Abstract. Background: The standard of care for locally advanced anal cancer has been concurrent chemoradiation. However, conventional treatment with 3-dimensional radiotherapy is associated with significant toxicity. The feasibility of new radiotherapy techniques such as image-guided radiotherapy (IGRT) in combination with chemotherapy for the treatment of this malignancy was assessed. Patients and Methods: A retrospective review of five patients with locally advanced anal carcinoma treated with Tomotherapy-based IGRT was conducted. All the patients received concurrent chemotherapy. Results: Gastrointestinal toxicity remained the limiting factor as four patients experienced grade 3-4 enteritis requiring a break during treatment. No patient experienced grade 3-4 hematological toxicity. Despite the large tumor size, three patients achieved local control at a median follow-up of 19 months. Conclusion: Tomotherapy-based IGRT may be a promising treatment for locally advanced anal cancer and needs to be investigated in further prospective trials.

Anal carcinoma represents a treatment challenge because of its pattern of spread to the inguinal and pelvic lymph nodes requiring radiation treatment to a large volume of normal tissues such as the bowels, bladder, and bone marrow resulting in severe toxicity when combined with chemotherapy (1, 2). In addition large tumors (T3-T4) require a high radiation dose for better local control (1, 3). The skin of the perineum is usually contaminated by fecal material and tends to break down with high radiation dose exposing the patient to risks of infection in the setting of bone marrow suppression induced by chemotherapy (4). Conventional treatment with two antero-posterior and postero-anterior fields to cover the inguinal areas is frequently associated with severe side-effects requiring a break during treatment and may compromise patient cure, if the patient cannot tolerate high radiation dose to the tumor (1, 2, 4). Recently, intensity-modulated radiotherapy (IMRT) has been introduced to decrease the side-effects of irradiation because of its ability to spare the normal tissues from excessive radiation dose (5). Preliminary results of IMRT have been promising because of reduced toxicity and in selected studies improved local control was also observed compared to the conventional radiotherapy technique (6-8). Helical Tomotherapy is an image-guided radiotherapy (IGRT) technique incorporating daily megavolt (MV) computed tomography (CT) planning and dynamic rotational IMRT. This special method of IMRT delivery produces a sharper dose fall-off compared to conventional IMRT and allows better sparing of the normal pelvic tissues (9). Preliminary results indicated that IGRT may improve treatment tolerance in rectal cancer patients undergoing preoperative chemoradiation (10) and prompted us to conduct this retrospective study to assess the feasibility of this new radiotherapy technique for the treatment of locally advanced anal carcinomas.

Patients and Methods

Five patients with locally advanced squamous cell carcinoma of the anal canal treated with concurrent chemoradiation at the University of Arizona Radiation Oncology department from 2008 to 2010 were retrospectively identified. Two were male and three female. Tomotherapy-based IGRT had been performed following...
institutional review board (IRB) approval. All the patients had biopsy-proven squamous cell carcinoma of the anus. One patient had stage II, one had stage IIIA and three had stage IIIB disease. Three patients had clinically palpable inguinal lymph nodes unilaterally (2) or bilaterally (1). Except for one patient, all the patients had large tumors (>5 cm). In addition, three patients had tumor invasion of adjacent organs: bladder (1), vagina and perineum (1), prostate and perineum (1). All the patients had a complete history and physical examination, digital rectal examination, CT scan of the chest, abdomen and pelvis. Laboratory tests included a complete blood count (CBC), electrolytes, creatinine, blood urea nitrogen (BUN), liver transaminases, γ-glutamyltransferase, alkaline phosphatase, total bilirubin and carcinoembryonic antigen.

Before treatment, each patient was simulated in the supine position with the legs abducted in the frog-leg position. A body vacuum bag was made for treatment immobilization. An anal marker was placed to indicate the location of the anus. A rectal tube was inserted following rectal examination for barium contrast study to assess the extent of the cancer. A 0.5 cm bolus was placed on the inguinal area(s) in the cases of involved inguinal lymph nodes at clinical examination or on CT scan. The abdomen and pelvis were scanned with a slice thickness of 3 mm with and without intravenous (i.v.) contrast. Rectal and i.v. contrast were employed to aid tumor localization and to identify grossly enlarged lymph nodes for target volume delineation.

Radiotherapy planning was performed on the noncontrast-enhanced CT scan to avoid possible interference of contrast density with isodose distribution calculations. Diagnostic positron emission tomography (PET)-CT scan for tumor imaging was incorporated with CT planning when available. Normal organs at risk (OAR) for complications were outlined for treatment planning (small bowel, bladder, femoral heads and genital area). The gross tumor volume (GTV) was outlined integrating information obtained from the CT scan with i.v. and rectal contrast, rectal examination and PET scanning when available. The clinical target volume (CTV) included the mesorectum, presacral space, external and internal iliac and inguinal lymph nodes. The inguinal lymph node if clinically enlarged on CT scan, was outlined separately for possible additional boost. The planning target volume (PTV) was generated by isotropically expanding the CTV by a 1 cm margin. The PTV was treated 45 Gy at 1.8 Gy/fraction. Two patients had an integrated boost technique where the GTV inside the PTV was treated 50 Gy at 2 Gy/fraction. Following 45 Gy, the GTV was boosted to a final dose of 54 to 60 Gy at 1.8 to 2 Gy/fraction. Enlarged inguinal lymph nodes were boosted to 50 to 60.8 Gy in 1.8 to 2 Gy/fraction if they were still clinically palpable at 45 Gy.

Target volume coverage was specified to be at least 95% of the prescribed dose. Dose constraints for normal OAR for complications were: small bowel volume receiving 45 Gy (V45) <10%, bladder: V45 <50%, femoral head volumes receiving 40 Gy (V40) <50% and genital area: V45 <30%.

Chemotherapy. Except for one patient who refused i.v. chemotherapy, all the patients were treated with two cycles of 5-fluorouracil (5-FU) (1000 mg/m² per day) in continuous i.v. infusion on days 1-5 and days 29-33 of IGRT and mitomycin C (MMC) (10 mg/m² i.v. bolus) on days 1 and 29 of IGRT. The patient who refused i.v. chemotherapy was treated with capecitabine at an oral dose of 825 mg/m² twice per daily, seven days weekly, beginning on the first day of radiotherapy and ending on the last day. The patients were monitored during treatment with weekly CBC, liver enzymes, electrolytes, BUN, and creatinine. Acute and late treatment toxicity were scored according to the Radiation Therapy Oncology Group (RTOG) scale (http://ctep.cancer.gov).

Following treatment, all the patients had regular clinical visits one month after treatment and every three months afterwards for the first two years. The presence or absence of fecal incontinence was assessed at each follow-up visit. A proctoscopic examination was performed four months after treatment and yearly afterward. All suspicious areas observed on proctoscopy were biopsied to exclude recurrence. A CT scan of chest, abdomen, and pelvis was performed four, and ten months after treatment and yearly afterwards. A PET-CT scan was performed if the patient had biopsy proven recurrence before salvage with surgery or chemotherapy.

Results

The gross tumor dose ranged from 45 Gy to 60.8 Gy. Table I summarizes the patient characteristics.

During treatment, four patients developed grade 3-4 radiation enteritis requiring a break in the treatment ranging from 12 to 21 days. One patient with a history of severe colitis prior to radiotherapy could not complete the whole pelvic radiotherapy because of severe diarrhea and dehydration. His second cycle of chemotherapy was discontinued. The GTV was boosted to 55.8 Gy after pelvic irradiation of 32.4 Gy and a treatment break of 21 days. The weight loss in the whole group ranged from 3 to 20 pounds (mean: 13.6 pounds). Four patients developed grade 3-4 skin reaction in the perineum.
However, no patient developed grade 3-4 hematological toxicity. The median follow-up was 19 months and one patient died from locoregional recurrence. One patient developed locoregional recurrence and bony metastases and underwent salvage chemotherapy. The other three patients were cancer-free at their last follow-up. One patient had fecal incontinence. She was incontinent prior to radiation because the tumor was massive; destroying the anal sphincter, invading the perineum, rectum and vagina (Figure 1).

**Discussion**

To our knowledge, this is the first study looking at the feasibility of Tomotherapy-based IGRT for the treatment of locally advanced anal cancer. All the patients in the study presented with poor prognostic factors for recurrences either because of the size of the lesion, invasion of adjacent organs or inguinal lymph node metastases at presentation. In a review of 644 patients with anal cancer treated with concurrent chemoradiation, tumor size (>5 cm) was shown to be the most predictive prognostic factor for colostomy-free survival (11). The 5-year colostomy rate was respectively 9% and 19% for tumors less than or above 5 cm in size. Eighty percent of the colostomies were performed for local recurrence. Patients with clinically positive inguinal lymph nodes also had poor disease-free survival compared to inguinal node negative patients (11). Other studies also corroborated the high rate of local failure associated with tumor size, and/or invasion of adjacent organs (1, 3). As the present study illustrated, given the size of the tumor and the presence of positive inguinal lymph nodes, irradiation of a large volume of bowel is unavoidable leading to radiation enteritis, weight loss and treatment breaks. However, it should be noted that only one patient with a past history of severe colitis and chronic diarrhea did not complete the pelvic radiation to 45 Gy as planned. Figure 1 illustrates the difficulty of treating a locally advanced tumor which completely destroyed the anal sphincter and invaded the rectum, vagina and perineum. Both GTV and inguinal lymph nodes were treated to 60.8 Gy leading to clinical remission 19 months after treatment. As the dose-volume histogram of Figure 1 illustrates, Tomotherapy allowed significant sparing of the iliac crest and the femoral heads from the high radiation dose and may have contributed to bone marrow sparing. Such sparing from excessive radiation may explain the absence of grade 3-4 hematological toxicity in this study. Though the study patient number was small, no grade 3-4 hematological toxicity which was very common with chemotherapy and conventional radiotherapy for anal carcinomas (1-4) and ranged from 21 to 54% with the IMRT technique (5-7, 12, 13) was observed. Tomotherapy has been demonstrated to spare the bone marrow from excessive radiation compared to conventional IMRT (14), most likely because of the sharp dose fall-off which allows decreased radiation dose even in smaller organs such as the cochlea in head and neck cancer (9, 15). However, further prospective studies should be conducted in a large number of patients with pelvic malignancies to assess the dosimetric bone marrow sparing properties of Tomotherapy as well as their clinical significance.

![Image 1](image1.png)

Figure 1. Illustration of the role of Tomotherapy in sparing the normal pelvic organs in a 89 year old patient with a massive anal cancer completely destroying the anal sphincter and invading the rectum, vagina and perineum. A fixed 4-5 cm right inguinal lymph node was also present. The dose-volume histogram illustrated the first phase of the treatment when the whole pelvis was irradiated. The red line represents the gross tumor volume and inguinal lymph node treated to 50 Gy in 2 Gy fraction while the green line outlines the clinical target volume treated to 45 Gy in 1.8 Gy/fraction. The orange, black, light blue and pink lines represents the bladder, small bowel, right and left femoral head respectively. Only 50% of the small bowel received more than 25 Gy with a maximal bowel dose of 47 Gy.
The limitations of the study include the small number of patients, the retrospective nature, and the short follow-up. Nevertheless, the absence of serious hematological toxicity effects is intriguing and merits further investigations.

Conclusion

Tomotherapy-based IGRT is feasible for the treatment of locally advanced anal cancer and should be investigated in future prospective trials to assess treatment efficacy and toxicity.

Conflict of Interest

The Authors have no conflict of interest and have no external source of funding.

References


Received August 28, 2011
Revised October 24, 2011
Accepted October 25, 2011