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Physics Contribution

Setup Variations in Radiotherapy of Anal Cancer: Advantages of Target Volume Reduction Using Image-Guided Radiation Treatment

Yi-Jen Chen, M.D., Ph.D.,* Steve Suh, Ph.D.,* Rebecca A. Nelson, Ph.D.,† An Liu, Ph.D.,* Richard D. Pezner, M.D.,* and Jeffrey Y.C. Wong, M.D.*

*Divisions of *Radiation Oncology and †Information Sciences, City of Hope Medical Center, Duarte, CA*

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Summary

To determine the optimal definition of target margins for patients with anal cancer treated by radiotherapy (RT), a retrospective evaluation of setup variations in patients with anal cancer treated by a tomotherapy image-guided RT (IGRT) program was performed. We concluded that daily volumetric scanning before each treatment can effectively detect setup errors and thereby reduce planning target volume (PTV) margins. This would reduce the radiation dose to surrounding critical organs and provide satisfactory clinical outcomes and favorable toxicities.

Purpose: To define setup variations in the radiation treatment (RT) of anal cancer and to report the advantages of image-guided RT (IGRT) in terms of reduction of target volume and treatment-related side effects.

Methods and Materials: Twelve consecutive patients with anal cancer treated by combined chemoradiation by use of helical tomotherapy from March 2007 to November 2008 were selected. With patients immobilized and positioned in place, megavoltage computed tomography (MVCT) scans were performed before each treatment and were automatically registered to planning CT scans. Patients were shifted per the registration data and treated. A total of 365 MVCT scans were analyzed. The primary site received a median dose of 55 Gy. To evaluate the potential dosimetric advantage(s) of IGRT, cases were replanned according to Radiation Therapy Oncology Group 0529, with and without adding recommended setup variations from the current study.

Results: Significant setup variations were observed throughout the course of RT. The standard deviations for systematic setup correction in the anterior–posterior (AP), lateral, and superior–inferior (SI) directions and roll rotation were 1.1, 3.6, and 3.2 mm, and 0.3°, respectively. The average random setup variations were 3.8, 5.5, and 2.9 mm, and 0.5°, respectively. Without daily IGRT, margins of 4.9, 11.1, and 8.5 mm in the AP, lateral, and SI directions would have been needed to ensure that the planning target volume (PTV) received ≥95% of the prescribed dose. Conversely, daily IGRT required no extra margins on PTV and resulted in a significant reduction of V15 and V45 of intestine and V10 of pelvic bone marrow. Favorable toxicities were observed, except for acute hematologic toxicity.

Conclusions: Daily MVCT scans before each treatment can effectively detect setup variations and thereby reduce PTV margins in the treatment of anal cancer. The use of concurrent chemotherapy and IGRT provided favorable toxicities, except for acute hematologic toxicity.

Keywords: Image-guided radiation therapy, Setup variation, Radiotherapy, Anal cancer

Reprint requests to: Yi-Jen Chen, M.D., Ph.D., Division of Radiation Oncology, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010-3000l. Tel: (626) 301-8247; Fax: (626) 930-5334; E-mail: yichen@coh.org

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Introduction

In 2010, an estimated 5260 Americans received diagnoses of anal margin or anal canal cancer, and approximately 720 died as a result of their disease (1). More than 80% of anal cancers are squamous cell carcinomas, and most of these cases present with locoregional disease (2). Before the 1970s, abdominoperineal resection was the treatment of choice, but this approach resulted not only in a permanent colostomy but also in a disappointing 5-year survival rate of just 40% to 70% (2). Nigro *et al.* revolutionized the treatment of anal cancer with the concept of combined chemotherapy and RT to preserve the anal canal (3). This strategy was widely adopted and validated by other investigators, who demonstrated a 5-year colostomy-free survival rate of approximately 70% and a 5-year overall survival rate of 70% (4–8). The current standard of care for patients with anal cancer is composed of combined chemotherapy using 5-fluorouracil and mitomycin and RT up to 45 to 59 Gy; however, the combined chemoradiation is quite toxic, with substantial acute and late morbidity. Acute toxic events include dermatitis, proctitis, dysuria, and hematologic events; late sequelae include perineal skin fibrosis, atrophy, chronic rectal ulcer, dyspareunia, and bony insufficiency fracture. In the Radiation Therapy Oncology Group (RTOG) 98-11 trial, after treatment with fluorouracil, mitomycin, and RT, acute nonhematologic and hematologic Grade 3 or 4 toxicity occurred in 74% and 61% of patients, respectively. The rate of long-term Grade 3 or 4 toxicity was 36% (8). Furthermore, in the RTOG 87-04 trial, 2.7% of patients experienced fatal toxicity as the result of neutropenic sepsis (5). Thus, despite the high clinical cure rate, a significant reduction of acute toxic events in the treatment of anal cancer would greatly improve the clinical outcomes for patients.

Intensity-modulated radiation therapy (IMRT) is a highly promising and cutting-edge technology that allows for the delivery of radiation to target tissues in a more conformal manner while sparing surrounding structures by modulating the intensity of radiation beams from different angles. In a dosimetric study, Chen *et al.* demonstrated superior target coverage with IMRT compared with other approaches while simultaneously achieving significantly reduced radiation doses to the surrounding organs at risk (OARs), including the femoral head and neck and the external genitalia (9). In a multicenter trial, preliminary outcomes of 53 patients treated with concurrent chemotherapy and IMRT suggest that the treatment is effective and tolerated favorably compared with the historical standard; however, acute Grade 3 gastrointestinal (GI) and dermatologic toxicity still occurred in 15.1% and 37.7% of patients, respectively, and acute Grade 4 hematologic toxicity occurred in 39.6% of patients (10). Because of treatment-related toxicity, treatment breaks occurred in 41.5% of patients, which likely compromised the overall results of the study. It should also be noted that volumetric-modulated arc radiotherapy, a new form of IMRT, can provide even better sparing of OARs with less monitor unit and treatment time than fixed-angles IMRT (11, 12).

To achieve successful treatment with IMRT, it is essential to contour precisely the primary cancer in the anal canal and the regional lymph nodes at risk in the pelvic and groin area. To spare surrounding normal structures from unnecessary RT and reduce treatment-related side effects, a more restricted target volume definition is appealing, but this approach may compromise the outcome because of therapeutic uncertainties, such as inaccurate patient positioning and internal organ motion. To ensure adequate target coverage during RT, one commonly used strategy is to expand the margins around the clinical target volume (CTV) to arrive at a planning target volume (PTV) (13). For example, a minimum of 1 cm around the CTV is required in all directions by a recently completed RTOG 0529 study (Phase II trial evaluating use of IMRT in combination with chemotherapy in the treatment of anal canal carcinoma) (14). Another method to achieve accurate delivery of radiation to the target requires the implementation of a verification process, such as comparing portal images with simulation films. Conventional setup correction based on portal film examination is performed weekly, but this frequency is now considered to be less than ideal (15–17). Although studies have been published on the advantages of daily online correction to eliminate setup variation in the settings of lung and prostate cancer (18, 19), data for online correction in the treatment of anal cancer are nonexistent.

Helical tomotherapy is a novel form of IMRT that features a 360° radiation delivery system and image-guided RT (IGRT) through comparison of pretreatment megavoltage CT (MVCT) scans with CT scans performed at the time of simulation for treatment planning (20). The tomotherapy system includes software for automatic registration of bony structures from MVCT to planning CT scans for translational and rotational corrections (21). In comparison with to step-and-shoot IMRT, tomotherapy has been shown to provide better dose homogeneity in the PTV, better dose conformity around the PTV, and therefore better sparing of nearby OARs in the treatment of anal cancer (22).

To define setup variation in the treatment of anal cancer and to evaluate the potential advantage(s) of IGRT in terms of target volume reduction, 12 consecutive patients treated with helical tomotherapy were retrospectively reviewed. In addition, we reviewed our initial clinical experiences of treating anal cancer with helical tomotherapy.

Methods and Materials

From March 2007 to November 2008, 12 consecutive patients with localized anal cancer were treated with combined chemotherapy and RT by tomotherapy at City of Hope Medical Center. Demographic characteristics, stages, and treatment details are given in Table 1.

Before beginning RT, all patients underwent CT scan simulation in the supine position with a Vac-Lok device (CIVCO Medical Solutions Inc., Kalona, IA) for immobilization of the lower extremities. The patients were scanned feet first with a full bladder. Three small tattoos were placed on the lower torso (right and left iliac crests, and between the pubic bone and umbilicus) to serve as reference points for daily treatment setups. Spiral CT scans were performed by use of a 3×3 mm stacked axial slice technique with a pitch of 1.7. The resolution of the CT images was 512×512 pixels. The images were transferred to the Eclipse treatment planning system (Varian Medical Systems, Inc., Palo Alta, CA) for contouring. The gross tumor volume (GTV), CTV, PTV, and avoidance structures including the bowel, bladder, external genitalia, and hip joints were contoured, and the data were sent to the tomotherapy planning station by use of the DICOM-RT protocol. This set of reference images was used for automatic registration with MVCT scans before each fraction of treatment. The GTV included radiographically visible and clinically identifiable disease in the anal canal and enlarged lymph nodes. The CTV consisted of the GTV plus 2 cm expansion and the pelvic and inguinal lymph nodal areas