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Overview

Bone Health and Pelvic Radiotherapy

C.E. Higham *†, S. Faithfull ‡

* Department of Endocrinology, The Christie Hospital NHS Foundation Trust, Manchester, UK
† Centre for Endocrinology and Diabetes, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
‡ School of Health Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK

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Abstract

Survivors who have received pelvic radiotherapy make up many of the long-term cancer population, with therapies for gynaecological, bowel, bladder and prostate malignancies. Individuals who receive radiotherapy to the pelvis as part of their cancer treatment are at risk of insufficiency fractures. Symptoms of insufficiency fractures include pelvic and back pain and immobility, which can affect substantially quality of life. This constellation of symptoms can occur within 2 months of radiotherapy up to 63 months post-treatment, with a median incidence of 6–20 months. As a condition it is under reported and evidence is poor as to the contributing risk factors, causation and best management to improve the patient's bone health and mobility. As radiotherapy advances, chronic symptoms, such as insufficiency fractures, as a consequence of treatment need to be better understood and reviewed. This overview explores the current evidence for the effect of radiotherapy on bone health and insufficiency fractures and identifies what we know and where gaps in our knowledge lie. The overview concludes with the need to take seriously complaints of pelvic pain from patients after pelvic radiotherapy and to investigate and manage these symptoms more effectively. There is a clear need for definitive research in this field to provide the evidence-based guidance much needed in practice.

Key words: Bone health; insufficiency fractures; pelvic pain; pelvic radiotherapy

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search strategy has been defined.

Introduction

About 30 000 patients per year in the UK are treated with pelvic radiotherapy, predominantly for cancers of the bowel, bladder, prostate, cervix and endometrium, with up to 150 000–300 000 people treated annually across the developed world [1,2]. Many of these individuals now survive their cancer and experience symptoms as a consequence of their treatment.

Bone toxicity as a late effect of cancer treatment has a rising profile [3]. Symptoms such as pain as a result of fracture can have significant morbidity and mortality for individuals. The consequences of fracture in the general population in terms of excess mortality, morbidity and financial burden are well described [4–6]. The chronic effects and impact of poor bone health and osteoporosis after cancer treatments such as endocrine therapies and chemotherapy have also been well described [7,8]. The effect of radiotherapy on the bone is less well known. Insufficiency fractures as a result of radiotherapy are causing problems for cancer survivors and pathways of care need to be developed. There are potentially simple measures that can be put in place to mitigate the risk and reduce the insufficiency fracture symptoms exercised by survivors.

This overview focuses on the bone toxicity caused by pelvic radiotherapy, the current evidence with regards to pathophysiology, clinical consequences and potential management are considered.

Author for correspondence: C.E. Higham, Department of Endocrinology, The Christie Hospital NHS Foundation Trust, Manchester M20 4BX, UK.
E-mail address: Claire.Higham@christie.nhs.uk (C.E. Higham).

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How Does Radiotherapy Affect Bone?

A full understanding of the pathophysiology underlying the effects of radiation on bone is still elusive, despite being described since the early twentieth century. There is also a need to consider the wider cancer therapies, age, menopausal status and genetic risk factors that all affect fracture risk [9].

There are a number of components that coordinate to maintain healthy bone; osteocytes and osteoblasts forming bone, osteoclasts resorbing bone, the non-mineral bone matrix and inorganic mineral salts. In addition, healthy bone requires an adequate vascular and nerve supply. All components are potentially affected by radiation and contribute to bone health.

Cell culture studies show that irradiation reduces osteoblast number, arrests osteoblast cell cycle progression and increases susceptibility to apoptosis, implying that reduced bone formation is a major contributor to radiotherapy-induced bone damage [10–14]. Data for osteoclasts are less clear. A reduction in osteoclast number and activity has been described [15–17], whereas others have shown an increase, suggesting that increased bone resorption may also play a role [18–20].

Animal studies have provided useful models of potential clinical impact. Murine models of total body irradiation in skeletally mature mice are consistent in their finding of early increased osteoclastic activity, but how closely total body irradiation models relate to localised radiotherapy is unclear [21]. A small animal radiation research platform model has been developed [22] to replicate focal clinical irradiation, mimicking typical dose constraints used for whole pelvic radiotherapy in humans [23].

Irradiation of rat tibia using this technique induced osteoblast apoptosis, loss of small trabeculae, a 50% reduction in trabecular bone stiffness and severely impaired mechanical strength at 28 days. In contrast to the murine total body irradiation model, there was a reduction in osteoclast number and activity and the authors concluded that reduced bone formation rather than excess resorption best explained the bone features, which is the closest mimic to pelvic radiotherapy in humans currently available [23].

There is also evidence of radiation causing damage to bone matrix [24–26], increasing marrow adiposity [27] and a degradation in the vascular supply to bone, all probably contributing to the direct effects of radiotherapy on bone function and strength. These animal models help our clinical understanding of biological mechanisms and provide potential targets for clinical intervention.

Is Bone Mineral Density Reduced after Pelvic Radiotherapy?

Despite an increasing body of basic research investigating the effects of irradiation on bone structure and function, there are limited data with regards to bone mineral density (BMD) and bone health in the radiotherapy patient group.

Pelvic radiotherapy significantly reduced BMD by 11.1% in the only prospective, longitudinal study (compared with a 15.2% reduction with chemotherapy and 24% in radiotherapy/chemotherapy combined). This bone loss occurred quickly, with changes being seen as early as 6 months after radiotherapy [28].

BMD (measured at L4 and proximal femur) in women who had received chemoradiation for cervical cancer was significantly lower than that seen in matched controls [29]. By contrast, Chen *et al.* [30] did not show any difference in L5 BMD in 40 post-menopausal women 1–7 years after pelvic radiotherapy compared with matched controls. BMD was also unchanged in men undergoing orchidectomy and para-aortic radiotherapy for stage I seminoma of the testis [31].

Finally, Uezono *et al.* [32] retrospectively analysed computed tomography images of patients undergoing pelvic radiotherapy for cervical cancer and determined a BMD measurement from selected areas within L5 and the sacrum. This value predicted the likelihood of insufficiency fracture, but the technique has not been widely validated.

BMD may change as a result of many factors and in multimodality therapy and long-term management it is often hard to isolate the causative factor for bone loss. Therefore it is important to review not only summary scores but the detail of BMD.

How do the Radiotherapy Effects on Bone Manifest?

There are a number of ways in which radiotherapy-induced bone damage can manifest, not only in signs but patient symptoms. The most common presentation is a pelvic insufficiency fracture (PIF), which occurs as a result of normal stress in underlying abnormal bone. This can result in complaints of patient pelvic and back pain and mobility reductions.

Insufficiency fractures are a relatively common occurrence in elderly post-menopausal females with osteoporosis [33], but osteoporosis is not a prerequisite, insufficiency fractures are also seen in those with underlying abnormal bone as a result of excess glucocorticoids, osteomalacia, Paget's disease, primary hyperparathyroidism, rheumatoid arthritis and osteogenesis imperfecta [34–38].

Fragility fractures of the femoral neck and vertebrae (if these are within the radiotherapy field) are also a less frequent but recognised complication, as is avascular necrosis, particularly of the femoral head as a result of compromised vascular supply in 0.5–1% [39–41].

How Common are Pelvic Insufficiency Fractures after Radiotherapy?

At least 23 articles have been published since 1992 describing the incidence of PIFs after radiotherapy for the treatment of uterine, cervical [32,39–52], anal, rectal [53–57] and prostate carcinoma [58] (Table 1).