Radiation osteitis: MR imaging after irradiation of soft tissue sarcomas

Poster No.: C-1077
Congress: ECR 2011
Type: Educational Exhibit
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Keywords: Radiation therapy / Oncology, MR, Musculoskeletal bone, Bones
DOI: 10.1594/ecr2011/C-1077

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Learning objectives

To analyze the MR imaging findings that define radiation osteitis after radiotherapy (RT) for extremity soft tissue sarcomas (STS).

The patterns of differentiation from other radiation induced bone changes, bone metastasis and tumoral extension will also be reviewed.
Background

SOFT TISSUE SARCOMAS

STS are an uncommon histopathologically diverse group of malignant tumors that arise from connective tissue. They can occur anywhere in the body but most originate in an extremity (59%), the trunk (19%), retroperitoneum (15%) or the head and neck. They grow in a centrifugal fashion and compress surrounding normal structures, thus presenting most commonly as asymptomatic masses.

Pretreatment radiologic imaging is critical for defining the local extent of the tumor, staging the disease, guiding biopsies, and aiding in diagnosis. Imaging studies are also crucial in monitoring tumor changes after treatment, especially after preoperative chemotherapy or radiation therapy and in detecting recurrences after surgical resection.

Surgery is the main treatment of primary soft-tissue sarcoma. Current surgical therapy generally involves a limb-sparing procedure in which the tumour is removed along with a wide margin of normal surrounding tissue (2 to 5 cm). Amputation is considered only in selected cases, such as certain high-grade lesions involving the foot and ankle or when limb-sparing surgery would leave gross residual disease.

RT may be administered either preoperatively or postoperatively, depending on tumor size and extension. For large tumors, preoperative external irradiation may reduce tumor size, facilitating subsequent limb-sparing surgery. Postoperative external beam radiation is used to increase local control, as an adjuvant to wide local excision. Brachytherapy may be employed in those cases with locally invasive, inadequately resected or recurrent sarcomas. The role of chemotherapy in the treatment of extremity soft-tissue sarcomas continues to be evaluated. Nowadays it is utilized in an attempt to control distant recurrences such as lung metastases.

DEFINITION OF RADIATION OSTEITIS

Radiation osteitis is a delayed skeletal complication of radiation therapy and develops in the long bones as well as pelvis, spine, chest, sacroiliac joints and mandible. In 1926, Ewing defined different types of radiation induced bone changes under the heading "radiation osteitis" when he reviewed the effect of radiation upon bone.

Throughout the years it has been used to describe a wide varied range of potentially reversible delayed radiographic changes such as bone marrow edema, periostitis, bone...
sclerosis and ischemic necrosis \textsuperscript{3,4,5,6,17,18}. Furthermore, recent literature reported that some of these delayed bone changes, seen after treatment of STS in an extremity, might represent an early stage of gelatinous transformation of marrow, which is typically seen in AIDS, starvation, anorexia nervosa, cachexia, alcoholism and other disorders, but further study is needed to elucidate the underlying pathologic process \textsuperscript{2}.

**PATHOPHYSIOLOGY**

RT has numerous adverse effects on bone. The pathophysiology of the changes seen at radiation osteitis are not understood completely, but it seems to involve a radiation-induced inflammatory response in the blood vessels and bone cells that develop into an impairment of osteoblastic function and vascular fibrosis.

Due to direct effect of radiation upon osteoclasts and osteoblasts, their number may drastically reduce, giving rise to a diminished metabolic activity of bone, as measured by alkaline phosphatase levels, matrix weight and calcium uptake \textsuperscript{16}.

RT also causes edema, vascular congestion, and capillary injury to the fine vasculature of the mature bone which in turn leads to the resorption of the bone matrix and weakens bone structure \textsuperscript{3,10,19}.

All these changes are dose dependant and relate to total irradiation dose. Mature bone tolerates doses in the 65 to 70 Gy range, being the threshold for changes in bone 30 Gy with irreversible cell death at 50 Gy. Radiation osteitis may occur at a lower dosage of radiation (40 Gy) \textsuperscript{10}. However, recent literature shows some cases in which no clear correlation between the RT dose and the development of marrow changes was observed in long bones after RT for STS; in fact, the mean RT dose was slightly higher in patients without marrow changes than in those with marrow changes \textsuperscript{2}.

**EPIDEMIOLOGY**

These focal bone abnormalities occur lately after radiation is set, although the time of onset varies widely in the literature. Garner et al. reported a mean onset at 42 months (range, 8-49 months) and Hwang et al. at 9 months (range, 1-36 months) \textsuperscript{1,2}. The long latent period observed in the evolution of these changes may be related to injury in the vascular bed.
The same occurs with the incidence, with a variation between 0.45% - 21.9% of treated patients \(^1\), although Hwang et al. estimated that the incidence of radiation osteitis following patients who undergo radiation therapy for extremity tumors was of 37% \(^2\).

**CLINICAL SYMPTOMS**

Radiation osteitis is asymptomatic and it is usually an accidental discovery \(^1^8\). When symptoms occur, they are most often due to associated complications. Insufficiency fractures, necrosis of bone, ulceration or infection can be extremely painful and difficult to manage. It is important to bear in mind this fact, because when symptoms appear a detailed approach must be taken in order to diagnose complications apart from radiation osteitis that may worsen the prognosis of the patient.
Imaging findings OR Procedure details

We studied cases from the last 7 years at our institution. The presented cases include normal anatomy of long bones, and bone changes related to radiation osteitis aiming to highlight the condition, discuss the expected imaging features and show some of the potential imaging pitfalls.

From March 2004 to December 2010 21 patients (male, 10; female, 11) with diagnosis of extremity STS who underwent radical surgical resection and received high dosis of radiation were reviewed retrospectively to evaluate the frequency and study the appearance of radiation osteitis caused by RT.

3 cases of radiation osteitis were identified (prevalence of 14,2%). Among these patients with radiation osteitis the age range was 65-66 years (mean age, 65,6). 2 patients (66,6%) had a myxoid liposarcoma and 1 patient (33,3%) a high-grade fibrosarcoma. All of them where located in the lower extremity. All patients with radiation osteitis were treated using external beam RT with a mean dose of 55 Gy (range, 45-60 Gy) after surgical resection of the primary STS. Concomitant brachytherapy was used in 1 patient (33,3%). Chemotherapy was used only in 1 patient (33,3%) as neoadjuvant therapy. The median interval from treatment to first follow-up MRI was 10,6 months

DIAGNOSIS WITH MRI

Historically plain radiograph and CT have been widely used in the evaluation of radiation induced bone changes\(^3,4,5,6\). They enable an assessment of the structure and contour of bone within the treatment area and depict soft tissue calcification and the nature and pattern of mineralization. Nevertheless, magnetic resonance imaging (MRI) has nowadays become the preferred imaging modality due to its sensitiveness to changes in bone marrow signal and soft tissue\(^1,2,7,8,10,15\).

In contrast, not only literature describing the appearance of radiation osteitis on MR images is scant, but also alterations of bone marrow signal that occur at MRI after treatment of STS in an extremity have received poor attention in the radiology literature\(^1,2\).

The development and extent (focal or diffuse) of changes in the marrow signal within the region of the tumour bed, the morphology and the relative intensity of signal changes, overall heterogeneity of lesion enhancement (homogeneous or heterogeneous)
on available post gadolinium images and progression or regression of signal changes over time should be analyzed in each MRI examination for each sequence.

Some of the sequences that should be included in MRI examinations if bone changes related to radiation osteitis want to be seen are T1 weighted and either fat saturated, T2 weighted, short tau inversion recovery (STIR) and T1 weighted spectral presaturation with inversion recovery (SPIR) after intravenous injection of gadolinium.

Extremity marrow abnormalities in patients with radiation osteitis are seen as somewhat poorly defined areas of nonspecific signal intensity. Areas of low intensity in T1 weighted sequences (Figs. 1 on page 9 and 2 on page 9) and of high signal in T2 weighted and STIR sequences (Figs. 3 on page 9 and 4 on page 10) in the bone marrow of extremities are related to radiation osteitis. After intravenous administration of gadolinium, in T1 weighted SPIR sequences, slight heterogeneous enhanced of this areas could be seen (Fig. 5 on page 11). The gadolinium enhanced areas seem to be due to fibrotic change.

These signal changes are often focal, do not exist in the first MRI controls (if they are made 3-6 months after RT, or even 1 year after) and in some cases, they increase in size and number at subsequent follow-up imaging. These changes may become more prominent over the succeeding months before they stabilize.

The configuration of most of the changes is unspecific: linear or curvilinear, patchy (diffuse of poorly defined border), nodular (well defined round or oval shape) or a mixture of them (Fig. 6 on page 12).

Bone destruction or associated soft-tissue masses are notably absent in patients with radiation osteitis, a finding that may help differentiate this entity from infection and tumor (Fig. 7 on page 13).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of radiation osteitis includes insufficiency fractures, recurrent malignancy, metastatic bone tumour, radiation-induced sarcoma and infection.
A history of radiation therapy in the area of bone changes, confinement of those changes to the radiation field and stability of the changes at follow up studies suggests a diagnosis of radiation osteitis (Fig. 8 on page 14).

These changes have various non-mass-like configurations and therefore, should not be confused for interval development of osseous metastases. Given that local bone metastases are quite uncommon in STS of the extremities, it is important for radiologists to avoid "overcalling" these marrow changes.\(^2\)

Radiation induced insufficiency fractures (RIIF) often occur in areas of radiation osteitis. In both RIIF and radiation osteitis, areas of high signal intensity on T2 and STIR sequences and low signal intensity on T1 weighted sequences can be seen, but the detection of a fracture line or a vertical array (as a hypointense line, best seen in STIR sequences), the latent period of the changes and the clinical symptoms of the patient may be useful findings for distinguishing between both of them.\(^{10,11,14,19}\) So, STIR sequence should be added if radiation osteitis and associated insufficiency fractures are suspected.\(^{10}\)

Many metastatic bone tumors are round shaped and well enhanced by intravenous gadolinium. Other malignant lesions such as recurrent tumor and radiation induced sarcomas also enhance well with intravenous contrast and are accompanied by soft tissue masses.\(^1\) In contrast, radiation osteitis showed geographic distribution, a faint enhancement mainly in peripheral areas and is not accompanied by soft tissue mass (Fig. 9 on page 15). So, when needed the use of gadolinium contrast enhancement may help to better differentiate radiation osteitis from malignant disease.

**TREATMENT**

As radiation osteitis is asymptomatic no treatment is needed. What are really necessary to treat are related complications when they appear. Insufficiency fractures, necrosis of bone, ulceration or infection may worsen the basal status of the patient and need specific treatment.
Fig. 0: Figure 2

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Fig. 3. Radiation osteitis 3 years after radiotherapy. See how linear-curvilinear low signal intensity radiation osteitis changes, evident in marrow of femoral shaft in coronal T1-weighted images (A) (B), present as high signal intensity areas in STIR sequences (C), (D) (arrows).

Fig. 0: Figure 3

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Fig. 0: Figure 4

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Fig. 4. Radiation osteitis in a 66 year old woman with myxoid liposarcoma 8 months after surgical resection and radiotherapy (same patient as in figure X). On coronal (A), (B), (C) and axial (D), (E) STIR images patchy-nodular central areas of high signal intensity are demonstrated (arrows).
Fig. 0: Figure 5

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Fig. 6: T1-weighted coronal (A), (B) and axial (C) images of 3 different patients shows the heterogeneity of radiation osteitis configuration: (A) patchy, (B) linear-curvedural and (C) nodular (arrows).
Fig. 7. Radiation osteitis in a 66 year old woman with myxoid liposarcoma 8 months after radiotherapy. Radiation osteitis appears as nodular central areas of abnormal low signal intensity in T1-weighted axial images (A) and as high intensity areas in both axial T2-weighted (B) and STIR images. See how no bone destruction nor bone tissue masses that can lead to misdiagnosis of malignancy are present.

Fig. 0: Figure 7

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Fig. 8. Radiation osteitis shows low intensity on T1-weighted image (A), and high intensity both in STIR (B) and T2-weighted images (C). In (D), a faint enhancement is illustrated on gadolinium T1-weighted SPIR images.
Fig. 0: Figure 9

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Fig. 9. Radiation osteitis in a 65 year old man with high-grade fibrosarcoma 3 years after radiotherapy. (A), (B), (C) Axial T1-weighted SPIR images after intravenous administration of gadolinium show slight heterogeneous enhancement (arrows). Interpreted in isolation, this image could result in misdiagnosis of metastasis. However, correlation with T1-weighted (D) and STIR (E) sequences allows confident diagnosis of focal changes due to treatment.
Conclusion

- Although the diagnosis of radiation osteitis is feasible by plain radiograph or CT, MRI can illustrate abnormal bone change distribution and is useful for diagnosing this entity by characteristic intensity patterns on T1-weighted images with and without gadolinium and T2-weighted images and because of that is currently the best imaging method to evaluate radiation induced bone changes.

- Familiarity of the MRI features of radiation osteitis is crucial for its diagnosis and for differentiating from other diagnosis such as tumoral extension or metastasis.

- Although the chronological evolution of changes in marrow after RT and chemotherapy has been extensively studied in the spine and pelvis, information about focal changes at MRI in the long bones of the extremities after RT has received scant attention and needs to be better studied.
Personal Information

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