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Early dose-dependent cortical thinning of the femoral neck in anal cancer patients treated with pelvic radiation therapy

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ABSTRACT

Background and purpose: Anal cancer patients treated with radiation therapy (RT) have an increased risk of hip fractures after treatment. The mechanism of these fractures is unknown; however, femoral fractures have been correlated with cortical bone thinning. The objective of this study was to assess early changes in cortical bone thickness at common sites of femoral fracture in anal cancer patients treated with intensity modulated radiation therapy (IMRT).

Materials and methods: RT treatment plans and computed tomography (CT) scans from 23 anal cancer patients who underwent IMRT between November 2012 and December 2014 were retrospectively reviewed. Cortical thickness (Ct.Th) was mapped at homologous vertices within the proximal femur using pre-RT and post-RT (≤4 months) CT scans. The bone attenuation measurements were collected at homologous locations within the trabecular bone of the right femoral neck (FN). The percent change in Ct.Th and trabecular bone mineral density (trBMD) were assessed. FN cortical thinning was correlated to RT dose using linear regression. A logistic model for dose dependent cortical thinning was constructed.

Results: Twenty-two patients were analyzed. Significant post-treatment cortical thinning was observed in the intertrochanteric crest, subcapital and inferior FN ($p < 0.05$). FN volume receiving ≥40 Gy (V40Gy) was a significant predictor of focal cortical thinning ≥30% ($p = 0.03$). A significant decrease in FN trBMD was observed (−6.4% [range −34.4 to 3.3%]; $p = 0.01$).

Conclusion: Significant early decrease in Ct.Th and trBMD occurs at the FN in patients treated with RT for anal cancer. FN V40Gy was predictive of clinically significant focal FN cortical thinning.

1. Introduction

Definitive chemo-radiation therapy (CRT) has become the standard of care for treating localized squamous cell carcinoma (SCC) of the anal canal [1]. Bone toxicity is a major concern after pelvic radiation therapy (RT) [2–4]. Incidence of femoral and pelvic insufficiency fracture is significantly higher in patients that receive pelvic RT [5–8]. Female anal cancer patients over the age of 65 treated with pelvic RT have a three-fold increase in pelvic and femoral fractures within the first five years following treatment based on Surveillance, Epidemiology, and End Results (SEER) cancer registry data [8]. Importantly, these fractures are associated with direct exposure of bone to ionizing radiation [8,9]. Femoral fractures tend to be located within the subcapsular femoral neck (FN) and intertrochanteric region [10,11].

Treating fractures in irradiated bone is complicated due to associated morbidity and mortality. The rate of non-union is high in RT-induced fractures [12,13]. Even with effective intervention, chronic pelvic and back pain and impaired mobility are common after fracture [14]. These complications are detrimental to quality of life [14]. Pelvic fractures, especially FN fractures, are particularly morbid in geriatric patients. Mortality rates are twice as high within five years following fracture due to associated complications [15].

Abbreviations: RT, radiation therapy; IMRT, intensity modulated radiation therapy; CT, computed tomography; Ct.Th, cortical thickness; FN, femoral neck; trBMD, trabecular bone mineral density; CRT, chemo-radiation therapy; SCC, squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results; OARs, organs at risk; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; DICOM, Digital Imaging and Communications in Medicine; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; HU, Hounsfield Unit; Ps.Pm, periosteal perimeter; vBMD, volumetric bone density; ROI, regions of interest.

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Significant toxicity after CRT for anal cancer has motivated the use of more conformal RT techniques, such as intensity-modulated radiotherapy (IMRT). IMRT conforms to a given target volume, allowing for sparing of higher RT doses to surrounding structures [16]. This technique reduces dose to organs at risk (OARs), but may increase the integral dose deposited to the surrounding tissue by each beamlet [17].

Anal cancer has a high propensity to spread to pelvic lymph nodes [2]. Involved inguinal nodes, which abut the FN, are usually treated in anal cancer. Nodal irradiation exposes the hip to a relatively high RT dose, even with highly conformal techniques [16,17]. Major Radiation Therapy Oncology Group (RTOG) prospective trials have included dose constraints for the femoral head in anal cancer patients; however constraints for the FN, a region biomechanically at risk for fracture, have not been employed [2].

The etiology of radiation-induced fracture is unclear, however, it appears fracture likely results from bone damage and deterioration [10–12, 18]. Cortical thickness (Ct.Th) is a major feature of bone strength, and thinning may reflect microstructural deterioration [10,18]. We have previously identified acute cortical bone thinning at sites within the ribcage that receive ≥10 Gy during thoracic stereotactic body radiation therapy (SBRT) for primary and metastatic lung lesions [19]. In this study, we examine early post-treatment changes in Ct.Th and trabecular bone mineral density (trBMD) of the proximal femur in anal cancer patients treated with IMRT and assess the dose-volume relationships between RT and focal cortical thinning within the FN.

2. Methods

2.1. Data collection

Pelvic computed tomography (CT) scans and RT plans of 23 patients treated for anal cancer with CRT from 2012 to 2014 at our institution were retrospectively reviewed as part of an Institutional Review Board-approved study. Patients were treated with dynamic multi-leaf collimator IMRT using 6–9 coplanar or non-coplanar, non-uniform beams. Doses, fractionation schemes, and treatment volumes were based on the guidelines used in the *RTOG 0529* protocol [2]. Mesorectal, inguinal, internal and external iliac nodes were treated in all patients.

Simulation CT scanning was performed in the supine position with resolution between 0.5 and 0.8 mm in the axial planes, and slice thickness of 1.8 mm. CT scans were examined for pelvic or femoral fractures or deformities. Patients with bone pathologies prior to treatment were excluded from analysis. Treatment planning was performed using Pinnacle TPS (Philips Radiation Oncology Systems, Fitchburg, WI). All patients received a follow-up CT scan within four months following RT. Digital Imaging and Communications in Medicine (DICOM) RT files and follow-up CT scans were exported and reconstructed in MIM Maestro (v6.4, MIM Software Inc., Cleveland, OH). Patient age, gender, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG), and incidence of post-radiation fracture within the first year after treatment were obtained retrospectively from patient medical records.

2.2. Cortical thickness mapping

For each CT scan, the pelvis was segmented from the top of the fifth lumbar vertebra to the proximal one third of both femurs using automated thresholding techniques and manual editing in Mimics (v16.0 Materialise, Leuven, Belgium). The pubic symphysis, bilateral sacroiliac joints, sacrotuberous ligaments, and sacrospinous ligaments were excluded as they are non-osseous tissues. The pelvis and femurs were used to establish the peak cortical bone BMD. Ct.Th was estimated and mapped along the surface of the proximal femur using a density-based automated cortical estimation method [19,20]. Ct.Th was estimated at approximately 20,000 vertices from the pre-treatment and post-treatment CT scans for each patient using Stradwin (v5.0, Cambridge, England). The baseline femur surface was spatially realigned with the post-treatment surface via rigid and affine deformation in 3D Slicer (v 3.6, http://www.slicer.org). The post-treatment Ct.Th at each vertex was compared to pre-treatment Ct.Th at each corresponding homologous vertex on the surface. Each femur was registered separately to achieve optimal surface alignment.

The FN was contoured bilaterally on the 3D femur surface using anatomical landmarks in GeoMagic Studio (v2014,Geomagic Inc., Morrisville, North Carolina). Specifically, the FN was medially defined by the line of junction with the head, and laterally by the intertrochanteric crest, and the greater and lesser trochanter. The centroid of the right FN surface was determined and the mid-femoral neck periosteal perimeter (Ps.Pm) was estimated for each 3D femoral surface using GeoMagic Studio. The mean pre-RT and post-RT Ps.Pm and Ct.Th were determined for each patient. Mean percent difference in Ct.Th at homologous vertices across patients was mapped using Matlab (v.2014a Mathworks, Natick, MA).

2.3. Trabecular BMD

Mean Hounsfield Unit (HU) values were collected in Mimics from homologous regions of interest (ROI) within the trabecular bone of the FN, right psoas major muscle, and anterior subcutaneous fat for the baseline and follow-up CT scans. FN ROI were obtained from the pre-RT CT scan in a standard sized region that was placed at the centroid of the 3D femoral neck surface. Region size was selected such that the cortical bone of the FN was avoided in each patient. Attenuation values in the homologous post-RT FN were obtained by registering the pre-RT ROI to the post-RT CT coordinate system using the transform calculated earlier. The HU were converted to volumetric bone density (vBMD) units using calibrated HU measurements collected at homologous locations. Briefly, the actual density of fat and muscle were determined using 20 scans including phantom ports with known mg/cm^3 values and the experimental fat and muscle HU values were linearly regressed against the known values. The percent change in mean FN trBMD at the time of follow-up imaging was calculated relative to the pre-RT CT scan for each patient.

2.4. Dosimetric analysis

DICOM-RT files were exported from Pinnacle and were then reconstructed in MIM Maestro. The proximal femurs were contoured bilaterally. Point doses were calculated within each contour using the treatment plan. Point doses were mapped to the corresponding Ct.Th values using iterative closest point (ICP) registration in Matlab. Mean point dose to homologous vertices across patients was calculated and mapped using Matlab.

A logistic model was constructed for RT dose-dependent thinning of the FN. The binary outcome variable was ≥30% cortical thinning in at least 1 cm^2 of the FN surface. This threshold was based on a prior study that reported patients experiencing FN fracture had 30% thinner cortical bone at the femoral head-neck junction than age-matched controls [10]. The patient treatment plans (DICOM-RT) were used to determine the absolute volume of the femoral neck receiving a given dose, $V_{D(Gy)}$, for the entire dose range in 0.1 Gy intervals in MIM Maestro. Serial logistic regressions were performed for the predictor variable $V_{D(Gy)}$ for each discrete dose between 0 Gy and the maximum FN dose received by any patient, at 0.1 Gy intervals. The most statistically significant predictor was used to develop a logistic model for cortical thinning based on volumetric dose.

2.5. Statistical analysis

Paired *t*-tests were performed to assess the significance of the change in mean FN trBMD and Ct.Th post-RT relative to the initial values. The relationship between cortical thinning and absorbed point dose was examined using univariate linear regression at homologous vertices within the FN across patients. Linear regression was used to assess the association between the outcome variables and patient gender, and BMI.