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ARTICLE

Michael L. Richardson
Gordon C. Zink-Brody
Randall M. Patten
Wui-Jin Koh
Ernest U. Conrad

MR characterization of post-irradiation soft tissue edema

M.L. Richardson, M.D. (✉)
R.M. Patten, M.D.
Department of Radiology SB-05,
University of Washington,
Seattle, WA 98195, USA

G.C. Zink-Brody, M.D.
Department of Diagnostic Radiology,
Kaiser Permanente Medical Center,
Hayward, California, USA

W.-J. Koh, M.D.
Department of Radiation Oncology RC-08,
University of Washington,
Seattle, Washington, USA

E.U. Conrad, M.D.
Department of Orthopedic Surgery RG-28,
University of Washington,
Seattle, Washington, USA

Abstract *Objective.* Radiation therapy is often used to treat bone und soft tissue neoplasms, and commonly results in soft tissue edema in the radiation field. However, the time course, distribution and degree of this edema have not been well characterized. Our study was carried out to better define these features of the edema seen following neutron and photon radiation therapy.
Design and patients. Two hundred and twenty-six patients underwent radiation therapy as part of combined modality management for musculoskeletal sarcomas between 1985 and 1993. Of these, 15 had surgical resection of their neoplasm, had no clinical evidence of recurrent disease, and had adequate MR follow-up that allowed sequential assessment of soft tissue following irradiation. Ten patients received photons with an average dose of 52.8 Gy. Five patients received neutrons with an average dose of 17.3 nGy. Sequential MR follow-up was available in these patients for an average of 22.8 months following radiation therapy. On each of the serial MR imaging studies, subcutaneous fat, muscle, and the intramuscular septa/fascial planes were graded subjectively as to size and signal intensity.
Results. In general, soft tissue signal intensity in the radiation field initially increased over time, peaking at about 6 months for neutron-treated patients and at about 12–18 months for photon-treated patients. Signal intensity then decreased slowly over time. However, at the end of the follow-up period, signal intensity remained elevated for most patients in both groups. Signal intensity in a particular tissue was greater and tended to persist longer on STIR sequences than on T2-weighted sequences. Survival analysis of signal intensity demonstrated much longer edema survival times for neutron-treated patients than for photon-treated patients. Signal intensity increase in the intramuscular septa persisted for much longer than for fat or muscle. A mild increase in size was noted in the subcutaneous fat and intramuscular septa. Muscle, on the other hand, showed a decrease in size following treatment. This was mild for the photon-treated group and more marked for the neutron-treated group.
Conclusions. There is a relatively wide variation in the duration and degree of post-irradiation edema in soft tissues. This edema seems to persist longer in the intramuscular septa than in fat or muscle. Although the duration of follow-up was limited, our study suggests that this edema resolves in roughly half the photon-treated patients within 2–3 years post-treatment and in less than 20% of neutron-treated patients by 3–4 years post-treatment. Muscle atrophy was seen in both photon- and neutron-treated patients, but was more severe in the neutron-treated group.

Key words Magnetic resonance imaging · Radiation therapy · Edema

Introduction

Magnetic resonance imaging is frequently used to monitor patients during treatment for musculoskeletal neoplasms [1, 2]. Patients undergoing therapeutic irradiation often develop increased soft tissue magnetic resonance (MR) signal intensity on T2-weighted (T2W) and short-tau inversion recovery (STIR) sequences [1, 3], which is felt to represent edema. However, the distribution, degree, duration and time course of this edema have not been well characterized. Indeed, it is not known when or even if this edema ever completely subsides.

Materials and methods

We reviewed the records of the 226 oncology patients who underwent radiation therapy for musculoskeletal sarcomas between January 1985 and August 1993. Of those patients with adequate MR follow-up that allowed sequential assessment of soft tissue post-irradiation, 15 had no clinical or radiographic evidence of tumor recurrence at the time of their most recent examination, and formed our study population.

These 15 patients included seven women and eight men with an average age of 49.9 years (range 24–71 years). Ten of the patients received photon radiotherapy, with an average dose of 52.8 Gy (range 20–64.8 Gy). Five patients received neutron radiotherapy, receiving an average of 17.3 neutron Gy (nGy) (range 15–20 nGy). One of the photon-treated patients received intraoperative radiotherapy.

All patients underwent excision of the primary neoplasm (five liposarcomas, four leiomyosarcomas, three synovial sarcomas, one Ewing sarcoma, one low-grade sarcoma, one angiomyosarcoma.). Eleven of these patients also received intraoperative chemotherapy. The average interval between surgery and initiation of radiation therapy was 13 weeks. All subjects were followed with post-irradiation MR and clinical examinations with an average follow-up of 22.8 months (range 8–42 months).

All MR studies were obtained on a 1.5 T clinical imager (Signa, GE Medical Systems, Milwaukee, WI) at our medical center. STIR sequence images were unavailable for one subject, and T2W images were unavailable for another subject. In the other 13 subjects, both STIR and T2W images were available. Fourteen subjects were studied with 55 STIR studies. Fourteen subjects were also studied with 55 standard spin-echo T2W examinations. MR examinations obtained prior to irradiation were available in 11 patients. Scanning parameters such as TR, TE, TI, slice thickness, and imaging matrix were variable because of the retrospective nature of the study and the broad time frame (and the resulting technical changes) encompassed in this study.

The T2W and STIR images of these patients were reviewed independently by three radiologists with expertise in musculoskeletal MRI (M.L.R., G.Z.B., R.M.P.). Each observer graded the signal intensity of three anatomic areas (muscle, intramuscular septa and perimuscular fascia, and subcutaneous fat) on a six-point subjective scale relative to normal tissue (0, no change; 1, mild increase; 2, mild to moderate increase; 3, moderate increase; 4, moderate to marked increase; 5, marked increase). Each anatomic area was also graded on an 11-point subjective scale as to its size, relative to normal tissues (0, no change; +/–1, mild increase or decrease; +/–2, mild to moderate increase or decrease; +/–3, moderate increase or decrease; +/–4, moderate to marked increase or decrease; +/–5, marked increase or decrease).

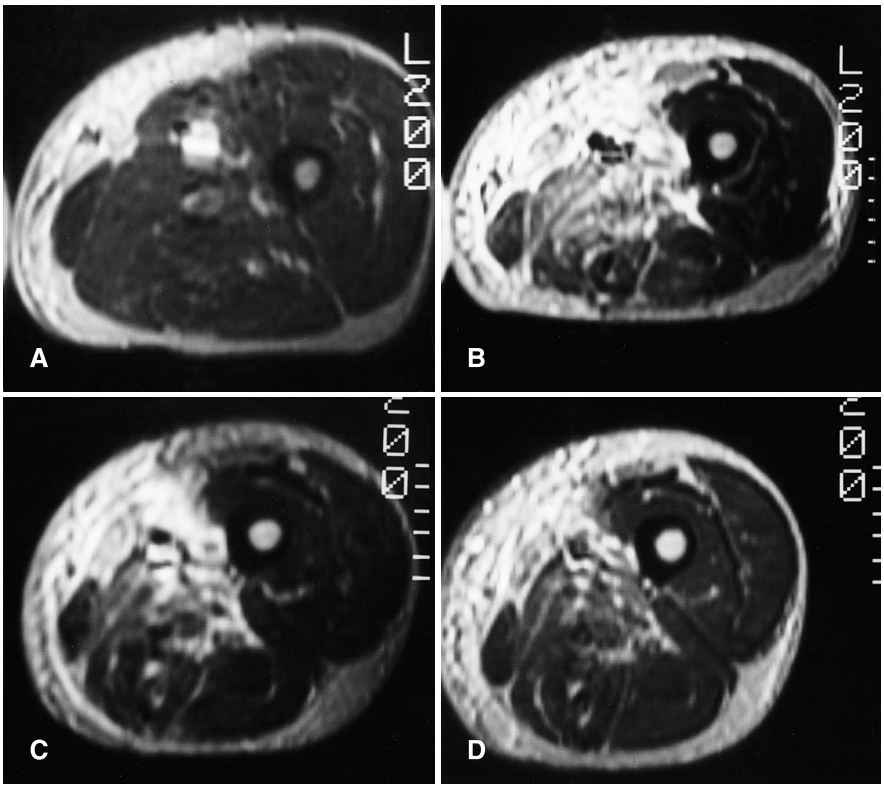

Fig. 1A–D A 61-year-old man treated for a liposarcoma of the left thigh with 15 Gy of fast neutron irradiation. Multiple axial T2-weighted images are shown. **A** Two months prior to irradiation. TR/TE=2000/80 ms. Normal soft tissue signal intensity is noted in all tissues. **B** Six months post-irradiation. TR/TE = 2000/80 ms. Markedly increased signal intensity is noted in a geographic distribution in the medial left thigh in all tissues. Diminished muscle volume is noted in the irradiated area. **C** One year post-irradiation. TR/TE=2000/80 ms. The overall signal intensity has decreased significantly since the previous examination. **D** Two and a half years post-irradiation. TR/TE=2200/70 ms. The muscle signal intensity has returned to normal, but the intramuscular septa and subcutaneous fat continue to demonstrate increased signal intensity

Statistical methods

Statistical analysis was performed using Statview 4.0 (Abacus Concepts, Berkeley, Calif.), Egret (Statistics and Epidemiology Research Corporation, Seattle, Wash.) and the S-Plus programming language (AT&T Bell Laboratories, Warren, N.J.). The lowess (locally weighted regression scatter plot smoothing) procedure [4–6] was used to estimate the empirical local distribution of changes in tissue signal intensity as a function of time following the last radiation treatment. Pointwise 95% confidence limits were then calculated for the smoothed regression lines.

The Kaplan-Meier technique was used to estimate the survival of post-irradiation edema as a function of time following irradiation. For this purpose, a patient was considered to have zero signal intensity if at least two observers graded the tissue as zero and the third observer graded it no higher than grade 1.

Results

Signal intensity

Tissue signal intensity was elevated in general (subjective intensity of 1–2) in all tissues prior to radiotherapy in both the photon- and neutron-treated groups. In general, this signal intensity then increased over time, peaking at about 6 months for neutron-treated patients and at about 12–18 months for photon-treated patients (Figs. 1, 2). Considerable variability was noted in the intensity changes among patients (Fig. 3). Tissue intensity then decreased slowly over time. Even at the end of the follow-up period, signal intensity remained elevated for most patients in both groups (Fig. 2). Signal intensity in a particular tissue was greater on STIR sequences than on T2W sequences.

Edema persisted much longer in patients treated with neutron radiation than in those treated with photons. For example, only 35–55% of photon-treated patients still demonstrated edema within the subcutaneous fat at the end of the follow-up period, compared with over 75% of neutron-treated patients. Increased signal intensity tended to persist longer on the STIR images than on the T2W images. The signal intensity increase in the intramuscular septa persisted for much longer than for fat or muscle.

Size

Following radiotherapy, a mild increase in size was noted in the subcutaneous fat, intramuscular septa and perimuscular fascia (Fig. 4). In the photon-treated group, the thick-

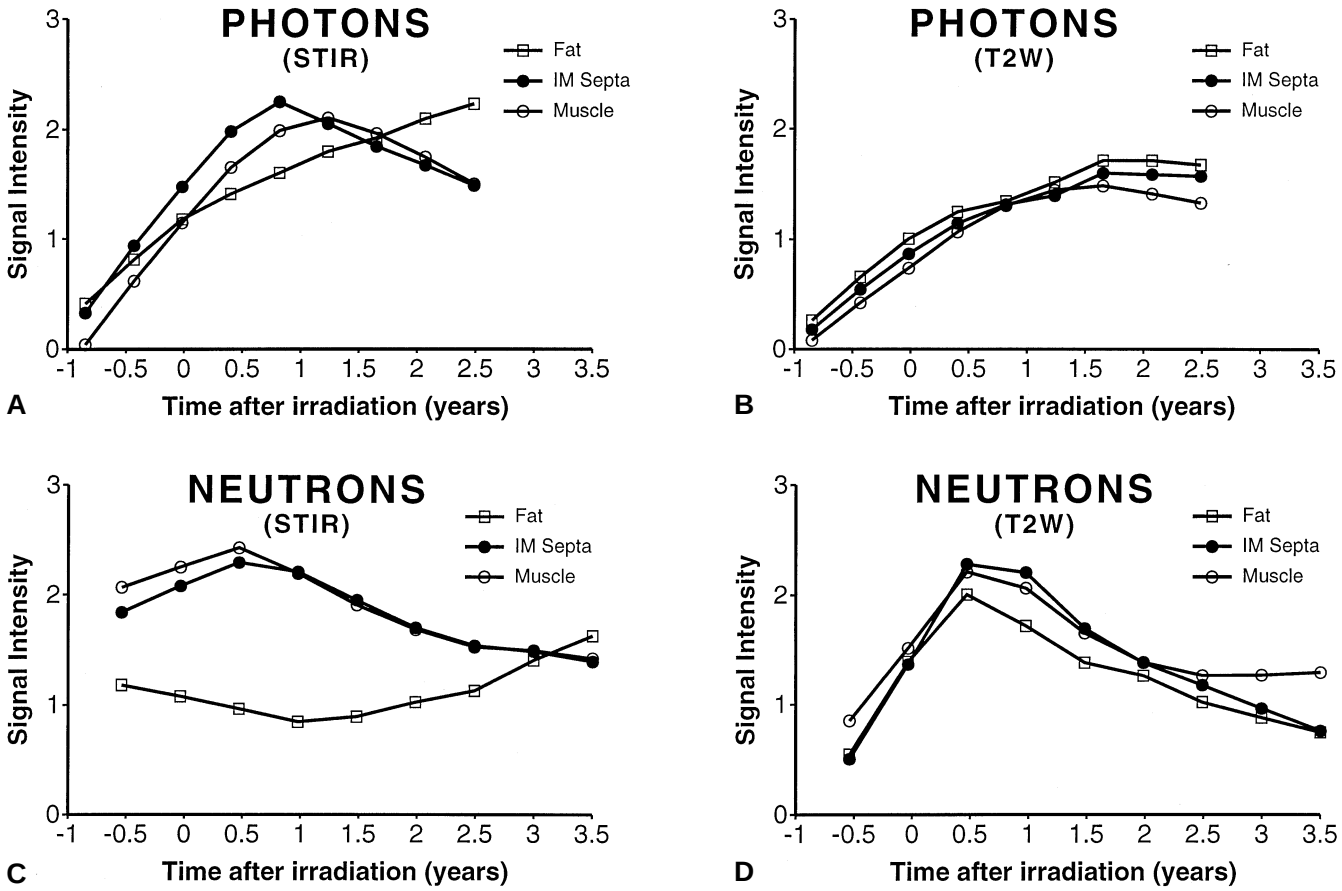

Fig. 2A–D Variation in tissue signal intensity as a function of time after the final radiotherapy treatment. **A** Photon-treated patients imaged with short-tau inversion recovery (STIR) sequence. **B** Photon-treated patients imaged with T2-weighted (T2W) sequence. **C** Neutron-treated patients imaged with STIR sequence. **D** Neutron-treated patients imaged with T2W sequence. *IM* Intramuscular

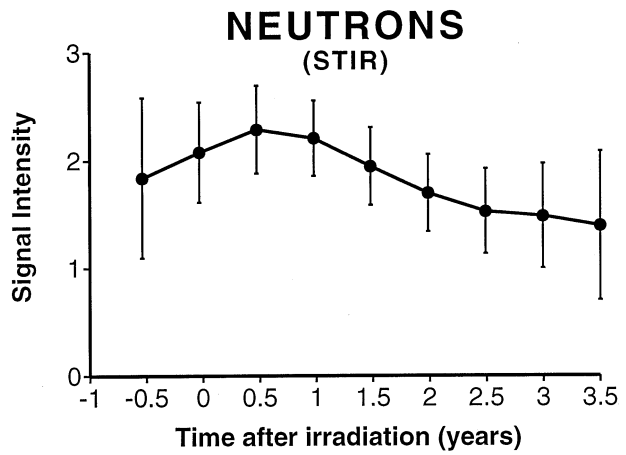

Fig. 3 Variation in signal intensity of intramuscular septa in neutron-treated patients. The error bars show the pointwise 95% confidence limits for the lowess regression line.

ness of the subcutaneous fat continued to increase throughout the follow-up period, whereas the size and thickness of the fascia had already peaked and had begun to decrease. In the neutron-treated group, the mild increase in size of these soft tissues peaked at about 6 months, and gradually decreased throughout the follow-up period.

Muscle, on the other hand, showed a decrease in size following treatment. This was mild for the photon-treated group and more marked for the neutron-treated group. In addition, this effect tended to flatten out in the photon-treated patients at about 18 months. In the neutron-treated groups, muscle size continued to decrease throughout the follow-up period.

Of the tissues studied, intramuscular septa and muscle demonstrated the most dramatic changes over the observation period (Fig. 2). On average, these tissues demonstrated normal signal on preoperative studies; however, on sequential scans after radiotherapy, these areas showed gradually increasing to mildly increased signal on T2W and mild to moderately increased on STIR sequences, peaking between 6 and 12 months.

Discussion

MR imaging is the imaging modality of choice for diagnosis and post-treatment surveillance of musculoskeletal neoplasms. Tumor recurrence typically manifests as an area of high signal intensity on T2W and STIR sequences. Unfortunately, all methods of tumor treatment commonly result in local edema in the tumor bed, making it more difficult to rule out subsequent tumor recurrence. To complicate the picture further, peritumoral edema, tumor necrosis and hemorrhage, and postoperative fibrosis can also cause increased signal intensity. Distinguishing among the many possible causes of increased signal intensity may be difficult or impossible. Prior investigators have used a variety of parameters to deal with this problem, including signal intensity, geometrical and textural patterns, and contrast enhancement of the lesion.

The absolute signal intensity of the tumor bed was reviewed by Vanel et al. [1] in 60 patients who had undergone surgery, radiation or a combined therapy for their primary musculoskeletal tumors. They found that low signal intensity lesions seen on T2W images following treatment were unlikely (1/20=4%) to represent tumor. Similar results have been obtained in the female pelvis [7], the thorax [8, 9], and the nasopharynx [10]. High signal intensity areas, on the other hand, may represent tumor recurrence, radiation fibrosis or seroma, and differentiating these entities may be problematic [1, 2, 11]. Ebner et al. [7], using a 1.5 T system, reported that significant overlap existed between the signal intensities of early radiation fibrosis and recurrent tumor, and only late radiation fibrosis could be reliably distinguished from recurrent gynecologic tumors following pelvic radiation.

Fletcher et al. [3] stated that errors in discriminating radiation changes from recurrent tumor could usually be avoided by noting the geometric, rather than anatomic configuration of the radiation changes. Other investigators relied on analysis of “textural patterns” to help distinguish recurrent tumor from other processes. If the fascicular architecture of muscle on T1-weighted images was preserved, tumor recurrence was felt to be unlikely [2]. The pattern and time course of gadolinium enhancement has been suggested as a further discriminator between recurrent tumor and other entities. In a study by Vanel et al. [11], most non-enhancing masses (16/17=94%) were hygromas and most enhancing masses were recurrent tumor (28/29=96%). However, some cases of post-irradiation reactive lesions also demonstrated enhancement.

While Vanel et al. [1] noted anecdotally that increased signal intensity can be seen from 1 month to 4 years following irradiation, they did not attempt to characterize these changes further . Our average length of follow-up was 22.8 months, and most of our patients still exhibited increased tissue signal intensity at the end of the study. In the jargon of survival analysis, observations for these patients are considered “censored” (meaning truncated). In the presence of censored observations, standard statistical procedures such as *t*-tests, analysis of variance, or least-squares regression are not appropriate for analyzing the rate at which signal intensity returns to normal. Such standard techniques tend to underestimate the mean survival time of post-irradiation edema that would be observed if all patients were completely followed until their findings resolved. The Kaplan-Meier technique controls for the effects of censoring and allows a more accurate estimate of the duration of post-irradiation edema [12].

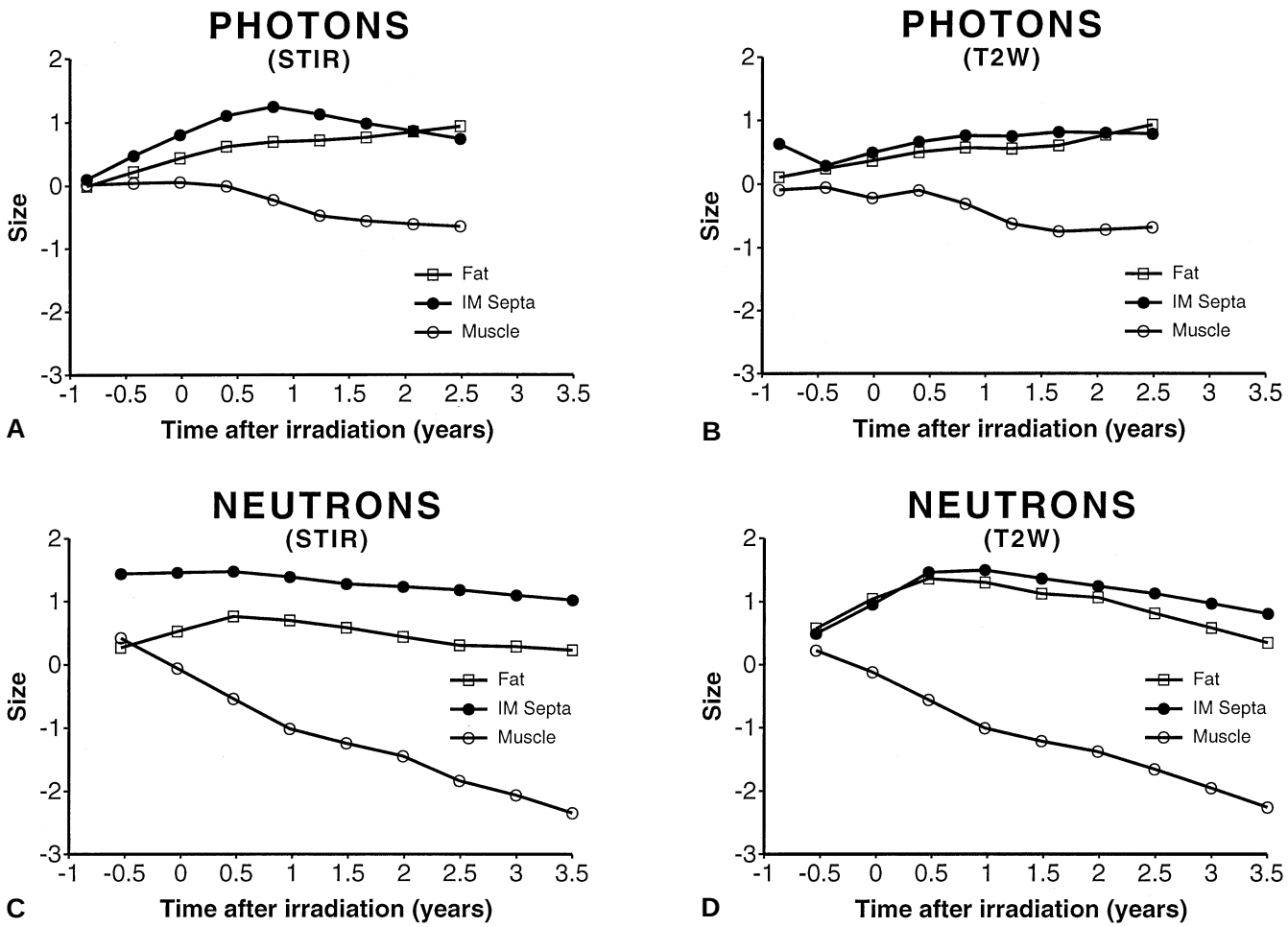

Fig. 4A–D Variation in tissue size as a function of time following the final radiotherapy treatment. **A** Photon-treated patients imaged with STIR sequence. **B** Photon-treated patients imaged with T2W sequence. **C** Neutron-treated patients imaged with STIR sequence. **D** Neutron-treated patients imaged with T2W sequence

Our study was not designed to determine whether post-irradiation edema could be separated from tumor recurrence, but was carried out only to study post-irradiation signal changes, and the duration of such changes. We found a relatively wide variation in the duration and degree of post-irradiation edema in soft tissues. This edema seems to persist longer in the intramuscular septa than in fat or muscle. Our findings show that post-irradiation edema peaked quicker for the neutron-treated patients than for those treated with photons. In addition, this edema persisted much longer in the neutron-treated groups. Although our follow-up time was limited, our study suggests that this edema resolves in roughly half the photon-treated patients within 2–3 years post-treatment but in less than 20% of neutron-treated patients by 3–4 years post-treatment.

The perceived amount of edema was greater and persisted longer on STIR images than on T2W images. This is not surprising, as STIR images are more sensitive than T2W images for the presence of edema. This finding is consistent with a prior study comparing the conspicuity of STIR images with those produced by more conventional sequences [13].

Muscle decreased in size over the study period. This atrophy was seen in both groups of patients, but was much more prominent in the neutron-treated group. This atrophy appeared to level off in the photon-treated group at about 18 months post-treatment. Patients in the neutron-treated group, however, demonstrated a steady decrease in muscle size throughout the observation period.

As compared with photons, fast neutrons are less dependent on the cell cycle phases and state of oxygenation of the target tissue cells, and allow less likelihood of cellular repair of radiation-induced injury. Therefore, fast neutrons may inflict greater damage to tissues that are considered relatively radioresistant to photons [14]. These biophysical characteristics of fast neutrons may

help to explain the increased muscle atrophy seen after neutron irradiation.

We did observe some increase in size in both fat and the intramuscular septa following irradiation. This tended to be mild. Early on, this was most likely due to edema in these tissues. However, this apparent increase in size persisted after the signal intensity had normalized. This is most likely due to increased conspicuity of the subcutaneous and septal fat due to accompanying muscle atrophy.

Marrow signal was normal in the majority of our patients, principally due to its exclusion from the radiation port. These results, therefore, should not be extrapolated to a population in which the marrow is the primary target of irradiation. In one of our patients, the marrow space was the primary target of the radiation (for a Ewing sarcoma of the pelvis), and it demonstrated prolonged marrow signal hyperintensity on T2W and STIR images at 27 months post-irradiation.

Our study is limited by its relatively small population size. This sample size seems somewhat paradoxical, given the large experience that our radiation oncology department has in the treatment of primary musculoskeletal neoplasms. However, our criteria for entry into the study were somewhat stringent in that we included only patients whose tumors had been resected, who were clinically and radiographically tumor-free and who had adequate MR follow-up. To perform a more definitive study with a larger population, a multicenter study may be necessary.

Another limitation of our study is that the increased signal intensity seen in our patients was not caused by radiation changes alone. Indeed, we found that signal intensity was generally elevated (subjective intensity of 1–2) in all soft tissues in most patients prior to the onset of treatment in both the photon- and neutron-treated groups (Fig. 2). This was almost certainly due to a combination of residual peritumoral edema [15–18], postoperative edema [19], and edema following chemotherapy [20, 21]. Edema from these causes may appear identical on MR images. However, we feel that postoperative edema is unlikely to be seen after 1 year. In any event, much of the increased signal intensity that we noted on sequential follow-up scans was in areas relatively distant from the original operative bed. Many of our subjects were treated with chemotherapy. In our experience, however, only occasional patients have manifested changes which were attributable to a direct toxic effect from the chemotherapy. Such findings have been seen predominantly in muscle, and have resolved within 1 year [22]. Therefore, we feel that increased soft tissue signal intensity seen more than 1 year after irradiation represents either irradiation effect or tumor recurrence. In the absence of a discrete mass, we feel that recurrent tumor is unlikely. Therefore, we are confident that the majority of the increased signal intensity noted in our study was due to radiation.

We conclude that there is a relatively wide variation in the duration and degree of post-irradiation edema in soft tissues. This edema seems to persist longer in the intramuscular septa than in fat or muscle. Although our follow-up time was limited, our study suggests that this edema does resolve in roughly half the photon-treated patients within 2–3 years post-treatment and in less than 20% of neutron-treated patients by 3–4 years post-treatment. Muscle atrophy was noted in both photon- and neutron-treated patients and was more severe in the neutron-treated group.

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