease Control and Survival Rates after Irradiation and Chemotherapy for Anal Cancer in Selected Series

| First Author/ Reference | No. Pts | Median FU (mo) | Total RT Dose (Gy) | Tumor Extent | Chemo Agent | Local Failure No. (%) | Overall Survival (%) |
|---|---|---|---|---|---|---|---|
| Rich[134] | 39 | 54 | 45-66 | T0-T4 | 5-FU[a] | 13/39 (33) | 74 |
| Cummings[74] | 66 | 24 | 48-50 | T1-T4 | 5-FU | 26/65 (40) | 64 |
| Hughes[135] | 25 | 30 | 45-66 | T0-T4 | 5-FU[b] | 8/24 (33) | 96 (2-year) |
| Martenson[95] | 50 | NR | 50-53 | T1-T4 | 5-FU, MMC | (20)[c] | 58 |
| Allal[75] | 68 | 48 | 50-55[d] | T1-T4 | 5-FU, MMC | 22/68 (32) | 65 |
| Doci[136] | 56 | 49 | 54-56 | T1-T3 | 5-FU, MMC | 12/49 (24) | 81 |
| Tanum[78] | 86 | >36[e] | 50 | T0-T4 | 5-FU, MMC | — | 72 |
| Cummings[74] | 69 | 36 (min) | 48-60 | T1-T4 | 5-FU, MMC | 10/69 (14) | 76 |
| Sischy[85] | 26 | 32 | 40.8 | <3 cm | 5-FU, MMC | 4/26 (15) | 85 (3-year) |
| | 50 | | 40.8 | ≥3 cm | 5-FU, MMC | 18/50 (36) | 68 (3-year) |
| Rich[134] | 19 | 20 | 54-60 | T2-T4 | 5-FU, CCDP | 2/19 (11) | 85 (3-year) |
| Doci[137] | 35 | 37 | 54-58 | T1-T3 | 5-FU, CDDP | 4/35 (11)[f] | 97[f] |
| Defoe[138] | 78 | 16 | 45-67.6 | T1-T4 | 5-FU, MMC | 7/78 (9.8) | 87 (2-year) |
| Eng[138a] | 201 | 103 | 34-69.9 | T1-T4 | 5-FU, CDDP | 22/201 (11) | 86 (5-year) |

5-FU, *5-Fluorouracil;* CDDP, *cisplatin;* Chemo, *chemotherapy; cm, centimeters;* FU, *follow-up;* Gy, *Gray;* min, *minimum;* MMC, *mitomycin C;* mo, *months;* No. Pts, *number of patient;* NR, *not reported* RT, *radiotherapy.*

[a]*5-FU, 250-300 mg/m$^2$/day, by infusion 5 days or 7 days weekly throughout radiotherapy.*

[b]*5-FU, 300 mg/m$^2$/day throughout radiotherapy.*

[c]*Kaplan-Meier estimate at 5 years.*

[d]*Usually, 30 Gy of external beam radiation therapy (EBRT) in 10 fractions plus 20 Gy with interstitial implant.*

[e]*Investigators monitored for more than 3 years.*

[f]*Crude.*

**TABLE 52-4** 3-Year Disease Control and Survival in Phase III Studies Comparing Radiotherapy Alone with Radiation and Chemotherapy

| Study | Pt No. | Median FU (mo) | Complete Response* | | Local Control† | | Distant Mets, Crude (%) | Overall Survival | |
|---|---|---|---|---|---|---|---|---|---|
| | | | % | *p* Value | % | *p* Value | | % | *p* Value |
| **EORTC** | 103 | 42 | | | | | | | |
| RT | 52 | | 54 | | 55 | | 21 | 64 | |
| RT plus 5-FU, MMC | 51 | | 80 | 0.02 | 69 | 0.02 | 18 | 69 | 0.17 |
| **UKCCCR** | 577 | 42 | | | | | | | |
| RT | 285 | | 30 | | 39 | | 17 | 58 | |
| RT plus 5-FU, MMC | 292 | | 39 | 0.08 | 61 | <0.001 | 10 | 65 | 0.25 |

5-FU, *5-Fluorouracil;* EORTC, *European Organization for Research and Treatment of Cancer;* Mets, *metastases;* MMC, *mitomycin C;* mo, *months;* Pt. No., *patient numbers;* RT, *radiotherapy;* UKCCCR, *United Kingdom Coordinating Committee on Cancer Research.*

**Assessment of complete response was 6 weeks after 45 Gy (before radiotherapy boost) in UKCCCR trial and 6 weeks after completion of 60 Gy to 65 Gy in EORTC trial.*

*†Patients who had surgery to achieve local control at the completion of radiotherapy were considered locally controlled in the EORTC trial; in the UKCCCR trial, patients who had surgery at the completion of radiotherapy were considered local treatment failures, as were all patients who had surgery for treatment morbidity.*

**TABLE 52-5** 4-Year Disease Control, Survival, and Toxicity after Radiotherapy and 5-FU Alone or Plus Mitomycin C: Results of RTOG 8704/ECOG 1289 Phase III Trial[104]

| Treatment Arm | N | Total Radiotherapy Dose (Gy) | Negative Biopsy | | Local Control | | Colostomy Rate | | Colostomy-Free Survival | | Disease-Free Survival | | Overall Survival | | Grades 4-5 Toxicity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | % | *p* Value | % | *p* Value | % | *p* Value | % | *p* Value | % | *p* Value | % | *p* Value | % | *p* Value |
| RT plus 5-FU | 145 | 45-50.4 | 85 | | 66 | | 22 | | 59 | | 51 | | 67 | | 8 | |
| RT + 5-FU/MMC | 146 | 45-50.4 | 92 | 0.135 | 84 | 0.0008 | 9 | 0.002 | 71 | 0.014 | 73 | 0.003 | 76 | 0.31 | 26 | ≤0.001 |

5-FU, *5-Fluorouracil;* ECOG, *Eastern Cooperative Oncology Group;* Gy, *Gray;* MMC, *mitomycin C;* RT, *radiotherapy;* RTOG, *Radiation Therapy Oncology Group.*

the UKCCCR trial. However, this endpoint was measured 6 weeks after the initiation of therapy compared with 6 weeks after the completion of all therapy in the EORTC trial. In both studies, local control was significantly improved with the addition of concurrent chemotherapy. Local control with radiotherapy alone was surprisingly low (39% at 3 years) in the UKCCCR study. The definition of local failure included tumor reduction of less than 50% 6 weeks after 45 Gy of irradiation, surgery for morbidity, and failure to close a pretreatment colostomy for any reason. Conversely, EORTC investigators considered patients locally controlled even if they had to undergo surgery to achieve a complete response at the completion of radiotherapy. Neither study reported any significant impact of chemotherapy on the incidence of distant metastases or on OS, although absolute survival at 3 years slightly favored the chemoradiation arms numerically in both trials.

The EORTC and UKCCCR trials established combined-modality therapy as the standard of care for patients with anal cancer. Further refinement in the understanding of optimal therapy is provided by the results of a Phase III study conducted by RTOG and the Eastern Cooperative Oncology Group (ECOG). In the RTOG/ECOG study (Table 52-5), patients were treated with radiotherapy (45 Gy to 50.4 Gy in 25 to 28 fractions) and 5-FU and were randomized to receive or not receive MMC.[139] The addition of MMC was associated with fewer colostomies, higher local control, and better DFS. The addition of MMC also significantly increased the risk of major toxicity. Survival was slightly higher in the MMC arm of the study, but the difference was not statistically significant. The chemotherapy regimen in this trial differed from that of the European trials because two doses of MMC 10 mg/m$^2$ were delivered on day 1 and day 29 instead of a single dose. Two of the four treatment-related deaths in the MMC arm were felt to be caused by a failure to follow protocol dose-reduction guidelines for the second MMC dose.

The biologic basis for improved outcome with the addition of chemotherapy to the treatment regimen is not known. However, the fact that several studies have reported no significant reduction in distant failure with chemotherapy suggests that the effect is predominantly locoregional, possibly because of an interaction with irradiation.[74] For example, in the PMH experience, distant failure occurred in 18% of patients treated with radiotherapy alone, in 17% of those who received MMC and 5-FU, and in 10% of those receiving 5-FU alone.[74,140] Synergistic interactions between irradiation and 5-FU or MMC and between 5-FU and MMC have been demonstrated in mammalian tumor cell lines in vitro.[141] Hypoxic mammalian tumor cells also have an increased sensitivity to mitomycin C in vitro, although whether the hypoxia has any effect when anal cancer is treated with fractionated radiotherapy is not known.[142] Laboratory studies have also shown increased cytotoxicity associated with continuous infusion 5-FU compared with 5-FU delivery by intermittent bolus.[143]

It cannot be assumed that sequential therapy will duplicate the excellent results achieved with concomitant chemoradiation. Complete pathologic response rates 6 weeks after 50 Gy of irradiation, 5-FU, and MMC are in the range of 85% to 95%.[80,144,145] In contrast, only 45% of 42 patients who received

**TABLE 52-6** 5-Year Disease Control and Survival after Radiotherapy and 5-FU Plus Mitomycin C or Cisplatin: Results of RTOG 98-11 and ACT II Phase III Trials

| | | Colostomy-Free Survival | | Disease-Free Survival | | Overall Survival | |
|---|---|---|---|---|---|---|---|
| **Study** | **Pt. No.** | **%** | ***p* Value** | **%** | ***p* Value** | **%** | ***p* Value** |
| **RTOG 98-11**[*152] | 649 | | | | | | |
| RT plus FU/MMC | 325 | 71.9 (5-year) | 0.05 | 67.8 (5-year) | 0.006 | 78.3 (5-year) | 0.026 |
| RT plus FU/CDDP | 324 | 65 | | 57.8 | | 70.7 | |
| **ACT II**[†153] | | | | | | | |
| RT plus FU/MMC | 472 | 68 (3-year) | 0.94 | 69 (3-year) | 0.63 | 79 (3-year) | 0.7 |
| RT plus FU/CDDP | 468 | 67 | | 69 | | 77 | |

5-FU, *5-Fluorouracil;* CDDP, *cisplatin;* MMC, *mitomycin C;* mo, *months;* Pt. No., *patient numbers;* RT, *radiotherapy;* RTOG, *Radiation Therapy Oncology Group.*
**5-year outcomes reported for RTOG 98-11.*
*†3-year outcomes reported for ACT II Study.*

sequential 5-FU and MMC, followed by radiotherapy, had a complete pathologic response.[111]

### *Radiation Plus 5-FU and MMC versus 5-FU and Cisplatin*

In addition to the concurrent use of MMC and 5-FU during radiotherapy, multiple single institutions[134,136,146,147] and prospective Phase II trials[148-150] have reported favorable results with concurrent cisplatin (CDDP) and 5-FU, with or without an induction chemotherapy phase of treatment. A U.S. Gastrointestinal Intergroup Phase III trial (RTOG 9811) was conducted to compare the efficacy of concurrent cisplatin-based therapy with standard MMC-based therapy.[151,152] Six hundred forty-four patients with T2 category or higher (any N category) carcinoma of the anal canal were randomized to two cycles of induction CDDP (75 mg/m$^2$) and 5-FU (1000 mg/m$^2$ for 4 days) followed by 45 Gy to 59 Gy of irradiation with two concurrent cycles of the same regimen versus MMC (10 mg/m$^2$) and 5-FU (1000 mg/m$^2$ for 4 days) given twice concurrently during radiotherapy (no induction phase). For the cisplatin- and MMC-based arms, 5-year OS was 70.7% and 78.3%, respectively ($p = 0.026$), and 5-year DFS was 57.8% and 67.8%, respectively ($p = 0.006$) (Table 52-6). There was a trend toward statistical significance for colostomy-free survival (CFS), locoregional failure (LRF), and colostomy failure (CF) ($p = 0.05$, $p = 0.087$, and $p = 0.074$, respectively).[152] Based on this trial, a regimen of MMC and 5-FU given concurrently with radiotherapy remains the standard of care for anal cancer. It is unclear whether the delayed use of radiotherapy or difference in radiosensitization of cisplatin compared with MMC played a role in the inferior colostomy rate observed in the experimental arm of this study.

In contrast, the largest Phase III trial, the UK ACT II study, was theoretically a direct comparison of CDDP versus MMC (gave two doses of CDDP versus only one of MMC) and also examined the role of maintenance (adjuvant) treatment. The ACT II trial enrolled 940 patients in a 2 × 2 randomized trial with a control arm of 5-FU (1000 mg/m$^2$, days 1-4, 29-32) and MMC (12 mg/m$^2$, day 1) versus an experimental arm of + 5-FU (1000 mg/m$^2$, days 1-4, 29-32) and cisplatin (60 mg/m$^2$, day 1 and 29) with a primary endpoint of 6-month response rate.[153] Patients were subsequently randomized to receive either no maintenance versus maintenance therapy of 5-FU (1000 mg/m$^2$, days 1-4, 29-32) and CDDP (60 mg/m$^2$, days 1 and 29) to be initiated 4 weeks after the completion of radiotherapy, with a primary endpoint of relapse-free survival (RFS). With a median follow-up of 5.1 years, 90.5% (391/432) patients in the MMC group compared to 89.6% (386/431) in the CDDP group had a complete response at 26 weeks ($p = 0.64$). Overall, toxic effects were similar in each group, although there were more grade-3 and grade-4 hematological toxicities in the MMC arm (26% versus 16%, $p = < 0.001$).[153] Maintenance chemotherapy (chemo) was not associated with an improvement in 3-year PFS (Table 52-6; 74% with maintenance chemo versus 73% without maintenance; HR, 0.95; 95% CI, 0.75 to 1.21; $p = 0.70$). Based on the results of this study, the largest in anal cancer to date, the authors concluded that administration of MMC, in combination with 5-FU and 50.4 Gy RT in 28 daily fractions without maintenance chemo, should remain standard practice because of similar efficacy and toxic effects, fewer cycles of chemo, fewer nonchemotherapy drugs, less time in the chemo suite, less expense, and no risk of neuropathy compared with cisplatin.[153]

### Role of Dose Intensification

In patients with locally advanced anal cancer, based on the promising results of a Phase II trial of induction chemotherapy,[149] the role of induction chemo and dose intensification of the radiation boost was evaluated in the UNICANCER ACCORD 03 study.[154] In this study, 307 patients with tumors ≥4 cm or <4 cm and N1-3M0 were randomly assigned by 2 × 2 randomization to receive one of the following: (1) 2 cycles of induction 5FU-CDDP (5-FU 800 mg/m$^2$, day 1-4, 29-32) and CDDP (80 mg/m$^2$ intravenously, days 1 and 29), with EBRT (45 Gy in 25 fractions over 5 weeks, 5-FU–CDDP during weeks 1 and 5), and standard-dose boost (SD: 15 Gy); (2) 2 cycles of induction chemo, chemoRT, and high-dose boost (HD, 20 Gy to 25 Gy); (3) chemoRT and standard-dose boost; or (4) chemoRT and HD boost. With a median follow-up of 50 months, neither induction chemo nor dose intensification of the RT boost was associated with improvements in 5-year CFS (76.5% versus 75.0%, $p = 0.37$ for induction versus no induction, and 73.7% versus 77.8%, $p = 0.067$ for SD versus HD, respectively).

Although the primary study endpoint was negative, given the trend toward improved CFS in this study, further dose intensification studies, either with new drugs or new radiation techniques, may be warranted.[154]

## Treatment Tolerance

Anal function is preserved in 65% to 80% of patients after sphincter-sparing therapy.[74,75,94,135] The most common indication for abdominoperineal resection is local recurrence or disease persistence because 90% of patients for whom local control is achieved can be expected to maintain a functional anus.[74] Late treatment complications may result in the loss of anal function, and a colostomy may be required to manage complications in 2% to 10% of patients whose cancer is locally controlled.[74,75,77,91,94,128,137,155,156] A Danish multicenter cohort study of 235 patients reported a 5-year cumulative incidence

of therapy-related colostomy of 12%. Of the 12 patients who received therapy-related colostomies not part of an APR, indications included chronic anorectal ulcer, fecal incontinence, bowel obstruction, rectovaginal fistula, perianal skin injury, and anal canal fibrosis.[156]

## LOCALLY ADVANCED DISEASE AND PALLIATION

Tumor size appears to have a moderate impact on treatment outcome when combined-modality therapy is used. In the RTOG/ECOG study, 17% of patients with primary tumors 5 cm or more in diameter had positive biopsy findings 6 weeks after completion of therapy compared with 7% of those with a tumor less than 5 cm in diameter ($p = 0.02$). Preservation of anal function was also more likely in patients who had smaller tumors; 11% of patients with T1 or T2 cancer required a colostomy compared with 21% of those with T3 or T4 cancer.[139] Differences in local control have also been reported using tumor diameter cutoffs of less than 5 cm. In a previous RTOG study, local control at 3 years was 84% among patients with tumors smaller than 3 cm and 62% among those with tumors 3 cm or larger.[85] Similarly, local control among patients treated at PMH was 94% for those with tumors of 2 cm or less and 72% for those with larger tumors. No difference in local control was reported between the subgroups of patients with tumors of 2 cm to 5 cm or with larger tumors (>5 cm), unless invasion of adjacent structures was discovered, in which case local control was 62%.[74]

Secondary analyses of the U.S. Gastrointestinal Intergroup RTOG 9811 Phase III trial have been performed to further define prognostic factors for outcomes in patients treated with concurrent chemoradiation. The initial analysis found that a tumor size of more than 5 cm was the only pretreatment characteristic that independently predicted a subsequent need for colostomy (hazard ratio, 1.85; $p = 0.008$).[151]

A subsequent analysis of RTOG 98-11 was performed to determine if the TN category of disease (T2N0, T3N0, T4N0, T2N+, T3N+, T4N+) has an impact on DFS and OS, LRF, distant metastasis, or CF.[73] All endpoints showed statistically significant differences between the 6 TN categories of disease, including OS ($p < 0.0001$), DFS ($p < 0.0001$), LRF ($p < 0.0001$), distant metastasis ($p = 0.0011$), and CF ($p = 0.01$). The best outcomes for OS, DFS, and LRF were found with T2N0 and T3N0 categories of disease (5-year OS, 82% and 74%; DFS, 72% and 61%; and LRF, 17% and 18%). The poorest outcomes were with the T3N+ and T4N+ disease categories (5-year OS, 57% and 42%; DFS, 38% and 31%; and LRF, 44% and 60%). The 5-year CF was best for patients with T2N0 (11%) or T2N+ (11%) disease and worst for patients with T4N0 (26%), T3N+ (27%) and T4N+ (24%) disease.[73]

Preservation of anal function is possible in two thirds to three fourths of patients with locally advanced disease in both RTOG 98-11 (see earlier mention)[73] and PMH series.[74] In the PMH experience, two thirds of patients with tumors that invaded adjacent structures maintained anal function after radiotherapy and chemotherapy, as did two thirds of patients with tumors that involved more than 75% of the circumference of the anal canal.[74] Locally advanced disease is not an indication for abdominoperineal resection in patients who retain some measure of anal function at diagnosis.[74]

### Node Involvement

Involvement of the inguinal lymph nodes at diagnosis is associated with a worse prognosis. In the EORTC randomized trial, patients with involved lymph nodes had inferior local control and survival. However, the extent of nodal involvement did not add any prognostic information.[82] In a report from PMH, the 5-year cause-specific survival for patients who were clinically node-positive was 57% compared with 81% patients who were node-negative ($p = 0.07$). Combined-modality therapy was effective in the treatment of patients with involved nodes. In such patients, control of cancer in metastatically involved lymph nodes was achieved 87% of the time.[74] In an RTOG 9811 secondary analysis, 5-year DFS was 64% for patients who were node-negative and only 35% for patients who were node-positive ($p \leq 0.0001$).[157] As noted in the prior section, in a subsequent secondary analysis of RTOG 98-11, the poorest rates of OS, DFS, and LRF were with T3-4, N+ disease.[73]

Radiotherapy without chemotherapy has been used for patients with metastatically involved inguinal lymph nodes, with control of nodal disease reported in 60% to 70% of patients.[77,94] However, survival is poor for these patients with radiotherapy alone (range, 0% to 36% at 5 years), and combined-modality therapy with radiotherapy and concurrent chemotherapy is preferred.[89-91,94]

### Salvage Therapy

Patients with local failure after radiotherapy and chemotherapy should be considered for abdominoperineal resection. Local control can be achieved with abdominoperineal resection in as many as 60% of these patients.[74,75,77,88,91,94] Ultimate local control is obtained in more than 90% of patients with anal cancer, including patients who require surgery after radiotherapy for locally persistent or recurrent disease.[77,94]

Patients who have locally advanced recurrent disease that is not surgically resectable for cure may benefit from low-dose reirradiation plus concurrent chemo followed by surgical resection of gross disease and intraoperative radiotherapy (IORT). This aggressive combined-modality treatment approach may result in successful salvage as seen in a recent Mayo Clinic Rochester analysis.[158] Salvage surgical resection and IORT were used in a series of 32 patients between 1993 and 2012 who had either residual ($n = 9$) or recurrent ($n = 23$) disease following primary chemoradiation. Those with recurrent disease received low-dose preop chemoRT before resection or IORT. Five-year OS and DFS were 23% and 17%, respectively.

### Palliation

Although anal cancer is predominantly a locoregional disease, 5% to 10% of patients will have disease beyond the pelvis at diagnosis and distant metastases will develop in 10% to 20% after locoregional therapy.[71,74,75] The most common site of distant metastases reported in most series is the liver; metastases to the lungs, lymph nodes, skin, bones, and brain have also been reported.[71,75,77-80] Palliative chemotherapy with 5-FU plus either mitomycin C or cisplatin is associated with a 50% response rate and a median survival of 12 months.[71] Patients with brain metastases, symptomatic osseous metastases, or other localized symptomatic metastases should receive hypofractionated radiotherapy for palliation.

## IRRADIATION TECHNIQUES AND TOLERANCE

### Traditional Field Design

Radiotherapy field design should be based on an understanding of the spread of anal cancer. Historical results in patients treated by APR show that 35% to 46% had involvement of

pelvic lymph nodes and that 13% to 16% had a relapse in the inguinal lymph nodes.[76,84] Therefore, the pelvic and inguinal lymph nodes should be included in the radiotherapy fields.

A portion of the inguinal lymph node chain is superficial to the femoral head and neck. It is important to use radiotherapy fields that decrease the radiation dose to these structures. Large anteroposterior/posteroanterior (AP/PA) fields that include the inguinal lymph nodes will deliver the full radiation dose to the femoral head and neck. Patients treated in this way may be at risk for radiation-induced fracture.[159] Radiotherapy techniques that treat the lateral inguinal lymph nodes only through anterior fields will minimize the dose to the femoral head and neck. One method is to treat the primary tumor, pelvic nodes, and inguinal nodes with an anterior photon field that encompasses all these structures. The posterior field is designed to treat only the primary tumor and the pelvic lymph nodes. Electron fields are used to supplement the dose to the lateral superficial inguinal nodes that are not included in the posterior photon field (Figure 52-1). Another technique is to use CT-based simulation for optimal delineation of the inguinal lymph nodes and then to use this information to minimize the volume of the femur included within the radiotherapy field.

## Target Volumes and Normal Structures

Accurate target and normal structure identification is crucial to advanced treatment planning with three-dimensional radiotherapy or intensity-modulated radiation therapy (IMRT). The gross tumor volume (GTV) represents the maximal extent of the primary tumor and clinically involved lymph nodes based on the combined consideration of the physical examination, endoscopic findings, and diagnostic imaging studies. The clinical target volume (CTV) includes all

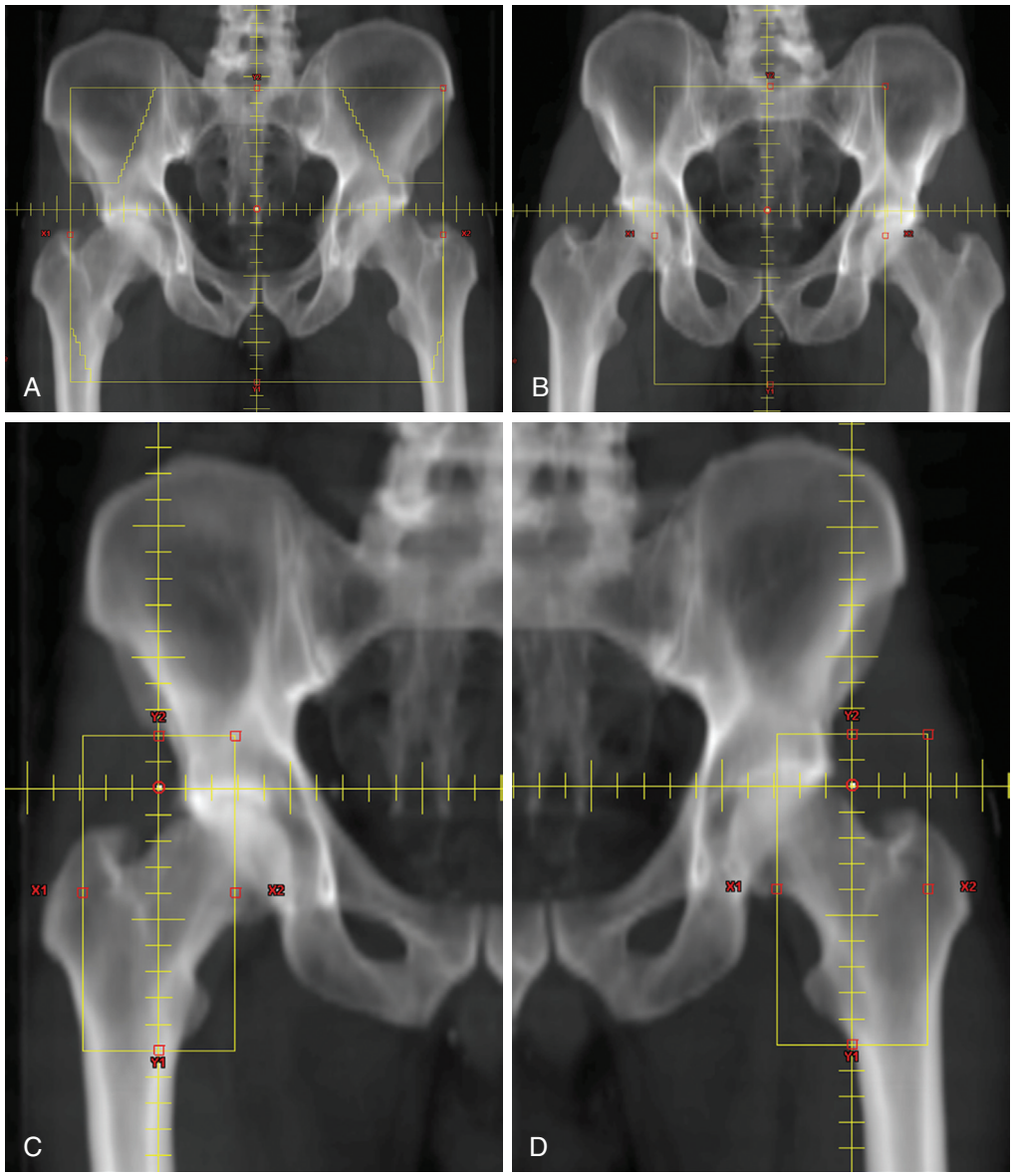


**Figure 52-1** Anal cancer fields: Wide anterior **(A)** and narrow posterior **(B)** photon fields. Electron fields are used to give a supplementary radiation dose to lateral inguinal nodes not included in the narrow posterior photon field **(C** and **D)**. The medial border of each electron field is placed at the posterior photon field's lateral exit point on the anterior abdominal wall.

tissues at risk of longitudinal or radial microscopic extension of the primary tumor as well as nodal areas at risk. These nodal regions include the perirectal nodes (including all of the mesorectum to the pelvic floor), inguinal nodes, presacral nodes, and internal and external iliac nodes. Multiple CTVs may be constructed based on differences in planned dose delivery to elective regions of treatment. The superior extent of the elective nodal coverage is generally at least to the iliac bifurcation or to the sacral promontory.

A retrospective review of 167 patients treated at the M. D. Anderson Cancer Center with definitive chemoradiation reported that all regional pelvic failures (21% of relapses) occurred among patients whose superior field border was placed at the bottom of the sacroiliac joint. The authors concluded that a superior field or target border at vertebrae L5/S1 may reduce such recurrences.[160]

In 2009, an RTOG panel reported consensus contouring guidelines and an atlas for elective CTV demarcation in anorectal cancer.[161] This reference serves as an excellent template and resource for lower gastrointestinal cancer treatment planning. Key normal structures that should be identified in the planning process and avoided include the femoral head and neck, bladder, and bowel. Excessive skin exposure should also be avoided in the perineum and groin.

## Intensity-Modulated Radiotherapy

Given the close proximity of the bladder, small bowel, femoral heads, and possibly pelvic bone marrow to target regions in the management of anal cancer, the improved conformality of IMRT compared with traditional techniques presents an opportunity for toxicity reduction[162,163] (Figure 52-2). A retrospective review of 53 patients treated at multiple institutions has reported favorable acute toxicity and efficacy rates with early follow-up among 53 patients treated with IMRT and concurrent chemotherapy.[164] More than 92% of patients had a complete clinical response, and acute grade-3 or higher gastrointestinal (GI) or dermatologic toxicities were observed in only 15% and 38% of patients, respectively. RTOG 0529, a Phase II trial of 52 patients treated with dose-painted IMRT and concurrent mitomycin C and 5-FU also shows favorable patient tolerance rates.[165] In this study, patients with T2-4N0-3M0 anal cancer received 5-FU and MMC on days 1 and 29 of dose-painted IMRT, prescribed per stage as follows: T2N0: 50.4 Gy to the anal primary PTV, 42 Gy to elective nodal PTV in 28 fractions; for T3-4, N0-3: 54 Gy to the anal primary PTV, 54 Gy to >3 cm metastatic nodal PTV, 50.4 Gy to ≤3 cm metastatic nodal PTV, and 45 Gy to elective nodal PTV. Compared with the historical benchmarks of RTOG 9811, there was significantly less grade 2+ hematologic toxicity (73% versus 85%; $p = 0.032$), grade 3+ GI or genitourinary toxicity (21% versus 36%; $p = 0.0082$) and grade 3+ dermatologic toxicity (23% versus 49%; $p < 0.0001$), with a favorable early clinical response reported.[165] Treatment interruptions because of toxicity were significantly less with dose painted IMRT with median treatment duration of 43 days compared with 49 days ($p < 0.0001$). Integration of IMRT requires rigorous quality assurance, however, to ensure appropriate target volume coverage, minimize marginal misses, and maximize normal tissue sparing with accurate identification of normal tissue structures. This was evidenced in RTOG 05-29, in that 81% of treatment plans required dose-painted-IMRT replanning on initial review and 46% of plans required multiple resubmissions.[165] Preliminary efficacy outcomes of RTOG 05-29 demonstrated similar 2-year outcomes to RTOG 98-11 (2-year LC: 20% versus 19%, 2-year OS: 88% versus 91%, 2-year DFS: 77% versus 76%, for RTOG 05-29 and RTOG 98-11, respectively).[166] Because of the associated acute toxicity sparing, DP-IMRT will be used as the platform and may allow for radiation dose escalation in future RTOG anal canal trials.

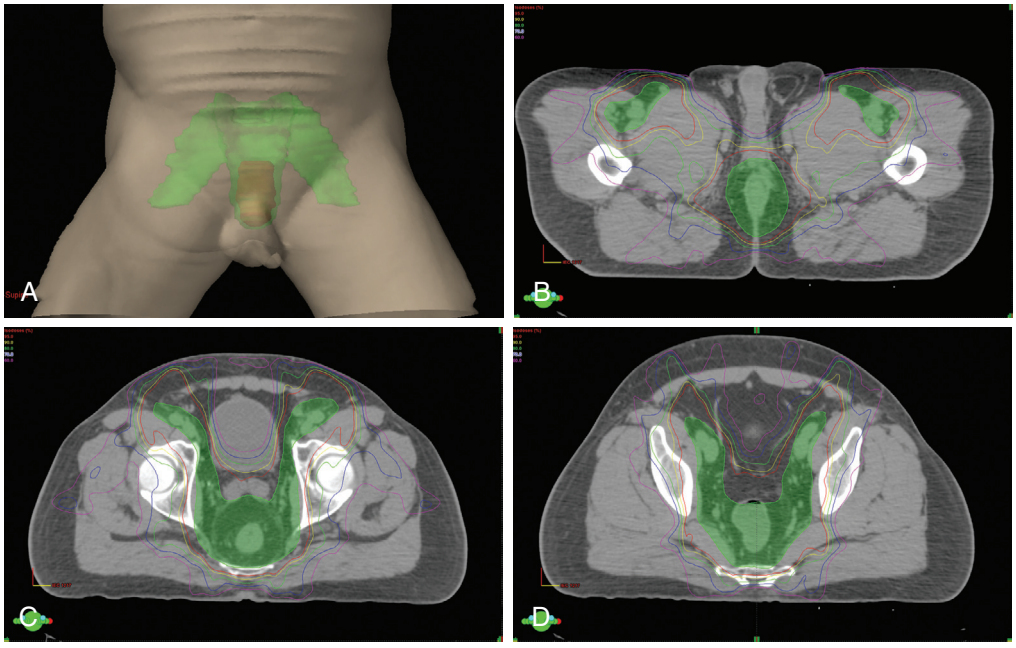


**Figure 52-2** Three-dimensional rendering **(A)** of the clinical target volume *(green)* and gross tumor volume in a 65-year-old male with T2N0M0 squamous cell carcinoma of the anal canal. Axial dosimetry using an eight-field intensity-modulated radiation therapy plan in the lower **(B)**, mid **(C)**, and upper pelvis **(D)**. *Red, yellow, green, blue,* and *purple lines* represent the 95%, 90%, 80%, 70%, and 60% isodose lines, respectively. (The planning tumor volume is not shown.)

## Radiation Dose and Fractionation

The RTOG/ECOG Phase III clinical trial provided useful information about the most favorable combination of radiation dose and chemotherapy agents.[139] The best local control rates resulted from an aggressive regimen of concurrent chemoradiation (5-FU, 1000 mg/m$^2$/d on days 1 to 4 and days 29 to 32 of EBRT; MCC, 10 mg/m$^2$ on day 1 and day 29 of EBRT). The primary tumor, pelvic lymph nodes, and inguinal lymph nodes received a total dose of 36 Gy of EBRT in 20 fractions, followed by a field reduction to include the primary tumor. An additional 9 Gy was administered in 5 fractions, for a total dose to the primary tumor of 45 Gy in 25 fractions. Patients who had residual tumor after 45 Gy received an additional dose of 5.4 Gy in 3 fractions, for a total cumulative primary tumor dose of 50.4 Gy in 28 fractions. The medial inguinal lymph nodes received 45 Gy if clinically negative or 50.4 Gy if clinically positive. This combination of radiotherapy plus 5-FU and MMC resulted in 4-year local control of 84%, which was significantly better than 4-year local control of 66% in patients randomized to receive an identical dose of irradiation plus 5-FU alone ($p < 0.001$).

In the RTOG/ECOG study, 26% of the patients treated with radiation therapy plus 5FU-MMC experienced life-threatening or fatal toxicity, including a 3% treatment-related death rate. It is not yet known whether increasing the radiation dose to more than 50.4 Gy in conjunction with 5-FU and mitomycin C chemotherapy will improve the therapeutic ratio of local control to treatment tolerance. In the subsequent U.S. Gastrointestinal Intergroup clinical trial RTOG 98-11, the recommended final boost dose was 55 Gy to 59 Gy for patients with T3 to T4 disease, positive nodes, or T2 disease with residual disease after 45 Gy.[151,152] Locoregional relapse continued to be a problem even with these slightly higher radiotherapy doses, as noted previously (5-year LRF range of 17% [T2N0] to 60% [T4N+] by TN disease category).[73] In RTOG 05-29 with dose-painted IMRT, recommended final doses were 54 Gy in 30 fractions for patients with T3 to T4 or node positive disease and 50.4 Gy in 28 fractions for patients with T2N0 disease.[165] Preliminary outcomes demonstrate equivalent rates of 2-year local control with this dose fractionation schema compared to RTOG 98-11.[166]

The hypothesis that there will be fewer local failures when the irradiation dose is increased to more than 50.4 Gy with concurrent 5-FU and mitomycin C has not been tested in prospective trials. Three retrospective series have contributed to the formation of this hypothesis. At the University of Texas M. D. Anderson Cancer Center, patients with anal cancer who were treated with radiotherapy and continuous infusion 5-FU 300 mg/m$^2$ during the entire radiotherapy course had better local control with radiation doses of 55 Gy to 66 Gy (9 of 10 patients) than with lower doses of 45 Gy to 49 Gy (7 of 14 patients).[135] Researchers at the University of Kansas evaluated treatment with or without chemotherapy and found local control of 92% for radiation doses of more than 55 Gy, 77% for 45 Gy to 55 Gy, and 64% for 45 Gy or less.[167] Similarly, a retrospective review from the Medical University of Vienna demonstrated 14% local recurrence with doses of 54 Gy or more compared with 70% with doses of less than 54 Gy among patients with T3 or T4 tumors.[168]

In contrast to dose escalation for locally advanced tumors, more moderate doses of irradiation with chemotherapy may be adequate for early tumors or after local excision of a small tumor. In addition to the original experience with complete responses to 30 Gy reported by Nigro et al,[133] at least two other institutions have reported local control of over 95% with 30 Gy and concurrent chemotherapy among a limited number of patients with early tumors or after local excision.[169,170] Such a strategy has not been evaluated in a prospective clinical trial.

EBRT alone is appropriate for a few patients who are not candidates for combined-modality therapy because of clinically significant comorbid illness or other reasons. A high rate of tumor control has been found in patients with small tumors treated with a radiation dose of 45 Gy in 25 fractions to the pelvis, inguinal lymph nodes, and primary tumor, followed by a boost dose to the primary tumor, for a total cumulative dose of 60 Gy to 70 Gy in 33 to 35 fractions.[86,128]

Nearly all patients who receive concomitant chemoradiation for anal cancer will have perineal skin reactions, and more than half will have confluent moist desquamation. The severity of such acute reactions is influenced by the radiation fraction size and treatment technique. In a PMH study of 50 Gy in 20 fractions (2.5 Gy per fraction), the acute and late toxicities were considered unacceptably high.[74] Less severe toxicity was reported with the same fractionation schedule and a break in treatment or with a fractionation schedule of 48 Gy in 24 fractions.[74] The use of IMRT appears to decrease both severity and volume of perineal skin reactions, hematologic suppression, and gastrointestinal toxicity in single institution and group studies. Improvement in acute treatment-related toxicities with IMRT may lead to decreased requirement for treatment break and shorter overall treatment times.

The overall treatment time may affect the outcome of radiotherapy or chemoradiation. In an RTOG pilot study evaluating 59.4 Gy with 5-FU and MMC that included a planned treatment break, 30% of patients required a colostomy by year 2 compared with only 7% in the RTOG/ECOG randomized trial, which did not use planned treatment breaks.[171] Pooled data analysis of RTOG 8704 and 9811 determined that each increase in treatment duration by 14 days was associated with a 9.4% increase in risk of failure requiring colostomy.[172]

## Tumor Regression

Tumor regression may be slow after radiation therapy alone or chemoradiation, with the time to complete regression ranging from 2 to 36 weeks (median, 12 weeks).[74] Preliminary results from a secondary analysis from the ACT II study evaluating optimal time to assess clinical complete response (CCR) found that 29% of patients not in CCR at 11 weeks achieved CCR at 26 weeks. As early surgical salvage would not have been appropriate for these patients, CCR at 26 weeks has been recommended as the optimal timing of response for future trials.[173]

An alternate approach in patients with high risk of local persistence or relapse (T4N0, T3-4N+) would be to use PET-CT response instead of CCR to determine when surgical salvage is indicated. This may lead to better rates of surgical salvage and allow the possibility of local excision instead of APR in select patients.

Most recurrences at the primary site manifest within 2 years of treatment.[74] When concurrent chemotherapy is not used, tumor regression may be even more prolonged. In a French study of 193 patients with anal cancer treated with radiation therapy alone, the mean time to a complete response was 3 months after the completion of therapy, and some patients required as long as 12 months for a complete response.[91] However, the rapidity of the clinical response to therapy may also be prognostic. Another institution from France reported that patients with T3 to T4 tumors who had a tumor reduction of 80% or less at the completion of the first phase of radiotherapy (30 Gy to 45 Gy of EBRT) had 5-year CFS of only 24.8% compared with 65% among patients with a response of more than 80% ($p = 0.002$).[174]

Although routine biopsies have been required 4 to 6 weeks after the completion of therapy in several studies,[80,144,145] routine biopsies should not be performed on patients with regressing or clinically absent tumors. Treatment with 30 Gy to 50 Gy plus 5FU-MMC is associated with negative biopsy findings in 85% to 90% of patients 4 to 6 weeks after completion of radiotherapy.[80,144,145] Because of accelerated repopulation in surviving clonogens, a low-dose radiation boost after a 6-week break is unlikely to provide any benefit. The purported benefit of additional therapy for 7 of 22 patients in the RTOG/ECOG study is more likely a result of continued slow tumor regression after initial therapy than the result of the addition of 9 Gy of irradiation and cisplatin chemotherapy.

## Treatment Tolerance

The acute toxicity associated with therapy for anal cancer may depend in part on the radiation fraction size and schedule and how chemotherapy is used. Investigators at PMH reported a decrease from 75% to 40% in acute grade-3 toxicities when the fraction size was reduced from 2.5 Gy to 2 Gy or when a planned treatment break was used.[74] Acute toxicity is markedly higher when MMC is added to 5-FU and radiotherapy. In the RTOG/ECOG trial, 26% of patients who received 5-FU and MMC together experienced grade-4 or grade-5 toxicity (3% treatment-related deaths), compared with only 7% of patients receiving 5-FU (0.7% treatment-related deaths).[139] As noted previously, IMRT appears to decrease the incidence of grade-3 or higher treatment intolerance.[165]

For patients receiving both MMC and 5-FU, the most common life-threatening toxicity is bone marrow suppression resulting in neutropenic sepsis. In addition, essentially all patients will experience a perineal skin reaction.[85] In the RTOG/ECOG study, confluent moist desquamation was reported in 55% of patients treated with this combination.[171] Mild to moderate diarrhea may be experienced by two thirds of patients, and nausea and vomiting by 25% and 15%, respectively.[85]

Late treatment-related complications are usually diagnosed within 2 years of treatment.[90] Asymptomatic or minimally symptomatic perineal fibrosis, telangiectasia, and minor intermittent bleeding from the anorectal region or bladder may be observed.[175] Severe late effects that affect a patient's social life or require surgical intervention have been reported in as many as 15% of patients.[74,78,91] These effects include anal incontinence, intestinal obstruction, chronic diarrhea, chronic pelvic pain, fistula, or bladder dysfunction.[78] Elderly women may be at increased risk for fractures of the femoral head and neck, especially if the radiotherapy fields encompass the entire femoral head and neck in both anterior and posterior treatment fields.[128,159] Late complications may necessitate colostomy for management in 2% to 10% of patients.[74,75,77,91,94,128,156] Whether the use of IMRT will reduce late toxicity remains to be seen.

Late complications of radiotherapy may be more likely when treatment is delivered with fraction sizes larger than 2 Gy.[74] Late complications are also more common in patients with locally advanced tumors; one series reported late effects in 23% of patients with T3 or T4 tumors compared with only 6% of patients with T1 or T2 tumors.[90]

Some investigators have reported that patients who are positive for HIV with anal cancer have reduced tolerance for combined chemoradiation regimens.[176,177] Compared with patients who are HIV-negative, patients who are HIV-positive are more likely to require treatment breaks, hospitalization for acute reactions, and chemotherapy dose reductions.[176,178] In addition, survival of patients with HIV is often limited; one report found a 29% 2-year survival for patients who are HIV-positive compared with 71% at 4 years for patients who are HIV-negative.[176] Although the best treatment strategy is unknown, low-dose chemoradiation in a small series of patients has been reported to result in a satisfactory tolerance and response in patients who are HIV-positive and in patients with AIDS without major opportunistic infections.[178]

The advent of highly active antiretroviral therapy (HAART) in the management of patients who are HIV-positive appears to have led to improved tolerance and treatment outcomes among patients who are HIV-positive. A pooled retrospective analysis from four institutions of 121 patients with anal cancer treated in the HAART era revealed similar clinical complete response rates (≥92%) and OS among patients who are HIV-positive and HIV-negative.[179] However, patients who are HIV-positive were much more likely to fail locally by 5 years (62% versus 13%; $p = 0.008$) and had increased dermatologic and hematologic acute toxicity with therapy. Other institutions have reported successful treatment and acceptable toxicity with standard anal cancer chemoradiation regimens among patients who are HIV-positive in the HAART era,[180-184] but some have also noted inferior long-term local control rates despite excellent initial response rates.[185]

# TREATMENT ALGORITHM AND FUTURE DIRECTIONS

Figure 52-3 is a diagnostic and treatment algorithm for patients with newly diagnosed anal cancer.

Future investigations in the clinical management of anal cancer should be focused on improving efficacy among patients with locally advanced disease but also reductions in acute and long-term morbidity from therapy. The continued advances in treatment target definition, radiation conformality (e.g., IMRT), and accuracy of radiotherapy delivery through image-guided radiation therapy (IGRT) afford the opportunity for the prospective study of dose escalation among patients with locally advanced disease at presentation. In addition, these technologies provide opportunity for reducing treatment toxicity by limiting the dose to the genitalia, femora, bladder, bowel, and bone marrow, as has been demonstrated with early clinical experience.

Though RTOG 9811 demonstrated a reduction in severe acute hematologic toxicity with the experimental cisplatin-based arm, there is an opportunity for study of newer cytotoxic, radiosensitizing agents in an attempt to improve efficacy or reduce chemotherapy-related side effects. In addition, the incorporation of biologic agents with treatment has the potential to improve efficacy. There is no role for maintenance chemotherapy after definitive chemoradiation at this time.

Advances in imaging may also improve therapy and medical decision making in the management of anal cancer. As discussed, PET/CT imaging improves the initial staging of anal cancer and may aid in evaluation of the response. The value of early reimaging with PET as a predictor of response to therapy and possibly to guide selection of the total radiotherapy dose and earlier surgical salvage (local excision, APR) has not yet been investigated.

Despite the rarity of anal cancer, major advances in the laboratory and clinic have led to an increased understanding of anal neoplasia that has improved treatment outcomes. As pathways leading to anal carcinogenesis are more fully described and the influences of HPV and other infectious agents are better defined, expanded research efforts focusing on prevention will be possible. However, further advances in the prevention and treatment of anal cancer will require continued commitment to prospective trials.

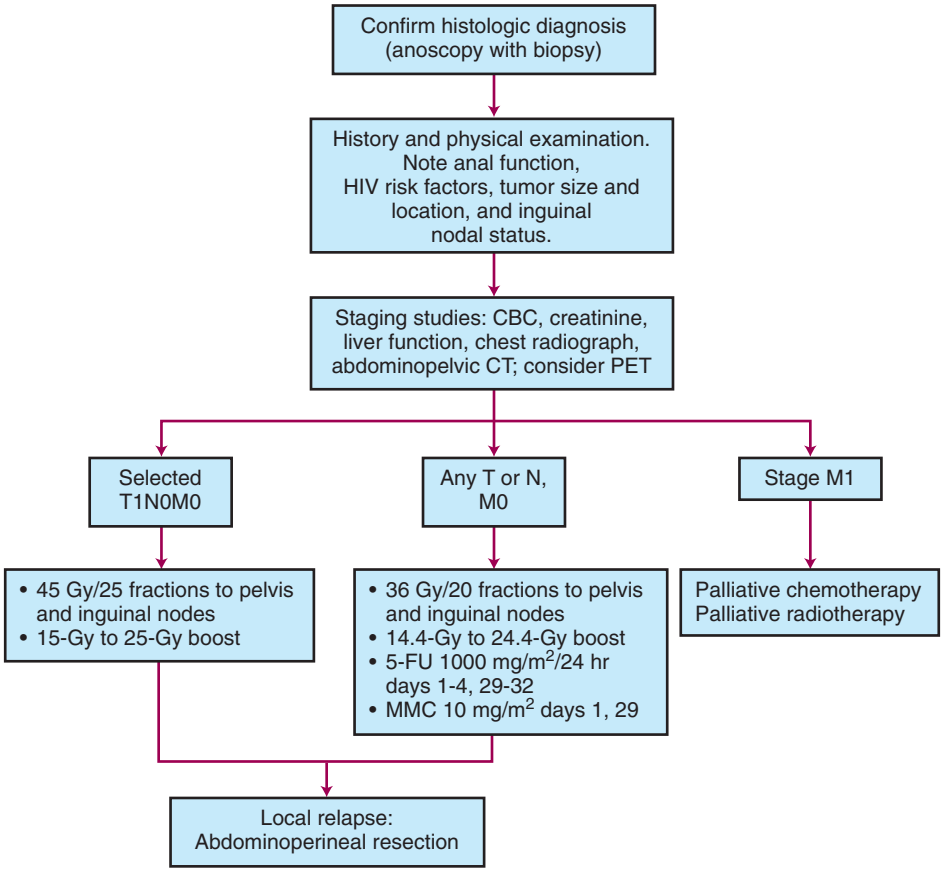


**Figure 52-3 Diagnostic and treatment algorithm for newly diagnosed anal cancer.** *5-FU*, 5-fluorouracil; *CBC*, complete blood count; *HIV*, human immunodeficiency virus; *MMC*, mitomycin C; *PET*, positron emission tomography.

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