Radiotherapy-Associated Pelvic Insufficiency Fracture Treated by Romosozumab: Course of CT Attenuations at L1 and L5

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Abstract

Pelvic radiation therapy (RT) is a risk factor for pelvic insufficiency fracture, which may be accompanied by significant pain, decreased self-sufficiency, and impaired mobility. Assessment of bone density with “opportunistic” computed tomography (CT) attenuation of the L1 vertebral body can be used as a surrogate for dual-energy x-ray absorptiometry (DXA) scan and potentially be useful to follow bone changes in cancer patients who undergo surveillance CT imaging. The following is a case of a 60-year-old female who suffered a pelvic insufficiency fracture, after receiving chemotherapy and pelvic RT for endometrial cancer, for which she was treated with romosozumab, a sclerostin inhibitor used for postmenopausal women at high risk for insufficiency or fragility fracture. CT attenuation of the L1 and L5 vertebral bodies were measured prior to chemoradiation therapy, post-therapy, and before and after treatment with romosozumab. Pelvic RT was associated with declining CT attenuation, greater in magnitude at L5 vs L1 vertebral body, while treatment with romosozumab was associated with increase to baseline at L1, and improvement but not return to baseline at L5.

Key Words: pelvic insufficiency fracture, radiotherapy, CT attenuation, romosozumab, endometrial carcinoma

Abbreviations: BMD, bone mineral density; CT, computed tomography; CTX, C-telopeptide; DXA, dual-energy x-ray absorptiometry; HU, Hounsfield units; IV, intravenous; P1NP, procollagen type 1 amino-terminal propeptide; PTH, parathyroid hormone; RT, radiation therapy.

Radiotherapy (RT) has become a standard modality used in the treatment of gynecologic malignancy, but also results in localized bone loss [1]. Doses of radiation for gynecologic malignancies commonly exceed 50 Gy, with bone receiving up to half of this dose [2]. This occurs despite efforts to limit radiation exposure to noncancerous tissues with increased incidence of fractures at sites in the path of RT compared with other skeletal sites [3-7]. RT induces several changes in bone, including demineralization, thinning, sclerosis, and loss of trabecular bone volume [8-11]. RT results in osteoblast cell-cycle arrest, DNA damage, reduced collagen synthesis, and increased apoptosis leading to impaired bone formation [12-15]. RT also results in increased production of osteoclasts [16, 17] and elevates pro-resorptive inflammatory cytokines [18] that drive an increase in bone resorption. RT can also impair function of osteocytes or lead to apoptosis [10, 16, 19, 20], leading to decreased ability of bone to withstand dynamic loads. Bone vasculature is damaged and blood supply reduced [10], resulting in local hypoxia of the bone.

Incidence of radiation-induced insufficiency fracture after pelvic RT has been reported at 8.2% to 45.2% [21]. Patients who have received RT were previously only eligible for antiresorptive agents for treatment of osteoporosis and insufficiency fractures, which have been demonstrated to reduce bone resorption and loss of bone after radiation therapy [22].

Intermittent parathyroid hormone (PTH) administration may help reverse some of the deleterious effects of radiation. When administered intermittently, PTH promotes osteoblastogenesis, inhibits apoptosis of osteoblasts, and promotes matrix synthesis, resulting in increased callus formation and mechanical strength of bone [23]. Although teriparatide and abaloparatide are clinically indicated for treatment of postmenopausal osteoporosis at high risk for fracture, these agents are contraindicated in prior therapeutic radiation crossing bone due to increased risk of osteosarcoma [24]. A new dual action bone anabolic-anticatabolic pharmacologic agent for the treatment of postmenopausal osteoporosis—romosozumab—was approved by the Food and Drug Administration (FDA) in April 2019 and is not contraindicated by RT [25, 26].

CT scan has been proposed as a method to screen for osteoporosis, even if obtained for other purposes [27]. The International Society for Clinical Densitometry (ISCD) guidelines for DXA interpretation include assessment of “opportunistic CT” as a surrogate for DXA scan using L1 vertebral body attenuation, with threshold > 150 and < 100 Hounsfield units (HU) estimating the likelihood of normal bone density and osteoporosis, respectively [28]. We describe the clinical course and investigation including CT attenuation of a patient with RT-associated pelvic insufficiency treated with romosozumab.
Table 1. DXA scans

| Year      | 2013a | 2019b | 2021b |
|-----------|-------|-------|-------|
|           | BMD (g/cm²) | T-score | BMD (g/cm²) | T-score | BMD (g/cm²) | T-score |
| LS        | 1.209 +0.1 | 1.249 +0.4 | 1.276 +0.7 |
| LFN       | 0.838 −1.4 | 0.653 −2.8 | 0.670 −2.6 |
| LTH       | 0.960 −0.4 | 0.770 −1.9 | 0.792 −1.7 |
| RFN       | 0.749 −2.1 | 0.622 −3.0 | 0.631 −2.9 |
| RTH       | 0.886 −1.0 | 0.741 −2.1 | 0.765 −1.9 |
| L33%R     | N/A     | 0.814 −0.7 | 0.789 −1.0 |
| R         | N/A     | N/A     | N/A     |

2013: 3 years before RT; 2019: 2 years after RT, just before romosozumab; 2021: after romosozumab × 12 months and alendronate × 12 months.
Abbreviations: LS, L1-L4 spine; LFN, left femoral neck; LTH, left total hip; RFN, right femoral neck; RTH, right total hip; L33%R, Left 33% Radius.
aGE Lunar iDXA (outside facility).

Written consent was obtained from the patient to publish this report.

A 60-year-old female with history of endometrial adenocarcinoma was referred to the endocrinology clinic after suffering pelvic insufficiency fracture. She was diagnosed with stage IIIC1 mixed endometrioid and serous adenocarcinoma at age 57 for which she underwent total abdominal hysterectomy, 6 cycles of carboplatin/paclitaxel, and pelvic RT (4500 Gy in 25 fractions). Two years after completing treatment she developed right groin and low back pain associated with difficulty walking and without inciting event. MRI of the lumbar spine with and without contrast showed possible metastatic disease in the right sacral ala, S1-S4 vertebral bodies, left L5 pedicle, left sacral ala, and left iliac bones for which she underwent image guided bone biopsy of the right sacrum which was negative for carcinoma. CT of the pelvis demonstrated a right superior pubic ramus fracture and bilateral sacral ala fractures.

Laboratory evaluation showed serum calcium 10.0 mg/dL (reference range, 8.6-10.5), 25-hydroxy vitamin D 41.5 ng/mL (30.0-100.0), PTH 35.6 pg/mL (14.0-72.0), procollagen type 1 amino terminal propeptide (P1NP) 82 mcg/L (20-108), C-telopeptide (CTX) 362 pg/mL (postmenopausal reference range not provided; reference range for ages 40-49, 40-465). Serum protein electrophoresis and light chain assay did not show a monoclonal protein. 24-hour urinary calcium excretion was 117.8 mg/24 hours. Celiac screening with tissue transglutaminase IgG and IgA antibodies were negative.

Dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) T-scores (site) were +0.4 (L1-L4 spine), −2.8 (left femoral neck), −1.9 (left total hip), −3.0 (right femoral neck), −2.1 (right total hip), and −0.7 (left 33% radius) (Table 1). Presence of degenerative changes and scoliosis falsely elevated BMD measurement of the spine.

Four months after onset of right groin and low back pain she started romosozumab 210 mg subcutaneously monthly, completed a full course of 12 doses, followed by oral alendronate. She reported improvement in pain 6 months after starting romosozumab and resolution of pain at 10 months of therapy. CTX and P1NP at 3 months were 247 pg/mL and 178 mcg/L, respectively; at 8 months: 256 pg/mL and 84 mcg/L, respectively, and at 11 months: 258 pg/mL and 62 mcg/L, respectively (Fig. 1). L1 and L5 vertebral body CT scan attenuations before RT, at 4 months after RT, and at 13 months after RT show a decrease in CT attenuation at both L1 and L5 with greater magnitude of decrease seen at L5. CT scan attenuations after initiation of romosozumab at 10 months and 16 months show an increase in CT attenuation at both L1 and L5 with near return of L1 CT attenuation to baseline prior to RT (Table 2) (Fig. 2).

Two years after initiation of treatment with romosozumab followed by alendronate, the patient’s pain remains resolved and she reports no further fracture. BMD percent change from baseline prior to initiation of romosozumab to follow-up (after 1 year of romosozumab followed and 1 year of alendronate) DXA scans are: +2.2% (L1-L4 spine), +2.9% (left total hip), +3.2% (right total hip) (Table 1).
Table 2. CT scan attenuations over time

| CT attenuation (HU) | 5/2017 | 12/2017 | 8/2018 | 6/2020 | 12/2020 |
|---------------------|--------|---------|--------|--------|---------|
| L1                  | 150    | 121     | 116    | 145    | 147     |
| L5                  | 139    | 35      | 39     | 57     | 65      |

HU, Hounsfield Units.

Discussion

This case illustrates the use of CT measurements to follow bone changes associated with RT and osteoporosis pharmacologic therapy. CT attenuation change at L1 was −29 HU (−19.3%). L1 has been promoted as the bone site in published literature [27], but it is unclear what is the relative effect on lower to upper lumbar vertebrae after RT focused on the pelvis. Here, remarkably, a greater reduction is observed at L5, showing absolute change −104 HU (−74.8%) after receiving pelvic RT. The greater magnitude of effect on L5 compared with L1 could be explained by differential radiation exposures based on proximity to the pelvic radiation field. Further, there are no reports of CT attenuation changes after romosozumab. Here, CT attenuation changes at L1 were +31 HU (+26.7%) and L5 +26 HU (+66.7%) after initiation of romosozumab. Absolute increases in HU are comparable, as expected from systemic therapy. In comparing CT attenuations before RT and after treatment with romosozumab changes at L5, −74 HU (−53%) were greater in magnitude than at L1, −3 HU (−2%). This may be explained by the differential effect of RT to L5 followed by equal effect across bone sites by osteoporosis pharmacologic therapy. In addition, there may be a lasting effect of RT on L5 to a greater degree than at L1. CT attenuation was restored to baseline at L1 and improved but remained below baseline at L5 after romosozumab therapy. A limitation of this case relates to the use of different CT scanners over time: Phillips Gemini GXL 16 for 5/2017, 12/2017, and 8/2018 and Siemens Biograph20 CT for 6/2020 and 12/2020 scans. Use of dissimilar scan types may potentially introduce bias in measurement.

CT attenuation was measured as described by Pickhardt et al. (Fig. 3) [27]. CT tube voltage shows an inverse relationship with CT attenuation, thus when dealing with varying tube voltage caution is warranted and adjustments must be made [29]. Additionally, intravenous (IV) contrast also affects CT attenuation measurement and must be corrected for when comparing CT attenuation [30]. CT tube voltage prior to initiation of romosozumab was performed at 120 kV and after initiation of romosozumab at 100 kV. To convert CT attenuation to standard tube voltage of 120 kV, attenuations at 100 kV scans were multiplied by 0.88 as a linear function previously demonstrated [30]. All CT scans and HU measurements were done with IV contrast, therefore, were corrected for. To correct for IV contrast, the measured HU were subtracted by 11 [30]. BMD assessment at the spine was falsely elevated by scoliosis and abnormal bone geometry. DXA scan was repeated at our site in 2019 and despite the added imprecision in comparing across machines, there were large interval decreases in BMD T-scores at the left femoral neck from −1.4 to −2.8 and left total hip −0.4 to −1.9 (comparable changes at the right hip), but not at the L1-L4 spine, +0.1 to +0.4 (Table 1). Progression of degenerative changes at the spine may have accounted for this as well as the greater impact of RT based on proximity to site of bone measurement. Unexpectedly, the patient showed only modest changes in BMD by DXA scan 2 years after treatment with romosozumab and alendronate.

Bone turnover marker data shows an increase in bone formation marker, P1NP (Quest Diagnostics Nichols Institute, Chantilly, VA), of +117% at 4 months after initiation of romosozumab, followed by return to baseline; and a decrease in bone resorption marker, C-telopeptide (Quest Diagnostics Nichols Institute, Chantilly, VA), −31.8% at 4 months that sustained throughout the 12-month treatment course of romosozumab. The rise in P1NP of our patient after 4 months

CT Attenuation

![CT Attenuation Graph](image)

Figure 2. CT attenuation at L1 and L5. Lumbar CT attenuations were measured at L1 and L5 vertebral bodies at baseline prior to initiation of RT and after treatment with romosozumab.
of treatment was greater than the average percentage increase of P1NP of 37.9% at 3 months from McClung et al [31]. Additionally, the fall in CTX of our patient after 4 months of treatment was greater than the average percentage reduction of CTX of 7.4% at 3 months.

Prior to romosozumab, no anabolic agents were available for treatment of osteoporosis in patients who have received RT crossing bone, given the contraindications of using of PTH receptor agonist agents based on data showing increased risk of osteosarcoma in a rat model receiving teriparatide or abaloparatide [32]. When administered once daily, teriparatide stimulates bone formation on trabecular and cortical bone surfaces via preferential stimulation of osteoblasts over osteoclasts, with increases in bone formation and resorption markers [24]. Romosozumab inhibits sclerostin, an osteocyte-secreted protein that reduces bone formation by binding to low-density lipoprotein (LDL) receptor-related proteins 5/6 (LRP5/6) and antagonizing Wnt signaling [33]. Inhibition of the Wnt signaling pathway leads to inhibition of osteoblast proliferation and function, resulting in decreased bone formation. Inhibition of sclerostin with anti-sclerostin antibodies leads to activation of the Wnt signaling pathway which has been demonstrated to increase BMD and bone formation while decreasing bone resorption in postmenopausal women with low bone mass [31]. In the phase 2 clinical trial of romosozumab, bone formation markers (P1NP) had a transitory increase for 1 month after initial dose of romosozumab, with return and eventual fall to below baseline between months 2 through 9, while bone resorption markers (CTX) were decreased at month 12 [31]. In contrast, teriparatide and abaloparatide show increases in bone resorption markers (CTX) [34, 35]. While romosozumab is contraindicated in patients who have had a myocardial infarction or stroke within the previous year, a personal history of RT crossing the bone is not a contraindication [26]. With the availability of romosozumab, treatment options are potentially expanded for this population. Our patient was followed in the gynecological oncology clinic for clinical examination and underwent serial CT imaging every 6 months with no evidence of cancer recurrence. This case suggests the potential to investigate the effects of RT on CT attenuation of bone, evaluation of CT-based predictors of fragility/insufficiency fracture, and monitoring response to this pharmacologic agent.

**Conclusion**

In this patient who received pelvic RT for gynecological malignancy, longitudinal measurements of CT attenuation of the lumbar vertebrae showed greater decreases at L5 compared to L1, while romosozumab treatment led to comparable increases at both sites. The pattern of change restored CT attenuation to baseline at L1 and toward but not to baseline at L5.

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**Data Availability**

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

**References**

1. Williams HJ, Davies AM. The effect of X-rays on bone: a pictorial review. *Eur Radiol*. 2006;16(3):619-633.
