Intensity-Modulated Radiation Therapy for Anal Cancer: Toxicity versus Outcomes

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The treatment of cancer of the anal canal has changed significantly over the past several decades. Although the abdominoperineal resection (APR) was the historical standard of care, a therapeutic paradigm shift occurred with the seminal work of Nigro, who reported that anal canal cancer could be treated with definitive chemoradiation, with APR reserved for salvage therapy only. This remains an attractive approach for patients and physicians alike and the standard of care in this disease. Now, nearly four decades later, a similar approach continues to be utilized, albeit with higher radiation doses; however, this strategy remains fraught with considerable treatment-related morbidities. With the advent of intensity-modulated radiation therapy (IMRT), many oncologists are beginning to utilize this technology in the treatment of anal cancer in order to decrease these toxicities while maintaining similar treatment efficacy. This article reviews the relevant literature leading up to the modern treatment of anal canal cancer, and discusses IMRT-related toxicity and disease-related outcomes in the context of outcomes of conventionally treated anal cancer.

Introduction

Cancer of the anal canal is an uncommon malignancy, with an estimated 5,290 cases diagnosed in the United States in 2009; however, its incidence has been increasing over the past several decades (www.cancer.gov). Historically, first-line therapy was an abdominoperineal resection (APR), resulting in a permanent colostomy. Long-term cure rates following resection alone have varied in the literature, but results as high as 71% have been reported. For most patients, however, avoidance of radical resection and permanent colostomy placement are highly desirable.[1]

Nigro and colleagues at Wayne State University pioneered the non-operative treatment paradigm for anal canal cancers.[2,3] Their initial investigation consisted of three patients treated with approximately 30 Gy radiation therapy (RT) with concurrent 5-fluorouracil (5FU) and mitomycin C (MMC). Two patients underwent planned APR with no residual disease demonstrated by pathologic assessment and the third patient declined surgical intervention, with no disease relapse in follow-up. This important preliminary data spawned numerous investigations of non-operative management of anal canal cancer.

Randomized Trials of Chemoradiotherapy

Two simultaneously conducted randomized phase III trials from Europe established the superiority of chemoradiation to radiation therapy alone.[4,5] The larger of these was conducted by the United Kingdom Coordinating Committee on Cancer Research (UKCCCR), and included 585 patients (ACT I trial). This trial randomized patients to treatment with radiotherapy alone versus radiotherapy with concomitant 5FU and MMC. Similar to the UKCCCR trial, the European Organization for Research and Treatment of Cancer (EORTC) trial randomized 110 patients to treatment with radiotherapy alone (45 Gy) versus radiotherapy (45 Gy) with concomitant 5FU and MMC. Both trials mandated a treatment break prior to an additional “boost” dose of radiation (15-20 Gy), based on tumor response. In both cases, an improvement in local control (LC) and colostomy-free survival (CFS) with combined modality therapy was reported, with no significant difference in overall survival (OS), although the risk of death from anal cancer was reduced by 29% (P = .02) in the UKCCCR trial. Locoregional failure (LRF) decreased from 50% to 32% with the addition of chemotherapy to radiation in the...
Toxicity and treatment efficacy from selected anal canal cancer studies

Recently, the UKCCCR updated their results with a median follow-up of 13 years. The LRF rate was 32% at five years with the use of combined modality therapy versus 57% in patients treated with radiation therapy only.[6] These results highlight that concurrent chemotherapy has an important role in the treatment of anal canal cancer, but that local failure occurs frequently, even with definitive chemoradiotherapy.

Acute and significant toxicities were reported in both trials (Table 1). Although no differences in acute gastrointestinal (GI) or dermatologic side effects were reported between the two treatment groups in the EORTC trial, higher rates of late anal ulceration were observed in the combined modality group.[5] There were two grade 4-5 hematologic toxicities reported with the addition of chemotherapy. In contrast, the UKCCCR reported significantly more acute hematologic, GI, dermatologic, and genitourinary (GU) toxicities with addition of 5FU/MMC, but no increase in late morbidity.[4]

Different Chemotherapy Regimens

MMC contributes significantly to the acute toxicity profile of combined-modality therapy in anal cancer, and studies have been undertaken to examine its potential role in this treatment program.[7–9] A trial by the Radiation Therapy Oncology Group (RTOG) randomized patients to receive radiotherapy and 5FU, with or without MMC (RTOG 87-04).[7] Even though OS was similar in both groups, disease-free and colostomy-free survivals were inferior in patients treated with radiation therapy and 5FU without MMC versus patients treated with radiation therapy, 5FU and MMC. These results justified the use of MMC as an important therapeutic element. While there was no reported difference in acute non-hematologic toxicities between the two groups, 26% of patients receiving MMC (versus 8% who received 5FU alone) experienced grade 4-5 hematologic toxicity.[7]

The RTOG conducted another study (RTOG 98-11), which randomized patients to both induction/concurrent CDDP and 5FU with radiation versus concurrent chemoradiation (45 Gy plus a 10-14 Gy boost) using 5FU and MMC (without induction chemotherapy).[8] It is important to note that this trial was not a direct comparison of 5FU and MMC vs 5FU and cisplatin (CDDP). Complicating the analysis of the trial were the following considerations in the CDDP arm of the trial: (1) the added total length of time of therapy; (2) the initiation of chemotherapy alone followed by chemoradiation; and (3) the toxicity of chemoradiation. Importantly, it was unknown at the time of the design of the trial whether induction chemotherapy was even beneficial, or whether chemoradiation followed by adjuvant chemotherapy was a more effective strategy. Five-year OS rates were not significantly different between the two treatment arms—at 70% in the CDDP-based arm and at 75% in the MMC-based arm, with locoregional recurrence rates of 33% in the CDDP-based arm and 25% in the MMC-based arm, respectively (P = NS). However, patients receiving CDDP/5FU experienced a statistically higher colostomy rate of 19%, versus 10% (P = .02) in patients randomized to 5FU and MMC. Still, it is unknown whether the increased colostomy rate was instead influenced either by time under therapy or the delay in chemoradiation due to the use of induction chemotherapy. This is especially unclear given the influence of time under therapy in previous trials and the unproved efficacy of induction chemotherapy in anal cancer. Toxicity was substantial, with 74% of both groups experiencing acute grade 3-4 non-hematologic toxicity. Significantly, acute grade 3-4 hematologic toxicity occurred in 61% percent of the patients receiving MMC, versus 42% of those receiving CDDP, despite the more prolonged course of chemotherapy in the CDDP arm (P < .001). However, this did not translate into differences in the rate of long-term toxicities (11% versus 10%).

A phase III trial of 950 anal canal patients by the UKCCCR (ACT II) was recently reported in abstract form.[9] In this trial, patients were randomized to the same radiotherapy regimen (50.4 Gy, in 1.8-Gy
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fractions) with either concurrent 5FU and CDDP versus 5FU and MMC—followed by a second randomization to receive two cycles of 5FU/CDDP—or no further therapy following the completion of chemoradiation. With a median follow-up of three years, there were no differences in the rates of complete response, recurrence-free survival, OS, or colostomy requirements. Acute grade 3-4 hematologic toxicity rates were higher in patients receiving MMC (25%) versus CDDP (13%) ($P = \lt .001$). Preliminary results demonstrate no significant differences in recurrence-free or OS for patients who received adjuvant chemotherapy versus those who did not. Although no statistical difference was seen in rates of high-grade, acute non-hematologic toxicities between treatment arms (61% versus 65%), these figures remained high.

Radiation Dose Escalation

Radiation doses of sufficient magnitude to ensure high probability of disease control are frequently limited by the tolerance of surrounding normal tissues. In the treatment of anal canal cancer, the tolerance of small bowel, femoral heads, rectum, bladder and genitalia often dictate the total dose of radiation therapy administered. Because of these considerations, dose escalation using conventional radiotherapy is frequently challenging.

A series from UCSF reported that LC was enhanced when patients received $\geq 54$ Gy in $\leq 60$ days,[10] with a local progression-free probability of 89% versus 42% in patients who did not ($P = .01$). Other institutional experiences have also suggested that dose escalation improves LC.[11-13] The French Federation Nationale des Centres de Lutte Contre le Cancer ACCORD 03 trial randomized patients to receive 5FU and CDDP alone followed by combined chemoradiotherapy (radiation dose 45 Gy with 5FU/CDDP) versus combined chemoradiotherapy (with 5FU/CDDP). Patients then underwent a scheduled three-week treatment break, followed by a second randomization of additional boost radiation therapy to a dose of 15 Gy, or 20-25 Gy without chemotherapy. A preliminary report of this trial showed no difference between the four arms in 3-year colostomy-free survival [80-86%], cause-specific survival [79-89%] and OS rates [78%], although the influence of the planned break on these outcomes remains uncertain.[14]

Given the propensity for local failure following EBRT-only approaches, investigators have also employed brachytherapy (the temporary or permanent insertion of radioactive sources into a tumor and/or peritumoral tissues) as a mode of dose escalation, delivering an additional 15-30 Gy in addition to standard EBRT doses. Multiple reports from French investigators have demonstrated favorable outcomes in terms of disease-free survival and LC relative to EBRT-alone techniques, with high rates of anal preservation and adequate sphincter function.[15-18] Given the high rate of local failure in this disease, particularly in larger/more advanced lesions, radiation dose escalation, with or without additional chemotherapy, warrants further study.

Treatment Interruptions

A fundamental principle in radiation oncology is that once radiation therapy is initiated, treatment interruptions should be minimized to avoid the phenomenon of accelerated tumor repopulation.[19] As described previously, the conventional treatment of anal canal cancer may, unavoidably, result in significant toxicity requiring treatment breaks. Given this, many investigators have designed treatment courses with scheduled treatment breaks to mitigate acute toxicities. Illustrating the importance of overall treatment time, Ben-Josef and colleagues performed a pooled data analysis of RTOG 87-04 and 98-11 to investigate whether the length of radiation or the total treatment time were associated with outcomes.[20] On univariate analysis, colostomy failure was correlated with total treatment time; for each increase in duration beyond 14 days, there was a 9.4% increase in hazard for colostomy failure (HR 1.593, 95% CI 1.080-2.350, $P = .02$). On multivariate analysis, a trend was maintained for total treatment time and the risk for colostomy failure (HR 1.588, 95% CI 0.993-2.539, $P = .053$).

A review from Massachusetts General Hospital examined 50 patients with anal canal cancer treated with radiotherapy concurrently with 5FU and MMC.[11] The investigators found improved OS and LC in patients receiving $\geq 54$ Gy versus $< 54$ Gy (84% vs 47%, respectively, $P = .02$ for OS; 77% vs 61%, respectively, $P = .04$ for LC). A trend was also noted for improved OS and LC in patients who completed treatment in $< 40$ days, versus patients whose treatment time was $\geq 40$ days. Other institutional experiences have also demonstrated a negative influence on prolonged treatment times and disease-related outcomes.[21,22] Finally, the preliminary results of the UKCCCR ACT II randomized trial in anal cancer (described previously) showed high complete response (95%) and relapse-free survival rates (75% at three years), comparing favorably to the ACT I study results,
which (per trial investigators) were at least partially attributable to the absence of a scheduled RT break.[9] Given the potential of intensity-modulated radiation therapy to reduce acute treatment-related toxicity, a reduction in unintended (and intended) treatment breaks may be possible.[23]

**How is Standard Radiation Therapy Delivered?**

**FIGURE 1**

Conventional 2/3-dimensional radiation fields in the treatment of anal canal cancer.

Prior to CT-based three-dimensional treatment planning, early randomized studies used planning techniques in which radiation field designs were based primarily on boney landmarks. These fields were large, and consequently treated significant volumes of normal tissue. To reduce normal tissue toxicity, a series of radiation field reductions, or “cone-downs” (Figure 1) were employed. These randomized trials utilized standard radiation planning consisting of opposed antero-posterior (AP) and postero-anterior (PA) beams with blocks to shield normal tissue, such as small intestine or bladder. Sometimes lateral fields were also used to further decrease dose to these structures.

**What is IMRT?**

Intensity-modulated radiation therapy (IMRT) employs a physical modifier (e.g., a multi-leaf collimator, a static compensator) placed in the path of the beam to attenuate its dose distribution. By increasing the number of fields (typically 9-13 in pelvic malignancies) aimed at a given target, and adjusting the fluence of each beam, highly conformal radiation dose distributions are created around the target with minimal dose to adjacent critical normal tissues. Potential disadvantages of this technique include that a low-dose “bath” of radiation may be delivered to large volumes of surrounding normal tissues. This may be advantageous to treat potential microscopic nodal disease in the inguinal and pelvic regions; however, extrapolation from historic data is difficult based on delivered dose per fraction.[24] This is also particularly relevant when treating tumors in the vicinity of organs that are sensitive to lower doses of radiation, including large volumes of bone marrow in the treatment of anal cancer; however, radiation tolerance of sensitive organs is generally greater when radiation is delivered at a lower dose per fraction.

IMRT has been used with excellent results in numerous other malignancies adjacent to critical structures, such as tumors of the head and neck and the prostate.[25-29] Because of the challenges of the therapeutic ratio (a comparison of the amount of radiation required to cause the therapeutic effect with the amount that causes normal tissue injury) with conventional chemoradiotherapeutic approaches, the use of IMRT in anal cancer patients has been investigated. It is difficult to safely escalate dose and avoid acute radiation-induced toxicity (with associated and potentially detrimental treatment breaks) with conventional treatment modalities, and using IMRT to conform dose around target structures and away from critical normal tissues, as performed in other oncologic sites, is rational.

**Published Data Utilizing IMRT for Anal Cancer**

The majority of published data regarding the use of IMRT for anal canal cancer are from institutional series.[30-36] Salama et al published a multicenter report on the use of IMRT in 53 patients, with 48 patients receiving concomitant 5FU/MMC.[37] All grade 4 toxicities were hematologic, with 30% and 34% experiencing leucopenia and neutropenia, respectively. Acute grade 3 GI and dermatologic toxicity was experienced by 15% and 38% of patients, respectively, rates which are lower than those reported with conventional radiotherapy in RTOG 98-11 and in the UKCCR ACT I and ACT II trials. Treatment efficacy was also excellent, albeit with short median follow-up (14.5 months), with
18-month OS, freedom from local failure, freedom from distant failure, and CFS rates of 93%, 84%, 93% and 84%, respectively.
A report from Duke University evaluated 29 patients treated with IMRT to a median dose of 54 Gy with concurrent 5FU/MMC.[38] Early disease-related outcomes were excellent, with two-year OS, local-regional control, and CFS rates of 100%, 95%, and 91%, respectively. There were no grade 3-4 dermatologic toxicities seen, while three patients (10%) experienced grade 3 diarrhea. Seven patients (24%) experienced grade 3-4 hematologic toxicity. In addition, seven patients (24%)

required a treatment break, for a median of five days.

FIGURE 2
Axial image from conventional 3-dimensional radiation planning for a patient with a T2N2M0 (IIIB) squamous cell carcinoma of the anal canal.

FIGURE 3
Axial image from intensity-modulated radiation therapy planning for the same patient.

FIGURE 4
Sagittal image from conventional 3-dimensional radiation planning.

FIGURE 5
Sagittal image from intensity-modulated radiation therapy planning in the same patient.

![Sagittal Image](image-url)

**FIGURE 6**

Dose volume histogram for conventional 3-dimensional radiation treatment plan. Note relative large volumes of critical normal tissues receiving a large percentage of the prescription dose (54Gy). PTV54 = Planning Target Volume to receive 54 Gy

![Dose Volume Histogram](image-url)

**FIGURE 7**

Dose volume histogram for the intensity-modulated radiation therapy treatment plan. Note relative smaller volumes of critical normal tissues receiving higher radiation doses, especially small bowel and external genitalia. PTV54 = Planning Target Volume to receive 54 Gy

![Dose Volume Histogram](image-url)

**FIGURE 8**

Fluence map from intensity-modulated radiation therapy plan.

![Fluence Map](image-url)

**FIGURE 9**

Examples of differential sparing of bladder and femoral heads between intensity-modulated radiation therapy (top) and 3-dimensional (bottom) plans.

RTOG 05-29 is a prospective phase II efficacy trial utilizing IMRT in the treatment of anal canal cancer.[39] All patients received concurrent 5FU and MMC. In this study, IMRT was delivered by
“dose painting,” in which different target volumes are treated concurrently but different-sized radiation fractions are used for different target structures, which is achievable with IMRT. The doses prescribed to elective nodal areas depended on the stage of disease, and the total dose to gross disease ranged from 50.4 to 54 Gy. As an example, the patient depicted in Figures 2-9 with T2N2M0 disease might have received 1.5 Gy/day (to a total of 45 Gy) to the uninvolved (elective) inguinal and upper pelvic regions, 1.68 Gv/day (to a total of 50.4 Gy) to an involved right pelvic lymph node (which measured ≤ 3 cm), and 1.8 Gy/day (to a total of 54 Gy) to the gross anal canal tumor. On preliminary report, 63 patients were enrolled and 51 were analyzed. Thirty-nine patients (76%) experienced acute ≥ grade 2 GI or GU toxicities, which is comparable with toxicities seen in RTOG 98-11[8, 39] However, compared to RTOG 98-11, the use of IMRT led to a reduction in high-grade (≥ grade 3) GU/GI toxicities, at 22% versus 36% (P = .014). There were also significant differences between the two trials favoring IMRT for ≥ grade 2 dermatologic (69% versus 81%, P = .039) and ≥ grade 3 dermatologic adverse events (20% versus 47%, P < .0001). Of 51 patients, 42 were evaluated following completion of chemoradiation, and 34 (67%) had achieved a clinical complete response. Seven patients (14%) had clinical disease persistence without overt progression, and one had clinical progression. Further follow-up is needed to assess long-term clinical endpoints such as OS, LC and CFS.

Real-time quality assurance (QA) was performed in this multi-institutional trial, and a secondary endpoint was whether or not dose-painted IMRT could be performed in a broader setting. After the initial QA was performed, contours needed to be redrawn in 79% of cases, thus illustrating the challenge of implementing this new and complex planning technique in a cooperative group setting. (For comparison, there was a 35% rate of treatment plan deviations requiring pretherapy radiation field changes in the Intergroup 0116 gastric trial using non-IMRT techniques.[40]) After final review, there were only three patients with major deviations, and none of these deviations compromised dose to target (three allowed excessive dose above tolerance to small bowel, and one to femoral heads). The authors concluded that it was feasible to perform dose painted-IMRT on a broader scale.

Hematologic, Dermatologic and Gastrointestinal Toxicity: Dosimetric Parameters to Potentially Improve with IMRT

Hematologic toxicity is significant with current chemoradiation regimens for anal cancer, at least in part reflecting the use of MMC. One confounding and potentially contributing factor, however, is that radiation is also toxic to hematopoietic cells, even at low doses. Contouring the pelvic bones and imposing dose constraints on this structure is possible with IMRT. This was first attempted with gynecologic malignancies [41,42] and has now also been used for cancers involving the anal canal.[43] Mell and colleagues analyzed 48 patients and found that the pelvic bone marrow V5, V10, V15 and V20 (VX = the volume of bone marrow that receives ≥ x dose in Gy) significantly correlated with both leucopenia and neutropenia. This illustrates that, even with low-dose radiation, bone marrow is at risk for myelosuppression, and one must impose strict dose constraints if radiation-associated myelosuppression is to be reduced. Given that IMRT can potentially increase the volume of pelvic bone marrow receiving low doses of radiation compared to 2D or 3D radiation approaches, its impact on treatment-related hematologic toxicity with MMC needs to be further investigated. Alternatively, administration of 5FU with CDDP with less hematologic toxicity, rather than MMC, may improve the therapeutic ratio with IMRT.

Skin toxicity is a common dose-limiting side effect during chemoradiation for anal cancer given the skin folds in the perineal, perianal, genital, and inguinal regions, and significant acute morbidity can result, frequently leading to unintended treatment breaks. Randomized trials have reported high-grade dermatologic toxicity rates of approximately 50% and higher in patients receiving conventionally planned chemoradiation therapy.[5,8] With IMRT, there appears to be a reduction in high-grade skin toxicity compared to patients treated with conventional techniques. Although skin reactions in the perianal skin are significant with IMRT (given proximity to the primary tumor), high-grade skin toxicity in genitalia and other sites seems to be reduced. Data from IMRT studies have suggested that a significant diminution in dermatologic toxicity at these sites can be achieved with resultant improvement in treatment compliance.[23,33,44] However, when there is dermal extension of disease, notably in more extensive tumors, dermatologic toxicity in the involved region (usually perianal skin) is desirable in efforts to eradicate disease.

Gastrointestinal toxicity (diarrhea, dehydration, etc.) is also a major dose-limiting toxicity in the treatment of anal canal cancer. Investigators from Helsinki demonstrated a significant reduction in >
grade 3 diarrhea in anal cancer patients receiving IMRT versus patients treated with conventional
two-dimensional based treatments (0% versus 31%, \( P = .004 \)).[23] A multi-institutional review of
anal cancer patients treated with IMRT and concurrent chemotherapy was performed to investigate
dosimetric indices predicting for bowel toxicity.[45] The only statistically significant parameter found
was the bowel V30 (volume of bowel receiving \( \geq 30 \) Gy). In patients that had a V30 \( > 450 \) cc, the
incidence of clinically significant GI toxicity was 33%, versus 8% in patients with a V30 \( \leq 450 \) cc (\( P =
.003 \)). This volumetric parameter has not been further validated, but with the limited data available,
these represent reasonable constraints to impose on the bowel to mitigate toxicity. Reduced
diarrhea also reduces risk of secondary infection due to issues of hygiene.

Other studies analyzing dose–volume bowel effects have shown correlations between acute
treatment-related gastrointestinal toxicity and the amount of small bowel irradiated at each dose
level analyzed, especially volumes receiving low-dose irradiation. Therefore, thoughtful dose
constraints should be implemented in radiation planning for anal cancer.[46-47] Table 1 shows
toxicity rates and disease-related outcomes of randomized studies using conventional radiation
techniques versus larger reported series using IMRT techniques. Although the follow-up is shorter in
the IMRT-treated groups and there is wide variation in scoring of toxicity between trials, IMRT
appears promising in reducing treatment-related toxicities (and likely toxicity-related treatment
breaks) without compromising disease-related outcomes.

### Challenges of IMRT

One of the most challenging aspects of treating patients with IMRT is the accurate definition of target
volumes and normal tissue. With IMRT, there are very precise and conformal high-dose regions
enveloping the tumor with a steep dose gradient. If a target is not adequately defined in the desired
treatment volumes, there is the potential for under-dosing of disease and resultant clinical
failure.[48] Knowledge of patterns of failure and routes of spread are paramount, and to that end,
the RTOG gathered a consensus panel of experts to create an anorectal contouring atlas to assist in
target delineation for anal cancer treatment planning.[49] As evidenced by nearly 80% of contours
that required modification from quality assurance in RTOG 05-29, one must be certain accurate
target and normal tissue volumes are appropriately defined to ensure disease control and normal
tissue avoidance.[33]

### Conclusions

Acute toxicity in the treatment of anal cancer with chemoradiotherapy undermines the ability to
complete therapy in a timely manner and likely compromises disease-related outcomes in some
circumstances. Reductions in acute morbidity could potentially result in improved disease-related
outcomes by minimizing treatment interruptions. IMRT appears safe, decreases acute toxicities, and
results in excellent therapeutic outcomes, albeit with relatively short follow-up in most series.
Toxicity may be further improved with avoidance of normal structures (including nontarget bowel,
bladder, genitalia and potentially boney structures) by strict dose constraints while carefully defining
target structures. Importantly, further experience in the treatment of anal cancer patients with IMRT
is necessary to address whether the improved toxicity profile of IMRT results in favorable long-term
disease-related outcomes in this largely curable disease.

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