Carcinoma of the Anal Canal: Small Steps in Treatment Advances

Cathy Eng, MD, FACP

Dr. Eng is an Associate Professor in the Department of Gastrointestinal Medical Oncology, at the University of Texas MD Anderson Cancer Center in Houston, Texas.

Address correspondence to:
Cathy Eng, MD, FACP
Department of Gastrointestinal Medical Oncology
The University of Texas
MD Anderson Cancer Center
1515 Holcombe Boulevard, Unit 426
Houston, TX 77030
Phone: 713-792-8146
Fax: 713-794-1873
E-mail: ceng@mdanderson.org

Keywords
Anal, carcinoma, chemoradiation, squamous cell

Abstract: For locally advanced squamous cell carcinoma of the anal canal, efforts to discover effective treatments that would protect sphincter preservation led to the development of combined chemoradiotherapy, which, when administered appropriately, is curative. While the standard of combined modality chemoradiotherapy has minimally changed over the past 30 years, various chemotherapeutic and biologic agents, as well as novel methods for delivering radiation, have enhanced the treatment of anal carcinoma and are continuously being explored. This review examines the risk factors associated with anal carcinoma, and subsequently discusses the current standard of care from diagnosis through surveillance, paying attention to the pivotal trials that have shaped modern treatment paradigms.

Introduction

Carcinoma of the anal canal is a malignancy that will impact approximately 5,820 individuals in the United States in 2011, resulting in 770 deaths.[1] Globally, it is reported to have impacted 99,000 individuals in 2002; 60% of those being women.[2] It is a distinct malignancy in that treatment decisions may either cure the patient or leave residual disease, which will necessitate a permanent colostomy. What is commonly underrecognized is that the incidence of carcinoma of the anal canal continues to rise annually. Yet, modifications in treatment have been minimal, likely due to the high cure rate for early-stage disease. This review will focus on existing treatment paradigms as well as treatment advances that have developed over the past decade, the role of induction and adjuvant chemotherapy, and novel developments in clinical trial design.

A total of 90% of anal canal carcinomas are of squamous cell carcinoma origin. Other rare carcinomas include anal adenocarcinoma, melanoma, and neuroendocrine carcinoma of the anal canal. For the purpose of this article, the discussion will focus primarily on locally advanced squamous cell carcinoma of the anal canal.

Risk Factors

A common misconception about carcinoma of the anal canal is that its development is primarily associated with homosexual men or men that have sex with other men (MSM). However, the average patient is a woman in her 60s.[3] Other well-documented risk factors exist, including multiple sexual partners (>10); receptive anal intercourse; prior history of sexually transmitted diseases, including human papilloma virus (HPV); and chronically immunosuppressed states, including organ transplants, chronic steroid use, and HIV. Other less common risk factors include a history of tobacco use.

Globally, the HPV virus is the most common sexually transmitted disease, reportedly affecting 20 million individuals.[4] In the United States, a recent study showed that the prevalence of HPV is 26.8% (95% confidence interval [CI], 23.3–30.9%) in females aged 14–59 years (n=1,921).[5] The prevalence of HPV increases from 14–24 years (P<.001), with a gradual decline until 59 years (P=.06). Currently, over 140 subtypes of HPV have been identified, with subtypes 16, 18, and 31 being the most common and possessing malignant potential. The HPV subtype 16 genome consists of 2 oncogenes, E6 and E7.[6] The E6 oncoprotein results in destruction of the p53 tumor suppressor gene preventing programmed cell death; E7 results in destruction of the retinoblastoma (Rb) tumor suppressor protein. Identification of HPV as a causative factor not only impacts the development of anal cancer but also other HPV-associated cancers, including oropharyngeal cancers, cervical cancer, and vulvar, vaginal, and penile cancer. HPV is commonly contracted in the teens to early 20s, when individuals are the most sexually active. Yet, as stated earlier, the average age of a non-HIV-positive patient with anal carcinoma is 60 years, and the average age of an HIV-positive patient is early 40s.[7] Of note is the US Food and Drug Administration (FDA) approval of the quadrivalent vaccine against HPV subtypes 6, 11, 16, and 18.[8] It is currently FDA approved in girls and women ages 9–26 years for prevention of cervical cancer and genital warts attributed to HPV resulting in condyloma acuminata, and in boys and men ages 9–26 years for prevention of genital warts caused by subtypes 6 and 11. A recent amendment also included people aged 9–25 years for the prevention of anal cancer and carcinoma in situ attributed to subtypes 6, 11, 16, and 18. Ongoing phase I and II studies are under way to evaluate the role of the quadrivalent vaccine against HPV subtypes 6, 11, 16, and 18 in young (13–25 years), HIV-positive, MSM patients[9] and in HIV-positive and non–HIV-positive pre-adolescents, adolescents, and adults.[10] Following a diagnosis of anal carcinoma, it is unclear what capacity a diagnosis of HPV and its subtype will have on response and disease-free survival. The role of HPV has primarily been evaluated in squamous cell carcinoma of the anal canal, and its role in adenocarcinoma of the anal canal is largely unknown.

HIV-positive patients are 2–6 times more likely to contract HPV regardless of sexual practice.[11] HIV-positive patients are also likely to develop anal carcinoma at a younger age than non–HIV-positive patients.[3] Surprisingly, the incidence of anal carcinoma among HIV-positive patients has not declined during the era of antiretroviral therapy.[11] Despite the association of carcinoma of the anal canal with HIV-positive patients, it is not an AIDS-defining malignancy.

Diagnostic Approach

Although 80% of patients will present with locally advanced disease, distant disease may develop in approximately 15–20% of patients. Therefore, it is imperative that the patient is evaluated completely before initiating treatment. A full history should include discussion of previous and current sexual history and practices, and a review of any previous potentially immunosuppressed state, including risk factors for HPV, hepatitis, HIV, and chronic steroid use. The physical examination should include an evaluation by digital rectal examination of the perianal margin (<5 cm from the anal verge) and of all lymph nodes, especially the inguinal region. If there is any concern about an involved lymph node, a fine needle aspiration should be considered, as this will impact the pretreatment stage and possibly affect the radiation treatment fields. A proctoscopy is required of all patients by the treating surgeon at baseline for accuracy of T stage. Diagnostic radiographic imaging should include a computed tomography (CT) scan of the chest and a CT or magnetic resonance imaging (MRI) scan of the abdomen and pelvis. A positron emission tomography (PET) scan may be considered if the CT or MRI is inconclusive for locally advanced or metastatic disease. Currently, the supporting literature for PET scans as a diagnostic modality is limited. Current studies are evaluating the role of diagnostic modalities such as MRI and fludeoxyglucose (FDG)-PET/CT in predicting response to chemoradiation therapy.[12,13] A complete multidisciplinary assessment is needed for accurate staging and to ensure successful treatment of the patient.

American Joint Committee on Cancer Staging

Unlike other gastrointestinal malignancies, the staging of anal carcinoma remains unchanged following the revisions of the American Joint Committee on Cancer Staging (AJCC) version 7.0 system (Table 1). The size of the primary tumor and the degree of lymph node involve-

Table 1. Staging of Anal Cancer

AJCC	TNM		
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1	N1*	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N2†	M0
	Any T	N3§	M0
Stage IV	Any T	Any N	M1

*N1=involvement of perirectal lymph nodes.

†N2=involvement of unilateral internal iliac and/or inguinal lymph nodes.

§N3=involvement of perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.

AJCC=American Joint Committee on Cancer; TNM=tumor penetration, lymph node involvement, distant metastasis.

ment still remain the most significant prognostic factors.[14] Although initial interest regarding endoscopic ultrasound was investigated, it is still not considered a standard of care in the treatment of anal carcinoma, like it is in rectal cancer.

Treatment for Locally Advanced Disease

Surgery is curative for locally advanced squamous cell carcinoma (SCC) of the anal canal, but an abdominal perineal resection (APR) is required, resulting in complete loss of the anal sphincter. A permanent colostomy undoubtedly impacts the lifestyle of the patient and requires adjustment to the associated social and physical stigma. If conducted appropriately, combined chemoradiation therapy may be curative without the need for surgical intervention.

Radiation therapy as a single modality has been evaluated but is not as effective as combined modality therapy. One of the largest studies reported was a retrospective analysis of 305 patients.[15] A total of 81% of patients had T2–3 disease, with only 16% of patients having regional lymphadenopathy. The median dose of external beam radiation therapy (EBRT) was 45 Gy. A radiation boost of 20 Gy was provided after a median delay of 37 days in 279 patients (92%). At the conclusion of the analysis, it was determined that split-course radiation therapy was detrimental to outcome, increasing the risk of locoregional recurrence. Overall, radiation as a single modality resulted in local control in only 68% of all patients: T1–T2: 78–81%; T3: 63%; and T4: 33%. Chemoradiation therapy has since been determined to be the most effective means in curing these patients, but single-modality radiation therapy may be considered in select instances when systemic chemotherapy is not the best option, such as in poor-performance elderly patients.

The earliest signs of success of chemoradiation as a single treatment modality for curative intent were originally identified by Nigro and colleagues using the 5-FU and mitomycin-C (MMC) regimen.[16] Five of the first 6 patients to receive combined modality therapy were cured with chemoradiation therapy alone. The treatment consisted of radiation therapy (30 Gy in 15 fractions via AP/PA fields to the pelvis, medial inguinal lymph nodes, and the anal canal) and 5-fluorouracil (5-FU 1,000 mg/m^2/day × 4) plus MMC (15 mg/m^2 bolus, day 1). An exploratory expansion of 28 patients determined that 24 patients (86%) had a clinical complete response (CR) following combined concurrent chemoradiation therapy. APR was reserved for salvage only. Based on these principles, combined modality therapy became the standard of care for all patients with locally advanced disease.

Combined concurrent chemoradiation with a doublet regimen is now considered the standard of care for locally advanced squamous cell carcinoma of the anal canal. Chemotherapy with fluoropyrimidine/5-FU remains the foundation of all current treatment. MMC is a common pairing, and it has continued to remain a standard regimen for the past 3 decades.

One of the first phase III trials to investigate the Nigro concept with a single dose of MMC (12 mg/m^2, day 1) in combination with 5-FU versus radiation only was completed by the United Kingdom Coordinating Committee on Cancer Research (UKCCCR)–ACT I (Table 2).[17] Patients were required to have an epidermoid SCC of the anal canal of any stage. Metastatic patients were evaluated for the primary endpoint of local response. Tumor response was determined by biopsy at 6 weeks. APR was considered in all individuals who had a less than 50% response at 6 weeks. If there was a greater than 50% response but not a CR, patients were given the option of boost radiotherapy (25 Gy at 10 Gy per day). Evaluation of response was conducted at 8 weeks following the boost. After a median follow-up of 42 months, of 585 patients enrolled, the combined modality arm had a lower 3-year local failure rate (61% vs 39%; $P<.0001$; hazard ratio [HR], 0.54; 95% CI, 0.42–0.69) and 3-year overall mortality rate (39% vs 28%; $P<.02$), but no improvement in overall survival (OS) was observed. Only a small proportion of patients (3–4%) were found to have metastatic

Table 2. Selected Studies of Combined Chemoradiation Utilizing Mitomycin-C

Study	n	Treatment	CR (%)
Nigro et al (1983)[16]	28	5-FU plus MMC plus RT	86.0
UKCCCR (1996)[17]	585	5-FU plus MMC plus RT vs RT	39.0 30.0
Bartelink et al (1997)[19]	110	5-FU plus MMC plus RT vs RT	80.0 54.0
Cummings et al (1993)[20]	110	5-FU plus MMC plus RT vs 5-FU plus RT	87.0 58.0

CR=complete response; MMC=mitomycin-C; RT=radiation therapy.

disease in both arms. Concurrent chemotherapy resulted in 6 chemotherapy-related deaths within 18 months. Subsequent modifications were made for patients over 80 years of age—the dose of MMC was reduced to 8 mg/m^2. There were 3 late deaths attributed to radiation therapy, 2 deaths following salvage surgery, and 4 additional treatment-related deaths. After a median follow-up of 13 years, it was determined that for every 100 patients treated with combined modality therapy, 25.3 fewer patients developed locoregional relapse, and 12.5 fewer deaths were attributed to anal cancer versus radiation therapy alone.[18]

A smaller phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) specifically evaluated T3–4 N0–3 or T1–2 N1–3 SCC of the anal canal.[19] The primary endpoint was locoregional control (LRC). The 3-year LRC rate was 58% versus 39% (P<.02), favoring the doublet MMC regimen versus radiation alone. Of note, this regimen utilized a higher single dose of MMC, at 15 mg/m^2 on day 1.

Whether or not MMC was required in combination with 5-FU for effective radiation was answered by the Radiation Treatment Oncology Group (RTOG 87-04) phase III trial of 5-FU with or without MMC with concurrent radiation therapy.[20] Unlike the previous studies, the dose of MMC was split during days 1 and 29 at 10 mg/m^2. Multiple primary endpoints were examined, including LRC, disease-free survival (DFS), OS, and toxicity. The 4-year colostomy-free survival (CFS) and OS were superior in the doublet arm. If the biopsy was positive or regional lymph nodes remained positive, patients were offered salvage chemotherapy with a cisplatin-based regimen. Myelosuppression was significant in the doublet arm, with notably increased grade 4/5 toxicities in the MMC arm. Four deaths were attributed to neutropenic sepsis; 2 were due to failure of a dose reduction prior to cycle 2.

One area of discordance exists when reviewing these classic phase III trials—the variable dose and schedule of MMC. Hence, the dose and schedule is often left at the physician's discretion, with the consideration of the high risk of myelosuppression commonly associated with MMC.

Platinum-Based Therapy

Given the risk of myelosuppression commonly seen with MMC and the possible treatment-related morbidity associated with treatment, investigators sought another treatment option. Cisplatin is a well-recognized radiation sensitizer causing less myelosuppression. Prior prospective and retrospective studies evaluated cisplatin in combination with 5-FU and noted impressive response rates (Table 3). Hence, it appeared to have great potential to change the existing treatment paradigm. A retrospective analysis completed at our institution included 92 patients: 70 patients (76%) had T2–3 disease and 12 patients had T4 disease.[21] Cisplatin (4 mg/m^2/day) and 5-FU (250 mg/m^2/day) were given as a continuous infusion, 5 days each week, during radiation therapy. Patients received a median dose of radiation therapy of 55 Gy. After a median follow-up of 44 months, the investigators reported a 5-year OS rate of 85%, a DFS rate of 77%, and a CFS rate of 82%. LRC was maintained in 83% of patients: N1 (86%) and N2–3 (71%). No grade 3/4 hematologic toxicity was noted. Platinum-based therapy has since been utilized at our institution as the standard regimen of choice.

A 20-year retrospective review of 188 patients who were treated with 5-FU (300 mg/m^2) plus cisplatin (4 mg/m^2/day, M–F, or 20 mg/m^2, day 1 only of each week, M–F) at MD Anderson Cancer Center was recently presented.[22] The median radiation dose provided was 55 Gy in 30 fractions. After a median follow-up of 8.6 years, the investigators reported a 5-year DFS rate of 81%, a 5-year OS rate of 86%, and a 5-year CFS rate of 88%. By univariate analysis, N-stage was a poor prognostic factor for 5-year DFS (P=.02; 95% CI, 1.17–2.01) and the development of distant metastasis (P=.04, 95% CI, 1.09–2.13). Unlike prior studies, the cisplatin regimen provided is continuous throughout radiation treatment on a daily (M–F) or weekly bolus dose.

In a small phase II study of 33 patients with locally advanced anal carcinoma, radiation with 45 Gy was administered to the primary tumor and pelvic nodes, followed by a boost to the primary and involved nodes to 59.4 Gy.[23] A planned 2-week treatment break occurred after 36 Gy. Concurrent chemotherapy consisted of 1,000 mg/m^2/day of 5-FU on days 1–4 and cisplatin 75 mg/m^2 on day 1. A second course of 5-FU and cisplatin was given after radiation with 36 Gy. Eventually, an amendment was created removing the radiation break, and an additional 13 patients were enrolled. Clinical complete response (CCR)

Table 3. Selected Studies of Combined Chemoradiation Utilizing Cisplatin

Study	n	Treatment	CR (%)
Hung et al (2003)[21]	92	5-FU plus cisplatin plus RT	N/A
Eng et al (2011)[22]	181	5-FU plus cisplatin plus RT	93.0
Chakravarthy et al (2011)[23]	45	5-FU plus cisplatin plus RT	78.0

CR=complete response; N/A=Not available; RT=radiation therapy.

at 8 weeks was seen in 78% (90% CI, 63–89) of patients and was best in patients who did not receive a planned treatment break (92% vs 68%). The 5-year OS rate was 69%.

The Role of Induction Chemotherapy

The single-arm phase II Cancer and Leukemia Group B 9281 study[24] evaluated the role of induction chemotherapy in poor prognosis patients (T3–4 or N2–3) with a primary endpoint of pathologic CR (pCR). All patients received 2 cycles of induction 5-FU (1,000 mg/m^2)/cisplatin (100 mg/m^2, days 1 and 29) followed by chemoradiation therapy with 5-FU/MMC (10 mg/m^2, days 57–99). All patients were biopsied during weeks 17–18. All patients with residual disease were offered 5-FU and cisplatin again and re-biopsied on week 23. In this small phase II study of 45 patients, induction chemotherapy alone resulted in a pathologic CR (pCR) rate of 18% and a partial response of 47%. After completion of combined modality chemoradiation therapy, the pCR rate increased to an impressive 82% in these poor prognosis patients. The early results of this study served as the premise for the consideration of induction in one of the largest phase III studies in locally advanced anal cancer, RTOG 98-11.

RTOG 98-11 enrolled 682 patients in a randomized, nonblinded fashion to a control arm of 5-FU (1,000 mg/m^2 on days 1–4 and 29–32), MMC (10 mg/m^2 on days 1 and 29), and radiotherapy (45–59 Gy), or an investigational arm of induction 5-FU (1,000 mg/m^2 on days 1–4, 29–32, 57–60, and 85–88), cisplatin (75 mg/m^2 on days 1, 29, 57, and 85), and radiotherapy (45–59 Gy, starting day 57).[25] The primary endpoint was 5-year DFS. All patients received 45 Gy (1.8 Gy doses in 25 fractions over 5 weeks). Patients with residual disease, tumors greater than 5 cm, or T4 received an additional 10–14 Gy in 2 Gy fractions (total dose 55–59 Gy over 5.5–6.5 weeks). Clinical response was determined at 8 weeks after completion of therapy; a biopsy was required if a clinical CR was not achieved. Five-year DFS and OS were improved for the control arm of 5-FU plus MMC versus the investigational induction arm of 5-FU plus cisplatin (67.7 vs 57.6%; *P*=.0045; 78.2 vs 70.5%; *P*=.021), respectively. However, no statistical difference for CFS and locoregional failure (LCF; 71.8 vs 64.9%; *P*=.053 and 20 vs 26.5%; *P*=.092, respectively) was noted. One fault of the study design was the inability to directly compare MMC to cisplatin as a result of the inclusion of the induction segment in the investigational arm.[26] Hence, it is unclear if the worse outcome for 5-year DFS and OS is attributed to true inferiority of cisplatin or in fact to the inclusion of induction chemotherapy confounding the results of this analysis.

The Intergroup ACCORD 03 study also evaluated the role of induction chemotherapy in addition to the benefits of intensified boost radiation therapy.[27] Patients were required to have T2 greater than 4 cm or node-positive disease. A total of 306 patients were randomized to 1 of 4 arms: 1) control: 45 Gy/25 fractions plus boost of 15 Gy; 2) 45 Gy/25 fractions plus high-dose boost of 20–25 Gy); 3) induction chemotherapy with 2 cycles of 5-FU (800 mg/m^2 days 1–4) and cisplatin (80 mg/m^2, day 1) with standard radiation boost; or 4) induction chemotherapy with high-dose radiation boost. The primary objective was to improve 3-year CFS from 70% to 85%. With a median follow-up of 43 months, no difference in CFS was noted for induction or intensified boost therapy (*P*=.67) versus the control arm.

The Hazards of Treatment Breaks

Based on the 2 phase III trials, RTOG 98-11 and ACCORD 03, and earlier studies with planned treatment delays,[15,23,25,27,28] it is clear that any treatment delays in the initiation of, or during, chemoradiation therapy are deleterious for patient outcome. Should treatment-related toxicities be a concern, rather than withholding all chemoradiation therapy, chemotherapy may be deferred temporarily if needed, but radiation therapy should not be held for prolonged periods unless medically necessary.

Cisplatin Versus Mitomycin-C

Continued controversy exists surrounding the superiority of cisplatin versus MMC as an optimal radiation sensitizer when combined with 5-FU. Despite its initial intent, RTOG 98-11 was unable to answer this question adequately due to the study design. Both cisplatin and MMC appear to be very effective, but result in different treatment-related toxicities. MMC is commonly associated with myelosuppression, which may not be appropriate in a severely immunocompromised patient, whereas cisplatin may result in nausea/vomiting and nephrotoxicity. Brazilian investigators reported on their own personal experience of 179 patients with locally advanced anal canal carcinoma treated at the Instituto Nacional de Cáncer with 2 cycles of chemotherapy during weeks 1 and 5 of radiotherapy: 5-FU (750 mg/m^2

120-hour infusion or 1,000 mg/m^2 96-hour infusion) plus cisplatin (100 mg/m^2) on the first day of each cycle or MMC (10–15 mg/m^2, day 1) administered concurrently with radiotherapy (total dose, 55–59.4 Gy).[29] Approximately 57% had stage T3–4 tumors, and one-third of patients had node-positive disease. After a median follow-up of 83 months, the 5-year colostomy rate was not significant (*P*=.28). The 10-year OS and DFS rates for the cisplatin arm were 54% and 49%; in the MMC arm the rates were 52% and 53%, respectively (*P*=.32 and *P*=.92). Independent prognostic indicators included increased T stage and node-positive disease (Table 4).

The ACT II trial is the first and largest phase III trial (N=894) to provide a direct comparison of cisplatin to MMC.[30] The primary endpoint was 6-month CR rate. Patients were randomized to 5-FU (1,000 mg/m^2, days 1–4, 29–32) plus MMC (12 mg/m^2, day 1) or 5-FU plus cisplatin (60 mg/m^2, day 1 and 29) with a second randomization to 2 cycles of adjuvant or "maintenance" 5-FU plus cisplatin. Patients received 50.4 Gy in 28 fractions. As expected, hematologic toxicities were greater in the MMC arm (*P*<.001). The CCR at 6 months was equivalent (*P*=.53), and no difference in 3-year CFS was noted (*P*=.26). A benefit with maintenance therapy was not supported by recurrence-free survival (*P*=.67) or OS (*P*=.21). Final results are to be reported shortly.

Determination of Response

Historically, the earlier pivotal trials determined a CR by pathologic exam from a biopsy and not by clinical evaluation.[31-33] The drawback to this methodology was tissue necrosis, which caused ulceration and pain due to incomplete healing following radiation therapy, which led to an APR for palliation. Furthermore, earlier studies commonly evaluated clinical response prematurely at 4–6 weeks rather than the current accepted time frame of 8–12 weeks. Following this similar approach in delaying the assessment of adequate response, colorectal surgeons are investigating the benefits of delaying response of neoadjuvant chemoradiation from 6 weeks to 12 weeks before surgical resection of the primary rectal tumor.[34] For chronically immunocompromised anal carcinoma patients, it is not uncommon to have the multidisciplinary team reevaluate the patient at serial visits at 8, 12, and 16 weeks. A biopsy will be completed for confirmation in cases of suspicious residual disease or progressive tumor growth where salvage surgery (APR) will be recommended. Clinical and radiographic surveillance should be continued at regular intervals for a minimum of 2 years to rule out both local and distant recurrence. All women should continue regular gynecologic visits due to the risk of second HPV-associated malignancies.

Table 4. Studies Comparing the Efficacy of Chemoradiation Utilizing MMC Versus Cisplatin

Study	n	Treatment	CR (%)
Olivatto et al (2011)[29]	179	5-FU + cisplatin + RT vs 5-FU + MMC + RT	73.0 72.0
ACT II (2009)[30]	940	5-FU + cisplatin + RT vs 5-FU + MMC + RT	95.0 94.0
RTOG 98-11 (2008, 2011)[25, 53]	649	5-FU + cisplatin (induction) + 5-FU + cisplatin + RT vs 5-FU + MMC + RT	N/A

CR=complete response; MMC=mitomycin-C; N/A=not available; RT=radiation therapy.

Radiation Techniques

The most commonly used approach in the combined-modality treatment of carcinoma of the anal canal is continuous-course radiation (45 Gy in 1.8-Gy fractions using opposed anterior and posterior treatment fields with a boost to the primary tumor to 5.4 Gy) with concurrent chemotherapy. However, to minimize organ toxicity, intensity modulated radiation therapy (IMRT) has been incorporated.[35] RTOG formally evaluated this approach in 52 patients with T2 or higher disease in the hopes of reducing grade 2 gastrointestinal toxicities by more than 15% versus the toxicities seen in RTOG 98-11.[36] The investigators were unable to fulfill their primary endpoint, but the RTOG has opted to pursue IMRT as a standard treatment approach. Though IMRT has been adopted by many as a standard, to date, no formal phase III trial evaluating IMRT versus standard radiation therapy has been completed.

Novel Therapeutic Approaches

5-FU has remained the foundation of commonly used treatment regimens regardless of whether they are MMC- or cisplatin-based. However, the European Organization for Research and Treatment of Cancer (EORTC) addressed the significance of 5-FU in a doublet regimen of MMC/cisplatin in a randomized phase II study (EORTC 22011-40014) of 88 patients.[37] Enrollment criteria required patients to have a T2 of 4 cm or larger or to be node-positive. However, after 36 Gy, patients were given 2 weeks off, and then an additional 23.4 Gy was given. Patients were randomized to 5-FU (200 mg/m^2) and MMC (10 mg/m^2, day 1), or MMC (10 mg/m^2, day 1) and cisplatin (25 mg/m^2, weekly). Clinical

response rate (CRR; primary endpoint) was determined at 8 weeks after treatment was completed. The non-5-FU doublet resulted in a CRR of 91.9% versus 79.5% in the control arm. However, a greater number of patients stopped therapy on the investigational arm (11 [29.7%] vs 2 [5.1%]). Nine grade 3 hematologic toxicities were noted in the investigational arm; surprisingly, no hematologic toxicities were reported in the control arm. A pilot study of the triplet regimen of 5-FU, MMC, and cisplatin resulted in severe hematologic toxicity and deferment of further development.[38]

The oral fluoropyrimidine capecitabine is promising due to its radiation-sensitizing capabilities in lieu of continuous infusion 5-FU.[39] Two phase II trials have evaluated the role of capecitabine. One was the EXTRA-A (A Multicenter Phase II Study of Chemoradiation Using a 5 Day Per Week Oral Regimen of Capecitabine and Intravenous Mitomycin C in Anal Cancer) trial, in which patients (n=31) received MMC (12 mg/m^2, day 1), capecitabine (825 mg/m^2 twice per day, M–F), and radiation therapy (50.4 Gy in 28 fractions).[40] The primary endpoint was CR at 4 weeks. Twenty-four patients had a CR (77%). Three patients had grade 3 neutropenia. After a median follow-up of 14 months, 3 patients (9.6%) had locoregional recurrence.

In a phase II study at MD Anderson Cancer Center, the role of capecitabine, as well as the third generation platinum analogue oxaliplatin, was investigated.[41] Capecitabine (825 mg/m^2, M–F) in combination with oxaliplatin (50 mg/m^2, weeks 1–2, 4–5) plus radiation therapy (45–59 Gy with option for IMRT) resulted in a CCR of 90%. Primary toxicities included diarrhea. However, despite the increased convenience of capecitabine, it is not currently FDA approved for use in the treatment of anal carcinoma.

Interest in epidermal growth factor (EGFR) inhibitors such as cetuximab (Erbitux, ImClone) and panitumumab (Vectibix, Amgen) as radiation sensitizers and therapeutic agents originate from pivotal data in head and neck cancer, as well as other, more common squamous cell carcinomas.[42-44] A phase II study of 5-FU plus cisplatin plus cetuximab being led by the Eastern Cooperative Group (ECOG E3205) continues to enroll patients.[45] The early study design included induction prior to chemoradiation therapy, but it has since been amended. Unlike colorectal cancer, definitive predictive and prognostic biomarkers have not been identified and validated.[46,47] The proto-oncogene KRAS has not been determined to be present in tumor specimens of anal carcinoma patients.[48]

Treatment of HIV-Positive Patients

In all prior pivotal trials, HIV-positive patients were considered ineligible. However, in a companion study to E3205, the AIDS Malignancy Consortium has created a study specifically inclusive of HIV-positive patients.[49] The study is closed to enrollment, and final results are pending. This study will be the first formal prospective evaluation of the role of chemoradiation therapy in a chronically immunosuppressed patient population, and if the results are similar to those seen in E3205, this study may serve as the basis to enable the HIV-positive patient population to be eligible for future studies. Furthermore, recent reports indicate that the face of HIV-positive patients is changing, with the rise in the African American population suggesting further changes in patient demographics in the future.[50]

The Challenges of Metastatic Disease

Fortunately, less than 20% of patients will develop distant metastatic disease. Common sites of distant disease include liver, lungs, bones, and the brain.[51,52] However, when distant disease develops, there is no paradigm to guide treatment, so many providers commonly utilize chemotherapy regimens adapted from more common squamous cell carcinomas, including head and neck, cervical, and lung carcinoma. Platinum-based regimens are also commonly utilized. However, until a multi-institutional trial is completed, there will be no standardized method. Similar to other gastrointestinal malignancies, surgical resection of oligometastatic disease is encouraged for curative intent when feasible.

Conclusion

Squamous cell carcinoma of the anal canal is a malignancy that has historically been misunderstood as a malignancy common to immunosuppressed individuals. However, recent literature indicates this malignancy more often impacts the population at large, which is generally immunocompetent. Fortunately, combined chemoradiation can be curative for locally advanced disease, with 5-FU as the continued cornerstone of radiation sensitization, and either cisplatin or MMC as an integral component of the doublet. Given the risk of permanent loss of the anal sphincter, optimal outcome is best achieved with a well-informed patient and a well-versed, knowledgeable multidisciplinary team.

Acknowledgment

Thank you to Jonathan K. Phillips for his editorial contribution.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69-90.
2. WHO. Human Papillomavirus and Related Cancers. 2010; http://apps.who.int/hpvcentre/statistics/dynamic/ico/country_pdf/XWX.pdf?CFID=5151271&CFTOKEN=40027107. Accessed July 7, 2011.
3. Chiao EY, Giordano TP, Richardson P, El-Serag HB. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. *J Clin Oncol*. 2008;26:474-479.

4. CDC. Genital HPV Infection - CDC Fact Sheet. 2009; http://www.cdc.gov/std/HPV/STDFact-HPV.htm. Accessed July 7, 2011.
5. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA*. 2007;297:813-819.
6. Jakate SM, Saclarides TJ. Immunohistochemical detection of mutant P53 protein and human papillomavirus-related E6 protein in anal cancers. *Dis Colon Rectum*. 1993;36:1026-1029.
7. Madeleine M, Newcomer L. Cancer of the Anus. 2010; http://seer.cancer.gov/publications/survival/surv_anus.pdf. Accessed October 11,2010.
8. FDA.gov. Gardasil (Human Papillomavirus Vaccine) Questions and Answers. 2006; http://www.fda.gov/BiologicsBloodVaccines/Vaccines/QuestionsaboutVaccines/ucm096052.htm. Accessed April 1, 2011.
9. Clinicaltrials.gov. Vaccine therapy in preventing human papillomavirus infection in young HIV-positive male patients who have sex with males (NCT01209325). http://clinicaltrials.gov/ct2/show/NCT01209325.
10. Clinicaltrials.gov. Vaccine therapy in preventing human papillomavirus infection in young participants who are either HIV-positive or HIV-negative (NCT00798265). http://clinicaltrials.gov/ct2/show/NCT00798265.
11. D'Souza G, Wiley DJ, Li X, et al. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr.* 2008;48:491-499.
12. Clinicaltrials.gov. MRI for tumor during chemoradiation for anal canal and perianal cancer (NCT01053923). http://clinicaltrials.gov/ct2/show/NCT01053923.
13. Clinicaltrials.gov. Predictive value of FMISO-PET, FDG-PET-CT, DWI-MRI and DCE-MRI scans for patients with anal cancer receiving radiotherapy +/- chemotherapy (NCT01330186). http://clinicaltrials.gov/ct2/show/NCT01330186.
14. Ajani JA, Winter KA, Gunderson LL, et al. Prognostic factors derived from a prospective database dictate clinical biology of anal cancer: the intergroup trial (RTOG 98-11). *Cancer*. 2010;116:4007-4013.
15. Deniaud-Alexandre E, Touboul E, Tiret E, et al. Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. *Int J Radiat Oncol Biol Phys.* 2003;56:1259-1273.
16. Nigro ND, Seydel HG, Considine B, Vaitkevicius VK, Leichman L, Kinzie JJ. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer*. 1983;51:1826-1829.
17. UKCCCR. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet*. 1996;348:1049-1054.
18. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). *Br J Cance*r. 2010;102:1123-1128.
19. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol.* 1997;15:2040-2049.
20. Cummings BJ, Keane TJ, O'Sullivan B, Wong CS, Catton CN. Mitomycin in anal canal carcinoma. *Oncology*. 1993;50 Suppl 1:63-69.
21. Hung A, Crane C, Delclos M, et al. Cisplatin-based combined modality therapy for anal carcinoma: a wider therapeutic index. *Cancer*. 2003;97:1195-1202.
22. Eng C, Xing Y, You Y, et al. Cisplatin (C) based chemoradiation (CXRT) for locally advanced squamous cell carcinoma (SCCA) of the anal canal (AC): a 20-year perspective. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 482.
23. Chakravarthy AB, Catalano PJ, Martenson JA, et al. Long-term follow-up of a phase ii trial of high-dose radiation with concurrent 5-fluorouracil and cisplatin in patients with anal cancer (ECOG E4292). *Int J Radiat Oncol Biol Phys.* Apr 20 2011. Epub ahead of print.
24. Meropol NJ, Niedzwiecki D, Shank B, et al. Induction therapy for poor-prognosis anal canal carcinoma: a phase II study of the cancer and Leukemia Group B (CALGB 9281). *J Clin Oncol.* 2008;26:3229-3234.
25. Gunderson L, Winter K, Ajani J, et al. Long-term update of U.S. GI Intergroup RTOG 98-11 phase III trial for anal carcinoma: comparison of concurrent chemoradiation with 5FU-mitomycin versus 5FU-cisplatin for disease-free and overall survival. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 367.
26. Eng C, Crane CH, Rodriguez-Bigas MA. Should cisplatin be avoided in the treatment of locally advanced squamous cell carcinoma of the anal canal? *Nat Clin Pract Gastroenterol Hepatol*. 2009;6:16-17.
27. Conroy T, Ducreux M, Lemanski C, et al. Treatment intensification by induction chemotherapy (ICT) and radiation dose escalation in locally advanced squamous cell anal canal carcinoma (LAAC): definitive analysis of the intergroup ACCORD 03 trial. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27: Abstract 4033.
28. Konski A, Garcia M, Jr., John M, et al. Evaluation of planned treatment breaks during radiation therapy for anal cancer: update of RTOG 92-08. *Int J Radiat Oncol Biol Phys.* 2008;72:114-118.
29. Olivatto LO, Cabral V, Rosa A, et al. Mitomycin-C- or cisplatin-based chemoradiotherapy for anal canal carcinoma: long-term results. *Int J Radiat Oncol Biol Phys.* 2011;79:490-495.
30. James R, Wan S, Glynne-Jones R, et al. A randomized trial of chemoradiation using mitomycin or cisplatin, with or without maintenance cisplatin/5FU in squamous cell carcinoma of the anus (ACT II). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27: Abstract LBA4009.
31. Eng C, Abbruzzese J, Minsky BD. Chemotherapy and radiation of anal canal cancer: the first approach. *Surg Oncol Clin N Am*. 2004;13:309-320.
32. Eng C. Anal cancer: current and future methodology. *Cancer Invest.* 2006;24:535-544.
33. Huang J, Eng C. Anal Cancer. In: Kantarjian H, Wolff R, Koller C, eds. *The MD Anderson Manual of Medical Oncology.* Vol 1: New York, NY: McGraw-Hill; 2011:585-610.
34. Clinicaltrials.gov. Optimum timing for surgery after pre-operative radiotherapy (NCT01037049). http://clinicaltrials.gov/ct2/show/NCT01037049.
35. Hodges JC, Das P, Eng C, et al. Intensity-modulated radiation therapy for the treatment of squamous cell anal cancer with para-aortic nodal involvement. *Int J Radiat Oncol Biol Phys.* 2009;75:791-794.
36. Kachnic L, Winter K, Myerson R, et al. Two-year outcomes of RTOG 0529: a phase II evaluation of dose-painted IMRT in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 368.
37. Matzinger O, Roelofsen F, Mineur L, et al. Mitomycin C with continuous fluorouracil or with cisplatin in combination with radiotherapy for locally advanced anal cancer (European Organisation for Research and Treatment of Cancer phase II study 22011-40014). *Eur J Cancer.* 2009;45:2782-2791.
38. James R, Cunningham D, Davidson N, et al. Chemoradiation and maintenance chemotherapy for patients with anal carcinoma: A phase II trial of the UK Co-ordinating Committee for Cancer Research (UKCCCR) Anal Cancer Working Party. *Proc Am Soc Clin Oncol.* 2000;19: Abstract 1045.
39. Wadlow RC, Ryan DP. The role of targeted agents in preoperative chemoradiation for rectal cancer. *Cancer*. 2010;116:3537-3548.
40. Glynne-Jones R, Meadows H, Wan S, et al. EXTRA-a multicenter phase II study of chemoradiation using a 5 day per week oral regimen of capecitabine and intravenous mitomycin C in anal cancer. *Int J Radiat Oncol Biol Phys.* 2008;72:119-126.
41. Eng C, Chang G, Das P, et al. Phase II study of capecitabine and oxaliplatin with concurrent radiation therapy (XELOX-XRT) for squamous cell carcinoma of the anal canal. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27: Abstract 4116.
42. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354:567-578.
43. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet*. 2009;373:1525-1531.
44. Rosell R, Robinet G, Szczesna A, et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. *Ann Oncol.* 2008;19:362-369.
45. Clinicaltrials.gov. Cetuximab, cisplatin, fluorouracil, and radiation therapy in treating patients with stage I, stage II, or stage III anal cancer (NCT00316888). http://clinicaltrials.gov/ct2/show/NCT00316888.
46. Ajani JA, Wang X, Izzo JG, et al. Molecular biomarkers correlate with disease-free survival in patients with anal canal carcinoma treated with chemoradiation. *Dig Dis Sci*. 2010;55:1098-1105.
47. Lampejo T, Kavanagh D, Clark J, et al. Prognostic biomarkers in squamous cell carcinoma of the anus: a systematic review. *Br J Cancer.* 2010;103:1858-1869.
48. Van Damme N, Deron P, Van Roy N, et al. Epidermal growth factor receptor and K-RAS status in two cohorts of squamous cell carcinomas. *BMC Cancer*. 2010;10:189.
49. Clinicaltrials.gov. Cisplatin, fluorouracil, cetuximab, and radiation therapy in treating patients with HIV and stage I, stage II, or stage III anal cancer (NCT00324415). http://clinicaltrials.gov/ct2/show/NCT00324415.
50. CDC. HIV Surveillance–United States, 1981--2008. 2011; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6021a2.htm?s_cid=mm6021a2_w. Accessed July 7, 2011.
51. Eng C, Pathak P. Treatment options in metastatic squamous cell carcinoma of the anal canal. *Curr Treat Options Oncol*. 2008;9:400-407.
52. Silva N, Eng C. A case study: management of metastatic anal squamous cell carcinoma Following progression on traditional chemotherapy. *J Clin Oncol.* 2008;26(3 suppl).
53. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA*. 2008;299:1914-1921.