Acute and Chronic Complications After Treatment of Locoregional Anal Cancer: Prevention and Management Strategies

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ABSTRACT

Definitive chemoradiotherapy (CRT) for anal cancer spares patients the morbidity of a colostomy surgery and optimizes cancer outcomes. CRT, however, has introduced a unique acute and chronic toxicity profile, which has greatly improved over the years with the introduction of advanced radiotherapy techniques. This article provides the multidisciplinary care team with practical tools to mitigate and manage acute and chronic complications from definitive treatment of anal cancer.


Anal cancer diagnoses have increased over the past decade. In 2023, an estimated 9,760 new cases of anal cancer will be diagnosed in the United States, with 1,870 estimated deaths.1 Since its advent in the 1970s, definitive chemoradiotherapy (CRT) has replaced abdominoperineal resection (APR) as standard of care, with a priority given to maximizing cure rates, sphincter preservation, and patient quality of life (QoL). The role of surgery is now confined to node-negative distal anal canal and anal margin carcinomas <2 cm in diameter, for which wide local excision with negative margins is curative, and to salvage therapy for recurrences post CRT.

For the patient, definitive CRT remains one of the most challenging courses of cancer treatment to complete. The advent of advanced radiation delivery techniques has improved toxicity, and in turn, treatment breaks, but even with intensity-modulated radiation therapy (IMRT), the rates of grade $\geq$2 acute hematologic (heme), dermatologic (skin), gastrointestinal (GI), and genitourinary (GU) adverse events remain significant (73%, 75%, 73%, and 15%, respectively).2 As such, proactive toxicity management by the multidisciplinary care team is paramount.3 Patients undergoing definitive CRT should be monitored closely, with weekly attention to skin examinations, hematologic profile, and the patient’s GI, GU, nutritional, and overall status. This article provides practical tools to mitigate and manage both acute and late toxicities associated with definitive CRT for anal cancer. Table 1 provides a comprehensive summary of potential complications by organ system, as well as suggested management options. Figure 1 provides an example of a volumetric modulated arc therapy (VMAT) radiation plan, which is a newer radiation delivery method that combines inverse planning, intensity modulation, and arc therapy, to illustrate the typical radiation doses and planning volumes used for anal cancer. For recommended radiation dose constraints to normal organs for IMRT planning, refer to the ECOG-ACRIN Cancer Research Group website.4

Acute complications, defined as occurring within 90 days of radiotherapy (RT) completion, are the result of chemotherapy and radiation being delivered together, whereas late effects can occur months to years after...
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treatment completion. Both types of toxicities and their management are detailed herein.

Hematologic Toxicities
Standard combined modality therapy for anal cancer consists of concurrent fluorouracil (5-FU), mitomycin C (MMC), and RT or capecitabine, MMC, and RT. Hematologic (heme) toxicity is an important issue unique to patients with anal cancer receiving CRT, because MMC is especially toxic to marrow. Additionally, interstitial pulmonary lung disease and hemolytic uremic syndrome are MMC toxicities of which treating physicians should be aware.

The ACT I trial demonstrated that early morbidity was significantly increased for patients undergoing CRT versus RT alone. The addition of 5-FU and MMC brought with it the sequelae of increased “severe” treatment-related toxicities, primarily skin (50%), GI (14%), heme (6%), and GU (3%). In ACT I, heme toxicity was only observed in the chemotherapy arm, and later randomized studies would confirm MMC as the main driver of acute bone marrow suppression.

Recently, capecitabine has been increasingly used in place of infusional 5-FU, because it has been shown to have less grade $^3$ acute heme toxicity as well as fewer treatment interruptions. In the study reported by Goodman et al., 52% of patients experienced grade 3/4 neutropenia with 5-FU compared with 20% in the capecitabine group ($P = .001$). Treatment breaks related to grade $^3$ heme toxicity were found in 42% of patients treated with 5-FU compared with 16% of those treated with capecitabine.

Although 5-FU/MMC triggers myelosuppression, radiation directed to the hematopoietically active bone marrow also plays a crucial role, because circulating blood cells within bone marrow are extremely radiosensitive, leading to some degree of damage regardless of radiation dose received. Although opinions are mixed on whether we should focus on sparing low doses versus medium to high doses to the pelvic bone marrow (PBM), there is agreement that PBM is a parallel organ. In radiobiology, a parallel organ is defined by the fact that a certain fraction of a specific organ’s parenchyma, or functional subunits, can be rendered inactive, but the organ will still function. Based on this model, a mean bone marrow dose constraint of $<25$ Gy has been suggested to guide RT planning and has yielded rates of grade $^3$ heme toxicity of $<10%$.

For PBM contouring, Cheng et al. found that for the purposes of predicting grade $^3$ heme toxicity, whole-bone contouring was superior to marrow cavity contouring, and this is standard for anal cancer IMRT. Although the optimal treatment planning parameters for sparing heme toxicity remains an area of active investigation, bone marrow should be included as an organ at risk (OAR) for all definitive anal CRT plans to minimize heme toxicity.

During CRT, weekly peripheral blood counts (CBC with differential) are monitored. When heme toxicity develops, the radiation oncologist should be in close communication with medical oncology, and patients with cytopenias must be counseled about neutropenic fever and the potential

Figure 1. (A–C) Radiotherapy dose color wash images of a 61-year-old female with cT2N1aM0, stage III, HPV-positive anal squamous cell carcinoma. She received volumetric modulated arc therapy, 360-degree arcs, 30 fractions, with concurrent capecitabine and mitomycin C. Prescription was 5,400 cGy to the primary tumor’s PTV shown in yellow color wash, which included the entire anal canal and gross anal tumor outlined in red with a margin; 5,040 cGy to an involved <3 cm inguinal lymph node PTV shown in green color wash, and 4,500 cGy to the elective uninvolved pelvic lymph nodes shown in blue color wash. The patient was planned in the prone position on a bowel displacement board with a 175-mL filled bladder. No bolus was necessary because there was no exophytic component of the tumor. Abbreviation: PTV, planning target volume.
need for inpatient admission for intravenous antibiotics if this should arise. At the medical oncologist’s discretion, granulocyte colony-stimulating factor (G-CSF), red blood cell, and platelet support can be provided when needed. It should be noted that there is literature advising against the use of G-CSFs in patients with cancer undergoing RT; however, it may be necessary.17 Bone marrow recovery happens within 10 weeks status post CRT completion; however, in approximately 25% of cases, myelosuppression is cumulative, and counts may be slow to or never recover, depending on age, sex, and other comorbidities.38

**Dermatitis/Mucositis**

Brisk and intense skin reactions, consisting of dermatitis and mucositis within the gluteal cleft, inguinal folds, or inner vaginal lining, are almost certainly guaranteed in patients undergoing CRT. This toxicity is difficult to avoid, because all patients will receive a high radiation dose to the perianal skin that is sensitized further by the concurrent MMC.

RTOG 0529 demonstrated significantly less dermatologic toxicity using IMRT compared with RTOG 98–11 (75% vs 82%, respectively), and the grade ≥2 toxicity with IMRT generally occurs after week 5 of MMC infusion when the patient is nearing the end of treatment, thus limiting the need for treatment breaks due to this morbidity.19–21 IMRT planning strategies include reducing the radiation dose to the uninvolved skin surface, which may be particularly beneficial in the groin region where elective nodal coverage is targeted. It is important for the treating radiation oncology team to remember that in areas where tumor or nodes grossly involve skin, bolus is being used during RT to ensure effective treatment of disease. In these patients, careful attention should be paid to these areas, because bolus will result in more local skin toxicity.

Although most dermatitis can be managed conservatively with skin care without treatment interruption (Table 1), there is a small percentage of patients in whom infection develops, causing treatment breaks or the inability to complete treatment. Patients’ perianal, perivaginal, and inguinal skin should be examined at least weekly during RT on-treatment visits, or more as needed, as patients progress through their treatment course.

Dermatitis and mucositis often heal completely within 12 weeks of CRT completion; however, preventing and mitigating the severity of acute symptoms is beneficial. Effective treatments that can be used early in treatment before or after symptoms develop include barrier creams, which provide both skin lubrication and soothing comfort.22 For patients with increased loose stool and irritated skin, these can be particularly helpful to reduce pain and avoid infection, and can be most effective if applied prior to bowel movements to prevent further skin irritation. If patients are willing, sitz baths can also be repeated throughout treatment for symptomatic relief and cleansing properties.23

As desquamation of the skin and mucosa progresses, topical lidocaine ointment or gel and silver sulfadiazine creams can provide symptom relief and restoration.24 For desquamation, application of gauze soaked with chlorhexidine or Domeboro (Moberg Pharma North America LLC) or saline soaks may be useful by cleansing and exfoliating the skin of exudative debris.25–26 Following gauze removal, patients can then apply a topical silver sulfadiazine and lidocaine mixture to the clean surface, and this can be repeated 2 to 3 times per day as needed.25–27

Although acute skin reactions can impact treatment, there are long-term effects that are also important to counsel patients about, usually consisting of telangiectasias, hyperpigmentation, and skin dryness. In managing these, use of heavy moisturizers such as Aquaphor or CeraVe cream can help with chronic dryness and irritation.

**GI Toxicities**

Patients with anal cancer can experience significant acute and chronic GI symptoms related to CRT; however, a recent study using patient-reported outcomes (PROs) demonstrated that most patients return to baseline at 3 months status post CRT completion, based on the EPIC questionnaire.28

Practical RT planning strategies that can be used to reduce GI toxicity include the use of prone positioning in selected patients to move the large and small bowel up and out of the treatment field, and adequate and repeated bladder filling. Dosimetrically, several studies have evaluated predictive parameters for acute GI toxicity during CRT. The University of Pittsburgh retrospectively reviewed 58 patients undergoing IMRT. The volume of bowel, using the bowel bag contouring technique, receiving 30 and 40 Gy (V30 Gy and V40 Gy, respectively) were powerful predictors of grade ≥3 GI toxicity. In patients with V30 Gy >310 mL, the rate of toxicity was 39% compared with 9% if the V30 Gy <310 mL (P=.016). In patients with V40 Gy <70 mL, the rate of toxicity was 6% compared with 36% if the V40 Gy >70 mL (P=.045).29 In general, close attention to reducing small bowel doses can improve the rates of grade ≥3 GI toxicity.30

Although rates of diarrhea continue to decline as treatment optimization improves, some patients can still experience loose and frequent bowel movements that not only are unpleasant but also can exacerbate open skin wounds from treatment. Dietary modifications are a useful first step in preventing acute GI issues. Patients should be advised that a low-fat, lactose-free, and low-residue diet can mitigate diarrhea, and consultation with a dietitian, if available, should be arranged for a detailed review of provoking foods and meal ideas. In cases where dietary changes are not enough, antidiarrheal medications...
will often be required. A common approach is to have the patient begin with over-the-counter loperamide. For those with more continual symptoms, a secondary agent such as atropine/diphenoxylate may be added. An often-forgotten fact is the connection between bile acid malabsorption and diarrhea that may be occurring in these patients, for which bile acid binders, such as cholestyramine powder, may also aid in symptom relief.31

Other commonly seen GI toxicities that can span both the acute and chronic timeline are tenesmus, anorectal dysfunction, and rectal pain. Treating tenesmus may require a multimodal approach, with one beginning with use of anti-inflammatory aminosalicylates, as well as pain relief medications applied topically inside the anus and rectum with a suppository, a form of medication delivery that can also be painful due to tumor and mucositis. If refractory, anticholinergic drugs can be tried, as well as smooth muscle relaxers or anticonvulsants.32 Anorectal dysfunction, which is often present at diagnosis, especially with bulkier tumors, encompasses anal incontinence, urge, and clustering (numerous bowel movements occurring within a short period of time). This toxicity is correlated most closely to radiation dose to the sphincter muscles, with dose to the internal sphincter muscles being more impactful than dose to the external.33 Although reducing dose to these muscles would be optimal, this is most often impossible in the treatment of anal cancer because the anal canal receives full radiation dose. Strategies to manage anorectal dysfunction include more conservative measures, ranging from diet modification and use of bulking agents to the use of pelvic rehabilitation specialists for Kegel exercises and consideration of a sacral stimulator in refractory cases.34 Similarly, for anorectal pain, a multimodal approach will often be needed. Medications including calcium channel blockers (diltiazem is commonly used), vasodilators (nifedipine), anti-inflammatory agents, and opioids are found to be helpful. Other interventions if anorectal pain proves refractory include lidocaine, nerve blocks, and referral to pelvic floor rehabilitation.35

Late GI toxicities include radiation enteropathy, chronic anorectal dysfunction, chronic urgency/leakage, chronic diarrhea/alternating constipation, rectal bleeding, rectovaginal fistula, and fecal incontinence. It is important to note that rectovaginal fistulas do not occur without T4 tumors and arise from a combination of both mechanical tumor effect and radiation exposure. RT-induced telangiectasia development can cause rectal bleeding and is initially managed through endoscopic evaluation followed by bowel habit optimization and medical therapy, including sucralfate enemas and oral metronidazole with or without concurrent formalin.36 For refractory rectal bleeding, hyperbaric oxygen therapy can be used and may benefit selected patients.37 In patients who develop fecal incontinence, this is managed with physical therapy referral/pelvic floor exercises, bulking agents, dietary modification, antidiarrheal medications, biofeedback techniques, surgical sphincter repair, and sacral nerve stimulation.38 Lastly, refractory sphincter dysfunction due to prior tumor infiltration and treatment toxicity can be an indication for diverting colostomy.

In cases of massive diarrhea, some medical oncologists will test patients for dihydroyrimidine dehydrogenase (DPD) deficiency, which causes 5-FU and capecitabine metabolism to malfunction, prior to starting treatment with 5-FU or capecitabine. This is not considered standard of care, however, given that the incidence rates in the population are very low. Only 3% to 5% of patients with cancer will have partial DPD deficiency, and even fewer experience full deficiency.39 In cases where no testing was performed and patients develop severe diarrhea and acute mucosal toxicity (skin or GI) early during therapy, the treating physician should consider DPD deficiency. If a patient is found to have DPD deficiency, the medical oncologist will need to dose-reduce or discontinue fluoropyrimidine-based chemotherapy.

**GU Toxicity**

Patients undergoing definitive CRT for anal cancer will often experience acute urinary symptoms, which may include urinary frequency and dysuria. IMRT has been shown to decrease the rate of grade ≥3 GU toxicity.40 Dosimetric parameters for urinary toxicity mitigation in patients with anal cancer are less defined compared with other organs at risk, and this may be due to the overall low rates of grade ≥3 GU toxicity seen throughout the anal cancer CRT literature.40

It is important to elicit a detailed history regarding a patient’s urinary symptoms, including any signs of infection, as well as when pain occurs in relation to urinary strain. Any signs of infection, which are usually dysuria and frequency, should prompt a urinalysis/urine culture with appropriate use of antibiotics as indicated. Patients with early dysuria, meaning it occurs early in the urinary stream, may be experiencing periurethral irritation, and a peri bottle may provide symptom relief. The patient can be directed to use the bottle to cleanse the skin during and after the urinary stream. Suprapubic pain at the end of the urinary stream, often described as cramping, may imply cystitis, and antispasmodics or phenazopyridine may offer symptomatic relief.41 The risk of late effects has not been well reported, likely due to the total mean radiation dose to the bladder being relatively low with IMRT for this cancer, compared with RT for other pelvic malignancies.

**Sexual Function Toxicity**

A very commonly missed (both in evaluation and up-front counseling) acute and chronic toxicity for patients with anal cancer is changes in physical and emotional...
sexual function posttreatment. QoL series have demonstrated high rates of long-term sexual toxicity, with >50% of patients reporting decreased interest is sexual activity, dyspareunia, erectile dysfunction, and loss of feeling attractive. Vaginal stenosis, while uncommon in the IMRT-era, as demonstrated in RTOG 0529, is one of the most impactful physical changes impacting sexual activity. Prevention of vaginal stenosis is therefore imperative for healthy sexual function, as well as for allowing for proper vaginal examinations in the future, which is essential for monitoring other HPV-related malignancies.

One method to prevent or ameliorate mechanical stenosis centers on the patient's proper use of a vaginal dilator, which should be given to patients within 1 month of finishing CRT. A general recommendation for dilator use is 10 minutes at least 3 times per week, and patients should be repeatedly counseled and questioned about their use at follow-up visits. A prospective study assessing vaginal dilator use in patients with anal or rectal cancer found that patients with <40% dilator compliance had higher rates of vaginal stenosis. If a patient does develop vaginal stenosis, conservative measures include trying to slowly redilate the canal with estrogen cream and progressive dilation. If this fails, surgical reconstruction may be offered, often necessitating split-thickness skin grafts for vaginal lengthening and myocutaneous grafts for vaginal reconstruction.

In women who experience vaginal dryness, a combination of topical estrogen and moisturizers/lubricants can be offered. For men, phosphodiesterase inhibitors are typically used to improve erectile dysfunction and sexual functionality, although the rate of erectile dysfunction has been shown to be low with modern IMRT. For emotional issues related to sexual dysfunction, patients should be referred to a psychologist with training in postradiotherapy sexual dysfunction when necessary or requested. For premenopausal women and men who desire future children, fertility consultation should occur early in the workup prior to treatment to discuss egg harvesting and sperm banking, respectively. For young women wishing ovarian endocrine preservation, discussion with a gynecologic oncologist within the multidisciplinary care team is warranted and ovarian transposition outside of the IMRT field should be considered. In women who experience premature menopause after treatment, hormone replacement therapy (HRT) and intravaginal estrogen may be used, if appropriate. For men who experience low testosterone following treatment, HRT may be considered.

**Bone Toxicity**

Another often overlooked toxicity in the chronic setting is bone morbidity. RT to bone increases fracture risk by reducing bone osteoblasts and vascularity, while increasing marrow adiposity. Late effects can include insufficiency fractures of the femoral heads or sacrum, causing chronic pain and reduced QoL.

In a 2020 meta-analysis examining 6,488 patients who received pelvic RT, the crude incidence of pelvic insufficiency fractures (PIFs) was 9.4%, and in another 2,131 patients examined, the 5-year actuarial incidence was 15.3%. Patient education regarding insufficiency fractures is important; the median time to PIF development in this meta-analysis was 8 to 39 months status post RT, and the sacrum was the most common location for fracture development. Patient characteristics associated with increased risk of fracture include age, weight, female sex, low body mass index, menopausal status, use of HRT, birth history of >3 deliveries, and smoking status. Medical comorbidities associated with risk of PIF development are rheumatoid arthritis, type 2 diabetes mellitus, and osteoporosis. From 18 studies examined, 58.5% of PIFs presented symptomatically, with pain being the most common symptom.

It is worth noting that the patients who experienced PIF received a heterogenous group of RT modalities and there are few data describing rates of PIFs in the IMRT era. Two studies have shown an association between dose and insufficiency fracture development using IMRT. Bazire et al demonstrated insufficiency fracture sites received a higher maximum dose compared with nonfracture sites (50 vs 45 Gy, respectively). Ramlov et al found a dose–effect relationship between $D_{50\%}$ to the sacrum and PIF risk, with higher doses to the sacrum associated with an increased risk of PIF development. Based on their model, decreasing sacral $D_{50\%}$ from 40 to 35 Gy would reduce the risk of PIF from 45% to 22% (absolute risk reduction of 23%).

Currently, there are no consensus guidelines for the management of RT-associated PIFs. Management is most often conservative, involving analgesics, bed rest, and observation. In a minority of cases, surgery (hip replacement, vertebroplasty) or hospitalization for pain control is required. Bone-directed therapies (bisphosphonates, calcium, vitamin D, and HRT in women) can allow for improved fracture healing, with one series reporting a higher proportion of radiographic fracture healing (83%) compared with observation alone (40%). The time to pain resolution ranged from <1 month to 35 months (median, 3 months).

Potential interventions during CRT to prevent insufficiency fractures include avoidance of the femoral heads and reducing dose to the sacrum through IMRT planning. Women who have completed CRT who are postmenopausal or in menopause due to treatment effect experience both radiation-related bone effects and low estrogen levels, and may therefore benefit from routine DEXA scans, allowing for appropriate treatments and lifestyle modifications to be advised. Bone-directed therapies such as bisphosphonates and HRT have been shown...
to reduce the risk of osteoporotic fractures; however, their prophylactic use for insufficient fractures is limited only to prostate studies.5,44 For all patients, general education on ameliorating bone loss through weight-bearing exercises, increasing dietary calcium and vitamin D, smoking cessation, and limiting alcohol intake should be provided at treatment completion. A Cochrane review highlighted the need for additional studies to elucidate appropriate pharmacologic interventions and their timing relative to RT.55

Conclusions
Definitive CRT for anal cancer spares patients the morbidity of surgery; however, it causes a very complex acute and chronic toxicity profile that must be managed diligently by all treating physicians involved in the patient’s care. Preventing and optimally treating adverse effects is imperative to supporting patients through completion of treatment without treatment breaks in the interest of improving overall clinical outcomes and patient QoL.

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