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Radiation-Induced Bone Toxicity

Catherine Okoukoni[1] · Michael Farris[1] · Ryan T. Hughes[1] · Emory R. McTyre[1] · Corbin A. Helis[1] · Michael T. Munley[1] · Jeffrey S. Willey[1]

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Abstract
Purpose of Review Normal bone is commonly irradiated during radiation therapy (RT). The true impact of focal radiation on bone tissue remains unclear. The goal of this paper is to present the current understanding of radiation effects on the bone as it pertains to clinically observed radiation side effects.
Recent Findings An increased risk of local fracture has been associated with RT-induced bone loss in the pelvis, vertebrae, and ribs. This bone loss appears to occur early after and/or during treatment, which suggests that reactive remodeling of the bone via osteoclast activity is a primary contributor to bone loss and fractures.
Summary Several reports have quantified the structural and histological changes observed after bone irradiation. These include changes in bone density and cortical thickness, as well as alterations in both the number and activity of the cells responsible for bone turnover that arise from hematopoietic and mesenchymal lineages: namely, osteoclasts and osteoblasts. All of these changes likely play an important role in the increased risk of fracture reported with RT. However, more research is needed to fully understand the mechanisms of bone damage and its relationship to modifiable factors such as beam energy, dose, photon or charged particle radiation, linear energy transfer (LET), fractionation, and field size.

Keywords Bone · Fracture · Rib · Pelvis · Vertebral compression fractures

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✉ Jeffrey S. Willey
jwilley@wakehealth.edu

Catherine Okoukoni
cokoukon@wakehealth.edu

Michael Farris
mfarris@wakehealth.edu

Ryan T. Hughes
ryhughes@wakehealth.edu

Emory R. McTyre
emctrye@wakehealth.edu

Corbin A. Helis
chelis@wakehealth.edu

Michael T. Munley
mmunley@wakehealth.edu

[1] Department of Radiation Oncology and Comprehensive Cancer Center, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

Introduction

The skeletal tissue has previously been described as a relatively radiation-resistant tissue [1, 2], and the bone is frequently included in radiation portals either deliberately for the treatment of bone lesions or incidentally when treating nearby tumors. The true impact of focal radiation therapy (RT) on normal bone tissue is difficult to determine. Many clinical studies are confounded by other known detrimental factors such as chemotherapy use [3–11], steroid use [6, 10, 12–16], reduced mobility [5, 14, 15, 17], and even direct tumor infiltration of the bone [18–20].

Toxicity studies suggest a relatively low α/β ratio of 1.8–2.8 Gy for the bone, implying that the bone is a relatively slow or late responding tissue with the capacity for sublethal DNA damage repair [1]. Acute reactive changes, however, including decreased osteoblast numbers, diminished collagen production,

and increased osteoclast activity, have been observed within days of RT exposure [1, 21–25]. Clinically, an increased risk of local fracture has been associated with RT to the pelvis, vertebrae, and ribs in cancer patients. Acute cortical bone loss has been reported in the ribcage within 4 months of thoracic stereotactic body radiation therapy (SBRT) [26, 27]. These findings clearly illustrate that the bone is actually an acute responding tissue. The effects of RT on early responding skeletal locations will be the focus of this review.

Cellular Response

The multipotent mesenchymal and hematopoietic stem cells (MSCs and HSCs) which share similar niches within the bone marrow serve as progenitors for cells that lead to bone formation and resorption [28]. Depletion of one population of these osteoprogenitor cells can disrupt the other [29, 30] in various ways, such as altered cell signaling or damaged vascularity within the marrow [29, 30]. In regard to bone turnover, osteoclasts are derived from hematopoietic lineage precursors [28], and the osteoblast/osteocyte is derived from mesenchymal origin [31]. Recent studies examining the effects of irradiation on the bone have largely focused on the osteogenic potential and colony-forming ability of MSCs post-RT [29, 32]. Reduced numbers of osteoblasts have been identified within irradiated bones [1, 24, 28, 33] with reactive oxygen species-mediated DNA damage [34] and subsequent apoptosis as a likely mechanism for cell death [33, 35, 36]. An increase in adiposity within the irradiated volume [37] could indicate a preferential shift of MSCs toward adipocytes at the expense of osteoblasts [29, 34]. Direct RT-induced osteoblast damage impairs matrix production and lowers bone mineral density (BMD) which increases bone fragility [1, 22, 38–41]. The prolonged and/or transient reduction in bone formation via effects on MSCs and osteoblasts can serve to reduce new bone formation and compromise the microstructure and mechanical properties of the bone [42].

The osteoclast is derived from HSC lineage precursors and serves to resorb the bone. The damaging effects by radiation on hematopoietic cells are well-documented historically. The lethality of total body high-dose irradiation was initially described in animals as early as the 1930s where fatal hematopoietic collapse was observed following irradiation [43]. Later, studies of those affected by the Japanese atomic bombs also showed that hematopoietic injury was the primary cause of death [44]. Multiple investigators have reported reduced osteoclast number and activity post-exposure [23, 28, 45]. The reduced turnover resulting from lowered bone formation and resorption could embrittle the bone [46]. However, similar to other stressors such as crack formation or mechanical deformation, radiation can also initiate acute bone remodeling via early reactive osteoclast activation [23, 37, 45, 47–49, 50••, 51]; this early, transient increase can occur prior to the observed reduction in osteoclast numbers. Disproportional activation promotes excessive resorption, lowers bone mass, and diminishes bone quality and strength [24, 52, 53]. The cause for this early increased activity is unclear. Material properties of the organic components of the bone can likewise be altered and can contribute to the embrittlement of the bone [41, 54, 55]. Substantial bone loss occurring as an early response due to elevated osteoclast activity, coupled with prolonged periods of reduced turnover and subsequent embrittlement of the bone [46], could contribute to the etiology of radiation-induced insufficiency fractures, as are detailed below in multiple skeletal locations.

Radiation-Induced Rib Fracture

Thoracic RT has been associated with osteitis, osteonecrosis, and/or fracture of both the ribs and the vertebrae [56]. These osseous changes are a source of concern, particularly for lung and breast cancer patients. Chest wall pain and rib fracture have been described after conventionally fractionated breast radiotherapy [1, 3, 57, 58]. Since the advent of breast-conserving therapies, the role of RT in the management of early-stage breast cancer has steadily increased [59]. In a review of over 1600 patients treated for early-stage breast cancer between 1968 and 1985, Pierce et al. identified rib fracture in 1.8% of the patients, occurring at a median duration of 12 months since completion of therapy [60]. Upon stratification by beam energy, patients treated with 4-MV photons were significantly more likely to develop rib fractures than those treated with 6–8-MV photons. Analyses of more modern cohorts receiving whole-breast irradiation with various fractionation schedules have reported rates of radiation-induced rib fracture approximating 0.2–1.5% [58, 61, 62].

Though severe osseous rib complications after breast RT are rare, osteoradionecrosis has been reported. Nicholls et al. described a case of a 43-year-old female who underwent conventionally fractionated adjuvant RT for a stage I breast cancer and subsequently developed ipsilateral chest wall pain 1 year after treatment [63]. Follow-up imaging revealed healing fractures of the second through the sixth right anterior ribs with fatty marrow replacement on magnetic resonance imaging (MRI) and increased uptake on bone scan. The patient received treatment for osteoradionecrosis with pentoxifylline, vitamin E, and hyperbaric oxygen. Over the course of 2.5 years, her pain gradually subsided, but a persistent nonunion of two rib fractures with sclerosis was observed.

Normal rib tissue is also unavoidably included in radiation portals during treatment of lung cancer. SBRT, which is a form of RT utilizing focused high doses of radiation per fraction, is increasingly being utilized as a primary therapeutic modality

for patients with early-stage lung cancer. The risk of rib fracture is particularly concerning when treating peripheral lung tumors near the ribs. Earlier studies reporting rib toxicity after SBRT for stage I non-small-cell lung cancer (NSCLC) included a German series which reported rib fractures in 3 of 68 patients (4.4%) [64] and another Swedish series reporting 13 rib fractures in 7 of 33 patients (21.2%) [65]. The rate of rib fractures that occur in the first year post-SBRT ranges from 1.6–41% [66–69, 70•, 71, 72]. Thus, fractures can occur as an early response.

Following these initial reports, there have been several studies attempting to quantify the risk of rib fracture with dosimetric data [70•, 73, 74]. In 2010, Dunlap et al. [74] reported dosimetric results for 60 patients treated for NSCLC with SBRT. Their results indicated that limiting the volume of the chest wall receiving 30 Gy (V_{30}) to less than 30 cm^3 minimized the risk of chest wall pain and rib fracture. These two toxicities were not evaluated individually, however, so it is difficult to determine if this constraint is directly applicable to rib fracture alone [74]. Similarly, a 2012 review of chest wall toxicity (including skin toxicity, chest wall pain, and symptomatic rib fracture) after SBRT found that limiting the V_{30} to < 30 cm^3 and/or V_{60} to < 3 cm^3 results in toxicity rates of less than 10% [75]. A risk-adapted strategy using variable fractionation (54 Gy in 3 fractions or 50–60 Gy in 5 fractions) to maintain $V_{30} < 30$ cm^3 resulted in an overall rib fracture rate of 6.9% [70•]. In 2011, Andolino et al. reviewed the dosimetric data for 347 NSCLC patients treated with SBRT and found that limiting the max dose to the chest wall and ribs to less than 50 Gy and limiting the volume receiving 40 Gy to less than 5 cm^3 also minimized rib toxicity, but this study also did not specifically evaluate dose constraints for rib fracture alone [73]. In 2015, however, Aoki et al. evaluated the incidence of rib fracture in 41 patients treated for lung cancer with SBRT and found that a maximum rib dose > 54 Gy resulted in significantly more rib fractures, as did the treatment delivered at a higher dose per fraction [70•].

Risk factors for chest wall toxicity after SBRT have been reported, but few studies evaluate predictive factors specifically for rib fracture. Throughout the literature, chest wall toxicity has generally encompassed skin and subcutaneous tissue changes, chest wall pain, and rib fracture (either asymptomatic or symptomatic). Patient-related factors such as gender, age, race, tobacco use, hypertension, and peripheral vascular disease have not been associated with risk of such chest wall toxicity; the impact of obesity and diabetes remains controversial [75, 76]. Total planning target volume (PTV) volume and its distance from the chest wall were not associated with chest wall toxicity after correction for dosimetric factors such as V_{30Gy} [75, 77]. While the etiology remains unclear, chest wall pain syndrome after hypofractionated RT has been associated with rib cortical thinning on CT imaging and elevated uptake on nuclear medicine bone scans, which can also contribute to fracture. Okoukoni et al. recently identified significant longitudinal bone loss in the ribs of patients treated with SBRT for peripheral lung lesions by only 3 months after the initiation of treatment at all sites that absorbed ≥ 10 Gy and the highest degree of cortical thinning occurring at sites absorbing ≥ 20 Gy [27]. Of the 28 patients examined, 2 experienced rib fractures during the 15 month follow-up period at the site of significant cortical thinning. Thus, early and late longitudinal cortical thinnings could serve as a predictive measure for chest wall pain and/or fracture.

RT-induced rib damage remains a concern for patients undergoing thoracic irradiation for cancers in close proximity to the chest wall. Further investigation into the effects of SBRT on rib cortical thickness and bone mineral density would allow better quantification of the relationship between RT dose and the risk for significant changes in bone structure that could lead to rib fracture.

Vertebral Compression Fractures

Vertebral compression fractures (VCFs) are the most common osteoporotic fracture [78]. Although the majority of cases are asymptomatic, approximately one third of cases can lead to significant pain, reduced mobility, and decreased quality of life [79, 80]. RT has been associated with an increased risk of VCF in cancer patients [81–83, 84•, 85–87]. While VCFs are possible after conventional RT, the rates of new VCF or progression increase significantly with high-dose-per-fraction radiation regimens such as spine SBRT. In some series, SBRT-associated VCF incidence has been reported as high as 39% [88], with the majority of reports indicating a VCF rate of 10–20% and most fractures occurring within 3–4 months of treatment [81]. Furthermore, the development of one vertebral fracture is associated with an increased risk of developing additional vertebral and non-vertebral fractures, especially in the period immediately following the initial fracture [79].

BMD and cortical thickness (Ct.Th) losses have also been shown to predispose a VCF to progressive collapse, resulting in symptoms [10, 19, 89, 90]. Several reports have quantified structural degradation in the bone after radiation to the vertebra [90–92] in the acute setting. Vertebral bodies receiving as little as 5 Gy had significant BMD loss (>20%) within 4 months of treatment [84•]. Furthermore, BMD reduction persisted at the subsequent 9 month follow-up.

The implication of the effects of RT on bone strength is perhaps most relevant in patients treated with RT prior to reaching full bone maturity [1]. Significant decreases in the vertical and axial growths of vertebral bodies have been reported in pediatric patients treated with extensive abdominal radiation fields for neuroblastoma [93]. A strong relationship between growth impairment and RT dose in pediatric patients is

demonstrated with doses greater than 15 Gy [56, 94, 95]. Pediatric cancer survivors are at an increased risk of developing degenerative bone pathologies, including vertebral fractures, earlier [96].

The pathophysiology of post-RT VCF is not well understood. Several studies have examined the effects of large fractional doses of RT on vertebral bodies (VB). Two post-mortem case studies, for example, reported significant necrosis and fibrosis in patients exposed to SBRT for cancer metastasis to the VB [84•]. Further quantitative studies are needed to better understand the development and evolution of post-RT VCF.

Pelvic and Femoral Insufficiency Fractures

Bone structural failures resulting from load-bearing forces are often manifested through pelvic or proximal femoral insufficiency fractures (IF) [97, 98]. These areas serve as the primary attachment sites for major muscle groups governing gait and posture. Force distribution is complex and changes with posture and activity [98].

When sitting or standing, the pubic symphysis is under constant tension and the posterior complex is compressed as it moves caudally [99]. With walking, however, the distribution of forces changes dramatically, placing significant transverse stress in the sacrum, particularly in S1 and S2 [100]. Sacral insufficiency fractures are commonly seen in these regions of high transverse stress [101]. Furthermore, fracture at any one site further alters the distribution of load stress and makes subsequent fractures at other locations more likely [102–105].

RT is a known risk factor for IF in both the pelvis and femoral heads [57, 103, 106–110]. Fractures of the femoral heads, pubic rami, and symphysis, as well as acetabular failures and avascular necrosis, have all been reported after RT as early as 1926. The incidence of pelvic IF varies considerably across studies, ranging from 1.7–89% [57, 92, 102, 103, 106–110]. Two prospective studies examining fracture incidence following RT with MRI reported 2-year pelvic IF incidence rates of 36.9 and 89% [107, 110]. The use of two-dimensional RT techniques which expose more normal bone to radiation may have influenced the rates reported in those studies. These data also included hairline fractures, which often remain asymptomatic [103, 106, 107]. The incidence of symptomatic fractures is much lower, in the range of 1.7–6.8%, indicating that a large number of asymptomatic pelvic IF remain undiagnosed [57, 102, 103, 106–109, 111].

The time course of fracture varies across studies. An early retrospective Japanese study assessed pelvic insufficiency fracture (PIF) in 80 women treated for uterine cancer with RT and reported a PIF rate of 34% in the radiation field within 6–48 months of treatment [106]. The prospective MR study examining the evolution of radiation-induced IF in females treated with RT for advanced cervical carcinoma reported fractures at 3–12 months after RT, with multiple fractures developing within 24 months [107, 110]. In the early 1990s, Bliss et al. reported painful fracture in five patients with cervical cancer as early as 1 month post-RT [112]. In the early 2000s, a larger retrospective study by Schmeler et al. examining 300 cervical cancer patients treated with RT reported a median time to imaging detection of pelvic IF as 14 months (range 2–63) post-RT [113]. Another retrospective study examining 134 prostate cancer patients treated with RT reported a median time to fracture of 20 months post-RT (range, 5–52 months) [114]. A more recent case study examining symptomatic PIF in female patients treated for rectal cancer had a time to fracture on the order of 3 years after RT [115]. This discrepancy between studies may be due in part to changes in RT technique and improved imaging sensitivity over time [111].

The largest retrospective study examining fracture incidence in women over the age of 65 with pelvic malignancies found that those who received pelvic RT were more likely to have a pelvic fracture than those who did not, with an overall hazard ratio of 1.65 [116]. The cumulative 5-year fracture rate for women with anal cancer was 14.0 vs 7.5%; for women with cervical cancer, it was 8.2 vs 5.9%; and for women with rectal cancer, it was 11.2 vs 8.7%. Interestingly, this study did not report an increase in osteoporotic fractures in non-irradiated sites. While RT increased the relative risk of fracture for all disease sites, patients with anal cancer had the highest increase in post-RT fracture rates. The substantial increase in fracture risk associated with anal cancer may reflect the radiation therapy technique used to treat this disease. Inguinal lymph nodes are commonly involved and must be included in the treatment field. The femoral neck and head may absorb higher RT doses in the treatment of anal cancer patients due to the close proximity of inguinal lymph nodes. The increased fracture risk in anal cancer patients suggests that the decline in pelvic bone strength is dose-dependent. However, differences in chemotherapy regimens between anal, rectal, and cervical patients may have also contributed to the increased relative fracture risk.

One major shortcoming of the available literature on pelvic insufficiency fractures is the paucity of outcome data from patients treated using modern conformal techniques. Historically, pelvic malignancies have been treated using evenly weighted parallel anterior and posterior fields, as well as opposed lateral beams. Although simple, easily reproducible, and capable of providing excellent tumor coverage, this comes at a high cost of substantial pelvis and femoral bone exposures [26].

Intensity-modulated radiation therapy (IMRT) is a more conformal method of RT delivery that can sometimes allow for better sparing of normal tissues when compared to static three-dimensional RT fields. The introduction and widespread

use of IMRT reduced the volume of pelvic bones receiving the highest radiation doses, but increased the bone volume receiving lower doses. The clinical significance of such low-dose RT has not been well-established. Interestingly, when comparing IMRT and three-dimensional RT delivery, as well as different dose fractionation schemes, there was no significant impact on the incidence or time to fractures. A retrospective study including 650 gynecological cancer survivors treated with RT observed that the mean absorbed external beam dose above 52.5 Gy to the pubic bone was associated with the occurrence of reportable pain and pelvic insufficiency fractures [117, 118].

There remains a paucity of data on the mechanisms of PIFs in RT patients. Several studies have quantified bone loss in the femoral neck and spine [8, 14, 19, 90–92, 119, 120]. Hui et al. conducted a longitudinal assessment of spine and femoral neck (FN) volumetric BMDs (vBMDs) in 40 gynecologic cancer patients treated with chemotherapy and radiation [8]. Significant bone loss was observed in the spine and femur within the first year of chemotherapy, radiation, and a combination of radiation and chemotherapy. The percent reduction in vBMD (± SE) at the L1–L2 spine and the FN was 11% (± 5.68) and 15.8% (± 2.56) in the radiation group and 21.0% (± 7.03) and 3.6% (± 3.3.7) in the combined therapy group. However, structural changes at the sites with the highest incidence of post-radiation fractures, namely, the sacrum, pubis, iliac crest, and femoral head, have not been assessed. Okoukoni et al. retrospectively examined trabecular and cortical bone losses in anal cancer patients treated using IMRT techniques [26]. They observed rapid dose-dependent bone loss in the proximal femur within 1–2 months of RT completion. These findings suggested that rapid bone resorption after RT exposure, similar to the bone loss described in preclinical studies, may predispose pelvic RT patients to fracture.

Due to the complex structure of the pelvis and proximal femur, the study of pelvic insufficiency fractures is difficult. Insufficiency fractures after pelvic radiation exposure are further complicated by potential difference in the local effects of RT on the bone. In the proximal femur, dose-dependent cortical thinning was observed in discrete locations. Structural features, such as cortical volume, minimal cross-sectional area, and trabecular BMD, were independently related to increased hip fracture risk in a number of studies [121]. However, the effects of regional changes, such as those observed in pelvic RT patients, on fracture risk are unclear. Because therapies vary in their impact on various components of the structure, it is important to understand the effects of RT on the bones of the pelvis to mitigate RT-induced bone damage.

Conclusion

Bone health is a vital component of overall health and quality of life. As a dynamic tissue that is continually changing over the lifetime of an organism, it is especially sensitive to environmental insults, such as RT or systemic agents. The cells responsible for bone formation and resorption have been identified as especially radiosensitive, reacting within days of RT exposure. Pre-clinical studies have shown a significant correlation between RT exposure and the early upregulation of bone-reabsorbing cells, as well as a decline in bone quantity and quality [23, 24]. Further research is needed to more fully understand the pathophysiology of the RT toxicities at various anatomic sites. However, there is ample evidence that RT is detrimental to bone health and that the bone is a radiation-sensitive, acute responding tissue.

Compliance with Ethical Standards

Conflict of Interest Catherine Okoukoni, Michael Farris, Ryan T. Hughes, Emory R. McTyre, Corbin A. Helis, Michael T. Munley, and Jeffrey S. Willey declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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