

104 NEOPLASMS OF THE ANUS

BRENDA SHANK, MD, PhD
WARREN E. ENKER, MD
MARSHALL S. FLAM, MD

Anal canal carcinoma no longer requires colostomy, with its dire consequences of anal sphincter loss and a highly uncertain prognosis. Successful multi-modality therapy has allowed sphincter preservation for even large primary tumors. Even patients with inguinal node metastases can have a high cure rate with this approach, without an extensive superficial and deep inguinal node dissection.

Melanoma of the anal canal, in contrast, continues to have a dismal prognosis; only innovative therapies hold any hope for improvement in this disease.

GROSS AND MICROSCOPIC ANATOMY

Reproducible landmarks define the limits of the anal canal. Surgically, the anal canal extends from the anal verge distally to the anorectal ring proximally. The anorectal ring is defined as the junction where the anal canal meets the rectum. This junction corresponds to the proximal level of the pelvic diaphragm, that is, the levator ani or the muscular floor of the pelvis. The anal canal changes from its cylindrical shape to the more capacious barrel shape of the rectum.¹

Distally, the junction of the anal verge is defined by the visible anus and its entry into the anal canal. This landmark is further defined by the transition from normal skin with its keratinized stratified squamous epithelium, perianal hyperpigmentation, and hair follicles to hairless, stratified squamous epithelium that is grossly lacking in cutaneous pigment.

Between the anal verge and the anorectal ring are two other landmarks: the intersphincteric groove and the dentate line. The intersphincteric groove, often more palpable than visible, defines a plane that separates the internal from the external voluntary sphincters. The dentate line is defined by the columns of Morgagni.

Anal canal carcinomas are defined as tumors that are either wholly or partially situated across the dentate line.¹ Tumors below the dentate line are considered anal margin carcinomas. Practically, few anal margin tumors extend into the anal canal. Significant differences in treatment and in survival separate the anal margin from anal canal tumors. The histology of the anal canal, from the anorectal ring down to and including the perianal skin, varies from the strictly columnar epithelium of the intestinal mucosa to the strictly stratified squamous keratinized epithelium of the skin with hair follicles and pigment. Overlap is the rule so that the keratinizing squamous stratified epithelium diminishes proximally, while the columnar epithelium of the intestinal mucosa gives rise to cuboidal epithelium, within the anal canal, and fades gradually when the strictly cutaneous epithelium of the perianal skin is encountered.

The anal transitional zone as described by Fenger² incorporates all forms of epithelium, giving rise to a wide array of histologic types of anal epidermoid carcinomas. These can be divided into two categories, basalioid (cloacogenic), or squamous cell carcinoma. While some investigators have attributed prognostic significance to the basalioid type, most have found no difference in clinical outcome and believe all histologic variants to be subsets of anal epidermoid carcinoma. See Figure 104.1 (Plate 22) for an example of an anal canal epidermoid carcinoma.

On the other hand, keratinizing squamous carcinoma of the perianal skin, that is, the anal margin (within 5 cm of the anal verge), does have a markedly improved outlook with minimal intervention, when compared with anal canal carcinomas of any other histologic subtype.¹ Some tumors situated below the dentate line but above the anal verge remain difficult to classify anatomically.

Anorectal melanoma is defined as cutaneous melanoma arising in the perianal skin or as melanoma of the mucous membrane arising in the anorectal region.

EPIDEMIOLOGY

Cancer in the anal region is rare, with only 2 to 3% of large bowel tumors arising in this area.³ The incidence has been increasing for both men and women; data from the Connecticut Tumor Registry for 1940 to 1988 indicate a 1.9-fold increase among men and a 2.3-fold increase among women since 1960 in that state.⁴ In the past, it was most commonly seen in middle age (50 to 60 years), but more recently, the age distribution has been shifting to a younger age. In a study from southern California, only 24% of patients were less than 64 years old in the period 1955 to 1965, but for 1986 to 1995, 75% were less than 64 years of age.⁵ This disease has been more common in females than in males, with a ratio currently of about 4:3.³ In the United States, there has been an increase in incidence in men under 45 years of age.⁶ This has reversed the sex ratio in this younger group.

ETIOLOGY

In the majority of patients with carcinoma of the anus, no etiologic factor has been identified. Male homosexuality has been shown to play a role. In a case-control study of 148 patients,⁷ a history of anal-receptive intercourse in men (but not in women) was strongly associated with anal cancer (relative risk [RR] = 33.1). A case-control study from Denmark and Sweden demonstrated a statistically significant association in women between anal cancer risk and anal intercourse, young age at first anal intercourse (< 30 years), and the number of anal-sex partners.⁸ The relative risk of developing anal cancer has risen dramatically among never-married men compared with ever-married men in urban areas; it has gone from 5.8 in 1973 to 1978 to 10.3 in 1985 to 1989.⁴ It has been suggested that spermatozoa and seminal fluid may be etiologic agents and/or cofactors.⁹ This would imply that sexual behavior, not sexual preference, would be a primary factor in anal cancer development.

One prime suspect as a causative agent has emerged—the human papilloma virus (HPV). There is a relationship between this virus and the development of genital warts (condylomata acuminata), which can evolve into anal cancer after 5 to 40 years.¹⁰ In Daling's study,⁷ squamous cell carcinoma was strongly associated with genital warts (RR = 26.9 in males and 32.5 in females). In addition, 64% of the 14 patients who had tumors that were positive for HPV had a history of genital warts. DNA from HPV type 16 has been found most frequently in studies of anal squamous cell carcinoma (Table 104.1).¹¹⁻¹⁸ The prevalence of type 16 DNA in anal carcinoma varies with geographic area, being significantly lower in India (3%) and South Africa (11%).¹⁹ In a study of 589 men who have sex with men, it was found that the non-prototype-like variant of HPV 16 had a 3.2 times higher risk of developing in situ anal carcinoma than the prototype-like variant, but the biologic mechanism responsible for this increased risk is unknown.²⁰ In another study, women and homosexual men were more likely to have tumors that were high-risk HPV (hrHPV) positive and to have anal canal tumors rather than perianal tumors when compared with heterosexual men.²¹ Anal canal tumors, in that study, were hrHPV positive 95% and 83% of the time in women and men, respectively, compared with only 80% and 28% in perianal skin tumors.

In a study of 82 patients who underwent anal epithelial biopsy during endoscopy, 23 with HPV infection by DNA hybridization had evidence of a premalignant condition, anal intraepithelial neoplasia (AIN).²² In this study, AIN was significantly higher in homosexual men with HPV (17 of 28) as compared with heterosexual men with HPV (1 of 26); in women with anal HPV, AIN was found only when cervical intraepithelial neoplasia (CIN) was also found. In a later study by the same group, 29 (19%) of 152 women with CIN grade III had histologic AIN, in whom 11 were grade III, and 2 had invasive anal squamous cell carcinomas. In this group with high-grade CIN, 18 of 35 (51%) had HPV 16 DNA identified in anal biopsies, whereas only 14% (7 of 50) in a control group with no history of anogenital neoplasia had HPV 16 DNA identified in anal biopsies.

Type 16 HPV was associated with high-grade AIN and invasive cancer in another study,¹⁵ while types 6 and 11 were associated with condyloma and low-grade AIN. Other studies have also correlated abnormal anal cytologic smears and HPV positivity,²⁴⁻²⁷ and some

Table 104.1. Frequency of HPV DNA Types in Anal Squamous Cell Carcinoma

No. Patients	HPV DNA Types (%)							Total	Reference
	6	11	16	18	31	33	Unc.*		
70	12	0	14	1	—	—	6	33	11
41	0	0	56	5	—	—	—	61	16
18	6	6	22	6	—	6	28	78 [†]	18
99	♂ 0 ♀ 0	0	52	4	0	0	—	56	13
		0	84	3	5	5	—	89	
13	0	0	0	0	—	—	—	0	12
4	—	—	100	25	—	—	—	100	14
	6/11								
12	8		17	0	0	0	0	25	17
24	15		77	0	23	8	—	85	15

*Unc. = unclassified.

[†] Includes one patient (6%) with a mixture of three types.

have suggested relationships among immunosuppression, HPV infection, and AIN.^{26,27} In a Norwegian study, 100% of HPV-infected anal canal carcinoma cases had evidence of viral integration into the host cell DNA, and 67% also had evidence of episomal virus DNA.¹³

The E6 oncoprotein of HPV viruses inactivates the growth-controlling p53 suppressor gene product,²⁸ which may also play a role in the pathogenesis of anal cancer. Consistent with inactivation of the p53 gene product is the finding that the presence of HPV in tumor cells is significantly associated with an increased proliferative rate and aneuploidy as compared with HPV-negative tumors. In one study, there was a high level of nuclear p53 expression in invasive anal cancer and in high-grade AIN (60 to 75%); only very low concentrations were expressed in low-grade AIN and none in normal anal squamous epithelium.³⁰ In another study, mutant p53 protein was found in a high percentage of anal cancer patients: 42% of squamous carcinomas and 86% of adenocarcinomas.²⁸ Coexpression of the HPV 16 and 18 E6 protein and mutant p53 was only found in 3 of 29 cases (10%).

Anal canal carcinomas have also been associated with prior irradiation and many benign conditions, such as fistulas and hemorrhoids, but rigorous studies of relative risk have rarely been reported. A Danish analysis found no evidence of benign anal lesions causing anal cancer, in spite of a strong temporal association between these diagnoses.³¹ An analysis of African American and Caucasian American men in VA hospitals supported the conclusion that benign anal lesions do not increase the risk for anal cancer, but instead may represent the early symptoms of these cancers, since the risk of anal cancer is very high in the first year after the benign diagnosis and rapidly declines thereafter.³²

Immunosuppression clearly plays a role. There is a 100-fold increase in anogenital tumors in kidney transplant patients (who have a high incidence of condylomata and herpes genitalis) compared with the nontransplanted population.³³

Smoking has also been pinpointed as a major risk factor.^{7,34} In the Daling study, there is an RR of 7.7 in women and 9.4 in men for current cigarette smoking.⁷ In a case-control study from Denmark and Sweden, an increased risk of anal cancer associated with smoking was restricted to premenopausal women.³⁵ The risk was highest in premenopausal women who currently smoked (multivariate odds ratio: 5.6) and increased linearly by 6.7% per pack-year smoked. The authors have proposed an antiestrogenic mechanism of action for smoking in anal carcinogenesis.

Although the human immunodeficiency virus (HIV) as a causative agent has been suggested in homosexual men,³⁶ a large study of 435 HIV-associated tumors in Italy demonstrated that in intravenous (IV) drug abusers, anal tumors were extremely rare.³⁷ In homosexual men, high incidence rates of high-grade intraepithelial anal neoplasia were associated with HIV positivity as well as lower CD4 levels and HPV infection.³⁸ A study utilizing data from AIDS and cancer registries in seven U.S. health departments,³⁹ concluded that there was a strikingly increased risk of anal cancer among both homosexual patients (RR = 84) and nonhomosexual patients (RR = 38) with AIDS. This may

reflect the known risk of immunosuppression rather than a risk of HIV directly. It should be noted that patients with HIV and anal cancer have increased toxic reactions to irradiation, thus requiring treatment interruptions and, often, hospitalization.⁴⁰

PATHOLOGY

Different histologic subtypes of cancer may occur in the anal canal, but the overwhelming majority are variants of epidermoid carcinoma (see Figure 104.1). Anal canal carcinoma may be divided into keratinizing and nonkeratinizing squamous cancers. The keratinizing carcinomas are most often well differentiated. The cutaneous or anal margin carcinomas are most often derived from keratinizing squamous epithelium. Among the nonkeratinizing types, the typical squamous cell and the basaloid (cloacogenic) carcinomas are the most common.

Etiologic differences may be apparent in the histologic variation. Of 14 cloacogenic carcinomas, all were negative for human papilloma virus (HPV), while of 21 squamous carcinomas studied, two-thirds were positive for HPV, types 16/18 in 12 cases and types 6/11 in two of the cases referenced.⁴¹

Anal canal carcinomas may spread to involve local structures. They may extend into the sphincter muscles or even beyond into the ischiorectal space laterally or the vagina anteriorly. Massive tumors involving all of the pelvic structures including the urinary tract are responsible for the clinical name "cloacogenic."

Lymphatic spread can occur in three directions. From the inferior anal canal, cancers can spread to the superficial inguinal lymph nodes, or from the upper canal to the superior hemorrhoidal vessels and the mesorectal lymph nodes. Cancers of the anal canal can also spread to the internal iliac distribution, that is, the middle hemorrhoidal and hypogastric lymph nodes, and laterally to the obturator lymph nodes. The incidence of pelvic or inguinal lymphadenopathy is hard to pinpoint. Many of the papers on natural history span five to eight decades of patient accrual. Judging lymph node involvement from the late clinical presentation seen in the early half of the 20th century may not be relevant to the extent of lymph node spread in patients seen currently. While older reports attribute lymph node spread to over 50% of patients, current data would suggest that approximately one-third of the patients have lymph node spread at the time of presentation.^{42,43}

While mesenteric lymph node involvement is reported in one-third to one-half of patients undergoing abdominoperineal resection, the span of many decades combined with the selection of patients for abdominoperineal resection who have failed initial chemotherapy and radiation makes it difficult to ascertain an accurate incidence.

Hematogenous metastasis is rare. Few, if any, patients present initially with widespread metastatic disease. Failure following definitive treatment is primarily loco-regional. Nevertheless, failure after attempted treatment of loco-regional failure is associated with widespread metastases in approximately two-thirds of patients who succumb to their disease.⁴⁴ The disease may be viewed as largely loco-regional until relatively late in its natural history. Prognosis is generally

based on a combination of clinical features including size, depth of invasion, and involvement of nodes.

DIAGNOSIS

A differential diagnosis of multiple benign conditions exists. Coexistent conditions (i.e., anal fistula, anal fissure, or hemorrhoids) are common. Most commonly, patients notice a palpable mass or bleeding. If pain or spasm is present, a rectal examination may be difficult and physician-related delay may result. A high index of suspicion in the presence of a mass is warranted. Core needle biopsy or incisional biopsy is the definitive method of establishing (1) the initial diagnosis, (2) the effectiveness of anal conservation treatment, and (3) the diagnosis of recurrent disease. Should fear, pain, or any other condition interfere with adequate biopsy, examination and biopsy under anesthesia are warranted. Anal cytology and anoscopy may prove to be useful screening methods for detecting, in high risk individuals, squamous intraepithelial lesions and other abnormalities related to HPV infection.^{44a,44b}

Treatment is based on an appropriate assessment of the extent of disease. Excision prior to staging is unwarranted, particularly because the majority of patients are not treatable by excision alone. Physical examination should include a search for supraclavicular adenopathy, hepatomegaly, abdominal masses or ascites, inguinal lymphadenopathy, and satellite lesions in the intergluteal folds or leading to the inguinal region, and a careful assessment of the primary lesion itself by digital examination, anoscopy, and proctoscopy. The primary lesion should be evaluated for size, location, depth of invasion, and the presence or absence of inguinal lymphadenopathy.

STAGING

Further workup should include a chest radiography, a computed tomographic (CT) scan of the abdomen and pelvis,⁴⁵ a complete blood count (CBC), and liver function tests. Transrectal ultrasonography remains investigational.⁴⁶ Tumor-associated antigens are currently under investigation but have not proven useful. The overall approach to patients with anal carcinoma is diagrammed in Fig. 104.2.

In a review of multiple studies,⁴⁷ tumor size, depth of invasion, location, and the presence or absence of inguinal lymphadenopathy proved to be statistically significant prognostic factors. The AJCC/UICC staging for anal canal and anal margin reflects these prognostic factors.⁴⁸ As the majority of most anal canal cancers are currently treated by nonsurgical methods, the staging system has become more clinical than pathologic.

Tumor grade has been reflective of prognosis.⁴⁹ DNA ploidy and proliferative indices remain investigational.^{49,50} Overexpression of p53 occurs in approximately 50% of tumors and correlates with inferior loco-regional control and disease-free survival.⁵¹

A search for perianal premalignant conditions, including Bowen's disease, anal intraepithelial neoplasia (AIN), HIV positivity, and the presence of HPV should be considered.

TREATMENT

LOCO-REGIONAL DISEASE Local Excision. Various series report the successful treatment of small, early superficial carcinoma of the anal canal by excision alone. T1 lesions (2 cm or less in diameter) without sphincter invasion qualify for such treatment. Nevertheless, such lesions are rare (fewer than 10%) at the time of presentation. Excision alone is associated with a 60 to 90% survival when such small, superficial lesions are selected for local therapy.^{52,53}

Multimodality Therapy. Over the past 25 years, the preferred treatment has evolved from radical surgery to definitive chemoradiation which has proven to be highly effective in achieving cures and preserving anal sphincter function with acceptable toxicity. Surgical intervention is limited to diagnostic biopsy of the primary tumor and suspicious regional lymph nodes and post-treatment biopsy when indicated.

In 1974, Nigro and colleagues first reported a preoperative regimen employing low-dose (30 Gy) irradiation (RT) and concomitant chemotherapy with 5-fluorouracil (5-FU) infusion and mitomycin-C (MMC).⁵⁴ At abdominoperineal resection (APR), performed in 6 patients 6 weeks after chemoradiation, 5 were pathologically free of

tumor. Subsequently, other investigators employed variations of this preoperative regimen in single-arm studies with impressive results.

By 1982 to 1983, other investigators had extended these observations with studies using chemoradiation as a definitive nonsurgical treatment.⁵⁵⁻⁵⁷ Over the next 10 years, many other investigators confirmed the efficacy of this regimen in over 500 patients in nonrandomized series with 5-year survivals of 75 to 85% and sphincter preservation in 80 to 90% of patients. The results in series with 25 or more patients are shown in Table 104.2.⁵⁸⁻⁶⁸ With higher doses of radiation (45-50 Gy), negative biopsies were obtained more frequently, and thus more patients could potentially be spared an APR. The majority of patients received two cycles of 5-FU by continuous infusion (1,000 mg/m²/d x 4 d CI) and one to two doses of MMC (10-15 mg/m² as bolus) concomitantly with radiation during weeks 1 and 5.

Sischy and colleagues demonstrated the effectiveness of this approach in the first multi-institutional group study (single-arm) conducted by the Radiation Therapy Oncology Group (RTOG 8314).⁶³ Overall survival was 73% at 3 years, with no significant difference in survival associated with tumor size. Adherence to the protocol was extremely important; overall survival was 92% for no or minor deviations from the regimen, but only 45% when the deviations were major (p = .03).

The RTOG later conducted a pilot study with 47 patients (RTOG 9208) employing 5-FU/MMC in standard dosage concomitantly with RT to 59.6 Gy administered over 8.5 weeks, with a 2-week planned therapy break to minimize the anticipated acute local toxicity of the higher RT dose.⁶⁹ When compared with patients treated on the 5-FU/MMC + 45-Gy RT arm of the RTOG 8704 trial described below,^{70,71} a significant increase in colostomy rates due to persistent local disease was observed (23% at 1 year and 30% at 2 years in RTOG 9208 versus 6% at 1 year and 7% at 2 years in RTOG 8704).⁶⁹ This increased colostomy rate (along with a decreased incidence of dermal toxicity) was thought to be attributable to the split-course delivery of chemoradiation.

Attempts have been made to eliminate MMC from the regimen because of its hematologic toxicity,⁷² but in larger studies, inferior local control rates were achieved when MMC was omitted.^{66,73,74} In the nonrandomized study by Cummings and colleagues, local control with 5-FU/MMC + RT was 86% in 69 patients in contrast with 60% local control in 65 patients with only 5-FU + RT.⁶⁶

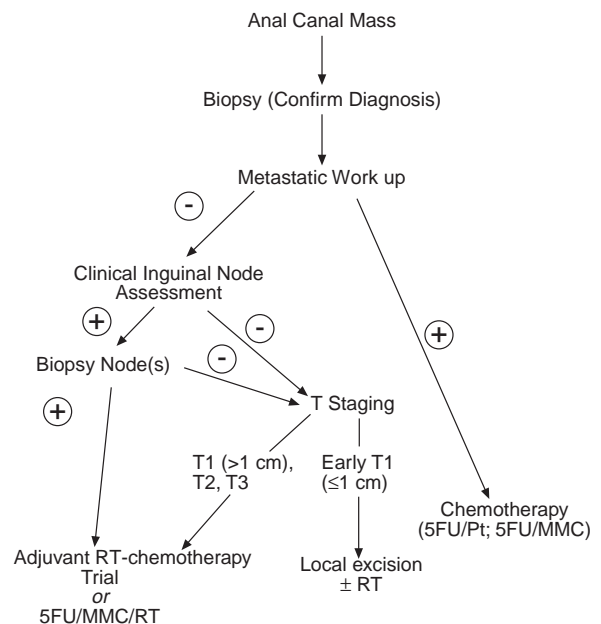


Figure 104.2. Flow diagram of staging and treatment of anal canal carcinoma.

Despite its associated morbidity, MMC has been shown to be necessary for effective treatment. In an intergroup study (RTOG 8704), 310 patients received 45-Gy irradiation and two cycles of 5-FU with or without MMC by randomization.^{70,71} Patients with negative post-treatment biopsies received no further treatment. Additional treatment (9 Gy boost RT plus 5-FU and cisplatin [Pt]) was given to those with positive biopsies. The positive biopsy rate was lower when MMC was given (8% versus 14%), but this was of borderline statistical significance ($p = .135$).⁷³ At 5 years, the MMC-treated patients demonstrated a highly significant improvement in loco-regional failure rates (36% for 5-FU versus 17% for 5-FU/MMC, $p = .014$), colostomy rates (22% 5-FU versus 11% (5-FU/MMC, $p = .019$), and disease-free survival (50% 5-FU versus 67% 5-FU/MMC, $p = .006$).⁷¹ Although colostomy-free survival was significantly different at 4 years, it was not at 5 years (58% 5-FU versus 64% 5-FU/MMC, $p = .17$). Deaths due to other causes, for example, second malignancies and cardiovascular disease, was the major contributor to the decline in colostomy-free survival in the MMC-treated group. Overall 5-year survivals were not significantly different (65% 5-FU versus 67% 5-FU/MMC, $p = .70$). Grade 4/5 toxicities were higher with MMC than without it (26% versus 7% with $p = .001$). In a study of 62 patients treated with 5-FU/MMC + RT, MMC dose influenced disease-free survival.⁷⁵

Since Pt as a single agent or in combination with 5-FU has activity in metastatic anal carcinoma, Pt/5-FU has been used as neoadjuvant treatment prior to definitive chemoradiation.⁷⁶ Of 22 patients treated, 6 (27%) experienced complete remission (CR) and 13 (59%) achieved partial remission (PR), with 20 patients achieving no-evidence-of-disease (NED) status following subsequent chemoradiation. In a nonrandomized study, the M.D. Anderson group compared two groups of patients treated with CI chemotherapy throughout their irradiation course: 39 patients on 5-FU (250-300 mg/m²/d) for 5 to 7 days a week and 18 patients on 5-FU/Pt (250 mg/m²/d and 4 mg/m²/d, respectively) for 5 days a week.⁷⁷ Although follow-up was shorter for those receiving Pt, the actuarial local control rate was 85% at 2 years, compared with 77% for those who received only 5-FU, and late morbidity was absent.

Two European prospective nonrandomized trials have demonstrated substantial efficacy of 5-FU/Pt + RT as definitive treatment.^{78,79} Peifert and colleagues treated 39 high-risk patients ($T > 4$ cm, N+) with two cycles of neoadjuvant 5-FU (800 mg/m² day 1) followed by two concomitant cycles of the same chemotherapy + RT to 45 Gy followed by an RT boost (15-20 Gy) 6 weeks later.⁷⁸ Two months after completion of the entire regimen, 96% of patients achieved a CR. Doci and colleagues treated 35 favorable patients (T1, T2, T3) with 2 to 3 cycles of 5-FU (750 mg/m² x 4 days) and Pt (100 mg/m² day 1) with concomitant RT (36-38 Gy) followed by a perineal and metastatic inguinal node boost of 18 to 24 Gy.⁷⁹ A CR was obtained in 33 patients (94%) including in all 9 patients with lymph node metastases. At a median follow-up of 37 months, 94% were disease-free and 86% were colostomy-free. These nonrandomized trials suggest that 5-FU/Pt may be at least as effective as 5-FU/MMC in combination with RT.

The Cancer and Leukemia Group B evaluated a program (CALGB 9281) in 45 poor-prognosis patients (T3/T4 or N2/N3). The induction was 5-FU (1,000 mg/m²/d CI x 5 d) + Pt (100mg/m²) on weeks 1 and 5, followed by 45 Gy RT on weeks 9 to 17 (19-day break after 30.6 Gy) with concurrent 5-FU (1,000 mg/m²/d CI x 4 d) + MMC (10 mg/m²) on weeks 9 and 15.⁸⁰ If residual disease persisted, 9 Gy RT with concurrent 5-FU (800 mg/m²/d CI x 5 d) + Pt (100 mg/m²) was given. Eight CRs and 21 PRs were obtained after induction chemotherapy. After all therapy, there were 36 CRs and 5 PRs. Ten patients required a colostomy for persistent or recurrent disease and 10 have died, 7 from progressive disease and 2 from toxicity). Of those, 35/45 (78%) who remain alive, 30 (67%) are disease-free and 25 (56%) are colostomy- and disease-free at 21 months follow-up.

Carboplatin may be as effective as Pt. Of 31 patients with locoregionally advanced anal cancer ($T > 4$ cm, or T4 or N+) treated with one to three cycles of neoadjuvant carboplatin (300-375 mg/m²) + 5-FU (1000 mg/m²/d x 5 d), 29 (94%) achieved NED status prior to radiation and a 5-year disease-free survival of 80%.⁸¹ An intergroup randomized trial (RTOG 98-11) is underway which compares 5-FU/MMC + 45 Gy RT with two cycles of 5-FU/Pt induction, followed by two cycles of concurrent 5-FU/Pt + 45 Gy RT. The RT dose is augmented to 55 to 59 Gy in both arms for high-risk patients (T3, T4, or N+ disease, or T2 lesions, if residual disease is present after 45 Gy).

Table 104.2. Multi-modality Therapy for Loco-regional Anal Canal Carcinoma

Study	Chemotherapy regimen	Radiation regimen	No. evaluable patients	No.(%) APR performed	Treatment-related deaths	5-Year survival (%)
Wayne State ⁵⁸	5-FU: 1,000 mg/m ² /4 d x 2 +MMC: 15 mg/m ² d 1	30 Gy/15 fx	44	17(39)	0	79
Memorial Sloan-Kettering ⁵⁹	5-FU: 750 mg/m ² /5 d + MMC: 15 mg/m ² d 1	30 Gy/15 fx	42	23(55)	0	82 87 ^a
Kaiser Permanente, Los Angeles ⁶⁰	5-FU: 1,000 mg/m ² /4 d x 2 + MMC: 10 mg/m ² d 1	30 Gy/15 fx	42	7(17)	0	—
Highland Hospital ⁶¹	5-FU: 1,000 mg/m ² /4 d x 2 +MMC: 10 mg/m ² d 2	50–57.5 Gy/25-32 fx	33	4(12)	0	64 70 ^a
Fresno Community Hospital ⁶²	5-FU: 1,000 mg/m ² /4 d x 2 +MMC: 10-15 mg/m ² d 2	41–50 Gy/23-28 fx	30	1(3)	0	90
RTOG ⁶³	5-FU: 1,000 mg/m ² /4 d x 2 + MMC: 10 mg/m ² d 2	40.8 Gy/24 fx	79	8(10)	0	79(3 yr)
Instituto Nazionale Tumori, Milan ⁶⁴	5-FU: 750 mg/m ² /5 d x 2–3 +MMC: 15 mg/m ² d 1	54 Gy/30 fx(split)	56	15(27)	1	81
Norwegian Radium Hospital ⁶⁵	5-FU: 1,000 mg/m ² /4 d + MMC: 10–15 mg/m ² d 1	50 Gy/25 fx	94	17(18)	3	72
Princess Margaret ⁶⁶	5-FU: 1,000 mg/m ² /4 d + MMC: 10 mg/m ² d 1	48-50 Gy/24-20 fx (split or continous)	69	10(14)	0	76 ^a
Massachusetts General Hospital ⁶⁷	5-FU: 1,000 mg/m ² /4 d + MMC: 10 mg/m ² d 1	≤54 Gy/<30 fx >54 Gy/>30 fx	14 13	6? ^b (43) 0(0)	1 0	79(3 yr) 100(3yr)
University Hospital Erlangen ⁶⁸	5-FU: 1,000 mg/m ² /4 d x 1–2 +MMC: 10 mg/m ² d 1	50 Gy/25–28 fx	44	8(18)	3	84

RTOG = Radiation Therapy Oncology Group; 5-FU = 5-fluorouracil; mmc = mitomycin-C; fx = (NEED TO FILL IN).

^aCause-specific 5-year survival.

[†]?unclear in abstract.

At present, MMC must be considered an essential component of standard therapy for all but the smallest tumors, in view of the outcome of RTOG 8704. The efficacy and toxicity of 5-FU/Pt + higher RT doses for more advanced tumors awaits the results of ongoing clinical trials.

External Irradiation. External irradiation may be a valid alternative for patients who may not be able to tolerate chemotherapy due to age, poor renal function, AIDS, or some other medical condition. The total dose of irradiation required is high (60 to 75 Gy), and as a result, complications requiring surgery arise in about 5 to 15% of patients treated (Table 104.3).^{66,82-89} In the studies shown in Table 104.3, 5-year survival varied from 94 to 50%, with local control rates from 56 to 100%. When lesions were small (T1, T2, or less than 5 cm in diameter), local control and 5-year survival were high (80% to 90%) in many of these series.

A British randomized trial⁹⁰ and a European randomized trial⁹¹ comparing multi-modality therapy with radiation therapy alone have shown quite clearly that the addition of chemotherapy is of value for prevention of local recurrence when given with irradiation. Early results of the European trial (EORTC) for patients with tumors larger than 4 cm, demonstrate an increase in the CR rate from 53 to 77% with the addition of chemotherapy; this resulted in a significant improvement of both loco-regional control (by 18%) and colostomy-free rate (by 32%) at 5 years ($p = .02$ and $.002$, respectively), with a similar overall survival rate in both arms.⁹¹ There was no significant increase in severe side effects between the two arms. The British randomized trial (UKCCCR) has shown a 46% decrease in local recurrence when chemotherapy with 5-FU/MMC is given during radiation therapy (101/283 patients or 36%) compared with irradiation alone (164/279 patients or 59%).⁹⁰ The relative risk of death from anal cancer was 0.71 in the chemotherapy arm ($p = .02$), but there was no significant advantage in overall survival.

Interstitial Irradiation. Interstitial irradiation therapy alone, either radium or Iridium-192 (Ir-192), has been used for early anal cancer.^{92,93} However, the local recurrence rates have been relatively high, especially in tumors over 5 cm in diameter (77% local recurrence), as one might expect with such localized treatment.⁹² Local necrosis has also been high (15 to 25%).⁹³ Therefore, it is inadvisable to use interstitial irradiation alone as first-line therapy.

Combined Interstitial and External Irradiation. Local control was considerably better when interstitial irradiation was combined with external irradiation, but complication rates still were high as a result of the high total dose of irradiation that is necessary.^{94,95}

The most extensive series is that of Papillon and colleagues.^{96,97} Chemotherapy (5-FU/MMC) was used in approximately a third of these patients. Ir-192 was used as a boost dose about 2 months after external beam therapy to a total dose of 35 Gy. At 5 years, 66% of patients were alive and well; 61% were alive with their sphincters preserved. Even patients with large lesions achieved excellent local control (90% in 89 patients with T3 tumors larger than 4 cm); 78 historic control patients treated with similar irradiation without chemotherapy achieved only 70% local control ($p = .02$).⁹⁸

Two other retrospective studies used combined external and interstitial irradiation plus chemotherapy.^{95,99} Neither showed an increase in efficacy with the addition of chemotherapy. In the French study,⁹⁵ 96 of 108 patients received an Ir-192 implant after external beam irradiation; 5-FU/Pt was used in 59 patients. Survival in the entire group was 64% and cause-specific survival was 72%. In the Swiss study, 108 of 125 patients had an Ir-192 implant and 68 had chemotherapy (5-FU/MMC).⁹⁹ Overall survival was 66% at 5 years. In an update of the Swiss study with 137 patients, the only analyzed factor which influ-

Table 104.3. Treatment of Anal Carcinoma with External Radiation Therapy Alone

Investigation	No. of patients	Primary site dose (Gy)	Follow-up (years)	Complications requiring surgery (%)	5-Year survival by size or stage*	Local control (%)	
Institut Curie ⁸²	183	60-65	3-14	8	All	59	69
					T ≤ 4cm	70	
					T > 4cm, but ≤ 6 cm	57	
Institut Gustave Roussy ⁸³	64	60-65	2-13	14	All	50	81
					T1,T2	72	91
					T3	35	76
					T4		67
St. Francis Memorial Hospital ^{84,85}	39	65	0.5-8.5	10	All	79	80
					NO, <5 cm	92	77
Princess Margaret Hospital ⁶⁶	57	45-60	10-30	8†	All	68§	56
CRLC Val d'Aurelle ⁸⁶	28	60-65	5-14	4	T1-3	85	61
					T1	86	71
					T2	92	67
					T3	75	57
Hôpital Tenon ⁸⁷	147	60-65	1-17	10	All	61§	7
					T2(5 cm)‡	71§	77
					T3‡	60§	70
					T4‡	42§	60
Mayo Clinic ⁸⁸	18	45-67	2.5-11.2	17	All	94	100
British Columbia Cancer Agency ⁸⁹	72	50	2-20	3	All	66	76
					T1‡		89
					T2‡		79
					T3‡		75
					T4‡		50

*UICC 1978 stage.

† Two of these refused surgery.

‡ UICC 1987 stage.

§ Cancer-specific survival.

enced local control was overall treatment time.¹⁰⁰ If treatment time was > 75 days, 5-year actuarial local control was only 69% versus 85% for shorter times, significant in univariate analysis but only of borderline significance in multivariate analysis ($p = .09$).

Pulsed dose rate brachytherapy has been used as boost treatment in a small pilot study of 17 patients,¹⁰¹ with 25.2 Gy given in 42 0.6-Gy hourly pulses after 46 Gy in 25 fractions with external beam; 13 patients (76%) had necrosis develop within 1 to 49 weeks after implantation, an unacceptably high rate. In a French analysis of factors predicting for late complications when interstitial Ir-192 has been combined with external beam irradiation, the only statistically significant factor contributing to necrosis was the extrapolated response dose for late-responding tissues which is a representation of the total effective dose from both modalities.¹⁰²

Such boost treatment or additional chemotherapy (possibly Pt/5-FU) with external irradiation may be found to be of value in large lesions, but in the studies which have been published to date, the use of an interstitial boost has not contributed to any better survival results compared with studies without such a boost.

Radical Surgery. Initial Treatment. Prior to the current era, in which the majority of patients are treated by combined multi-disciplinary therapy, over 90% of patients with potentially curable carcinomas of the anal canal were treated by APR. Such surgery was often accompanied by adjacent organ resection, that is, posterior vaginectomy, in an effort to achieve wide margins of resection combined with the pathways of lymphatic spread.¹⁰³ Indications for adjacent organ resection and for pelvic (i.e., hypogastric) lymphadenectomy have been modified over the past 15 years as studies have demonstrated the lack of routine value of either approach beyond APR with total mesorectal excision.

Results vary widely by patient stage and associated conditions; the 5-year overall survival of patients undergoing primary treatment by APR is in the range of 50%. A typical result is represented by 144 patients treated by radical surgery at the Memorial Sloan-Kettering Cancer Center, where a 55% 5-year survival rate was reported.¹⁰⁴ All patients had tumors involving the dentate line, and no cancers of the anal margin were included in these results.

Salvage Treatment. An APR of the rectum is reserved today for patients who have failed combined multi-disciplinary treatment. For patients with either persistent disease or recurrent loco-regional disease, salvage APR may be offered as definitive therapy. Conceptually, it is difficult to separate persistent disease from locally recurrent disease in these patients, particularly in patients with lesions larger than 5 cm at the time of presentation.¹⁰⁵ The role of APR in the management of patients with lesions > 5 cm is debatable.

Alternative approaches to treatment have been advocated, such as the addition of a further small increment of radiation and of Pt-based chemotherapy.^{106,107} A retrospective study of patients from all of the VA hospitals suggested that salvage surgery was superior to conservative salvage attempts;¹⁰⁸ surgery was successful in 53% of patients with recurrences, compared with salvage chemotherapy with or without RT, which was successful in only 19%. That study undoubtedly was subject to biases in the choice of therapy, but, at present, an APR is recommended for patients with persistent disease well beyond the initial period of treatment or with histologically proven recurrent disease.

In a series of 38 patients treated over a 12-year period at the Memorial Sloan-Kettering Cancer Center, an actuarial survival rate of 44% was achieved by salvage APR for persistent/recurrent disease following combined chemotherapy and radiotherapy for epidermoid carcinoma of the anus.¹⁰⁵ Inguinal adenopathy at the time of initial presentation, fixation of tumor to the pelvic side wall, and pathologic involvement of perirectal fat adversely affected survival. Age, gender, the initial response to chemotherapy and radiation, the initial stage of the primary tumor, the histologic involvement of the levator muscles, or the status of the perirectal lymph nodes did not affect survival.

A high rate of disseminated failure was ultimately evident in those patients who had recurrences despite the APR. This suggests that definitive chemotherapy, as well as definitive surgery, may be neces-

sary if patients with persistent/recurrent disease are to be salvaged after combined modality therapy.

INGUINAL NODE INVOLVEMENT With surgical resection, the prognosis has been dismal for synchronous inguinal node involvement, typified by the results reported from Memorial Sloan-Kettering Cancer Center.¹⁰⁹ Only 2 of 13 patients had their disease controlled after an APR followed by inguinal lymphadenectomy. Radiation alone has been able to control, on average, about 65% of inguinal nodes, but with multi-modality therapy, over 90% of synchronous inguinal nodes may be controlled.^{110,111} Nodal involvement is predictive of survival; in one study of 118 patients treated with curative intent, patients with negative inguinal nodes had a 9-year survival of 73% compared with only 52% when these nodes were involved.¹⁰² Multi-modality treatment should clearly be the treatment of choice for positive inguinal nodes. Surgery should be for diagnosis, consisting of a limited sampling of the suspected node(s), or for salvage after an isolated inguinal recurrence. Metachronous inguinal node relapse can be treated with a lymph node dissection; disease-free survival at 3 years in one series by Papillon was 64%.¹¹² Combinations of lesser surgery, radiation, and chemotherapy may also be used successfully, although reports have been only anecdotal.

METASTATIC DISEASE The rarity of anal cancer, its limited propensity for early dissemination, and the success of definitive chemoradiation have resulted in few patients who require systemic chemotherapy without radiation. This topic has been reviewed by Flam.¹¹³ Individual case reports suggest some, but limited, activity of 5-FU + MMC against metastatic and recurrent disease when employed without radiation.^{97,114-117} Single-agent Pt has shown activity in metastatic disease,¹¹⁸⁻¹²⁰ and the combination of 5-FU/Pt has shown substantial activity in patients with metastatic disease.^{107,117,121-124} Tanum reported that 3 of 8 patients achieved a CR with 5-FU/Pt, of whom 2 were 5-year survivors.¹¹⁷ Some of these patients had failed 5-FU/MMC/RT, suggesting a lack of cross-resistance between MMC and Pt.

Limited activity has been found for a variety of other combinations, including bleomycin, vincristine, and high-dose methotrexate (BOM), a regimen which proved toxic, with 4 toxic deaths in 12 patients.¹²⁵ Pt, vinblastine, and bleomycin (CVB) and Pt plus methotrexate, vinblastine, and Adriamycin (MVAC), produced 6 of 21 (29%) major responses.¹²⁶ Sequential MTX/5-FU/leucovorin produced 4 CRs and 4 PRs in 9 patients.¹¹³ New promising drugs with activity against squamous carcinomas and substantial radiosensitizing properties such as gemcitabine and the taxanes have yet to be evaluated. One of the authors (MSF) has observed excellent responses to Taxol in 4 patients with metastatic disease, including a sustained unmaintained CR exceeding 1 year.

MELANOMA

Anorectal melanoma is an exceedingly rare disease accounting for 1 or 2% of all anal cancers. In contrast to anal canal carcinoma, where survival approaches 80% for patients undergoing combined multi-disciplinary therapy, the prognosis in anorectal melanoma is uniformly poor, with 90% or more of patients dying despite aggressive surgical or multi-disciplinary treatment. In view of the rarity of the disease, consistently useful adjuvant therapy has not been developed.

As in all melanomas, prognosis is related to the thickness of the primary tumor. Because of a delay in diagnosis (i.e., the disease often being mistaken for hemorrhoids), anorectal melanoma is generally diagnosed when the primary tumor is locally advanced. Most patients present with bleeding, the detection of a mass, or pain. Several patients in each series present with melanoma discovered on pathologic analysis of a hemorrhoidectomy specimen. In a review of 85 patients from the Memorial Sloan-Kettering Cancer Center, the median tumor size was 3.3 cm and the median depth of tumor invasion was 7.5 mm.¹²⁷ An intermediate-size cutaneous melanoma is 0.75 to 1.5 mm by AJCC/UICC staging.⁴⁸ Regional node involvement at diagnosis is frequent; it was 69% in one series of patients who underwent an APR for cure.¹²⁸

In the 85 patients described above, no statistically significant survival difference was observed in those undergoing APR of the rectum as compared with wide local excision.¹²⁷ Only 1 of 18 patients with positive mesenteric lymph nodes survived, and no patients survived with positive lymph nodes at elective or therapeutic inguinal lym-

phadenectomy. A subset of female patients who had an APR fared best; of 10 long-term survivors, all were female and 9 had undergone an APR. Among the 10 survivors, 3 had tumors that were less than 2 mm in depth and 3 had their melanoma discovered as an incidental finding at hemorrhoidectomy. These data suggest that an APR of the rectum in women with resectable minimal disease may be associated with a rewarding survival.

Distant and multiple sites of recurrence are common despite aggressive operative treatment by APR. Lymph node distribution is similar to the distribution seen in anal canal carcinoma, that is, to mesenteric, pelvic, or inguinal lymph nodes. Local recurrence is rarer and widespread metastases are the rule.

There is no established way to prevent or treat systemic disease, but there have been some 5-year survivors when chemotherapy was added to local excision.¹²⁹ Others have reported no advantage to chemotherapy in advanced pelvic or metastatic anal melanoma.¹³⁰ Adjuvant immunotherapy using irradiated melanoma cells with bacille Calmette-Guérin (BCG) resulted in no cures. The treatment for metastatic disease may consist of chemotherapy and/or immunotherapy with cytokines, modulators of chemotherapy, or adoptive immunotherapy,¹³¹ as utilized for the treatment of melanomas arising in other sites. These tumors are desperate threats, regardless of the extent of resection; therefore, such patients should be considered for trials investigating aggressive adjuvant therapy.

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