Radiation Therapy Advances for Treatment of Anal Cancer

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Abstract
Radiation therapy (RT) is established as the primary treatment of squamous cell carcinoma of the anus. Multiple randomized trials have shown that combined modality therapy with RT, 5-fluorouracil, and mitomycin-C results in high rates of local control, disease-free survival, and sphincter preservation. However, treatment-related toxicity using conventional radiation approaches remains high and may compromise therapeutic efficacy because of prolonged treatment breaks and inability to deliver adequate radiation dose. Recent developments, including the use of PET for staging, radiation planning, and response assessment, and advanced RT planning using intensity-modulated radiation therapy (IMRT), may decrease acute and late treatment-related toxicity, provide high-dose target conformity, and permit safe radiation dose escalation. This article reviews the basic principles of IMRT and highlights current literature on these recent advances and the application of new RT techniques. (JNCCN 2010;8:123–129)

Techniques for the treatment of anal cancer have developed in parallel with technologic advances in radiation therapy (RT). Combined chemotherapy and RT has replaced radical surgical resection as the cornerstone of treatment for anal malignancies since the report by Nigro et al.1 was published in 1974. These initial results documented that 5-fluorouracil (5-FU) and mitomycin-C (MMC) combined with pelvic RT yielded improved local control rates with sphincter preservation. Randomized trials have since shown that combined modality therapy with RT, 5-FU, and MMC improves long-term disease-free survival and sphincter preservation rates in patients with anal cancer compared with RT alone, neoadjuvant cisplatin-based chemotherapy alone, or RT combined with 5-FU alone.2–6 Mitigating these gains is the high rate of treatment-related morbidity associated with chemoradiation. For example, 87% of patients in the recent phase III Radiation Therapy Oncology Group (RTOG) 98-11 trial (which did not use intensity-modulated radiation therapy [IMRT] techniques) experienced grade 3 to 4 acute toxicity.5 RT interruptions, whether through intent or treatment-related toxicity, may compromise therapeutic efficacy.

Efforts to improve RT techniques, with the goal of minimizing treatment breaks, are under active investigation. Most anal cancer studies have used 2-dimensional planning, in which radiation treatment fields are defined using orthogonal radiographs with known anatomic landmarks. By the late 1980s, improvements in imaging modalities and radiation planning software allowed for an evolution from a 2-dimensional to 3-dimensional technique, enabling target and normal tissue structures to be identified using axial CT images. By the 1990s, IMRT was introduced as a more advanced form of 3-dimensional planning,7,8 and is now established as an effective treatment modality in head and neck and prostate cancers.9,10

Newer RT techniques, such as IMRT, are capable of reducing normal tissue dose and delivering high-dose conformity to target tissues. This approach may also permit safe radiation dose escalation, potentially resulting in improved local control rates. This article reviews the rationale and application of these radiation techniques and discusses recent advances in anal cancer treatment.
Anal Cancer Imaging and Radiation Planning

The application of fluorodeoxyglucose (FDG)-PET and PET/CT is an important advance for anal cancer staging and treatment planning. These imaging modalities have been integrated into clinical practice to more accurately define sites of macroscopic disease, including involvement of draining lymph node basins, which may not be detected with conventional imaging. Current literature supports the use of FDG-PET for anal cancer staging and advanced radiation treatment planning to better delineate target structures. Two recent series reported that 17% to 24% of patients with clinically or radiographically uninvolved lymph nodes according to CT showed PET-positive nodal metastases.11,12 Similarly, another large series from the United Kingdom reported that FDG-PET findings resulted in a change of tumor stage in 23% of patients, particularly those with more advanced disease, and altered RT fields in 13%. The authors concluded that FDG-PET increases sensitivity compared with conventional imaging and changes treatment intent or radiotherapy planning for a significant number of patients.13 Additionally, 2 series showed that PET scans resulted in modification of RT plans in approximately one fourth of patients.14,15

Although FDG-PET may not change radiation coverage of potential subclinical disease, it may alter radiation dose to sites of hypermetabolic gross disease that may not be appreciated on CT. Other investigators have shown no detriment in radiation dose reduction to CT-enlarged but PET-negative inguinal lymph nodes.16 Furthermore, in a prospective study, investigators at Washington University reported that patients with anal cancer showing incomplete metabolic response to chemoradiotherapy according to FDG-PET (performed at a median 2.0 months posttreatment) had inferior 2-year cause-specific and progression-free survival.17

In summary, FDG-PET assists radiation planning through identifying potential sites of disease spread undetected by conventional imaging, and may prevent excessive dose to metabolically inactive nodal basins. FDG-PET might also predict posttreatment outcomes (and guide further therapeutic intervention) through facilitating early identification of residual disease after combined modality therapy.

IMRT and Anal Cancer

The objectives of radiation treatment planning are 2-fold: to provide adequate dose coverage to the tumor and to minimize dose to normal tissue structures, or avoidance structures, adjacent to the tumor. Conventional 2- and 3-dimensional RT techniques, which use static treatment fields, can be effective in achieving these goals. However, administering an efficacious radiation dose while complying with normal tissue constraints is challenging. This is especially relevant when attempting to conform radiation dose coverage to irregularly shaped targets, such as a tumor volume or at-risk lymphatic basins.

In essence, IMRT delivers radiation dose by partitioning a given radiation field into multiple smaller fields of different shapes and sizes, varying the radiation dose intensity between each area.18 This is performed with either dynamic IMRT (where collimating leaves, or blocks, 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). Either method is particularly effective at conforming radiation dose to the target structures (particularly concave structures, as are often seen in pelvic nodal basins) while avoiding dose to normal tissues. To accomplish this, the radiation oncologist uses physical examination, endoscopic findings, CT, PET/CT, or MRI to define the primary or gross disease, referred to as the gross tumor volume (GTV); tissues at risk for subclinical tumor involvement, including draining nodal basins, referred to as the clinical target volume (CTV); and a third volume, referred to as the planning target volume (PTV), encompassing the gross and clinical target volumes with an additional “margin” accounting for organ motion and daily positional differences. In the treatment of anal cancer, multiple PTVs are often present, and the prescribed radiation doses to each are usually different, with lower doses to subclinical disease sites (draining nodal basins) and higher doses to sites of gross disease.

IMRT uses inverse planning, in which an intended radiation dose is placed on target volumes, such as the PTV, and radiation dose constraints are placed on avoidance structures. For anal cancer, IMRT requires delineation of avoidance structures, such as the bladder, rectum, small bowel, genitalia, and femoral heads. Because these normal organs are impossible to spare completely when irradiating the pelvis, radiation dose
constraints are placed on each structure during treatment planning. Thereafter, computer software algorithms can design treatment fields that would not otherwise be possible with standard planning methods. Physicians and medical physicists critically evaluate numerous plans until reasonable PTV coverage is attained and dose constraints are satisfactorily met. The result should be a series of radiation doses that closely conform to the target volumes while limiting dose to normal tissues (Figures 1–4).

The importance of target design during the treatment planning process cannot be overemphasized, as IMRT requires careful delineation of regions at risk for harboring subclinical disease and knowledge of patterns of spread. This is especially true for a malignancy that is curable in most patients and in which efficacy of salvage therapy is limited. In RTOG 05-29, a multi-institutional study examining IMRT feasibility, 79% of enrolled patients required a change in the radiation treatment planning volumes after pretreatment central review.19 This highlights practitioners’ learning curve and that knowledge of field design is critical in IMRT planning for anal carcinoma. CTV delineation is particularly important given that omission of potential sites of subclinical disease may result in a so-called “marginal miss” with resultant pelvic disease recurrence. Motivated in part by this trial, the RTOG has designed treatment and anatomic atlases to help better delineate clinical target structures for radiation planning.20

**Detriment of Treatment Breaks and the Role of Radiation Dose Escalation**

IMRT has promise as an effective tool to deliver a high degree of radiation dose conformality while minimizing treatment interruption through decreasing acute side effects, particularly when normal tissue toxicity may be considerable. When possible, treatment breaks should be avoided. To illustrate this point, a phase II RTOG study examined high-dose radiation and acute toxicity rates in patients with anal cancer. In this trial, 59.4 Gy was delivered over 8.5 weeks, including a mandated 2-week treatment rest to diminish treatment-related toxicity. Although not powered for comparison, the results of this study showed that overall disease- and colostomy-free survivals were inferior to results from previous trials using chemoradiotherapy with lower radiation doses without mandated treatment breaks.21

Similarly, a recent analysis from Memorial Sloan-Kettering Cancer Center (MSKCC) suggested that prolonged treatment breaks or inability to complete radiation because of toxicity predisposes patients to disease recurrence. In this study, patients were treated primarily using conventional radiation techniques, with 77% of their cohort requiring at least 1 treatment interruption. Bivariate analysis suggested that patients who had treatment breaks experienced higher rates of disease relapse, and failure to complete RT was a significant predictor for anal cancer relapse on multivariate analysis.22

Another study from Boston University showed improved overall survival, disease-free survival, and local control with radiation doses of 54 Gy or greater...
but suggested that prolonged treatment times (≥ 40 days) because of treatment-associated acute toxicity resulted in inferior disease-related treatment outcomes. Additionally, a University of California, San Francisco (UCSF) study showed improved local control for patients who received 54 Gy or greater in 60 days or less.

The preliminary results of the UKCCCR ACT II randomized trial in anal cancer comparing 5-FU/MMC–based chemoradiotherapy with cisplatin/5-FU–based chemoradiotherapy showed high complete response (95%) and relapse-free survival rates (75% at 3 years). The investigators judged that these favorable results were at least partially attributable to the absence of a scheduled RT break.

Finally, a recent analysis of 2 RTOG randomized trials showed a significant correlation between risk for colostomy and a protracted treatment course. For each 2-week increase in radiotherapy treatment duration, an estimated 9.4% increase was seen in the hazard of colostomy. The authors concluded that every effort should be made to avoid therapy interruptions. Although no randomized trial has directly evaluated the effect of treatment interruption on disease-related outcomes, available data suggest a detriment.

Given that IMRT has the potential to decrease dose to normal tissues, an argument could be made to use this approach to escalate radiation dose to sites of gross disease, particularly in larger tumors in which local relapse is common. Several institutional series have suggested that increasing radiation dose in the treatment of anal cancer may enhance local control and disease-free survival. Studies from Boston University and UCSF showed improved disease-related outcomes with radiation doses of 54 Gy or greater compared with lower doses. Similarly, a multi-institutional European study showed that radiation doses less than 54 Gy were associated with a significantly higher rate of local failure in advanced lesions. Investigators from M. D. Anderson Cancer Center showed local control rates of 50% for patients with all stages of disease receiving 45 to 49 Gy versus 90% for patients receiving 55 Gy or greater.

The role of dose escalation is being formally evaluated in a randomized French Fédération Nationale des Centres de Lutte Contre le Cancer ACCORD 03 trial, in which patients with stage II/III anal cancer are randomized to 1 of 4 treatment arms: 1) neoadjuvant 5-FU/cisplatin alone followed by 5-FU/cisplatin/RT (45 Gy), followed by a low-dose RT boost (15 Gy); 2) same treatment as in arm 1, except with a high-dose RT boost (20–25 Gy); 3) same treatment as in arm 1, but no neoadjuvant chemotherapy; or 4) same treatment 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

Acute toxicity rates from conventional radiation treatment for anal cancer are high; this can lead to...
radiation dose reduction and unintended treatment breaks, which may in turn lead to unfavorable disease outcomes. IMRT has shown potential in decreasing treatment-related morbidity. The normal organs most commonly affected by toxicity that leads to treatment breaks are skin, bowel, and bone marrow.

Skin is a common dose-limiting structure during chemoradiation for anal cancer because of skin folds in the perineal, perianal, genital, and inguinal regions. For example, in the recently reported RTOG 98-11 study, in which IMRT techniques were not used, 48% of patients receiving 5-FU/MMC experienced Common Terminology Criteria for Adverse Events (CTCAE) v2.0 grade 3 to 4 skin toxicity. Similarly, 57% of patients in the EORTC phase III trial had WHO grade 3 to 4 acute skin toxicity.

In contrast, Milano et al. showed that 100% of their patient cohort had grade 2 acute dermatologic toxicity (moist perianal desquamation) and no grade 3 toxicity when IMRT techniques were used. In the Duke University experience involving nearly 50 patients with anal cancer treated with IMRT, this article's authors found that 93% had CTCAE v3.0 grade 2 acute skin toxicity and none experienced grade 3 to 4 toxicity. Although skin reactions in the immediate perianal region are expected to remain significant with IMRT (given proximity to the primary tumor), high-grade skin toxicity seems to be reduced at other sites.

Rates of acute gastrointestinal toxicity from conventional chemoradiotherapy techniques may also be significant. For example, in an EORTC randomized trial, 20% of patients receiving MMC/5-FU with radiotherapy experienced WHO grade 3 diarrhea. Similarly, 24% of patients who underwent this same regimen in RTOG 98-11 had CTCAE v2.0 grade 3 to 4 gastrointestinal toxicity. Most analyses of acute gastrointestinal tolerance with IMRT stem from investigations of gynecologic and prostate malignancies. Mundt et al. found lower rates of acute and chronic gastrointestinal toxicity with IMRT compared with conventional radiation approaches for gynecologic patients. Additionally, investigators from MSKCC showed that IMRT reduced small bowel irritation in patients with prostate cancer compared with 3-dimensional conventional RT. Furthermore, University of Chicago investigators showed no cases of RTOG acute grade 3 gastrointestinal toxicity in their retrospective series of patients with anal cancer.

In the Duke cohort, most patients (80%) had mild diarrhea but only 9% experienced CTCAE v3.0 acute grade 3 diarrhea, and none had grade 4. Studies analyzing dose–volume parameters associated with acute small bowel toxicity in patients undergoing chemoradiation therapy for pelvic malignancies have indicated that incidental small bowel irradiation is a frequent cause of gastrointestinal toxicity. Multiple investigators have shown strong correlations between acute treatment-related gastrointestinal toxicity (including severe diarrhea) and the amount of small bowel irradiated at each dose-level analyzed, including volumes receiving low-dose irradiation.

Collectively, these data indicate that avoidance of small bowel irradiation should be prioritized in the treatment of anal cancer and that IMRT seems superior to standard techniques in reducing acute gastrointestinal toxicity.

Acute hematologic toxicity rates are also high in patients with anal cancer when treated with pelvic RT and concurrent 5-FU and MMC. This is principally caused by the highly immunosuppressive nature of MMC and high percentage (approximately 40%) of active bone marrow within the pelvis. For instance, a 61% CTCAE v2.0 grade 3 to 4 acute hematologic toxicity rate was seen in the RTOG 98-11 study arm receiving 5-FU and MMC. Although Salama et al. reported grade 3 to 4 toxicity of 59% in patients treated with IMRT-based chemoradiation, other investigators have suggested improved bone marrow sparing with this approach.

Brixey et al. found lower rates of acute hematologic toxicity among patients with cervical cancer treated with pelvic IMRT concurrently with cisplatin. 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 patients with cervical cancer irradiated with concurrent cisplatin and in those with anal cancer treated with IMRT and concurrent chemotherapy. However, further study is necessary given that IMRT has the potential to increase the volume of pelvic bone marrow receiving low doses of radiation.

Disease-Related Outcomes and IMRT

Although data are limited on IMRT with concurrent chemotherapy for anal cancer, early disease-related outcomes appear promising. A multi-institutional
study treating patients with anal cancer with IMRT-based chemoradiotherapy reported 18-month overall survival, local control, metastasis- and colostomy-free survival rates of 93%, 94%, 93%, and 84%, respectively. In the authors’ experience at Duke University, 2-year actuarial overall survival, local control, metastasis-free survival, and colostomy-free survival rates for 29 patients with squamous cell carcinoma treated with IMRT-based chemoradiotherapy were 100%, 95%, 100%, and 91%, respectively. These studies have also shown improved acute toxicity rates with comparable disease-related outcomes compared with previous clinical trials in which IMRT techniques were not used.

The recently completed RTOG 05-29 trial, a multi-institutional phase II study assessing the feasibility, acute toxicity, and disease-related outcomes of an IMRT-based combined-modality approach, showed encouraging rates of clinical complete response. However, longer follow-up from these and other studies is necessary to assess long-term disease outcomes and chronic toxicity rates. Nevertheless, based on early study results, IMRT-based chemoradiotherapy seems to reduce acute toxicity rates without compromising clinical outcomes in the treatment of anal cancer.

Summary
IMRT has the potential to reduce acute and chronic treatment-related morbidity associated with chemoradiation therapy and potentially permit radiation dose escalation in the treatment of anal cancer. Additionally, integrating PET/CT into staging and RT planning, and as a means to evaluate treatment response, represents a significant advance in the treatment of anal cancer. Preliminary treatment-related toxicity rates and disease-related outcomes using IMRT look encouraging. Although long-term follow-up data are limited with these approaches, further investigation is ongoing to fully explore the benefits of these radiotherapy advances.

References


