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Clinical Investigation: Gynecologic Cancer

Prospective Study of Functional Bone Marrow-Sparing Intensity Modulated Radiation Therapy With Concurrent Chemotherapy for Pelvic Malignancies

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Summary

Acute hematologic toxicity is a common complication of chemoradiation therapy for pelvic malignancies that leads to poor treatment tolerance and reduced treatment intensity. We have developed a technique using ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography and magnetic resonance imaging with quantitative IDEAL IQ (GE Healthcare, Waukesha, WI), in conjunction with intensity modulated radiation

Purpose: To test the hypothesis that intensity modulated radiation therapy (IMRT) can reduce radiation dose to functional bone marrow (BM) in patients with pelvic malignancies (phase IA) and estimate the clinical feasibility and acute toxicity associated with this technique (phase IB).
Methods and Materials: We enrolled 31 subjects (19 with gynecologic cancer and 12 with anal cancer) in an institutional review board-approved prospective trial (6 in the pilot study, 10 in phase IA, and 15 in phase IB). The mean age was 52 years; 8 of 31 patients (26%) were men. Twenty-one subjects completed ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) simulation and magnetic resonance imaging by use of quantitative IDEAL (IDEAL IQ; GE Healthcare, Waukesha, WI). The PET/CT and IDEAL IQ were registered, and BM subvolumes were segmented above the mean standardized uptake value and below the mean fat fraction within the pelvis and lumbar spine; their intersection was designated as functional BM for IMRT planning. Functional BM-sparing vs total BM-sparing IMRT plans were compared in 12 subjects; 10 were treated with functional BM-sparing pelvic IMRT per protocol.
Results: In gynecologic cancer patients, the mean functional BM V_{10} (volume receiving $\geq$10 Gy) and V_{20} (volume receiving $\geq$20 Gy) were 85% vs 94% ($P<.0001$) and 70% vs 82% ($P<.0001$), respectively, for functional BM-sparing IMRT vs total BM-sparing IMRT. In anal cancer patients, the corresponding values were 75% vs 77% ($P=.06$) and 62% vs 67% ($P=.002$), respectively. Of 10 subjects treated with functional BM-sparing pelvic IMRT, 3 (30%) had acute grade 3 hematologic toxicity or greater.

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therapy, to reduce radiation dose to functional pelvic bone marrow subregions. Preliminary results indicate that this technique is well tolerated and could reduce acute hematologic toxicity compared with standard pelvic radiation therapy techniques.

Conclusions: IMRT can reduce dose to BM subregions identified by ^{18}F-fluorodeoxyglucose-PET/CT and IDEAL IQ. The efficacy of BM-sparing IMRT is being tested in a phase II trial.

Introduction

Concurrent chemoradiation therapy is standard treatment for many pelvic malignancies. Randomized trials have found that chemoradiation therapy improves tumor control compared with radiation therapy (RT) alone (1-4) and that intensifying chemoradiation therapy improves patient outcomes (5-7). However, high-grade acute hematologic toxicity is a problem, occurring in up to 60% of patients (5-7). This can lead to reduced intensity of chemotherapy delivery, which has been associated with inferior outcomes (2, 8). Therefore, reducing hematologic toxicity is an important goal.

Both radiation and chemotherapy are myelosuppressive, but the extent to which radiation contributes to hematologic toxicity in patients undergoing chemoradiation therapy is not well-known. Radiation causes apoptosis of bone marrow (BM) stem cells and stromal damage, resulting in myelosuppression and characteristic pathologic and radiographic BM changes (9). Concurrent chemotherapy augments radiation-induced BM injury, leading to higher rates of toxicity than sequential chemotherapy and RT or either modality given alone (9). Clinical studies have shown that the extent of radiation-induced BM injury depends on both dose and volume of BM irradiated (10, 11). Conventional pelvic RT fields encompass large volumes of hematopoietically active BM, particularly in the pelvis and lower spine. We have therefore hypothesized that pelvic BM radiation could contribute to hematologic complications and poorer chemotherapy tolerance.

One approach to reducing BM irradiation is intensity modulated radiation therapy (IMRT). Multiple studies have shown that, compared with conventional techniques, IMRT reduces normal tissue dose, including BM (12, 13). A problem with standard IMRT plans is a large BM volume to avoid, which constrains optimization. It is known, however, that BM is composed of both hematopoietically active "red" marrow and inactive "yellow" marrow, which cannot be distinguished on computed tomography (CT) (14). By avoiding hematopoietically active, or "functional," (ie, red) BM, IMRT planning could be improved. Magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission CT have been used previously to reveal locations of functional BM (15, 16). However, the ability to image an organ does not guarantee that IMRT plans can be designed to spare it, because this also depends on the location of the organ with respect to the target and other normal tissues.

Our primary aim in this study was to test the hypothesis that functional BM-sparing IMRT can reduce radiation dose to functional BM in patients with pelvic malignancies (phase IA), compared with BM-sparing IMRT without using functional imaging. Our secondary aim was to determine the feasibility (ie, the ability to complete protocol therapy) and estimate acute hematologic toxicity using this technique (phase IB). The study was not designed to compare toxicity of this technique against the standard of care.

Methods and Materials

Patients

We enrolled 31 subjects in a prospective clinical trial approved by our institutional review board between September 2008 and December 2010. All subjects signed informed consent. Inclusion criteria were (*1*) histologically proven stage I-IV invasive carcinoma of the cervix or stage I-III carcinoma of the anal canal, (*2*) radical treatment intent with concurrent chemoradiation therapy, and (*3*) technical feasibility. Exclusion criteria were (*1*) a prior history of chemotherapy, pelvic irradiation, or hematopoietic growth factor use; (*2*) incarceration; or (*3*) the need for emergent care. Of 58 patients screened for participation, 31 consented to participate, 14 refused, 5 were excluded because of emergency, and 8 were excluded because of technical infeasibility (temporary IDEAL IQ [GE Healthcare, Waukesha, WI] license expiration).

^{18}F-Fluorodeoxyglucose-PET/CT simulation

All patients treated according to protocol underwent ^{18}F-fluorodeoxyglucose (FDG)-PET/CT simulation on a GE Healthcare scanner (64-slice Discovery VCT). Patients were simulated in the supine position, with custom immobilization to minimize setup variation. CT images were exported to Eclipse (Varian, Palo Alto, CA) for planning.

Quantitative MRI of fat fraction in BM

Before treatment, patients underwent imaging from the L4-5 interspace to the ischial tuberosities by use of an investigational MRI protocol, IDEAL IQ (17). The underlying principle is that the signals from fat and water exhibit resonant frequency/chemical shift differences that can be separated using multiple measurements taken at different time points after excitations. The end result is an individualized 3-dimensional fat fraction (ie, fat/[fat+water]) map (Fig. 1A). The intensity of the image provides an (inverse) quantitative index of BM cellularity.

Functional BM delineation

The simulation PET/CT and IDEAL IQ MRI studies were rigidly registered by use of Velocity AI software (Velocity Medical