European Journal of Radiology 69 (2009) 209–221

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Post-treatment complications of soft tissue tumours

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ARTICLE INFO

Article history:
Received 29 September 2008
Accepted 2 October 2008

Keywords:
Soft tissue sarcoma: MR imaging
Soft tissue sarcoma: recurrences
Soft tissue sarcoma: metastases
Soft tissue sarcoma: seromas
Radiotherapy: muscle

ABSTRACT

Purpose: To identify local and distant complications of patients with soft tissue tumours and evaluate their relationships to types of therapy.
Methods and materials: Fifty-one patients (29 males and 22 females, ages 14–80 years) with 34 malignant and 17 benign soft tissue tumours were evaluated for local and distant complications after resection or amputation only (26 patients) or after the addition of radiotherapy (25 patients: 17 patients had external beam therapy, 7 patients had external beam therapy and brachytherapy, and one patient had extracorporeal irradiation and reimplantation). Duration of follow-up averaged 3.75 years for malignant tumours and 2.79 years for benign tumours. Follow-up studies included radiography, T1- and T2-weighted magnetic resonance (MR) imaging, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), computed tomography for thoracic and abdominal metastases, and 3-phase technetium-99m-labeled-methylene-diphosphonate scintigraphy for bone metastases.
Results: Recurrent tumours were 2.2 times more frequent in patients who had undergone their initial resection at an outside hospital as compared with those first treated at the university hospital. Nine of 11 recurrences occurred after marginal surgery. Metastases from soft tissue sarcomas, most commonly to lung (nine patients) and to bone and muscle (five patients), showed no specific relationship to type of therapy. DCE-MRI differentiated rapidly enhancing soft tissue recurrences (11 patients) and residual tumours (6 patients) from slowly enhancing muscle inflammation, and non-enhancing fibrosis and seromas that usually did not enhance. Seromas developed in 76% of patients who had postoperative radiation therapy and in 7.7% of patients who had only surgery. Subcutaneous and cutaneous oedema and muscle inflammation was at least four times more frequent after adjunct radiotherapy than after resection alone. Irrespective of the type of treatment, inflammatory changes in muscle and subcutaneous and cutaneous tissue and the majority of seromas were evident at the first follow-up study. Although seromas after resection and external beam therapy resolved with time, seromas after additional brachytherapy persisted. Inflammatory changes in muscle and cutaneous and subcutaneous tissue after resection alone disappeared by the second follow-up study, whereas these changes after radiotherapy resolved months to years after treatment. Fourteen of 51 patients showed MR findings of chronic muscular atrophy, predominantly located in the lower extremity. Heterotopic ossification was seen in three patients after resection and amputation without radiotherapy. Except for one patient with aggressive fibromatosis, bone and nerve complications occurred in patients with soft tissue malignancy. Twelve patients had osteoporosis. Six patients sustained fractures in irradiated osteoporotic bone of the lower extremity, and one patient had a vertebral fracture in radiographically normal but irradiated bone. In addition, one patient was found to have a medullary infarct in an irradiated femur. In nerve entrapment, DCE-MRI demonstrated the rapidly enhancing recurrent tumour or non-enhancing fibrosis surrounding the slowly enhancing nerve. T1- and T2-weighted MR images displayed the acute and chronic sequelae of nerve entrapment and nerve transection with denervation as T2-hyperintense acute muscle atrophy or T1-hypertense chronic fatty muscular atrophy with decrease in muscle volume.

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0720-048X/$ – see front matter
doi:10.1016/j.ejrad.2008.10.008

Conclusion: This study suggests a possible relationship between types of treatment of soft tissue tumours and subsequent complications. Postoperative radiotherapy was associated with a significant number of patients with seromas, muscle, cutaneous and subcutaneous inflammation, and fractures. Incomplete or difficult surgery resulted in residual or recurrent tumours and heterotopic ossification. Muscle atrophy and nerve entrapment were related to both treatments (resection alone or radiotherapy after resection). Diligent follow-up of patients with soft tissue tumours with recognition of these complications and their differentiation from recurrent or residual tumour can help guide clinical care and may negate the need for surgery when benign disease is defined.

1. Introduction

For the past two decades, the estimated number of soft tissue sarcomas diagnosed and number of cancer deaths due to these tumours as compared with all malignancies are unchanged at less than 1% of all cancers as reported by the American Cancer Society [1,2]. Because these sarcomas are uncommon and are 100 times less frequent than benign tumours, they may be misdiagnosed in general practice with the result that patients may be understaged and inadequately resected with significant risk for recurrence [3–8]. In the follow-up of these patients, recognition of post-treatment complications and their differentiation from recurrent tumour is important for optimal evaluation of these patients.

Although investigators have described specific complications (recurrences, metastases, seromas, muscle inflammation) in patients who have had resection and radiotherapy of soft tissue tumours [3,5,6,9–12], they have not compared these various complications with specific treatments. The current study evaluated the imaging findings of these complications, their follow-up, and their relationship to therapy.

2. Materials and methods

2.1. Patient and tumour profiles and treatment

In this retrospective study at a university medical centre, 51 patients with histologically proved malignant (34) and benign (17) soft tissue tumours were evaluated for local and distant complications after resection with or without radiotherapy (Table 1). Twenty-four patients had postoperative external beam therapy. In seven patients with sarcomas, brachytherapy was given prior to external beam therapy. One patient had extracorporeal irradiation and re-implantation for a soft tissue hemangio-endothelioma that had invaded bone. Twenty-nine males and 22 females, ages 14–80 years, comprised the patient population. The mean age for patients with sarcomas was 56.7 years and for benign soft tissue tumours, 37.6 years. Patients with sarcomas were followed from 6 months to 11 years (mean of 3.75 years) and those with benign soft tissue tumours from 1 month to 7.6 years (mean of 2.79 years).

Table 1
Initial treatment of soft tissue tumours.

Treatment	Benign soft tissue tumours 17 patients	Malignant soft tissue tumours 34 patients
Resection without radiotherapy[a]		
Resection only	14	8
Resection and megaprosthesis	0	1
Amputation	0	3
Resection with radiotherapy[b]		
Resection and external beam therapy	3	13
Resection, external beam therapy, and brachytherapy	0	7
Resection, external beam therapy, and megaprosthesis	0	1
Resection and extracorporeal irradiation and implantation of bone, and megaprothesis	0	1

[a] Patients had resection or amputation without radiotherapy.
[b] Twenty-five patients had resection and radiotherapy.

The most common sites for the 34 malignant neoplasms were the pelvis and thigh in 52.9% of patients (18/34); other less frequent locations were the knee (2), leg (3), foot (3), shoulder (1), forearm (3), hand (2), paravertebral regions (2). The 17 benign soft tissue tumours demonstrated no predominant location with involvement of lower extremities (thigh [4], knee [2], leg [3], and ankle [2]) and upper extremities (shoulder [2], arm [2], and forearm [1]). In one patient, the pelvis was the site of benign tumour.

At the university medical centre, 35 patients underwent radical resection, and 2 had amputations for locally unresectable sarcomas with bone invasion. Of the 14 patients with initial surgery at a local hospital, 13 had radical resection, and 1 had an amputation. Three patients (two at the university hospital and one at an outside hospital) received femoral megaprostheses because of malignant extension into periarticular tissues.

Twenty-six patients had radical resection without radiotherapy (Table 1). Twenty-four patients received postoperative external beam therapy (Table 1). Approximately 3 weeks after resection, 50 Gy was applied to the extremity as a whole and an additional 6 Gy applied to the surgical bed with 5 cm margin. Pelvic soft tissue sarcomas were irradiated with 60 Gy to the pelvis and an additional 6 Gy to the surgical site, except for areas with intestines where the dose did not exceed 54 Gy. Prior to postoperative external beam therapy, seven patients with high-grade sarcomas also had brachytherapy (interstitial implants using iridium-192), which was started 3–5 days after resection in order to allow for wound healing. Brachytherapy (20 Gy) was applied for 40 h at 1 cm intervals to the resected tumour bed with margins of 2 cm. To prevent skin necrosis, brachytherapy was not given when the tumour was within 1 cm of the skin.

Besides the 24 patients who had external beam therapy with or without brachytherapy, one patient underwent extracorporeal irradiation and implantation of the ilium for a soft tissue hemangio-endothelioma that had invaded bone. During the procedure, the iliac bone with the tumour was removed, irradiated with 300 Gy extracorporeally, and then reinserted [13].

Adjunct postoperative chemotherapy was administered to seven younger patients with soft tissue sarcomas with poor prognosis and incomplete resection.

2.2. Imaging protocol

Follow-up examinations for both benign and malignant soft tissue tumours consisted of standard spin echo magnetic resonance (MR) imaging and dynamic contrast-enhanced-MRI (DCE-MRI), computed tomography (CT) of the chest and abdomen, 3-phase technetium-99m-labeled-methylene-diphosphonate bone scintigraphy, and standard radiographs. For soft tissue sarcomas, follow-up studies after the initial resection were obtained every

3 months for the first 2–3 years and every 6 months until the fifth year. Thereafter, patients without recurrences were followed yearly. With recurrent tumours, patients were followed postoperatively with the same protocol as for the primary tumour. The patients with benign tumours were followed once a year until the end of the fifth year or less depending on when the complications resolved.

Protocol for standard MR imaging (Siemens, 1.5 Tesla, Erlangen, Germany, 6–8 mm thickness) consisted of T1-weighted sequences (T1 [TR/TE: 450–600/10–15], matrix 256–512 × 256–512; and T2-weighted sequences [TR/TE: 3000–4800/60–120], matrix 256–512 × 256–512) in the axial plane and in an additional coronal or sagittal plane. MR images encompassed the entire tumour and the proximal and distal joints. The plane in which the tumour was best defined was selected for the DCE-MRI. An artery was included in this plane to determine and compare the time of arrival of the first bolus with the first pass of contrast through the tumour. Simultaneously with an intravenous bolus of gadopentetate-dimeglumine (Magnevist, Bayer Healthcare, Berlin, Germany) (0.5 ml/kg body weight), turbo-FLASH DCE-MRI was done in the selected plane with TR/TE [9/4], TI of 200 flip angle of 8 degrees, matrix (128 × 128), acquisition time per slice of 1.41 s per slice, and one acquisition [5,14,15]. This rapid acquisition of dynamic images from time of bolus through 3 min produced 180–200 dynamic images. The signal intensities of contrast enhancement from regions of interest were plotted against time to create time intensity curves that provided a graphical display of the early pharmacokinetics of the contrast agent during and immediately after the first pass. The slope of this curve represented the maximum enhancement rate during the first pass and was mainly determined by tissue vascularisation (i.e. number of vessels) and perfusion [5,14,15]. Qualitative analysis (subtraction images of noncontrast scan from enhanced scans) and quantitative analysis (time intensity curves from regions of interest) were used to differentiate between the early vascular phase synchronous with arterial enhancement and late vascular phase of tissue enhancement. The criterion for viable tumour was tissue that enhanced within 10 s after bolus injection, simultaneous with arterial enhancement.

Spiral 4-level low-dose CT of the thorax and abdomen (5 mm slice thickness) were obtained for metastases. After intravenous injection of 75 cc of iodixanol (Visipaque 320) (General Electric Healthcare, Pewaukee WI, USA) or iopromide (Ultravist 300 Bayer Healthcare, Berlin, Germany), additional spiral CT evaluated change in liver metastases in arterial, portal and venous phases. Other follow-up imaging studies included chest radiographs and radiographs of the involved extremity or axial skeleton and 3-phase bone scintigraphy.

2.3. Histopathological examination

All recurrences were proved by biopsy and resection. Metastases were biopsied when single. However, biopsies were not done on multiple new lung nodules that were consistent with metastases. Abscesses were aspirated or drained via catheter with CT or ultrasonography depending on the deep or superficial location respectively. Seromas were not resected but were followed with MR imaging.

3. Results

3.1. Recurrences, residual tumour and pseudotumours of inflammation

Eleven of 51 patients (9 patients with sarcomas and 2 patients with benign tumours) developed a recurrence from 6 to 60 months after initial resection (mean 26.9 months). Nine of these 11 patients with recurrent disease had marginal resections (5 patients had initial resection at a local hospital and 4 at the university hospital) (Table 2). Despite effective radical resection surgery with wide margins at the university hospital, two patients developed recurrences. Three patients had more than one recurrence 1.8–5 years after second resection. In addition to recurrences, residual tumour was found in six patients at the first postoperative follow-up study (three who had their initial resection at the local hospital and three at the university hospital). Thus patients that first were treated at local hospitals had 2.2 times the risk for developing recurrences and 2.6 times the probability of having residual disease as compared with those initially treated at the university medical centre although the numbers of patients with recurrent or residual tumours were small.

Table 2
Recurrences and residual tumours in patients treated at the university and local hospitals.

Location of resection	Recurrences		Residual tumours	
	No.	Percent	No.	Percent
University hospital	4/37[a] positive margin	10.8	3/37	8.1
	2/37 negative margin	5.4		
Local hospital	5/14[b] positive margin	35.7	3/14	21.4

[a] Thirty-seven patients had resection or amputation at the University Hospital.
[b] Fourteen patients had initial resection or amputation at a local hospital.

At DCE-MRI, recurrent and residual sarcomas and aggressive fibromatosis enhanced rapidly synchronous with arteries within the 10 s after bolus injection (Figs. 1 and 2). These neoplasms were distinguishable from the non-enhancing seromas and fibrosis and from the slowly enhancing normal muscle, diffuse inflammation of muscles and focal inflammatory pseudotumours (Figs. 2 and 3). Recurrences of two benign tumours (hemangioma and pigmented villonodular synovitis) did not show rapid enhancement in the early vascular phase but were diagnosed by their characteristic MR findings similar to the primary tumour. The hemangioma displayed fat separating tortuous vessels that enhanced after contrast. Pigmented villonodular synovitis consisted of multiple intra-articular masses with hemosiderin.

The 17 recurrent and residual tumours were histologically proved at further resections. Sixteen displayed the same histology as the primary tumour. One recurrent myxoid lipofibrosarcoma showed dedifferentiation but did not demonstrate distinguishing MR features that differentiated it from the primary tumour.

3.2. Metastases and lymphadenopathy

Soft tissue sarcomas most frequently metastasized to the lung (9 of 34 patients) and the musculoskeletal system (5 of 34 patients) including muscles (both ipsilateral and contralateral) and bone (skip and multiple distant bones of the axial and appendicular skeleton). Other metastases to lymph node and liver were synchronous with pulmonary and bone metastases in two patients.

Only 1 of 13 patients had metastases at presentation. The other 12 patients developed metastases from 3 to 60 months after resection (25% metastases within 3 months, 25% between 6 and 12 months, and 50% 12 months or later after resection). Mean time for metastatic development was 2.73 years. When radiography and/or CT detected multiple new pulmonary masses consistent with metastases, no biopsy was done. A single metastasis to any site was confirmed by biopsy.

3.3. Second malignancy

A second malignancy was found in three of 34 patients with soft tissue sarcomas. One patient presented with synchronous left

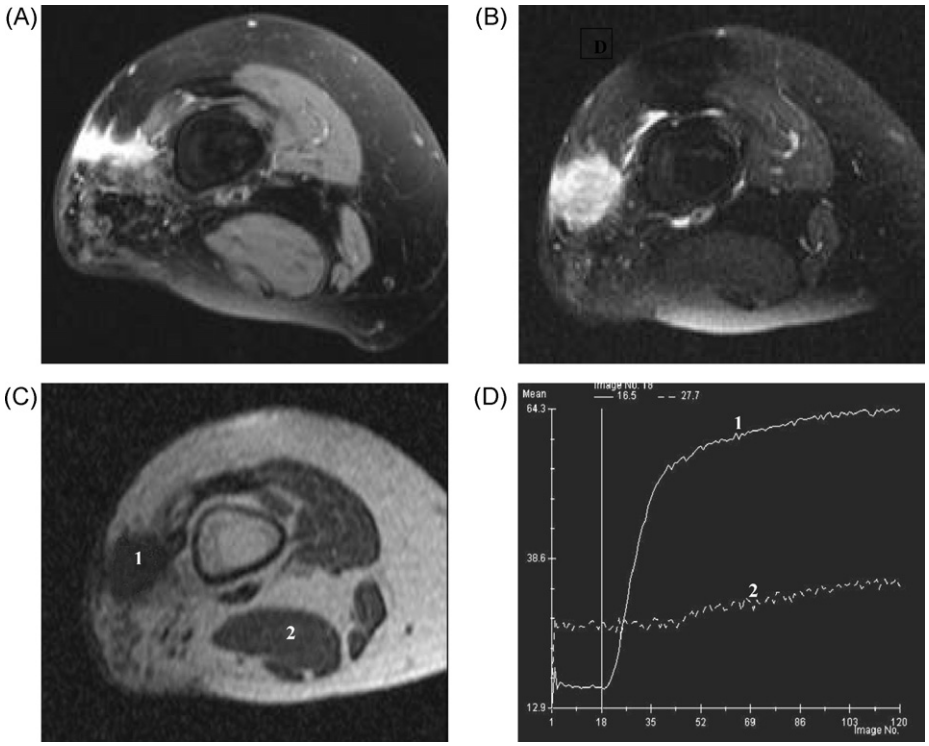

Fig. 1. 71-year-old woman 13 months after resection of a pleiomorphic sarcoma of the right thigh. (A) Axial fat-saturated FSE T2-weighted MR image shows irregular high-signal-intensity postoperative granulation tissue along the surgical pathway unchanged from prior studies. (B) Three months later, axial fat-saturated FSE T2-weighted MR image of the right thigh shows a high-signal-intensity nodular mass that has replaced the inflammatory tissue. (C) Axial T1-weighted MR image of the thigh for localizing regions of interest (1, mass; 2, normal muscle). (D) Time intensity curves from regions of interest show rapid enhancement of the mass (1, continuous line) during the first pass of contrast through the tumour and the slow enhancement of muscle (2, dashed line). The rapid first-pass with high-maximal enhancement represents tumour vascularisation and perfusion that are markedly greater than that in normal muscle. Resection proved the mass to be recurrent tumour.

heel leiomyosarcoma and renal cell carcinoma. Second tumours were diagnosed in two other patients at follow-up examinations. A melanoma of left hand was discovered in a 23-year-old woman 32 months after resection of an alveolar rhabdomyosarcoma of the right forearm. The third patient, a 46-year-old man, developed a gluteus maximus liposarcoma at the surgical site 4 years after resection and irradiation of a leiomyosarcoma. The pathologist did not consider this tumour to be radiation induced.

3.4. Response to postoperative chemotherapy

Seven patients, who had inadequate resections of their sarcomas and a poor prognosis, received postoperative chemotherapy. Three showed a good response with no demonstrable viable tumour at DCE-MRI, and four showed persistent fast-enhancing residual tumour. No specific complications were related to chemotherapeutic treatment.

3.5. Seromas and abscesses

At the first follow-up study, seromas were found in 2 of 26 patients (7.7%) who had resection alone. In contrast, seromas were diagnosed in 19 of 25 patients (76%) who had radiotherapy after resection (Table 3). When external beam patients were separated from those who also had additional brachytherapy, 12 of 17 of patients (70.6%) developed seromas after external beam therapy, whereas 6 of 7 patients (85.7%) were found to have seromas after combined brachytherapy and external beam therapy. A seroma was also detected in the patient who had extracorporeal irradiation and reimplantation. Seventy-two percent of post-irradiation seromas were evident within the first 3 months after radiation therapy; 9% between 3 and 6 months, and 18.1% between 6 and 12 months. Except for one seroma in the arm, all others were located in the lower extremity. Seromas varied in volume from 1 to 2610 cc (29 cm × 9 cm × 10 cm). After resection with or without external beam therapy, seromas progressively decreased in volume and finally resolved. In patients who received brachytherapy, seromas persisted.

Seromas were homogeneous or heterogeneous low-signal intensity on T1-weighted images unless T1-hyperintense proteinacious material or debris was present. On T2-weighted MR images, these collections became homogeneously hyperintense (Fig. 4) or heterogeneously hyperintense, when debris was present (Fig. 5). One seroma showed a fluid–fluid level. The pseudocapsule of the seroma was usually low-signal intensity on all MR sequences and appeared thickened particularly in patients who received brachytherapy (Figs. 4 and 5). At DCE-MRI, most seromas showed a flat curve without enhancement. Late-enhancing pseudocapsules that were also hyperintense on T2-weighted MR images were unusual and were not distinguishable from the late-enhancing capsules of abscesses. Aspiration of these seromas excluded infection.

3.6. Inflammatory changes of muscle, subcutaneous tissue, and skin

At the first postoperative follow-up study, MR imaging identified T2-hyperintense inflammation in muscle in 19.2% of patients who had resection with extensive muscle manipulation (Fig. 6) (Table 3). In contrast, 80% of patients who received postoperative radiotherapy showed T2-hyperintense inflammatory changes in one to three of the muscles in the radiation field. DCE-MRI showed late and slow enhancement of the inflamed muscle. On T1-weighted MR images, the muscle texture was preserved in both groups of patients. In the patients who had only resection, muscle

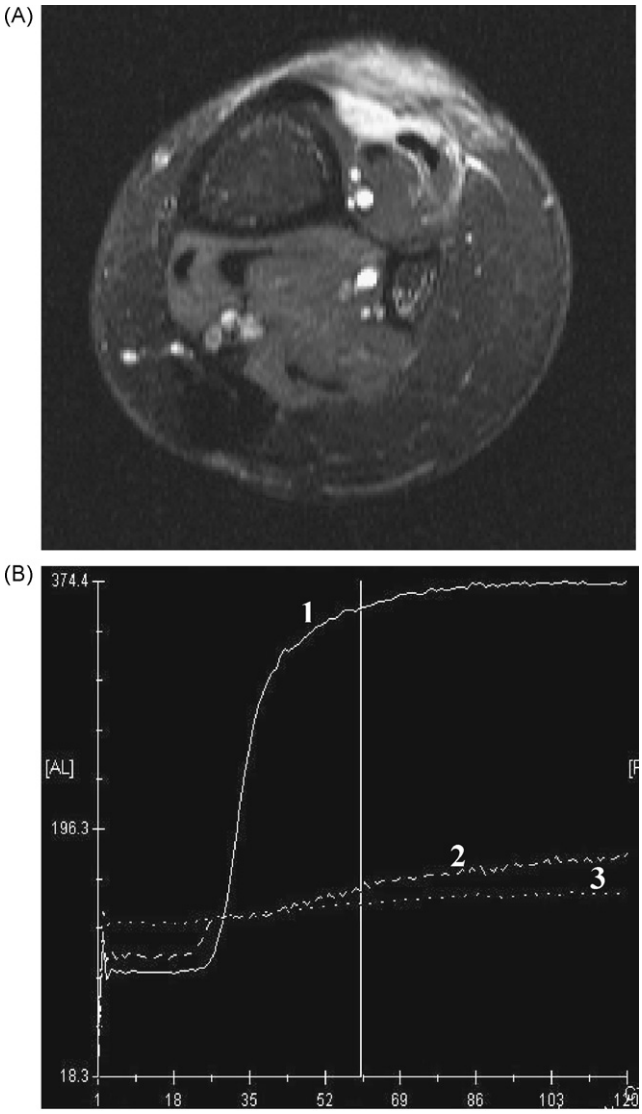

Fig. 2. 60-year-old woman 2 years after resection of a myxofibrosarcoma of the left leg. (A) Axial fat-saturated FSE T2-weighted MR image of the left lower leg shows high-signal intensity in the anterior subcutaneous tissue and in the anterior muscle compartment. (B) Time intensity curve from dynamic contrast-enhanced MR images shows rapid and intense enhancement in the anterior compartment consistent with recurrence (1, continuous line). The pseudotumoural inflammation in the subcutaneous tissues shows slower, less intense enhancement (2, dashed line) as compared with recurrence but mildly increased enhancement as compared with normal muscle (3, dotted line).

inflammation resolved by the second postoperative MR study. Radiation-related muscle inflammation progressively decreased and disappeared from 6 months to 9 years with a mean resolution time of 15 months (median of 25 months). Besides post-treatment inflammatory changes of muscle, three patients were diagnosed with infective myositis and concomitant abscess formation (Fig. 7); one patient had associated osteomyelitis. After positive aspirations and biopsies of the affected areas, patients were successfully treated with antibiotics.

The second most frequent muscular complication after inflammation was chronic atrophy in 14 of 51 patients with soft tissue tumours (2 patients after resection alone and 12 patients after resection and radiotherapy) (Table 3). In 86% of patients, chronic muscle atrophy was located in the lower extremity. At MR imaging, chronic atrophy appeared as a decrease in muscle size and/or as fatty replacement of muscle (Fig. 5). Chronic muscle atrophy was related to several factors (1) disuse atrophy of patients after extensive resection of lower extremity tumours, (2) sequela of muscle inflammation after radiotherapy, and (3) secondary effect of nerve entrapment and nerve transection with denervation. In the three patients with acute atrophy after nerve transection, MR imaging showed areas of diffuse T2-hyperintense oedema in the muscle innervated by the involved nerve (Fig. 7). These acute changes evolved into the chronic atrophic pattern within 6 months to 1 year after onset.

An uncommon postsurgical finding in muscle in three patients who had resection of soft tissue sarcomas was heterotopic ossification (proximal to the amputation site in one patient and near the resection site in two patients who had extensive muscle manipulation during surgery). None of these patients had received radiotherapy.

Postoperative and post-irradiation cutaneous and subcutaneous oedema and thickening were diagnosed in 54.9% (28 of 51) of patients (Table 3) at the first follow-up MR study and exhibited two patterns. Diffuse oedematous, T2-hyperintense skin thickening with subcutaneous oedema predominated in 23 patients who had undergone radiotherapy (Fig. 4). Changes after resection alone (five patients) appeared as low-T1/high-T2 reticular strands in skin and subcutaneous tissues and fascia of the underlying muscles. Post-resection oedema disappeared by the second follow-up study, whereas post-irradiation changes persisted for several months to years after treatment with eventual resolution or conversion to fibrosis.

3.7. Bone complications: osteoporosis, fractures, megaprosthesis complications

In this retrospective study, osteoporosis was diagnosed at radiography by comparing the contralateral extremity and/or a non-irradiated part of the same extremity with the involved bone because bone densitometry data were not available for review. Twelve patients with sarcomas had osteoporosis by these criteria (Table 3). Eleven of these patients had sarcomas located in the lower extremity (five had resection, six had resection and external beam therapy, and one extracorporeal irradiation and reimplantation). The 12th patient with osteoporosis had an upper extremity tumour treated with resection and radiotherapy.

Six of the patients who had lower extremity osteoporosis sustained fractures. Five of these patients had received radiotherapy; one had resection alone. One other patient, after resection and irradiation of myxolipofibrosarcoma of the left T1–T5 paravertebral region, fractured a thoracic vertebra that appeared normal density on radiographs. Three patients had more than one fracture, either refracturing of the same bone in the field of irradiation or fracturing another ipsilateral osteoporotic bone of the same extremity. Fractures occurred from 15 days (direct injury after resection) to 77 months after treatment. Although no patient developed epiphyseal avascular necrosis, MR imaging showed a well-demarcated infarct of the proximal femur after irradiation of a thigh sarcoma (Fig. 6). In addition to fractures and osteoporosis, one patient with a megaprothesis, had subluxation and loosening of his prosthesis and pseudo-arthrosis at the resection site.

3.8. Nerve complications

MR imaging detected complications related to peripheral nerves in eight patients (Table 3). T2-weighted MR images showed nerve entrapment as either hyperintense mass (three patients) or hypointense fibrosis (three patients) (Fig. 8) surrounding the involved nerve. DCE-MRI defined the causes of entrapment (rapidly

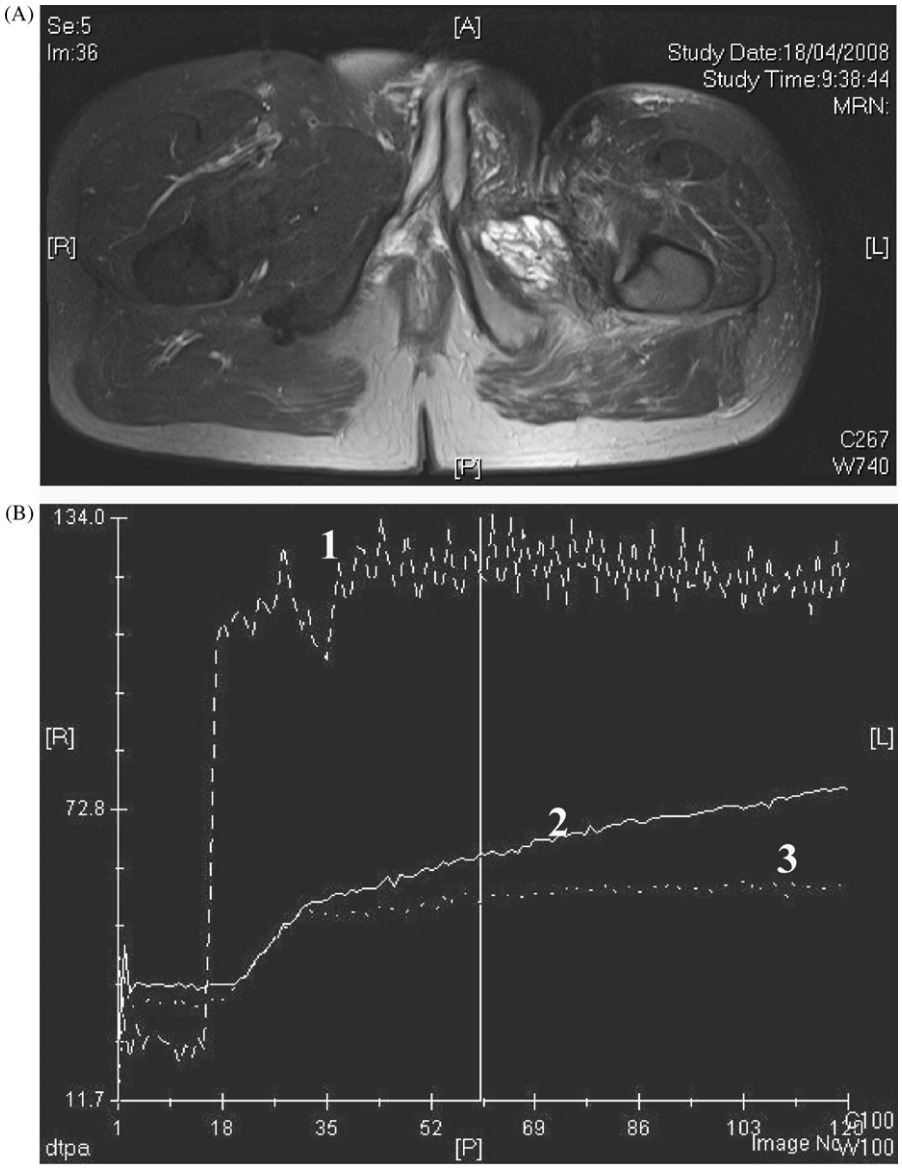

Fig. 3. 56-year-old man 1 year after resection of a pleiomorphic sarcoma of the left thigh. (A) Axial fat-saturated FSE T2-weighted MR image of the left thigh shows a heterogeneous high-signal-intensity mass suspicious for recurrence. (B) Time intensity curves from dynamic contrast-enhanced MR images show the rapid enhancement of the artery (1, hyphenated line) and only moderate enhancement of suspicious mass (2, continuous line) and of muscle (3, dotted line) during the first pass through the mass. After the first pass, the muscle shows no further enhancement (plateau phase), but the inflammatory pseudotumour shows mild increase in enhancement in its large interstitial space. In contrast, a recurrence, similar to arterial enhancement, would have shown rapid first pass enhancement and maintained high-overall enhancement during the interstitial phase.

enhancing tumour or non-enhancing fibrosis) and differentiated them from the slowly enhancing entrapped nerve. A secondary manifestation of nerve entrapment and nerve transection with denervation was muscle atrophy (acute in two patients and chronic in three patients). No findings of neuritis were evident at MR imaging.

4. Discussion

Since the 1970s, the development of new imaging techniques has enhanced staging of soft tissue tumours, and advances in conservative surgical and reconstructive procedures combined with radiotherapy have improved local tumour control rates [16]. However, despite continuing progress in diagnosing and treating these patients, tumours may recur with associated morbidity and decreased long-term survival [17,18]. Patients should be referred to a tertiary care hospital for appropriate diagnosis, surgical planning and procedure, adjunct therapy, and long-term follow-up. Biopsy-related problems and their subsequent adverse effects on clinical course were 2–12 times more frequent when biopsies were done in a referring hospital instead of a referral centre [19,20]. As presented in the current study and by other investigators, the recurrence rate was 1.3–2.2 times higher in patients referred after surgery to tertiary oncologic centres and was 2.4 times higher in patients not referred but treated at local hospitals [8]. The difference in the 5-year actuarial local control rate for extremity soft tissue sarcomas for negative [97%] and positive [82%] margins further emphasizes the need for adequate surgery and follow-up [21].

Early and precise detection of recurrent and residual soft tissue tumours can be enhanced by using an algorithmic MR imaging protocol with standard MR imaging and DCE-MRI [3,6,22]. However, for maximal interpretation of these studies, the radiologist should

Table 3
Non-neoplastic complications of soft tissue tumours after treatment.

Non-neoplastic complications	Resection or amputation (26 patients), no. (%)[a]	Resection + radiotherapy (25 patients), no. (%)[b]	All patients (51 patients), no. (%)[c]
Masses			
Seromas	2 (7.7%)	19 (76.0%)	21 (41.2%)
Inflammatory pseudotumours	3 (11.5%)	0	3 (5.9%)
Muscles, subcutaneous tissue, skin			
Cutaneous and subcutaneous oedema	5 (19.2%)	23 (92.0%)	28 (54.9%)
Muscle inflammation	5 (19.2%)	20 (80.0%)	25 (49.0%)
Chronic muscle atrophy	2 (7.7%)	12 (48.0%)	14 (27.5%)
Acute muscle atrophy	2 (7.7%)	0	2 (3.9%)
Heterotopic ossification	3 (11.5%)	0	3 (5.9%)
Bones			
Osteoporosis	5 (19.2%)	7 (28.0%)	12 (23.5%)
Fractures	0	7 (28.0%)	7 (13.7%)
Bone infarct	0	1 (4.0%)	1 (2.0%)
Megaprosthesis loosening	0	1 (4.0%)	1 (2.0%)
Nerves			
Nerve entrapment	1 (3.8%)	5 (20.0%)	6 (11.8%)
Nerve transection/denervation	2 (7.7%)	0	2 (3.9%)

[a] Percentage of patients who had resection or amputation without radiotherapy, i.e. percentage of 26 patients.
[b] Percentage of patients who had resection and radiotherapy, i.e. percentage of 25 patients.
[c] Percentage of total patients who had this complication, i.e. percentage of 51 patients.

be aware of the type of tumour treated, its imaging characteristics, the surgical and radiotherapy procedures, and the post-treatment complications [10]. The initial follow-up MR imaging sequence after resection and/or radiotherapy should be a fat-suppressed sequence, usually fat-saturated T2-weighted or short tau inversion recovery (STIR) when prostheses are present. Absence of high-signal intensity at the resection site or in adjacent areas on these sequences excludes recurrent or residual tumour in 99% of patients with two limitations. Rarely, isolated tumour cells without nodule formation such as soft tissue Ewing sarcoma may not produce adequate signal to be detected with the current MR scanners. In addition, malignant fibrous neoplasms theoretically could present as hypointense

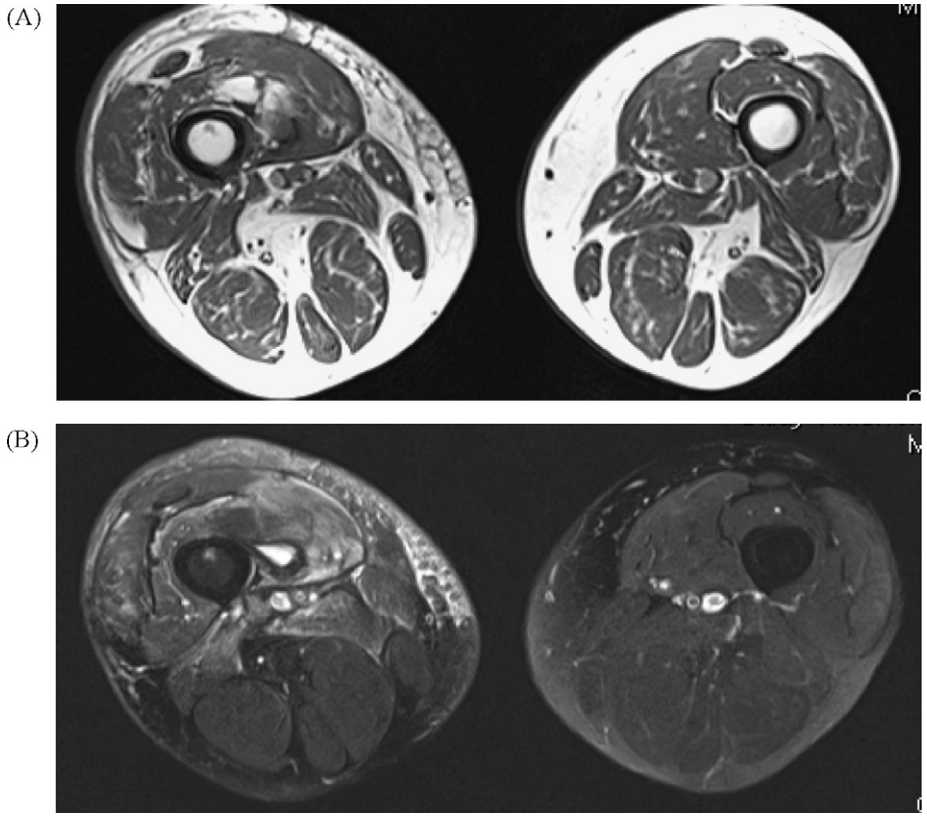

Fig. 4. 60-year-old man 1 year after resection, external beam irradiation, and brachytherapy of a liposarcoma of the right thigh. (A) Axial T1-weighted MR image shows low-signal-intensity oedema of the anterior and medial subcutaneous tissue and a low-signal-intensity seroma with thickened capsule. The seroma and subcutaneous oedema become hyperintense on fat-saturated FSE T2-weighted MR image (B), but the capsule remains low-signal intensity on both sequences. All muscles in the external beam radiation portal (anterior muscle compartment, adductor muscles and small area of biceps femoris) show increased T2-signal intensity, whereas the non-irradiated muscles display normal signal intensity.

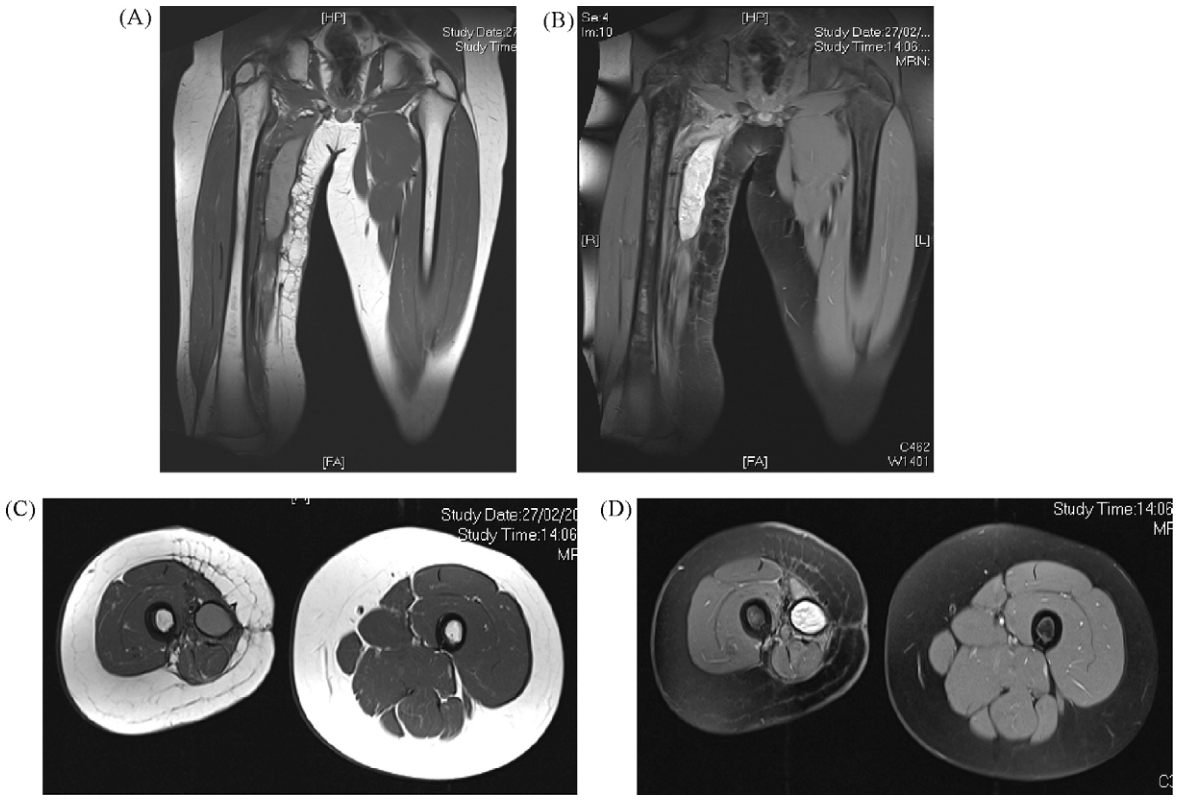

Fig. 5. 14-year-old girl with pleiomorphic sarcoma of the right thigh treated with postoperative external beam therapy and brachytherapy. Follow-up coronal T1-weighted (A) and fat-saturated FSE T2-weighted (B) and axial T1-weighted (C) and fat-saturated FSE T2-weighted (D) MR images of the right thigh show a T1- and T2-hyperintense protein-rich seroma with debris and thickened capsule (hypointense on both sequences). The pattern of hyperintense cutaneous thickening/oedema is typical of external beam irradiation with distribution from the anterior to posterior regions of the medial half of her thigh. The decrease in muscle volume is compatible with post-irradiation muscle atrophy.

masses without areas of high-signal intensity because of the collagen content present [3,5]. However, in the current series and prior studies, recurrent fibrous tumours were heterogeneous signal intensity with foci of high-signal intensity; none was homogeneously hypointense [3,5]. Another predictor of benign disease at T2-weighted imaging is the high-signal-intensity reticulation or thickening without mass in soft tissues (muscle, subcutaneous tissues, and skin). The preservation of textural features of muscle on T1-weighted images combined with the T2 findings further supports the diagnosis of benign inflammatory change [23], and DCE-MRI is not needed.

On fat-saturated T2-weighted MR images, a hyperintense mass may represent recurrent or residual tumour or may correspond to various non-neoplastic processes related to the surgical procedure or radiotherapy [3,5,9,10,12]. Saline spacers placed to elevate bowel from the radiation field and Avitene [microfibrillar collagen hemostat] packing into biopsy sites both may produce hyperintense masses [10]. After resection and radiotherapy, seromas are usually homogeneously hyperintense. However, when seromas have debris, fluid/fluid levels, or blood on T1/T2 MR images or enhancing walls after contrast injection, seromas may mimic abscesses, and aspiration may be needed for diagnosis and treatment [9,12]. Another T2-hyperintense mass, the subacute haematoma, is best defined by its T1 characteristics of hyperintense halo of extracellular methemoglobin that surrounds an intermediate-signal-intensity cavity with a hypointense outer rim [12]. In haematomas and in myxoid tumours, small sarcomatous nodules may not be conspicuous on T2-weighted MR images [6,12]. DCE-MRI can help detect and differentiate between small, rapidly enhancing sarcomatous nodules 3 mm or greater in size from the adjacent non-enhancing haematomas or myxoid areas of tumours [3,6]. DCE-MRI also separates the fast enhancement of viable tumour from the slow enhancement of inflammatory pseudotumours [5]. Rarely, when postoperative MR studies are inadvertently obtained at 3–4 weeks after resection rather than at first postoperative study at 3 months, inflammatory pseudotumours may demonstrate rapid enhancement during the arterial phase and give a false positive result. However, follow-up DCE-MRI within weeks shows the characteristic slow enhancement pattern of inflammation, and surgical confirmation is not necessary [5].

DCE-MRI not only distinguishes between local recurrences and post-treatment complications but also may determine the response of primary or recurrent soft tissue sarcomas and metastases to chemotherapy [3,5,11]. The presence of rapidly enhancing nodules correlates with a poor response to chemotherapy at histology, whereas diffuse slow enhancement or no enhancement in the resection site signifies a good chemotherapeutic response [3,5,11].

Metastases from soft tissue sarcomas tend to be haematogenous rather than lymphatic with the lung the most common site followed by bone, lymph nodes, liver, brain and subcutaneous tissue [24–26]. Twenty percent of patients with soft tissue sarcomas of the extremities develop isolated pulmonary metastases at some point in their clinical course [27]. Although the Society of Surgical Oncology recommends chest CT for follow-up of soft tissue sarcomas greater than 5 cm, grade II (moderately differentiated) or grade III (poorly differentiated) tumours, a recent study suggests that routine chest scanning is more cost effective for patients with high-grade tumours as compared with low-grade lesions and

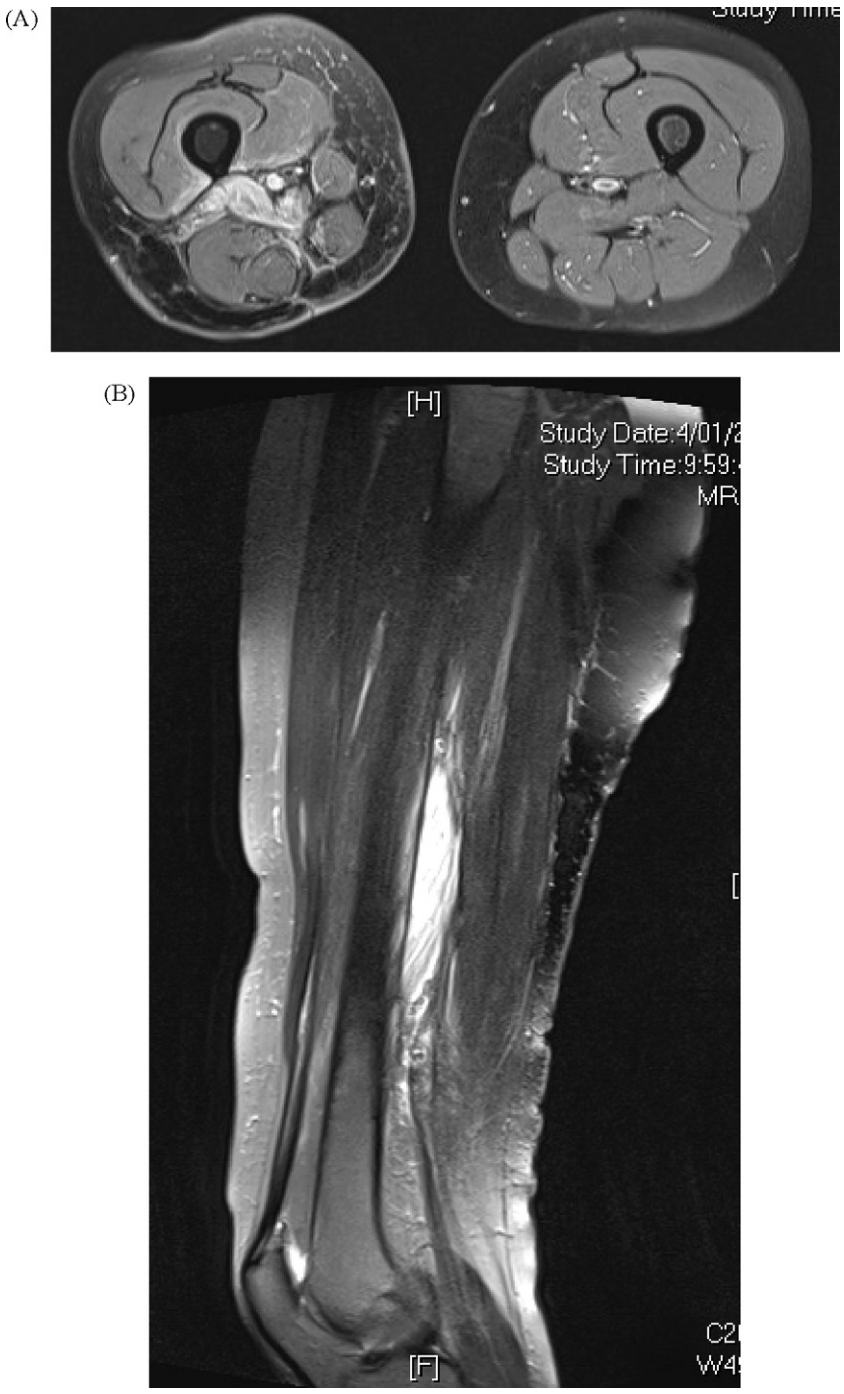

Fig. 6. 51-year-old woman 1 year after resection of a liposarcoma of the right thigh. No radiotherapy was given. Axial (A) and sagittal (B) fat-saturated FSE T2-weighted MR images of the right thigh show the hyperintense muscle fibres without loss of muscle anatomy consistent with acute oedema/inflammatory changes of muscles secondary to mechanical force of extensive manipulation at surgery and partial denervation.

retroperitoneal tumours [28,29]. The only effective treatment for pulmonary metastases is resection [30].

Metastases to bone are the second most common site for metastases from soft tissue sarcomas [24,25]. Usually the primary tumour is known or, if unknown, imaging survey identifies the primary neoplasm, which can then be biopsied. Occasionally, the primary tumour is never found, even at autopsy, because it may be sterilized by chemotherapy and radiotherapy [31]. However, the pathologist may establish the diagnosis by evaluating the metastatic bone biopsy specimen with immunohistochemistry and cytogenetics [31]. On radiographs, the majority of bone metastases from soft tissue sarcomas produce osteolysis with moth-eaten or permeative patterns and erosion or destruction of cortical bone confirmed at CT. Periosteal reaction is not present. Twenty-one percent of bone metastases are mixed; sclerotic lesions are rare [31,32]. MR imaging displays the metastases as homogeneous or heterogeneous T1-low-signal intensity and T2-high-signal intensity [32]. Most patients with bone metastases have pulmonary metastases; isolated bone metastases occur in less than 12% of patients. The spine is the most common site for bone metastases from soft tissue sarcomas. In

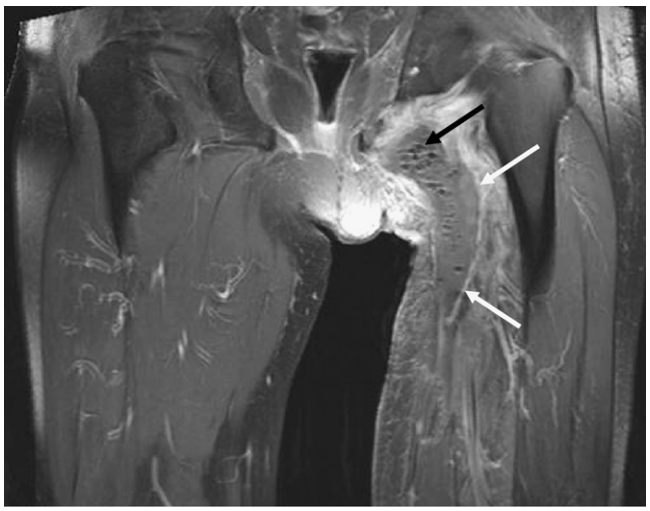

Fig. 7. 55-year-old-man, presenting with pain 3 months after resection of a malignant fibrous histiocytoma of the left thigh. Post-contrast coronal fat-saturated T1-weighted MR image shows enhancing inflammatory changes at the resection site and in adjacent muscle with a collection with enhancing rim (white arrows) and intraluminal hypointensities (black arrow) compatible with air in an abscess and infected myositis. Diagnosis was proved by aspiration and drainage.

the extremities, metastases are 3.5 times more likely to occur in bones ipsilateral to the primary tumour than in the contralateral extremity.

Besides metastases and recurrences, synchronous or metachronous second sarcomas occasionally may develop in patients with soft tissue sarcomas, including the rare radiation-induced sarcoma with a mean latency period of 4–17 years (range 2.75–55 years) [33,34]. Radiation-induced tumours account for 0.5 to 5.5% of all sarcomas and are rarely secondary to irradiation of a soft tissue malignancy [33]. The imaging features of radiation-induced sarcomas are not pathognomonic. However, the presence of bone destruction, an associated soft tissue mass, a change in the appearance of previously stable findings within or at the edge of the radiotherapy field after appropriate latency period should suggest a post-irradiation sarcoma [33,34]. The prognosis for these tumours is usually poor because they tend to be poorly differentiated and aggressive, are often unresponsive to therapy, and may be diagnosed late [33].

Acute effects of radiotherapy, more frequently after preoperative radiation, may result in wound complications and burns that are evident early after treatment and are often clinically recognizable [24,35,36]. With longer patient survival, late, chronic effects of radiotherapy have a greater probability of development, especially after postoperative irradiation with its larger fields and higher doses [36–38]. With post-irradiation fibrosis, clinical examination may be difficult, and inconclusive, and MR imaging is essential

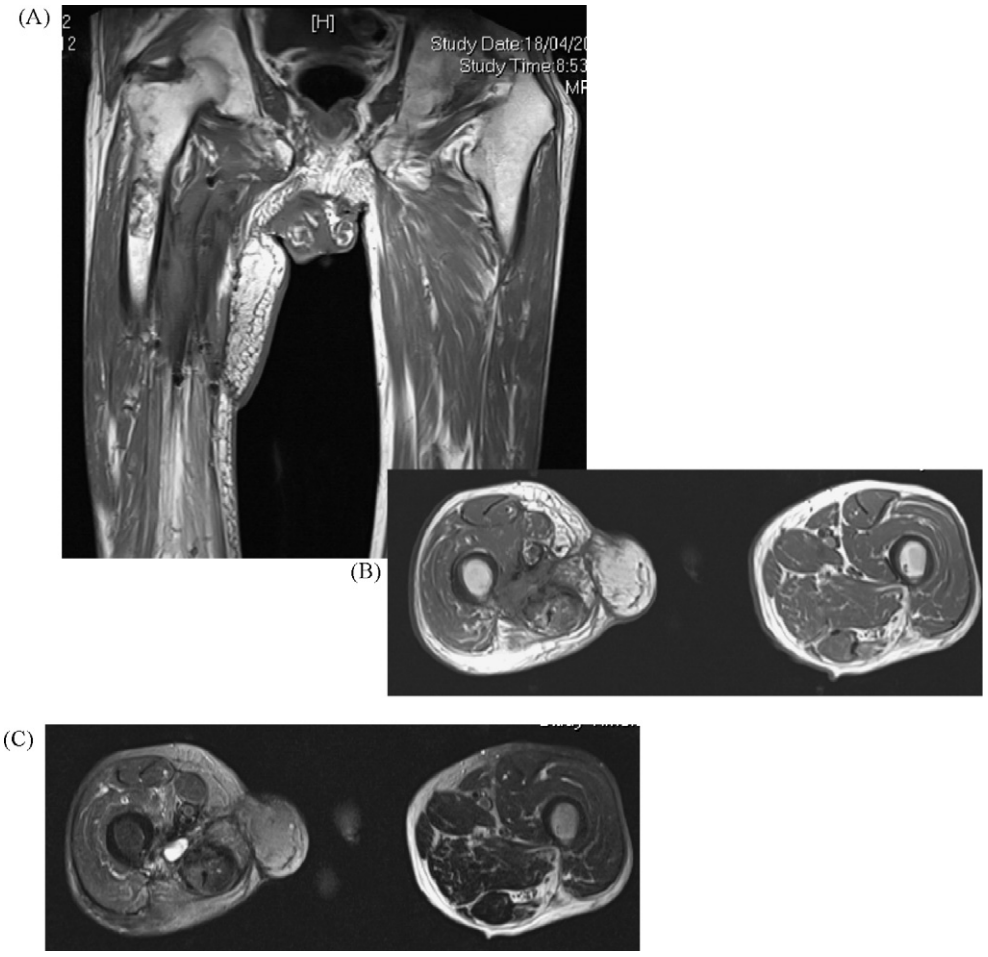

Fig. 8. 76-year-old man, 18 months after resection and radiotherapy of a pleiomorphic sarcoma of the right thigh. (A) Coronal T1-weighted MR image shows an infarct of the proximal diaphysis of the right femur which may have been related to his radiotherapy. Axial T1-weighted (B) and fat-saturated FSE T2-weighted (C) MR images show fibrous tissue entrapping the sciatic nerve, mild decrease in muscle volume compatible with mild muscle atrophy, and a seroma best seen on the T2-weighted MR image.

for detecting non-neoplastic masses and differentiating them from recurrences.

The most common benign mass after resection and radiation therapy of soft tissue tumours is the seroma, reported in 10–30% of patients [9,10] in prior studies and 41.2% in the current series. Prior reports did not discuss the occurrence of seromas with different treatments. In the current patients, seromas were almost 10 times more frequent after adjunct postoperative radiotherapy than after resection alone. Furthermore, with additional brachytherapy, 86% (6/7) patients developed seromas, although the number of patients is small. The reasons for the high percentage of seromas after external beam therapy and brachytherapy is uncertain. Postoperative radiotherapy can render soft tissues non-compliant or woody with the creation of a potential space at the soft tissue sarcoma resection site that will tend to fill with fluid [9]. This also may help explain the long-term persistence of seromas [9]. Seromas slowly change in size with rate of less than 2.4 cm^3/month [39]. Sixty-six percent of seromas decrease in size, 15% remain unchanged in size, and 16% increase in size [9]. In the current study, seromas decreased in size and resolved in patients treated with resection alone or with external beam therapy but persisted in the brachytherapy-treated patients.

Besides evaluating for seromas, studies on lower extremity sarcomas emphasize the importance of long-term surveillance of these patients to identify other late complications in muscle, subcutaneous tissue, and skin [38,40]. Several years after radiotherapy, patients may manifest changes in muscle strength, joint stiffness, impairment of joint mobility, and contractures related to progressive, sometimes disabling fibrosis [37,40]. In these patients, MR defines the extent of fibrosis or muscular atrophy.

Prior to the chronic stage, post-irradiation changes in muscle typically show T2-hyperintense oedema with straight, sharp margins that extend uninterrupted across muscle and subcutaneous fat [41]. The signal intensity peaks between 12 and 18 months and usually resolves by 2–3 years after treatment, although oedema can persist for 5–10 years [42]. A potential use for MR imaging is to quantify radiation effects on muscle in order to select the optimal radiation dose with the least adverse effects. A recent pilot investigation of pediatric sarcoma patients treated with radiotherapy showed that acute radiation effects in muscles were quantifiable and suggested that they may be correlated with patient parameters of radiation dose and clinical age [43]. In the older child, T2 increased linearly with increasing radiation dose during the first 12 weeks after the start of radiotherapy. This finding correlated with previous studies that showed post-irradiation soft tissue oedema with increased enhancement, particularly in areas receiving the highest dose [43].

In patients who have undergone resection, acute muscle inflammation also may be a consequence of tissue manipulation and exhibits a similar MR appearance as post-irradiation change. After amputation, uneven loading may lead to repeated microtraumata and inflammatory changes and adventitious bursae de novo in the soft tissues of the stump between the skin and muscle or bone and between bones and tendons [44]. At MR imaging, bursitis typically shows T1-low-signal intensity and T2-high-signal intensity and peripheral enhancement and intrabursal diffusion after contrast [45].

Another muscle complication in the sarcoma patient is heterotopic ossification. Although more frequently associated with severe trauma after auto accidents or military combat [46], heterotopic ossification may occur after extensive muscle manipulation at surgery, prosthesis placement, or amputation. When the amputation stump is not well covered with periosteum, spike-shaped heterotopic ossification may develop in the soft tissue, generating pain, inflammation, or ulceration [45]. For surgical planning, CT with three-dimensional reconstruction should be used to identify the distribution of the heterotopic ossification and its relationship to the neurovascular structures. MR imaging shows the extent of ulceration and inflammation of the affected soft tissues [45].

Besides heterotopic ossification, other complications related to prosthesis placement include mechanical component failure, fracture and aseptic loosening or migration of the prosthesis in patients with musculoskeletal tumours. Aseptic loosening of the femoral component and component failure occurs within 5–10 years after prosthetic placement in patients with bone tumours or metastatic tumours to bone [47]. The rate of aseptic loosening of megaprostheses was reported as 20% in one series of 91 patients who had megaprosthesis placement after bone tumour resection [48].

Radiotherapy also may be a contributing factor to bone complications, particularly osteonecrosis and fractures with sequelae of delayed or non-union and, in children, growth plate arrest [49–53]. After irradiation of lower extremity sarcomas, the rate of pathologic fractures varies from 1.2% to 10% with a non-union rate of 45% [50,53]. Patients who have received high-dose postoperative radiotherapy have 11.7 times the risk for fractures at 5 years as compared with those who had low-dose preoperative radiotherapy [50]. A surgical technique, periosteal stripping, combined with radiotherapy places patients at higher risk for pathologic fractures in the lower extremity [51,53]. When soft tissue tumours are adjacent to bone, periosteal stripping (excision of the periosteum) may be necessary to create a clear margin. Both periosteal stripping and radiotherapy with vasculitis can interrupt the blood supply to bone and compromise the cortical vascularity [54]. These treatments may also affect the osteoprogenitor cells in the cambium layer with delay in bone healing [54].

Decreased mobility with disuse osteoporosis may further weaken the bone in patients who have sarcoma resection and may also predispose to fractures particularly in the lower extremity. Because the standard approach for evaluating osteoporosis is bone densitometry, the data in the current study based on radiographs have limited usefulness and may have underestimated the percentage of patients with osteoporosis. Although decreased mobility and disuse are recognized factors that lead to osteoporosis in patients with lower extremity sarcoma surgery, a direct relationship between radiotherapy and osteoporosis has not been defined. Only one recent report from St. Judes's Hospital suggested a possible causal relationship between radiotherapy and the development of osteoporosis and fractures in children [55].

In the follow-up of patients with soft tissue tumours, peripheral nerve damage is a major clinical complication after radiotherapy in 7–13% of patients [24,40]. The MR findings of radiation-induced neuritis have not been reported in patients with soft tissue sarcomas and were not evident in the current patients. However, MR imaging can detect fibrosis and recurrent tumour entrapping nerves after surgery and radiotherapy. After denervation or resection, the remnants of the nerve usually are not visible at MR imaging, but the signal intensity changes in the muscles innervated by the abnormal nerve suggest the site of nerve damage [56]. Complete denervation typically produces high-signal-intensity changes affecting the entire muscle in a diffuse and homogeneous pattern without changes in adjacent subcutaneous tissue. These findings can be differentiated from the effects of trauma and radiotherapy that often produce changes in subcutaneous tissue. Acutely denervated muscle may not demonstrate signal intensity alterations. However, 2–4 weeks after denervation, muscle oedema in the involved region becomes evident. At this time, MR images show T2-high-signal intensity as a result of increased extracellular water content and decreased muscle fibre volume [56]. As denervation becomes chronic (greater than 1 year after injury), oedema-like changes in muscle gradually resolve, and muscle may

become atrophic with decrease in volume and T1-hyperintense fatty infiltration.

5. Conclusions

Patients who have undergone resection and radiotherapy may present a challenge to both medical and orthopaedic oncologist. Chronic changes may appear late, be obscured by postoperative or post-irradiation changes at clinical examination, and can be disabling. Imaging follow-up is essential for demonstrating and diagnosing complications and differentiating them from recurrent and residual disease. T1- and T2-weighted MR imaging, combined with DCE-MRI, can distinguish between viable tumour and non-neoplastic masses and inflammation. This study suggests that post-treatment complications and their resolution were related to types of therapy. Seromas, muscle and subcutaneous inflammation, and fractures were more frequently associated with radiotherapy than resection alone. Marginal resections predisposed to recurrences, and heterotopic ossification was found after extensive manipulation at surgery. Nerve entrapment and muscle atrophy were seen both after resection alone or after combined resection and radiotherapy. Most seromas, and muscle, cutaneous, and subcutaneous inflammation were detected within the first 6 months after resection and radiotherapy. Although seromas decreased in size and resolved in patients who had surgery with or without external beam therapy, seromas persisted in patients who had brachytherapy. By the second follow-up study, post-resection inflammatory changes in muscle, subcutaneous tissue and skin had resolved, whereas, after radiotherapy, muscle and other soft tissue inflammation persisted for months to years after treatment and finally resolved or were replaced by muscle atrophy and soft tissue fibrosis. The radiologist, using DCE-MRI and spin echo MR imaging, should be able to differentiate between post-treatment complications and recurrent or residual tumours, and thereby contribute significantly to the clinical care of patients with soft tissue tumours.

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