RESEARCH

Radiotherapy-related insufficiency fractures and bone mineral density: what is the connection?

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Abstract

Background: Radiotherapy-related insufficiency fractures (RRIFs) represent a common, burdensome consequence of pelvic radiotherapy. Their underlying mechanisms remain unclear, and data on the effect of osteoporosis are contradictory, with limited studies assessing bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA).
Methods: BMD by DXA (Hologic) scan and fracture risk following pelvic RRIF were retrospectively assessed in 39 patients (median age 68 years) at a tertiary cancer centre. Patient characteristics and treatment history are presented narratively; correlations were explored using univariate regression analyses.
Results: Additional cancer treatments included chemotherapy ($n = 31$), surgery ($n = 20$) and brachytherapy ($n = 19$). Median interval between initiation of radiotherapy and RRIF was 11 (7.5–20.8) and that between RRIF and DXA 3 was (1–6) months. Three patients had normal BMD, 16 had osteopenia and 16 osteoporosis, following World Health Organization classification. Four patients were <40 years at the time of DXA (all *Z*-scores > –2). Median 10-year risk for hip and major osteoporotic fracture was 3.1% (1.5–5.7) and 11.5% (7.1–13.8), respectively. Only 33.3% of patients had high fracture risk (hip fracture >4% and/or major osteoporotic >20%), and 31% fell above the intervention threshold per National Osteoporosis Guidelines Group (NOGG) guidance (2017). Higher BMD was predicted by lower pelvic radiotherapy dose (only in L3 and L4), concomitant chemotherapy and higher body mass index.
Conclusion: At the time of RRIF, most patients did not have osteoporosis, some had normal BMD and overall had low fracture risk. Whilst low BMD is a probable risk factor, it is unlikely to be the main mechanism underlying RRIFs, and further studies are required to understand the predictive value of BMD.

Key Words

- radiotherapy-related insufficiency fractures
- insufficiency fracture
- radiotherapy
- bone mineral density
- clinical predictors
- late effects of cancer therapy

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Introduction

With a constantly rising number of people receiving pelvic radiotherapy for various malignancies, including gynaecological, urological and anorectal, and living long beyond their cancer diagnosis and treatment (1, 2), the importance of cancer treatment late effects and survivorship is being increasingly recognised. Bone toxicity, and more specifically radiotherapy-related insufficiency fractures (RRIFs), are well-established late effects of pelvic radiotherapy, with significant implications for these patients' mobility, morbidity and quality of life (3, 4, 5). In contrast to traumatic fractures, insufficiency fractures develop with minimal effort on bones with reduced elastic resistance (6). The median time to diagnosis of RRIFs is 8–39 months (7), at a time point when new pelvic symptoms are often concerning for relapse of cancer. The occurrence of RRIFs in the absence of trauma further adds to this stress of patients.

RRIFs have been widely reported since the early twentieth century. Although their incidence varies due to differences in imaging and radiological reporting standards (3), a recent meta-analysis of almost 4000 patients with gynaecological malignancies treated with pelvic radiotherapy found an overall rate of 14% (8). Despite their frequency, the literature is notable for almost exclusively studies of retrospective design, with a sparsity of bone density data and conventional fracture risk assessment. In the only prospective study that assessed the incidence of pelvic RRIFs and changes in bone mineral density (BMD) after radiotherapy for gynaecological malignancies, Salcedo *et al.* found an increase in the proportion of patients with osteopenia/osteoporosis at 3 months, 1 year and 2 years following radiotherapy, compared to baseline. Sixteen patients (7.8%) sustained a pelvic RRIF; though they did not comment on the changes in their BMD over time, RRIFs were found to be associated with baseline osteoporosis (9).

Osteoporosis and low BMD prior or following radiotherapy have been suggested as risk factors for RRIFs (9, 10, 11). However, a definite correlation has not been confirmed, with some studies showing no differences in BMD between the irradiated and non-irradiated bone structures (12, 13, 14). The exact mechanisms and pathophysiology of RRIFs remain unclear. Understanding whether BMD measured by dual-energy x-ray absorptiometry (DXA) scan is related to future fractures and identifying patients at increased risk is crucial, as it could allow timely introduction of preventive measures.

This study aimed to assess the areal hip and lumbar spine BMD (aBMD) by DXA and conventional fracture risk at the time of an RRIF.

Methods

We performed a retrospective analysis of all patients who were referred for a DXA (Hologic) scan due to the diagnosis of RRIF between 2012 and 2021 at a tertiary referral cancer centre (Manchester, UK). Patient characteristics, including demographic information and conventional fracture risk factors, as well as underlying cancer diagnosis, staging and treatment history were captured from the patients' electronic medical records. Images and reports of all the scans, including DXA, as well as magnetic resonance imaging (MRI) or computed tomography (CT) (depending on the diagnostic modality used for the detection of RRIFs) were also reviewed. The study was assessed and approved by the Christie Hospital Quality Improvement and Clinical Audit committee (local project code: 2739). All data were pseudo-anonymised.

Patients that had a DXA scan beyond 12 months following the RRIF ($n = 9$) were excluded from our analysis, to ensure that the timing of the bone density assessment was close to the fracture. Three patients who had a DXA scan at the time of the fracture using a different DXA scanner were also excluded, to retain homogeneity in the scanning process. One patient who had treated disease at the site of RRIF (S2 body) was excluded, as the fracture could also be considered as pathological, though there was no disease apparent in this location at the time of reported fracture.

All patients had a conventional fracture risk assessment (FRAX® Fracture Risk Assessment Tool, University of Sheffield) as part of their DXA scan, which is routinely included in the scan report. In addition, based on the clinical information available on patients' electronic notes, FRAX scores were recalculated to ensure that these matched the reported; in a few cases of discrepancy, the most accurate scores were accepted.

Data were summarised using descriptive statistics. Non-normally distributed continuous variables were presented as median (interquartile range), normally distributed continuous variables were presented as mean ± standard deviation (S.D., and categorical variables as percentages. Histograms and Shapiro–Wilk test were used to assess the normal distribution of continuous variables. Student's *t*-test was used to compare normally distributed continuous data, Mann–Whitney *U*-test to compare non-normally distributed independent data

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and Wilcoxon signed ranks test for paired data (BMD L3 and L4). Univariate linear regression analyses were used to assess whether radiotherapy doses and body mass index (BMI) were associated with BMD, based on data from previous studies (8, 9, 15). A *P*-value of <0.05 was considered as significant. Statistical analyses were performed using SPSS (IBM software, version 25).

Results

Thirty-nine patients (37 females) were included, with a median age of 68 (55–74) years. Their demographic and baseline characteristics are summarised in Table 1.

All participants received pelvic radiotherapy for the underlying malignancy, while almost half (48.7%) additionally received brachytherapy, all of which had underlying gynaecological malignancies (cervical, endometrial and vaginal carcinoma). The number of patients treated with each therapeutic modality and the details on the radiotherapy doses are summarised in Table 2. The median interval between the initiation of pelvic radiotherapy and the scan that revealed the RRIF (MRI or CT) was 11 (7.5–20.8) months.

Twenty-one patients (53.8%) had no additional conventional risk factors for fracture beyond those associated with the underlying malignancy and cancer treatments. Of those, six patients were ex-smokers and five were prescribed oestrogen containing hormone-replacement therapy. The frequency of risk factors is described in Fig. 1. Sixteen patients were documented to be receiving calcium and vitamin D replacement. Only one patient was on bisphosphonate therapy at the time of the DXA scan, specifically on alendronic acid. However, this was started only 4 months prior to the scan, following right hip replacement for an undisplaced fracture and left hip replacement for complete left hip insufficiency fracture (index event); this participant's DXA scan revealed a bone density *T*-score in the lumbar spine of –2.8 and a 10-year risk of 8.8 for hip fracture and 28 for major osteoporotic fracture, falling above the intervention threshold.

Table 1 Demographic information and underlying oncological diagnosis.

All participants, *n* = 39			
Demographics		Underlying oncological diagnosis, *n* (%)	
Female sex, *n* (%)	37 (95%)	Cervical	13 (33.3%)
Ethnicity, white, *n* (%)	38 (97.4%)	Endometrial	8 (20.5%)
Age (years, median (IQR))	68 (55–74)	Anal	7 (18%)
Weight (kg, median (IQR))	66.3 (57–73.3)	Vaginal	6 (15.4%)
Height (cm, median (IQR))	160 (158–164)	Vulval	2 (5.1%)
BMI (kg/m^2, median (IQR))	25.5 (22.4–28.7)	Other[a]	3 (7.7%)

[a]Other: ovarian cancer, sarcoma of thigh and lymphoma.
BMI, body mass index; IQR, interquartile range.

Table 2 Number of patients that underwent different cancer treatment modalities and median radiotherapy doses.

Cancer therapies	**Number of patients** (*n* (%))	**Radiotherapy dose** (median (IQR)**, cGy)**
Pelvic radiotherapy	39 (100%)	4487.5 (4000–4525)
Pelvic radiotherapy boost	9 (23.1%)	2000 (1740–2000)
Brachytherapy	19 (48.7%)	1500 (1237.5–1900)
Chemotherapy	31 (79.5%)	
Surgery	20 (51.3%)	

Vitamin D status was available in 27 patients; of these, 16 patients had sufficient vitamin D levels (>50 nmol/L, as per local guidance from Greater Manchester Medicines Management Group), 7 had insufficiency (30-50 nmol/L) and 4 were vitamin D deficient (<30 nmol/L). Phosphate levels were available in 35 patients, and these were normal (0.8–1.5 mmol/L) in the majority of them ($n = 34$), with only one having a level below the range.

Diagnosis of RRIF was made due to symptoms of back or hip pain in 30 patients. In eight patients the scan that revealed the fracture was performed as part of routine surveillance post-radiotherapy, though two of them were symptomatic at the time of the scans. One patient had symptoms of lower limb paraesthesia as the indication for the MRI scan, which did not reveal any spinal abnormalities but a left sacral ala RRIF.

In most of the cases, the initial RRIFs were limited to the sacral alae (bilateral $n = 10$, right $n = 12$ and left $n = 7$). In addition to the sacral fractures, there were also RRIFs involving the pubic rami and/or symphyses ($n = 5$), left ischium ($n = 1$) and acetabular roof ($n = 1$). Only a few RRIFs did not affect the sacrum and were isolated to the pubic rami ($n = 2$) or pubic symphyses ($n = 1$) and femoral neck ($n = 2$). Follow-up scans were reviewed to look for the progression of RRIFs (median follow-up 22.5 months (11.3–32.5)). In five patients, the initial RRIF had healed by the time of the last scan without additional RRIFs, while four patients sustained further RRIFs, all of which had healed by the last follow-up. The fractures improved or remained stable but did not fully heal in 13 patients, and nine patients sustained further RRIFs without evidence of healing by the last scan. In eight patients, a follow-up scan was not available on our electronic system.

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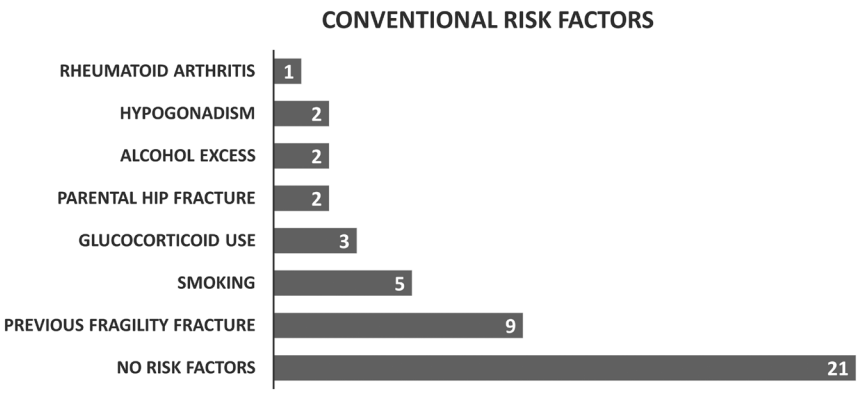

Figure 1
Number of patients with conventional fracture risk factors, which are included in the FRAX® Fracture Risk Assessment Tool. Hypogonadism refers to patients with premature menopause (<45 years) who did not receive oestrogen containing hormone-replacement therapy; alcohol excess is defined by 3 or more units of alcohol daily; glucocorticoid use includes current exposure to oral glucocorticoids or previous exposure for more than 3 months at a dose of prednisolone of 5 mg daily or more; current (but not previous) tobacco smoking is also a risk factor.

The median interval between fracture noted on imaging and DXA scan was 3 (1–6) months. Trabecular bone score analysis of the lumbar spine, an indicator of bone quality which has been shown to be related to bone microarchitecture and fracture risk, was performed in 27 patients. The results of the DXA scans are summarised in Table 3. In four patients, *T*-scores were not reported due to age <40 years at the time of the scan; all *Z*-scores in these patients were above –2. Of the remaining patients, 3 had normal BMD, with all *T*-scores above –1; 16 patients (41%) had osteopenia defined as at least one *T*-score between –1 and –2.5, and 16 patients had osteoporosis (as per World Health Organization definition, lowest *T*-score of two sites ≤ –2.5). Twenty-three patients (59%) had all *Z*-scores above –1, with only one patient having at least one *Z*-score below –2. Vertebral morphometry assessment was normal in 31 patients; underlying vertebral fractures were found in four patients, two had degenerative changes, and one patient had scoliosis.

In the group of 21 patients with no additional conventional risk factors for fracture, median BMD of lumbar spine, femoral neck and total hip was 0.9 (0.78–1), 0.69 (0.59–77) and 0.88 (0.76–0.95), respectively, compared to the group of patients with at least one risk factor that had median BMD lumbar spine, femoral neck and total hip of 0.81 (0.7–0.9), 0.62 (0.54–0.69) and 0.8 (0.7–0.84), respectively. Independent samples Mann–Whitney *U*-test did not reveal any statistically significant difference in BMD between the groups; however, the sample size is limited.

Only 13 of the participants (33.3%) had a high conventional fracture risk (10-year risk for hip fracture above 4% and/or for major osteoporotic fracture above 20%); in four patients, FRAX was not calculated due to age. When accounting for the RRIF as a previous fracture in the risk calculation, 17 patients (43.6%) had a high fracture risk, as defined above, but 18 were still not considered at high risk of fracture. Additionally, the NOGG intervention thresholds were assessed, based on FRAX probability, with only 12 patients (31%) falling above the intervention threshold; this increased to 43.6% if RRIF was included as a previous fragility fracture.

Our study included only patients with RRIFs; hence, identification of factors predicting these was not possible. However, the correlation of variables, previously identified as risk factors for RRIFs, with BMD was assessed.

Table 3 Summary of the results of DXA scans and FRAX calculation.

Variable	Median	Minimum	Maximum	Q25	Q75
T-score total LS	–1.8	–3.9	3.6	–3	–0.7
T-score femoral neck	–2	–4.1	1.6	–2.6	–1.4
T-score total hip	–1.2	–3.1	1.9	–1.9	–0.3
Z-score total LS	–0.5	–2.9	5.3	–1.6	1.3
Z-score femoral neck	–0.5	–2.8	2.1	–0.9	0.1
Z-score total hip	–0.1	–2.5	2.3	–0.5	0.7
BMD total LS	0.84	0.62	1.44	0.72	0.97
BMD femoral neck	0.67	0.39	1.07	0.57	0.74
BMD total hip	0.82	0.56	1.18	0.74	0.93
TBS score	1.21	0.974	1.454	1.15	1.27
TBS *T*-score	–2.8	–5.5	–0.2	–3.5	–2
TBS *Z*-score	–0.3	–2.6	1.7	–1.1	–0.1
FRAX hip	3.1	0.0	62	1.5	5.7
FRAX MO	11.5	2.6	66	7.1	13.8
FRAX hip (including RRIF)	4.5	0	70	2.8	7.3
FRAX MO (including RRIF)	17.5	4.9	73	12	21.8
FRAX hip (adjusted for TBS)	3.3	0	60	1.7	7
FRAX MO (adjusted for TBS)	12	2.2	68	7.9	17

BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry scan; FRAX hip, 10-year risk of hip fracture; FRAX MO, 10-year risk of major osteoporotic fracture; LS, lumbar spine; RRIF, radiotherapy-related insufficiency fracture; TBS, trabecular bone score.

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BMI was found to be positively correlated with BMD using simple linear regression analyses (BMD total lumbar spine: $P=0.00$, coefficient = 0.017; BMD femur neck: $P=0.022$, coefficient = 0.009; BMD total hip: $P=0.04$, coefficient = 0.008). In addition, the radiotherapy dose delivered to the pelvis was found to be negatively correlated with BMD L3 and L4, suggesting that every extra 10 Gy of radiotherapy dose were associated with 0.122 and 0.132 decrease in BMD, respectively ($P=0.02$ for L3 and $P=0.003$ for L4). Accordingly, a negative trend was found for BMD total lumbar spine, which did not reach statistical significance ($P=0.06$). Similar correlations were not observed for BMD of total hip and femoral neck. Moreover, no correlation was found with the brachytherapy or boost radiotherapy dose. To assess if potentially higher dose of radiotherapy delivered to L4 compared to L3 affected the bone density, we compared BMD L3 and L4, which did not reveal any significant difference ($P=0.344$). To assess if chemotherapy had any additional impact on the BMD, Mann–Whitney *U*-tests were used to compare the BMD between those treated with chemotherapy and those who were not. BMD of femoral neck, lumbar spine and total hip was lower among participants who did not receive chemotherapy (*P*-values 0.001, 0.041 and 0.019, respectively; median BMD values of different groups are described in Table 4).

Discussion

Our study showed that most patients wh sustained an RRIF did not have osteoporosis at the time of the fracture, with some patients having a normal BMD. While osteoporosis has been identified as a risk factor for RRIFs in numerous studies (8, 9, 11, 16, 17), our findings suggest that low BMD is not always present in patients at risk. The exact association remains unclear, as there are contradictory data regarding the differences in BMD post-radiotherapy between patients treated with radiotherapy and healthy controls. In a retrospective study comparing the aBMD of postmenopausal women with cervical cancer treated with concurrent chemoradiotherapy and matched controls with history of hysterectomy for leiomyomas, BMD of L4, total hip (left) and greater trochanter was significantly lower in the chemoradiotherapy-treated group compared to controls (18). On the other hand, Chen *et al.*, in a study comparing the aBMD (L2 to L5) between 40 postmenopausal women with cervical cancer treated with radiotherapy and 40 matched controls, found no significant difference in the BMD between the two groups, with L5 being included in the irradiation field, and no significant change 1–7 years after the therapy in the patient group (13). Similarly, BMD remained unchanged between the irradiated and non-irradiated hips of men treated with para-aortic radiotherapy for seminoma; while comparing to age-matched control data, the treated participants had a significant increase in mean bone density (14). In addition, a study that compared the aBMD of the irradiated site for sarcoma bone and the unirradiated side found an increase in mean bone density for all irradiated sites (12).

In our study, conventional fracture risk, as assessed with the routinely used FRAX score for fragility fractures, was below the accepted treatment thresholds in the majority of patients with RRIFs, who would hence not qualify for antiresorptive therapies on this basis. The applicability of this observation in clinical practice though is complex, as the effectiveness of antiresorptive therapy in RRIFs remains to be proven, with currently no available clinical studies looking specifically at the use of antiresorptive treatments in pelvic RRIFs (19).

Preclinical studies have also assessed the effect of bisphosphonates in murine models; zolendronate administered subcutaneously pre- and post hindlimb irradiation (20) and risedronate administered subcutaneously immediately post whole-body irradiation (21) prevented the radiation-induced bone loss compared to control; however this improvement did not lead to a biomechanical advantage in the mice treated with zolendronate (20). In contrast, alendronate treatment in mice irradiated with a small animal radiation research platform, which allows focal radiotherapy, better emulating the clinical setting, failed to maintain the bone integrity. However, this could be related to oral administration, which can be less accurate in murine models compared to intravenous (22).

Table 4 Comparison of BMD between patients receiving and not receiving chemotherapy and *P*-values from Mann–Whitney *U* -tests.

	Median (IQR) **BMD in non-chemotherapy group**	**Median** (IQR) **BMD in chemotherapy group**	***P*-value**
BMD total LS	0.7 (0.67–0.9)	0.87 (0.8–1)	0.041
BMD femoral neck	0.56 (0.53–0.59)	0.69 (0.6–0.77)	0.001
BMD total hip	0.74 (0.7–0.79)	0.85 (0.76–0.94)	0.019

BMD, bone mineral density, IQR, interquartile range; LS, lumbar spine.

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In addition, in patients with previous fractures, bisphosphonate treatment aims to prevent further fractures (23). Previous studies have presented the locations of RRIFs, with sacrum being the most common (8, 9); however, the frequency of recurrence has rarely been assessed, with one study reporting 28.1% of single-site fracture progressing to multiple (4). As described above, in our study, a majority of RRIFs were also limited to the sacrum, with 13 patients sustaining further RRIFs in the following scans.

In keeping with previous studies that have identified radiotherapy dose as a risk factor for RRIFs (15), higher pelvic radiotherapy dose was associated with lower BMD of L3 and L4. BMI was also positively correlated with BMD, which is in agreement with the low BMI identified as a risk factor in previous studies. Given though that obesity is a known risk factor for endometrial cancer (24), one of the most common gynaecological malignancies, and the deleterious effects it has been shown to have on the bone (25, 26), further studies are needed to investigate the effect of obesity on RRIFs.

An unexpected finding was the lower BMD in the group that did not receive chemotherapy. This might result from the younger age ($P=0.028$, median age 66 (53–73) and 73.5 (70–81.8) in chemotherapy and non-chemotherapy group, respectively) and hence better functional status of patients considered for chemotherapy. Interestingly, a recent retrospective study also found that patients who received chemotherapy developed fractures less frequently in L4 and L5 compared to the non-chemotherapy group (27), though there was no statistically significant difference in the sacral, iliac and pubic fractures. However, various other studies have reported the opposite (28, 29, 30, 31, 32), with most studies not yielding any significant difference in the incidence of RRIFs in the groups receiving additional chemotherapy, compared to radiotherapy alone (4, 7, 10, 11, 16, 17, 33, 34). This highlights the need for further prospective clinical and mechanistic studies to evaluate the interplay of chemotherapy and radiotherapy in the development of RRIFs.

Our study has several limitations. First, as this study was retrospective, data were collected from patients' electronic records and some clinical information may be incomplete. In addition, a control group was not included, and hence the prevalence of RRIFs or potential risk factors could not be assessed. Our study had a limited population; therefore, multivariate analyses regarding the factors affecting BMD could not be conducted, and the results are exploratory and would need further validation in larger studies. On the other hand, this study is the first to assess the BMD and conventional fracture risk of patients at the time of RRIFs, with a thorough clinical characterisation and assessment of cancer treatments given. Importantly, this exploratory study clearly demonstrates that RRIFs occur in patients with normal BMD and low conventional fracture risk.

Overall, the mechanism of RRIFs is likely different to osteoporotic fragility fractures and, whilst low BMD is a probable risk factor, further studies are required to understand the pathophysiology of RRIFs, identify predictive markers, determine how fracture risk should be best assessed and managed in these patients at baseline and explore the value of RRIFs in predicting future RRIFs/other osteoporotic fractures.

Declaration of interest

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