Intensity-Modulated Radiation Therapy for Anal Cancer

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By Brian G. Czito, MD [1], Joseph M. Pepek, MD [2], Jeffrey J. Meyer, MD [3], Sua Yoo, PhD [4], and Christopher G. Willett, MD [5]

Historically, the treatment of squamous cell carcinoma of the anal canal has been an abdominoperineal resection (APR), resulting in loss of the anus and rectum with need for a permanent colostomy.

ABSTRACT: The contemporary treatment of anal cancer is combined-modality therapy with radiation therapy, fluorouracil, and mitomycin. This therapy results in long-term disease-free survival and sphincter preservation in the majority of patients. Tempering these positive results is the high rate of treatment-related morbidity associated with chemoradiation therapy for anal cancer. The use of intensity-modulated radiation therapy (IMRT) has the potential to reduce acute and chronic treatment-related toxicity, minimize treatment breaks, and potentially improve disease-related outcomes by permitting radiation dose escalation in selected cases.

Historically, the treatment of squamous cell carcinoma of the anal canal has been an abdominoperineal resection (APR), resulting in loss of the anus and rectum with need for a permanent colostomy. In addition to loss of sphincter function, high rates of urinary/sexual dysfunction, wound morbidity, and perioperative mortality have been reported. Studies evaluating outcomes following APR reported 5-year survival rates of 30% to 71%, with locoregional recurrence occurring in 19% to 45% of patients.[1,2] TABLE 1

Randomized Trials for Anal Cancer: Toxicity and Disease-Related Outcomes

Given these poor results, Nigro and coinvestigators from Wayne State University treated three patients with low-dose (30 Gy) preoperative radiation therapy concurrently with continuous-infusional fluorouracil (5-FU) and mitomycin followed by APR. The surgical specimens of two patients showed no evidence of residual disease, whereas a third patient refused surgery and remained disease-free.[3] Since this report, similar studies have confirmed high rates of clinical and pathologic response using preoperative chemoradiotherapy and surgery,[4-8] leading to trials evaluating radiation therapy alone or combined chemoradiation as primary radical therapy, with surgery reserved for salvage. These studies demonstrated that the majority of patients treated by these approaches achieved long-term disease-free survival without surgery. The contemporary treatment of anal cancer is founded on the results of five randomized trials (Table 1). Collectively, these demonstrate that combined-modality therapy with radiation therapy, 5-FU, and mitomycin result in long-term disease-free survival and sphincter preservation in the majority of anal cancer patients. Furthermore, the combination of radiation therapy, 5-FU, and mitomycin was shown to be superior to radiation therapy alone, radiation therapy with 5-FU only, and induction cisplatin/5-FU followed by concurrent radiation, cisplatin, and 5-FU.[9-13]

FIGURE 1
Tempering these positive results is the high rate of treatment-related morbidity associated with chemoradiation for anal cancer (Table 1). The acute toxicity induced by these treatments can be severe. In the recent Radiation Therapy Oncology Group (RTOG) 98-11 trial, in which conventional radiation therapy techniques were employed (Figure 1), 87% of patients experienced grade 3/4 acute toxicity. Patients who received 5-FU/mitomycin with radiation therapy as part of this trial experienced Common Toxicity Criteria for Adverse Events (CTCAE) v2.0 grade 3/4 skin and gastrointestinal toxicity rates of 48% and 35%, respectively.[12] Similarly, preliminary results of a United Kingdom Coordinating Committee on Cancer Research (UKCCCR) study comparing 5-FU/mitomycin–based chemoradiotherapy to a cisplatin/5-FU–based chemoradiotherapy regimen reported a 61% grade 3/4 nonhematologic toxicity rate in the mitomycin arm.[13] Treatment breaks induced by or used to mitigate these high treatment-associated toxicity rates are common and likely compromise therapeutic efficacy (discussed below).

Although chemotherapy clearly enhances the acute toxicity of radiation therapy in the treatment of anal cancer, radiation therapy contributes to the majority of acute and chronic therapy-related toxicities. The use of intensity-modulated radiation therapy (IMRT) has the potential to reduce acute and chronic treatment-related toxicity, minimize treatment breaks due to excessive grade 3/4 skin toxicity (notably in skin outside of the immediate perianal region) and bowel toxicity, while potentially improving disease-related outcomes by permitting radiation dose escalation in selected cases (because radiation toxicity to the bowel is avoided).

**Intensity-Modulated Radiation Therapy**

![Conventional Radiotherapy Plan](image1)

**FIGURE 2**

Conventional Radiotherapy Plan

![IMRT Treatment Plan](image2)

**FIGURE 3**

IMRT Treatment Plan

The two goals of optimizing a radiation treatment plan are to provide adequate dose coverage to the tumor/target volume and to minimize dose to adjacent normal tissue structures. To date, most trials in anal cancer have used either two-dimensional (2D) planning, in which radiation treatment fields
are defined using orthogonal radiographs with known anatomic markers (primarily bony landmarks), or three-dimensional (3D or computed tomography [CT]-guided conformal) techniques, which allow for identification of target and normal tissue structures using axial CT images, facilitating improved treatment accuracy, delivery, and dose quantification. Both techniques, however, use uniform, static fields for radiation therapy delivery.

Imaging and radiation planning software improvements allowed for an evolution from 2D and 3D approaches in the late 1980s to the introduction of IMRT in the 1990s.[14,15] In contrast to 3D-based planning, where the physician designs treatment fields based on a “beam’s-eye view” of the target volumes and normal structures, IMRT-based planning entails setting strict radiation dose constraints to normal organs, a prescription dose to varying target volumes, and the use of “inverse planning” computer algorithms to design unconventional treatment fields that would not otherwise be possible with standard planning methods.

In essence, IMRT delivers the radiation dose by partitioning a radiation field into multiple smaller fields of varying shapes and sizes, varying the dose intensity between each area.[16] This is carried out with either dynamic IMRT (where collimating leaves move in and out of the radiation beam path during treatment) or “step-and-shoot” IMRT (where the leaves change the radiation field shape while the beam is turned off). The end result is that the intensity of the radiation beam for a given field varies. Ultimately, the cumulative effect of all treatment fields results in a radiation dose-distribution that closely conforms the prescription (high) radiation dose around the target volumes while significantly reducing the high doses to surrounding normal tissues, which could not be achieved through conventional planning methods. Compared to 2D or 3D techniques, IMRT is effective at conforming radiation dose to irregular target volumes (particularly concave structures as are often seen in pelvic nodal basins) while limiting high doses to delineated sensitive normal tissues.

To create an IMRT plan, the treating physician uses physical exam, endoscopic exam, CT, PET-CT, and/or MRI findings to define the primary/gross disease (gross tumor volume, or GTV), and tissues at risk for subclinical tumoral involvement, including draining nodal basins (adding to the GTV to make the clinical target volume, or CTV). A third volume encompasses the gross and clinical target volumes, allowing additional “margin” to account for organ motion and daily positional differences (planning target volume, or PTV). IMRT plans may have multiple PTV volumes receiving differing radiation doses during any given fraction. This is the concept of “dose painting.” Alternatively, “sequential” PTV boosts, as are commonly carried out in non-IMRT 3D-conformal therapy, may be employed.

The use of IMRT for anal cancers also requires delineation of critical normal (avoidance) structures such as bladder, small bowel, genitalia, and the femoral heads. Radiation oncologists must determine which structures are most critical and dose-weight those appropriately during the treatment planning process. Importantly, the greater the number of avoidance structures, the more challenging it is to meet all dose constraints and still ensure appropriate CTV/PTV coverage. Physicians and medical physicists critically evaluate numerous plans until dose constraints are satisfactorily met. The result should be a series of radiation doses that closely conform to the target volumes while minimizing dose to normal tissues. FIGURE 4

![DVH for 3D Plan](Image43x183 to 193x285)

FIGURE 5
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DVH for IMRT Plan

Figures 2 through 5 compare a 3D conformal radiation therapy plan (Figures 2 and 4) with an IMRT-based treatment plan (Figures 3 and 5). Figures 6 and 7 illustrate a representative IMRT field with associated dose fluence map. The differences in sagittal radiation dose distribution are shown between a 3D conformal plan (Figure 8) vs IMRT plan (Figure 9). A clinically significant advantage of IMRT includes a reduction in normal (high-dose) tissue irradiation resulting in less acute and chronic radiation-related toxicities, including nontarget bowel, bladder, and genitalia. These can often be significant using conventional radiation techniques, leading to potential treatment breaks with poor outcomes. Additionally, IMRT may permit safe radiation dose escalation in selected clinical situations.

Because the use of IMRT requires careful and accurate delineation of areas at risk for harboring subclinical disease spread and knowledge of patterns of dissemination, careful definition of target regions is critical, especially in light of the high cure rates and limitations of salvage therapies. In the multi-institutional RTOG 05-29 trial, which evaluated IMRT feasibility for anal cancer, 79% of patients enrolled required a change in the radiation treatment plan volumes following pretreatment central review,[17] illustrating the learning curve of practitioners in this process and that knowledge of field design and experience is critical when using this approach. Based in part on this trial, the RTOG has made significant efforts to help better define clinical target structures for IMRT-radiation planning purposes.[18]

In general, our practice has been to identify the following areas for inclusion in the CTV: the primary GTV (including nodal GTVs), the mesorectal space and presacral nodal basins, as well as the bilateral inguinal, internal, and external iliac nodal regions. CTVs may be modified based on concerns over the higher probability of poor treatment tolerance, such as for HIV patients with low CD4+ T-cell counts.[19]

Anal Cancer Imaging and Radiation Planning

FIGURE 6

IMRT Beam Orientation

FIGURE 7

Radiation Fluence Map

An important advance in the treatment of anal cancer is the use of $^{18}$F-fluorodeoxyglucose positron-emission tomography (FDG-PET) and combined PET/CT in staging and IMRT-based treatment planning. These images are being increasingly used in clinical practice to better define sites of gross disease, as well as draining lymph node basins, which may not be appreciated by conventional imaging techniques.

Recent literature supports the use of PET in anal cancer staging and in advanced radiation treatment planning to more accurately delineate target structures. In three recent series, 17% to 24% of patients with clinically or radiographically uninvolved lymph nodes by CT demonstrated PET-positive
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...nodal metastases.[20-22] It appears that PET increases sensitivity over conventional imaging and may change treatment goals or radiation therapy planning in a significant portion of patients.[22] Multiple series have also demonstrated that PET scan resulted in modification of radiation treatment plans in up to one-fourth of patients.[22-24] Other investigators showed no detriment in radiation dose reduction to CT-enlarged but PET-negative inguinal lymph nodes.[25] In a prospective study, Washington University investigators demonstrated that the findings of incomplete metabolic response to chemoradiotherapy on post-therapy PET (performed at a median 2.0 months post-treatment) predict for an inferior 2-year cause-specific and progression-free survival.[26] Thus, PET can guide radiation planning by preventing administration of insufficient doses to potential sites of disease (based on conventional imaging) as well as potentially avoiding excessive dose to metabolically inactive nodal basins. Moreover, PET may allow early prediction of outcomes to combined-modality therapy.

**Detriment From Treatment Breaks**

As discussed previously, IMRT holds promise as an effective tool to deliver high-dose radiation therapy with exact conformity resulting in less acute treatment toxicity and avoidance of treatment interruption. While some treatment breaks during combined therapy may be due to chemotherapy-related hematologic toxicity, the majority are due to radiation-related toxicities including bowel and skin toxicity. Treatment breaks should be minimized. One study by the RTOG examined radiation dose escalation and acute toxicity rates in anal cancer patients. In this phase II investigation, 59.4 Gy was delivered over 8.5 weeks, including a mandated 2-week treatment break to mitigate treatment-related toxicity. Overall, disease-free and colostomy-free survivals were lower than those seen in previous trials employing chemoradiotherapy with lower radiation doses and no mandated treatment break, although this study was not powered for comparison. The authors concluded that treatment interruptions should be avoided to optimize local control.[27] FIGURE 8

![Sagittal Radiation Dose With 3D Treatment](image)

**FIGURE 9**

Another recent analysis of anal cancer patients treated at Memorial Sloan-Kettering Cancer Center also suggested that prolonged treatment breaks or inability to complete radiation due to toxicity may be detrimental to outcome. Patients were treated primarily using conventional radiation techniques, with 77% of their cohort receiving at least one treatment break. Bivariate analysis showed that patients who required treatment breaks experienced higher rates of disease relapse, while failure to complete radiation therapy was associated with anal cancer relapse by multivariate analysis.[28] In a Boston University study, prolonged treatment times (≥ 40 days) due to treatment-associated acute toxicity had an adverse effect on disease-related treatment outcomes.[29] Similarly, a study from the University of California, San Francisco (UCSF) showed improved local control for patients
who received ≥ 54 Gy in 60 days or less.[30] Further, in evaluating the preliminary results of the largest randomized trial conducted in anal cancer to date—which showed high rates of complete response (95%) and relapse-free survival (3-years: 75%)—the authors concluded that the favorable results were influenced, in part, by the absence of a scheduled radiation therapy break.[13] Finally, a recent analysis of two RTOG randomized trials showed a significant correlation between risk of colostomy and a protracted treatment course, with an estimated 9.4% increase in the hazard of colostomy for each 2-week increase in radiation therapy duration. The authors concluded that every effort should be made to avoid therapy interruptions.[31] Although no randomized trial has directly evaluated the effect of treatment interruption on disease-related outcomes, available data suggest a clear detriment.

Radiation Dose Escalation

Given the potential dose reduction to normal organs and tissues by IMRT in anal cancer, and the fact that local failure rates remain high in larger and more advanced lesions using conventional radiation doses, it is rational to escalate radiation dose to gross disease in selected cases of anal cancer through IMRT. Several institutional series have suggested that increasing radiation dose in the treatment of anal cancer may enhance local control and disease-free survival. As described previously, studies from Boston University and UCSF showed improved disease-related outcomes with radiation doses ≥ 54 Gy compared to lesser doses.[29,30] Similarly, a multi-institutional European study also demonstrated that radiation doses < 54 Gy predicted for a significantly higher rate of local failure in advanced lesions.[32] Investigators from M.D. Anderson Cancer Center showed local control rates of 50% for all stages receiving 45 to 49 Gy vs 90% for patients receiving ≥ 55 Gy.[33]

The role of dose escalation is being formally evaluated in a randomized French Federation Nationale des Centres de Lutte Contre le Cancer ACCORD 03 trial, where patients with stage II/III anal cancer are randomized to one of four treatment arms: (1) neoadjuvant 5-FU/cisplatin alone followed by 5-FU/cisplatin/RT (45 Gy), followed by low-dose boost RT (15 Gy); (2) as in arm 1, except high-dose RT boost (20-25 Gy); (3) as in arm 1, but no neoadjuvant chemotherapy; (4) as in arm 2, but no neoadjuvant chemotherapy. In all arms, patients have a mandated 3-week break, and boost radiation treatments are delivered using external-beam radiation or brachytherapy techniques.

Treatment-Related Toxicity and IMRT

With conventional (2D or 3D) treatment approaches, acute side effects from chemoradiation-based therapy for anal cancer may be a significant handicap resulting in unintended treatment breaks and radiation dose-reduction, leading to unfavorable disease-related outcomes. In this treatment, the normal organs most commonly affected and leading to treatment breaks include skin, bowel, and bone marrow.

Skin is a dose-limiting structure during chemoradiation for anal cancer due to skin folds in the pelvis, perineal, perianal, genital, and inguinal regions. As an example, 48% of patients receiving 5-FU/mitomycin in the recently reported RTOG 98-11 study experienced CTCAE v2.0 grade 3/4 skin toxicity, where IMRT techniques were not used.[12] In contrast, Milano et al reported that 100% of their anal cancer patient cohort experienced grade 2 acute dermatologic toxicity (defined as moist perianal desquamation) with no grade 3 toxicity using IMRT techniques.[34] Similarly, in our experience of 45 anal cancer patients treated with IMRT at Duke University, 93% had CTCAE v3.0 grade 2 acute skin toxicity with no patients experiencing grade 3/4 toxicity.[35] Given the proximity of the primary tumor to the perianal tissues, it is expected that skin reactions in the immediate perianal skin will remain significant with IMRT. However, there appears to be a reduction in high-grade skin toxicity at other problematic sites, such as the genital, gluteal cleft, and inguinal regions.

Acute gastrointestinal toxicity from chemoradiotherapy approaches may also be substantial. For example, 35% of patients receiving mitomycin/5-FU with radiotherapy in RTOG 98-11 experienced CTCAE v2.0 grade 3/4 toxicity, primarily consisting of diarrhea.[12] Most acute gastrointestinal toxicity data associated with IMRT have stemmed from investigation of gynecologic and prostate malignancies. Mundt et al found lower rates of acute[36] and chronic[37] gastrointestinal toxicity with IMRT compared to conventional radiation approaches for gynecologic patients. Additionally, investigators from Memorial Sloan-Kettering showed that IMRT improved small bowel sparing compared to 3D-CRT for prostate cancer patients.[38] In anal cancer patients, a multi-institutional IMRT study by Salama et al showed a 15% CTCAE v2.0 grade 3 gastrointestinal acute toxicity rate
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and no grade 4 toxicity.[39] Similarly, we demonstrated a 9% rate of CTCAE v3.0 grade 3/4 diarrhea in anal cancer patients receiving concurrent chemoradiotherapy.[35] Based on presently available data, IMRT acute GI toxicity compares favorably with contemporary controls treated with conventional radiation techniques.

Acute hematologic toxicity rates are high in anal cancer patients treated with pelvic radiation therapy and concurrent 5-FU and mitomycin. For example, a 61% CTCAE v2.0 grade 3/4 acute hematologic toxicity was seen in the RTOG 98-11 study arm receiving 5-FU and mitomycin.[12] Although Salama et al reported a similar grade 3/4 toxicity rate of 59% in patients treated with IMRT-based chemoradiation with mitomycin,[39] other data suggest that improved bone marrow sparing can be achieved with IMRT. Brixey et al found lower rates of acute hematologic toxicity for cervical cancer patients treated with pelvic IMRT concurrently with cisplatin.[40] When examining dosimetric parameters, University of Chicago investigators found that bone marrow V10 and V20 (volumes receiving 10 and 20 Gy, respectively) correlated with greater hematologic toxicity in cervical cancer patients irradiated with concurrent cisplatin[41] and in anal cancer patients treated with IMRT and concurrent mitomycin chemotherapy.[42] Further study is necessary, given that IMRT can potentially increase the volume of pelvic bone marrow receiving low doses of radiation compared to 2D or 3D radiation approaches.

Treatment-related normal tissue toxicity will remain an important consideration because of the focus on integrating newer chemotherapeutic agents that also have potent radiosensitizing properties. Examples include a phase II trial combining cisplatin, 5-FU, and cetuximab (Erbitux) with radiation therapy being conducted through the Eastern Cooperative Oncology Group (ECOG). A similar trial is being conducted through the AIDS Associated Malignancies Clinical Trials Consortium in HIV-positive patients. In addition, a phase II study of the oral 5-FU prodrug capecitabine (Xeloda) and oxaliplatin (Eloxatin) combined with radiation therapy by investigators from M.D. Anderson is being conducted. All of these agents have the potential to further enhance acute treatment-related toxicities (for example, skin toxicity with cetuximab) that may be potentially reduced with IMRT.

IMRT Disease-Related Outcomes

It is important to demonstrate that any radiotherapy technology that limits normal tissue toxicity also provides established rates of tumor control. Although data on IMRT with concurrent chemotherapy for anal cancer are limited, early disease-related outcomes appear promising. A multi-institutional study treating anal cancer patients with IMRT-based chemoradiotherapy showed 18-month overall survival, local control, metastasis-free survival, and colostomy-free survival rates of 93%, 94%, 93%, and 84%, respectively.[39] In our series from Duke University, 2-year actuarial overall survival, local control, metastasis-free survival, and colostomy-free survival in 29 patients with squamous cell carcinoma were 100%, 95%, 100%, and 91%, respectively.[35] The recently completed prospective phase II RTOG 05-29 trial assessed the feasibility, acute toxicity, and disease-related outcomes of an IMRT-based combined-modality approach in a multi-institutional setting. Preliminary trial analysis showed that this approach is feasible and resulted in significant sparing of ≥ grade 2 dermatologic and ≥ grade 3 gastrointestinal and genitourinary acute toxicity when compared to conventionally treated patients from RTOG 98-11, with encouraging rates of clinical complete response.[17] Although these reports have small numbers of patients, collectively they indicate lower rates of acute toxicity and comparable disease-related outcomes compared to previous clinical trials where IMRT techniques were not employed. Therefore, IMRT-based chemoradiotherapy has the potential to improve acute toxicity without compromising clinical outcomes in the treatment of anal cancer.

Summary

REFERENCE GUIDE

Therapeutic Agents

Capecitabine (Xeloda)
IMRT has the potential to reduce acute and chronic treatment-related morbidity associated with chemoradiation therapy, reduce the incidence of potentially detrimental treatment breaks, and permit safe radiation dose escalation in selected anal cancer patients. Preliminary treatment-related toxicity rates and disease-related outcomes using IMRT appear encouraging. Additionally, the integration of PET/CT into staging and radiation therapy planning, and as a means to evaluate treatment response also represents an advance in the treatment of this disease. However, knowledge of patterns of disease spread and careful radiation target design is of critical importance given the significant dose conformity associated with IMRT and potential to underdose sites of subclinical disease. Further investigation is necessary to fully explore the benefits of these innovations in radiotherapy.

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