Postradiotherapeutic changes and their evolution in MRI in children with aggressive soft tissue tumors

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Summary

Background:
Magnetic resonance imaging is a commonly used method of monitoring of soft tissue tumours. The aim of the work was to describe precisely the typical changes within soft tissues and bones occurring after radiotherapy in children treated for sarcomas and other soft tissue tumours. With time, the changes undergo evolution and their characteristics and comparison with previous examinations help in a difficult differentiation between tumour lesions and posttherapeutic changes.

Material/Methods:
Fifteen children and young adolescents (9 boys and 6 girls) aged between 2 and 22 years (mean age of 13.4 years) with diagnosed aggressive soft tissue tumours, were treated with radiotherapy. There were 102 MRI examinations analysed in the period from February 2004 to February 2008. The examinations were performed with a 1.5T MRI scanner in the following sequences: SE T1, SE T1+fatsat, before and after gadolinium administration (Gd), FSE T2 and STIR in three planes, and, in some selected cases, a dynamic gadolinium-enhanced (DCE MRI) examination with FAME sequence. Histopathological examinations showed: rhabdomyosarcoma (RMS) in 8 cases, synovial sarcoma – 3, agressive desmoid fibroma – 3, mesenchymoma mal. – 1. MRI examinations were performed at different postradiotherapeutic stages, several times in one patient (12 times at the most).

Results:
Every postirradiation stage revealed a typical picture of posttherapeutic changes. We distinguished four stages and described changes in different sequences within soft tissues and bones, as well as features of contrast enhancement and enhancement curves in a dynamic study. The stages included: I stage – early, up to 3 months after rth, II stage – chronic, from 3 months to 12 months after rth, with some differences between the following periods: • 3–9 months; 9–12 months; III stage – late, from 1 to 3 years after rth, IV stage – distant, more than 3 years after rth.

In the early stage, there were 2 cases with a suspicious, equivocal image of postradiotherapeutic changes. In the chronic stage, there was one recurrence and one case of increasing changes after the therapy. However, the changes resolved in subsequent examinations. In the distant stage, we found two cases of a local recurrence.

Conclusions:
1. MRI is a method of choice in the monitoring of treatment of aggressive soft tissue tumours and in diagnosis of recurrence. 2. To interpret the examination results, it is very important to know the MRI characteristics of changes after radiotherapy and their evolution with time. 3. Interpretation of MRI images and differentiation between postradiotherapeutic and neoplastic changes is difficult, especially at an early postradiotherapeutic stage. 4. A dynamic MRI examination may be useful in the differentiation between postradiotherapeutic and neoplastic changes but it may be unreliable at an early postradiotherapeutic stage. 5. When interpreting the results, it is very important to compare the image with the previous ones. It is therefore indicated to carry out a baseline MRI in the early postradiotherapeutic stage, and then further follow-up images, at several-month intervals.

Key words: soft tissue sarcomas • magnetic resonance imaging (MRI) • radiotherapy (rth)
Background

Soft tissue sarcomas constitute approx. 1% of malignancies and require a combined treatment including chemotherapy, surgery and radiotherapy. Their prognosis (despite such an aggressive therapy) is uncertain. More than a half of the lesions result in a local recurrence [1,2]. Therefore, it is extremely important to monitor the patients constantly and to find such imaging methods that would help us to distinguish between postradiotherapeutic changes and recurrent lesions. In patients who underwent an aggressive course of therapy, often a few surgeries, chemo- or radiotherapy, the detection of the recurrence among postradiotherapeutic changes is very difficult [2]. Ultrasonography (US) and magnetic resonance (MRI) are renowned imaging methods used in monitoring of patients with soft tissue tumours. In case of changes after several surgeries and those after radiotherapy, especially in the early posttherapeutic stage, ultrasound evaluation may be difficult and unreliable. That is why, the method of choice is here the MRI [3]. Evaluation of changes in the early posttherapeutic period (first 3–6 months), even with MRI, is frequently ambiguous. That is why it is now attempted to find such imaging methods and sequences that would facilitate this differentiation. One of the applied methods is the dynamic MRI examination after contrast enhancement (DCE MRI), which, on the basis of the characteristics of enhancement curve changing with time, allows for differentiation between neoplastic lesions and postradiotherapeutic changes [4,5].

Postradiotherapeutic changes within soft tissues are very characteristic and evolve with time [6].

The aim of this work was to define precisely the characteristics of changes following radiotherapy in subsequent posttherapeutic stages, in different MRI sequences, with evaluation of changes within soft tissues and bones, assessment of evolution of contrast enhancement of those changes and evaluation of MRI efficiency in the detection of recurrences among postradiotherapeutic changes and other posttherapeutic changes.

Material and Method

The study group included 15 children and young adolescents (9 boys and 6 girls) aged from 2 to 22 years (mean age of 13.4 years) with diagnosed aggressive soft tissue tumours treated at the Institute of Mother and Child in Warsaw and subjected to radiotherapy.

Histopathological diagnosis included: rhabdomyosarcoma (RMS) – 8 cases, synovial sarcoma – 3, aggressive desmoid fibroma – 3, mesenchymoma malignum – 1. There were 102 MRI examinations analysed in the period from February 2004 to February 2008. The examinations were performed several times in every patient, in different treatment stages. The analysed tests included 80 examinations performed after radiotherapy. The examinations were carried out with a 1.5T MRI scanner (GE Signa) at the Institute of Mother and Child in Warsaw.

The following sequences were used: SE T1, SE T1+fatsat, FSE T2, STIR, SE T1 and SE T1+fatsat after i.v. gadolinium administration (Gd) in the dose of 0.2 mg/kg of body mass and, in some selected cases, a dynamic examination after Gd enhancement with the use of FAME sequence. Three planes were used: coronal, sagittal, and axial, selected depending on the visualised body area.

MRI examinations were performed at different treatment stages: before treatment, after initial chemotherapy, after surgery, after surgery and radiotherapy, and after several surgeries and radiotherapy. All but one patient after radiotherapy underwent surgeries of tumour resection.

MRI examinations after radiotherapy (n=80) were performed at different post-irradiation stages and were divided into the following groups:

I stage – early, up to 3 months after rth (n=11),
II stage – chronic, from 3 months to 12 months after rth,
   a. 3–9 months (n=10),
   b. 9–12 months (n=11),
III stage – late, from 1 to 3 years after rth (n=11),
IV stage – distant, more than 3 years after rth (n=37).

The MRI examinations were assessed for local recurrences and the presence of residual tumours. The characteristics of changes and their time-dependent posttherapeutic evolution was assessed as well.

Results

The MRI image of postradiotherapeutic changes was characteristic for every postirradiation period. The changes were presented in Table 1.

MRI image in the early stage (up to 3 months after rth) was the most difficult to interpret. Sometimes it was unclear due to the presence of a significantly increased signal in T2-weighted images (FSE T2 and STIR) and a strong and rapid contrast enhancement. In 2/11 cases, the image suggested a potential neoplasm. However, in both cases, further follow-up examinations showed regression of the lesions and revealed features of postradiotherapeutic changes.

In the early stage we may observe a diffuse, generalised signal increase in STIR and FSE T2 sequences, both within the subcutaneous and soft tissues (oedema, postirradiation inflammatory reaction). There are thickened intermuscular septa. In the examination after gadolinium administration, there follows a rapid and strong contrast enhancement. In the DCE MRI examination performed 3 weeks after rth, the enhancement curve was typical of a neoplastic lesion (a fast rise and plateau). Recurrence was suspected.

In the chronic stage (3–12 months after rth) there is a slow decrease in signal intensity in T2-weighted images. However, increasing changes are also possible. Increase in the number of postirradiation changes is possible within 6–9 months following rth. That is why the late stage was subdivided into two stages: 3–9 months after rth and 9–12 months after rth. In one of the patients, in the stage lasting until 9 months following rth, the thickness of the sinal mucosa was increasing and the mastoid process was airless in the irradiated area. Tumour regrowth was also
suspected but all the changes did not progress further and with time even regressed. Contrast enhancement at that stage is weaker and the characteristics of the enhancement curve change in the dynamic examination. There is a slow increase in the enhancement curve, typical of benign lesions. Characteristic for that stage are distinct postirradiation changes within the bone marrow, in the form of an increased signal in T1-weighted images, due to fatty degeneration of the bone marrow. There may appear regions of decreased signal intensity in the bone marrow with very non-homogeneous image of that structure. These foci correspond to areas of bone marrow destruction and gelatinous transformation [7]. There may as well appear diffuse regions of decreased signal intensity in the later posttherapeutic stage, corresponding to bone marrow reconversion. As far as soft tissues are concerned, there is oedema regression in the subcutaneous tissue and muscles and an increasing muscular atrophy.

In the late stage, i.e. from one year to 3 years after radiotherapy, the image undergoes a slow stabilisation. There may be some residual signal increase in the STIR sequence, a distinct muscular atrophy, increase in the amount of fatty tissue, thickened muscular septa and fascia. The bone marrow may reveal features of fatty degeneration which may regress at a different rate. Contrast enhancement is very weak and slowly increasing or absent.

Distant stage, i.e. more than 3 years following rth, is characterised by a stable image, fixed atrophic changes of the muscles, no contrast enhancement, different degree of fatty degeneration of the bone marrow.

Successful detection of local recurrences of soft tissue tumours depends on the time that passed from the completion of the rth. The results of MRI examinations indicating a recurrence or a suspected recurrence, confronted with the final diagnosis (histopathological examination or observation), at different postradiotherapeutic stages, were presented in Table 2.

In the most difficult (first) year after rth, there were 3 cases of an incorrect suspicion or diagnosis of tumour recurrence which turned out to be postradiotherapeutic changes.

Discussion

The main aim of imaging examinations in the management of patients with sarcomas and other aggressive soft tissue tumours is the detection of a local recurrence or disease dissemination.

MRI is currently a basic monitoring method in case of such patients. Normally, these are patients after a combined treatment including surgery and chemo- and radiotherapy.

It is extremely important to define the usefulness of the MRI examination in the detection of recurrences among postradiotherapeutic changes and in their differentiation.

Table 1. Changes of signal intensity and enhancement in MRI examinations after contrast medium administration, at different postirradiation stages.

| Stage after rth | Signal/soft tissues | Signal/bones | After gadolinium |
|----------------|---------------------|--------------|------------------|
| I – early 0–3 months | ↑T2, ↑STIR, oedema of the subcutaneous tissue and soft tissues | Slow ↑T1 ↑T2 (oedema) | Strong, early enhancement |
| II – chronic a. 3–9 months | Changes may increase, slow ↓T2 and STIR | Distinct ↑T1 – fatty degeneration of the bone marrow | Weaker enhancement |
| II – chronic b. 9–12 months | Distinct regression ↑T2, ↑STIR | ↑↑T1, possible foci ↓T1 or diffuse ↓T1 (reconversion) | Weak, slow enhancement |
| III – late 12–36 months | Residual ↑STIR, muscular atrophy, ↑fat | Fatty degeneration of the bone marrow (↑T1) | Weak or no enhancement |
| IV – distant >36 months | Stable image, muscular atrophy, preserved changes | Preserved, of different degree ↑T1 | No enhancement |

Table 2. Diagnostics of tumour recurrence with MRI examinations and diagnosis confirmation depending on the postradiotherapeutic stage.

| Stage after rth | Number of MRIs | MRI/recurrence | MRI/suspected | Histopathol. or follow-up |
|----------------|----------------|---------------|--------------|--------------------------|
| I (0–3 months) | 11 | 1 | 1* | 1 – changes after therapy 1* – changes after therapy |
| II (3–12 months) | 21 | 1 | 1* | 1 – recurrence 1* – changes after therapy |
| III (12–36 months) | 11 | 1 | – | 1 – recurrence |
| IV (>36 months) | 37 | 2 | – | 2 × recurrence |
An optimal protocol of the MRI examination and time intervals between subsequent follow-ups should be defined as well.

In the recent years, many authors have commented on the role of the dynamic MRI in the differentiation between neoplastic lesions and postradiotherapeutic changes [2,4,5]. Rijsvijk et al. [4] distinguished 5 types of curves of contrast enhancement in the dynamic MRI examination and determined that type IV and V, i.e. rapid enhancement in the first minute followed by plateau or wash-out of the contrast medium, speak for a malignancy. Type II or III, i.e. a slow increase in the enhancement curve, followed or not by a plateau, suggests benign lesions. Curve of type I is connected with no contrast enhancement.

Vanel et al. [2] found that late contrast enhancement in the dynamic study suggests inflammatory posttherapeutic changes. In such cases, the lesion may be just observed and not subjected to biopsy.

In our material, the dynamic examination performed at a very early postradiotherapeutic stage (3 weeks) showed a strong and early contrast enhancement. The curve was typical of malignancies. Therefore, in a very early postradiotherapeutic stage, conclusions based on the enhancement curve should be drawn with much caution, as the examination is not fully reliable.

In the later postradiotherapeutic stage (3–12 months), in the dynamic examination, there was a late, weak contrast enhancement, typical of benign lesions, indicating posttherapeutic changes.

Image of postradiotherapeutic changes and their evolution in the tumours of soft tissues was presented by Richardson et al. in 1996 [6]. They observed an increase in signal intensity in T2-weighted images and suggested that the changes increase until the sixth month after the therapy and then regress between the second and the third year following rth.

In our material, an extremely difficult for evaluation image was obtained during the first 3 months following rth. Postirradiation changes in that period reveal a significantly increased signal in the STIR and FSE T2 sequence, as well as a rapid and fast contrast enhancement, i.e. features similar to a neoplastic tissue (Figure 1A,B). In the early postradiotherapeutic stage, there may appear – apart from inflammatory and oedematous changes – seroma collections or haematomas that are easy to detect owing to the typical signal produced in the MRI. That soon after the treatment and after surgery (in most of the cases), the recurrence is unlikely, especially an extensive one, involving the whole postirradiation area. It is very difficult to detect a residual tumour among early postirradiation changes. There were some cases of overinterpretation of the MRIs in the material analysed at that stage. There are also other authors [5,6] that point to the difficulties with the assessment and differentiation of changes in the early posttherapeutic period. In such cases, it is helpful to use previous MRI results for comparison. Although the image is difficult to interpret at that stage (due to massive inflammatory and oedematous changes), it seems recommended to perform a baseline MRI in the early postradiotherapeutic period, for comparisons with further follow-up examinations, in the later posttherapeutic period.

Contrast enhancement and signal increase in T2-weighted images, especially STIR, typical of the early posttherapeutic period, resolve with time. Huang [8], in his animal studies, evaluated both the MRI images and histopathological changes in the first weeks following radiotherapy and found a decreased signal intensity and contrast enhancement starting with the fourth postoperative week. Histologically, at the beginning of the first 3 weeks, there were some oedematous changes, damaged vessels and, at the same time, an increasing fatty degeneration of the bone marrow, starting with the third postradiotherapeutic week.

Richardson et al. [6] found that in most of the MRI examinations following rth, there were no changes within the bone marrow. This remains in contrast to our results: a significant increase in signal intensity in T1-weighted images of the bone marrow of all patients. The changes appeared and progressed in the first few months following
radiotherapy and remained or partially disappeared during the first years following radiotherapy. These differences may result from the fact that our material included mostly children. Their bone marrow is red and thus the fatty transformation of the bone marrow following radiotherapy was much more visible in such cases (Figures 2C, 5B).

Postirradiation changes in soft tissues at more than 3 months following rth are very characteristic and evolve with time. There is an increasing muscular atrophy, increase in fat tissue volume, and fibrosis in the form of thickened intermuscular septa (Figure 3) [6]. In our material, the postradiotherapeutic changes witnessed an increasing progress until approx. 9 months following therapy. According to other authors, that was even until 1–1.5 year after the therapy [5,6]. Then, some of the changes may regress and their image becomes preserved and consolidated within the second – third posttherapeutic year, until a full stabilisation. In the late stage, muscular atrophy is still present (Figure 6) while the thickening of intermuscular septa and mucous membranes, as well as fatty degeneration of the bone marrow may regress at a different rate, for up to three years following therapy.

A distant period, after more than 3 years following therapy, is characterised by a fixed and stable image of the changes. In our material, there was a patient after ear rth due to RMS, with a thickening of sinal mucosa and an airless...
mastoid process at the irradiated side. The changes were progressing for 9 months following therapy, as revealed by subsequent follow-ups. Afterwards, they became stable (Figure 4A,B). According to Raviv et al. changes in sinuses following radiotherapy may persist or even progress for 30 months [9].

Late and distant changes and complications following radiotherapy of sarcomas in the limbs of children were presented by Paulino [10]. He found muscular atrophy and fibrosis in 80% of patients, disturbances of limb growth in 67%, limitation of limb mobility in 40%, and damage of peripheral nerves following radiotherapy in 13%.

Distant complications following radiotherapy include inter alia.: a second tumour in the irradiated region in 20% of patients. This high incidence shows that patient monitoring is required for many years after radiotherapy, not only because of potential recurrences.

In the monitoring of patients in the later postoperative stage, it is essential to exclude:
• Local recurrence,
• Metastases, especially to the bone marrow,
• Second tumour.
Schepper et al suggested a diagnostic algorithm of MRI in the monitoring of patients with soft tissue tumors following therapy [1].

First, it is necessary to perform the FSE T2+fat sat or STIR sequence:
- if there is no pathological mass or if there is one but of low signal intensity, the recurrence is improbable and monitoring may be continued (Figures 5A, 8D),
- if there is a hyperintense mass, then the SE T1 and contrast-enhanced SE T1 sequence should be introduced (Figure 8A, B).

If the tumor mass becomes enhanced after contrast administration, then the recurrence is well probable and a dynamic contrast-enhanced examination should be introduced, as it can differentiate between the recurrence and the inflammatory tumor.

In case of distant follow-ups, this protocol is justified.

Our patients underwent routine T2-weighted and T1-weighted imaging before and after gadolinium administration, and, in some selected cases, a dynamic MRI.

The dynamic MRI is a method of choice for the differentiation between inflammatory changes following radiotherapy and recurrences. Its late and slowly increasing contrast enhancement allows for further observation of posttherapeutic changes and resignation from diagnostic biopsies (Figure 9A, B) [2, 11].

Interpretation of the MRI results following surgery and radiotherapy is difficult and sometimes only a detailed analysis and comparison of several examinations allows for drawing proper conclusions. From our experiences and the literature data it follows that a baseline MRI within 4–6 weeks following radiotherapy and subsequent follow-ups every 3–6 months during the first posttherapeutic years are indicated [3]. Sometimes, only on the basis of a comparison with previous examination results and knowledge of the type and evolution of postirradiation changes with time, it is possible to decide whether the image corresponds to posttherapeutic changes or whether there is recurrence suspicion, requiring microscopic verification.

A difficult task is the evaluation of changes within the bone marrow following radiotherapy. It was found that after radiotherapy, the bone marrow undergoes fatty degeneration but there may also appear foci of altered signal: in T1-weighted images: signal of decreased intensity (between the one of signal from muscles and from fat), and in T2-weighted images: signal of increased intensity (between the one of signal from muscular tissue and from fluid). These changes undergo contrast enhancement, evolve with time, and may grow. Such an image may correspond to bone marrow damage in the first months (gelatinous degeneration after radiotherapy), and then to reconversion to the red bone marrow in the later stage [15]. In our material, there were areas of altered signal within the bone marrow which underwent evolution with time and corresponded to changes after radiotherapy and bone marrow reconversion (Figure 7).

It is difficult to differentiate between such changes and bone marrow metastases that produce a similarly decreased signal in T1-weighted images and an increased one in T2-weighted images. Metastases are normally better circumscribed, oval, produce in T1-weighted images signals of a lower intensity than the muscular tissue, and undergo a stronger contrast enhancement [16].

In the assessment of changes after radiotherapy only, it is important to evaluate reactions to treatment and degree of tumour regression. The static MRI study after gadolinium administration does not give us answer to the question in how far the tumour is alive and in how far there is a necrosis inside it. Assessment of the tumour size is not a reliable indicator of response to treatment either [12]. Attempts at differentiation of a living tumour from necrosis were undertaken with the application of diffusion imaging [13, 14].
In case of necrosis, there is a damage of cell membranes, which causes an increased diffusion of water particles within the necrotic part of the tumour. This manifests itself with an increased signal in diffusion imaging and a decreased signal in ADC images. A living tumour, on the other hand, reveals a decreased diffusion rate and is characterised by a low signal intensity in diffusion imaging and a high signal in ADC maps. In T2-weighted images, both the living tumour and the necrosis produce a higher signal and there is no possibility of their unambiguous differentiation [13]. Diffusion-weighted imaging may constitute an alternative for gadolinium-enhanced dynamic MRI in the assessment of treatment efficiency. There were also studies concerning the usefulness of this imaging method in the differentiation of tumours and posttherapeutic changes [13,14]. It was revealed that in the area of irradiated tissues, due to tissue fibrosis, the diffusion rate decreases and the signal intensity increases in ADC maps, which causes change of signal similar to the one in the nervous tissue [14]. DWI is an imaging technique that requires further studies and its value has not been yet well defined. However, it is now being evaluated in multiple clinical studies. Due to no appropriate technical capabilities of our scanner, we did not perform DWI in our patients, but in the nearest future we plan to introduce this sequence to a routine study protocol used in case of monitoring of therapy in patients with soft tissue tumours.

**Figure 8.** RMS of the left cheek after surgery and rth. (A) SE T1+C+fatsat cor, 7 months after rth, contrast enhancement in the region of the left parotid gland — local recurrence. (B) FSE T2+fatsat cor, 7 months after rth, high signal intensity within the tumour recurrence. (C) SE T1+C+fatsat cor, 2 years after surgery of tumour recurrence and intraoperative radiotherapy, slight contrast enhancement in the irradiated region. (D) FSE T2+fatsat cor, 2 years after surgery and rth of the recurrence, no enhanced signal intensity in the region of changes after treatment excludes tumour recurrence.
Conclusions

1. MRI is a method of choice in the assessment of changes and monitoring of treatment of aggressive soft tissue tumours.
2. To interpret the MRI results properly, it is very important to know the MRI characteristics of changes after radiotherapy and their evolution with time.
3. Interpretation of postradiotherapeutic changes is difficult, especially at an early postradiotherapeutic stage.
4. A dynamic MRI examination may be useful in the differentiation between postradiotherapeutic and neoplastic changes.
5. For a correct assessment of postradiotherapeutic MRI changes, it is useful to:
   - Apply a uniform study protocol,
   - Carry out a baseline examination at 4–6 weeks following rth and introduce regular follow-ups,
   - Draw comparisons with previous examination results.
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