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Clinical advances in musculoskeletal imaging: spondylodiscitis and pediatric oncology

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kasalak, Ö. (2019). *Clinical advances in musculoskeletal imaging: spondylodiscitis and pediatric oncology*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

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Chapter 8

Surveillance MRI for the detection of locally recurrent Ewing sarcoma seems futile

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Abstract

Purpose

To determine the frequency of locally recurrent Ewing sarcoma on surveillance MRI and the outcome of these patients.

Materials and Methods

This retrospective single-center study included all patients with newly diagnosed Ewing sarcoma who underwent surveillance MRI of the primary tumor location after primary treatment between 1997 and 2016.

Results

Thirty-two patients underwent a total of 176 local surveillance MRI scans, yielding an average of 5.5 ± 4.4 MRI scans per patient. Follow-up time of surveillance MRI after completion of primary treatment ranged between 1-111 months. Surveillance MRI detected 5 (15.6%) locally recurrent Ewing sarcomas, at 2, 4, 6, 6, and 7 months after completion of primary treatment, of whom 3 also had simultaneous recurrent (metastatic) disease elsewhere. Two patients had recurrent metastatic disease without any signs of locally recurrent disease on surveillance MRI. All 5 patients with locally recurrent disease on surveillance MRI died, at 2, 4, 5, 8, and 9 months after local recurrence detection. Patients with locally recurrent disease had a significantly worse overall survival than patients without locally recurrent disease (log-rank test, $P < 0.0001$).

Conclusion

A limited number of patients has locally recurrent Ewing sarcoma on surveillance MRI. These patients often have simultaneous recurrent (metastatic) disease elsewhere, and their outcome is poor. Moreover, some patients present without locally recurrent disease on MRI but disease recurrence elsewhere. Therefore, surveillance MRI currently seems to have little value and should be reconsidered, also given the costs and the repeated exposure of surviving patients to gadolinium-based contrast agents.

Introduction

Ewing sarcoma is an aggressive sarcoma of bone and/or soft tissue with a peak incidence during adolescence and young adulthood [1]. The overall annual incidence of Ewing sarcoma is approximately 2.93 cases/1,000,000 in the Western world [2]. Metastatic status at diagnosis is the strongest prognostic factor across different treatment strategies [1]. Estimated 5-year overall survival rates are 65-75% for patients with localized disease and 30% for those with initially metastatic disease [1]. The utility of follow-up imaging in Ewing sarcoma after primary treatment with curative intent is currently unknown. Nevertheless, it is common practice to perform routine surveillance magnetic resonance imaging (MRI) of the location of the primary tumor site, unless the patient has a tumor prosthesis (which causes severe artifacts) or metastatic disease without a dominant primary tumor. MRI has been reported to be an effective method for detecting local recurrence of Ewing sarcoma [3]. However, the general prognosis of recurrent Ewing sarcoma is very poor. For example, in a study that included 290 patients with recurrent Ewing sarcoma, the 5-year event free survival after the last relapse and overall survival were only 5.1% and 7.9%, respectively [4]. Other issues are that MRI is a relatively costly examination and that there are recent concerns regarding the use of gadolinium-based contrast agents (GBCAs). GBCAs are routinely administered for tumor detection with MRI, including surveillance MRI in treated Ewing sarcoma. Compelling evidence has shown that repeated administration of GBCAs causes gadolinium deposits in brain tissue, most notably in the dentate nucleus and globus pallidus [5]. Because the clinical significance of gadolinium accumulation in the brain remains unclear [5], caution is warranted and GBCA-enhanced MRI should only be used when clinically useful. This particularly applies to the approximately 70% of children and young adults with Ewing sarcoma who can be cured and who still have many life years ahead. Overall, it remains unclear if the potential benefits of surveillance MRI in treated Ewing sarcoma outweigh its disadvantages. The primary goal of surveillance MRI in this setting is to detect and treat local recurrent disease in a timely manner in order to improve survival, but there is a lack of evidence on this topic. The aim of this research was therefore to determine the frequency of locally recurrent Ewing sarcoma on surveillance MRI and the outcome of these patients.

Materials and Methods

Study design

This retrospective study was approved by the local institutional review board of the University Medical Center Groningen (IRB number: 201700179), and the requirement for informed consent was waived. The database of the University Medical Center Groningen, which is a regional/national referral center for sarcoma patients, was searched for all patients who were newly diagnosed with Ewing sarcoma and who underwent surveillance MRI after completing primary treatment between 1997 and 2016. If MRI is technically feasible (i.e. without suffering from severe artifacts such as in the case of an implanted tumor prosthesis), patients generally undergo surveillance MRI in our hospital every 6 months. After 2 years, MRI is generally only done if clinically indicated (e.g. in case of symptoms). However, there are no absolute guidelines, and the decision as to when and until when surveillance MRI should be done, is jointly made by the treating orthopedic surgeon and the patient or patient's representative, and is still highly variable. Inclusion criteria for this study were: newly diagnosed and histopathologically proven Ewing sarcoma and availability of at least one MRI scan after completion of primary treatment for surveillance purposes. Exclusion criteria for this study were: no clear histopathological diagnosis, death during primary treatment, therapy-refractory Ewing sarcoma, continuous maintenance treatment during follow-up, and MRI that was performed after recurrent disease had already been confirmed by means of another imaging examination.

Patient record review

Medical records of included patients were reviewed to determine patients' age, gender, primary tumor location and metastatic status at diagnosis (the latter as determined by means of bone marrow biopsy of the posterior iliac crest, chest computed tomography, and bone scintigraphy or ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography), type of therapy, number of surveillance MRI scans after completing primary treatment, number of patients with recurrent disease at the old primary tumor site on MRI, absence or presence of concomitant clinical symptoms, number of patients with simultaneous recurrent disease elsewhere, and overall survival (calculated from the date of primary/initial diagnosis until death as a result of any cause or, in surviving patients, censored at the date last known to be alive).

MRI

Surveillance MRI scans were performed using different clinical 1.5-T and 3.0-T systems. MRI protocols were therefore not uniform. Nevertheless, all patients were scanned with unenhanced T1-weighted, fat-suppressed T2-weighted, and contrast-enhanced T1-weighted sequences. GBCA-enhanced imaging was performed with 0.1 mmol gadoterate meglumine (Dotarem®; Guerbet) per kg of body weight in all patients. Slice thicknesses for each sequence varied between 0.9-5.0 mm. Images or reconstructed images (in case of a three-dimensional isotropic acquisition) were oriented in at least two perpendicular directions with regard to the primary tumor location. MRI scans were interpreted by musculoskeletal radiologists as part of routine clinical care.

Statistical analysis

The proportion of patients who were diagnosed with locally recurrent disease on surveillance MRI among all patients was calculated. Overall survival of patients with locally recurrent disease on surveillance MRI was assessed and compared to patients without locally recurrent disease (excluding patients without locally recurrent disease on MRI but disease recurrence elsewhere) using the Kaplan-Meier method with log-rank test. *P*-values less than 0.05 were considered statistically significant. Statistical analyses were executed using MedCalc version 17.9.7 Software (MedCalc, Mariakerke, Belgium).

Results

Patients

A total of 67 consecutive patients were diagnosed with Ewing sarcoma at our institution between 1997 and 2016. Excluding one patient without a clear histopathological diagnosis, 22 of 66 patients (33.3%) deceased at a median of 15.5 months (range: 4-53 months), whereas 44 of 66 patients (66.7%) survived at a median follow-up of 85 months (range: 12-243 months). Of the 66 Ewing sarcoma patients who were potentially eligible for inclusion, 24 were excluded because no surveillance MRI was performed, 8 were excluded because they died during primary treatment, 1 was excluded because of continuous maintenance chemotherapy during follow-up in a palliative setting, and 1 was excluded because MRI was performed after recurrent disease had already been confirmed. Thus, 32 patients (16 males and 16 females, with mean age of 20.8 ± 15.4 years [range: 5-64 years]) were finally included. Twenty-three patients had primary bone Ewing sarcoma (pelvic bone [n=8], vertebrae [n=3], femur [n=3], fibula [n=3], humerus

[n=2], skull [n=1], rib [n=1], sacrum [n=1], and tibia [n=1]), whereas 9 patients had primary extraosseous Ewing sarcoma (brain [n=2], spinal canal/paravertebral [n=2], extracranial temporal soft tissue [n=1], maxillary sinus [n=1], bladder [n=1], rectum [n=1], and soft tissue around the knee [n=1]). Four of 32 patients had metastatic disease at initial presentation (lungs [n=3] and lungs and bone [n=1]). Patients were treated with various regimens, including chemotherapy only (n=8), chemotherapy, radiation therapy, and resection (n=6), chemotherapy and resection (n=6), chemotherapy, proton therapy, and resection (n=4), chemotherapy and radiation therapy (n=4), chemotherapy and proton therapy (n=2), resection only (n=1), and chemotherapy and stem cell transplantation (n=1).

Surveillance MRI findings

The 32 included patients underwent a total of 176 surveillance MRI scans after completing primary treatment, yielding an average of 5.5 ± 4.4 MRI scans per patient (range: 1-14 MRI scans). Average follow-up time of surveillance MRI after completion of primary treatment was 23.1 ± 20.6 months (range: 1-111 months). Surveillance MRI detected 5 (15.6%) locally recurrent Ewing sarcomas (humerus, vertebra C7, vertebra L3, pelvic bone, and fibula), at 2, 4, 6, 6, and 7 months after completion of primary treatment, 2 of them were pathologically confirmed (**Figure 1**). Three of these 5 patients had no metastatic disease at initial diagnosis, whereas 2 of these 5 patients had metastatic disease (lung involvement) at initial diagnosis. Compared to surrounding muscle, 4 local recurrences appeared hypointense and 1 hyperintense on T1-weighted imaging, and all 5 appeared hyperintense on T2-weighted imaging and showed enhancement after GBCA administration. Mean maximum tumor diameter at relapse was 46 ± 22 mm (range: 18-80 mm). Of the 5 patients with locally recurrent disease on surveillance MRI, 4 had no concomitant clinical symptoms whereas 1 patient with recurrent disease in the C3 vertebra had a left arm paresis. Three of these 5 patients also had simultaneous recurrent (metastatic) disease elsewhere. Of note, 2 patients had recurrent metastatic disease without any signs of locally recurrent disease on surveillance MRI (these 2 patients did not have metastatic disease at initial diagnosis). Three patients with locally recurrent disease were treated with second-line chemotherapy, 1 received palliative chemotherapy, and 1 received no further therapy.



Figure 1. A 10-year-old girl who experienced locally recurrent Ewing sarcoma. Radiograph at initial presentation, before any treatment, shows focal periosteal elevation of the left humeral shaft (A, arrowhead). Coronal T1-weighted (B), fat-suppressed T2-weighted (C), and subtraction GBCA-enhanced images (D) show a tumor in the left humeral shaft with an extra-osseous soft tissue component, which proved to be Ewing sarcoma on histopathological examination after biopsy. There were no signs of metastases on whole-body ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) (not shown). After neo-adjuvant chemotherapy, tumor resection and fibular graft reconstruction were performed, as demonstrated on the postoperative radiograph (E). Additional radiation therapy and chemotherapy were administered. Posttreatment coronal T2-weighted (F) and subtraction GBCA-enhanced images (G) show no signs of residual tumor. Surveillance MRI nine months later suggested recurrent tumor in the soft tissue medial to the fibular graft, as shown on coronal T2-weighted (H, arrow) and subtraction GBCA-enhanced images (I, arrow) at the same level as (F) and (G). The patient had no symptoms at that time. Biopsy confirmed recurrent Ewing sarcoma. Whole-body FDG-PET/CT (not shown) did not identify any metastases. Despite second-line therapy, the patient developed lung metastases five months later and succumbed another five months later.

Patient outcome

The median follow-up time of surviving patients was 64 months (range: 22-243 months). Of 32 patients included, 7 patients (21.9%) died (i.e. end of overall survival). All 5 patients with locally recurrent disease on surveillance MRI died, at 2, 4, 5, 8, and 9 months after local recurrence detection on MRI. Patients with locally recurrent disease had a significantly worse overall survival (log-rank test, $P < 0.0001$) than patients without locally recurrent disease (excluding the 2 patients without locally recurrent disease on MRI but disease recurrence elsewhere, who died 7 and 32 months after recurrent metastatic disease detection) (**Figure 2**).

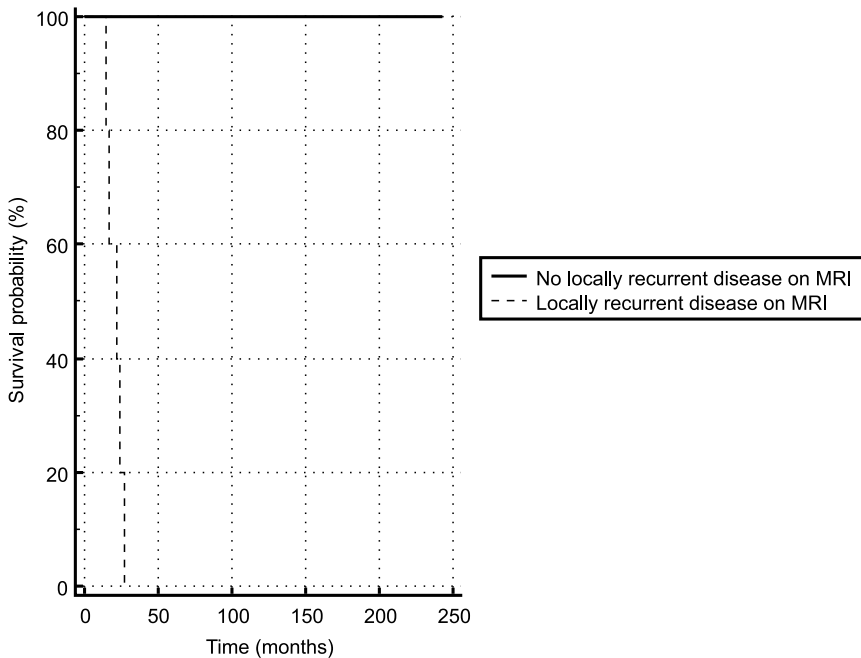


Figure 2. Kaplan-Meier curve for overall survival (calculated from the date of primary/initial diagnosis until death as a result of any cause or, in surviving patients, censored at the date last known to be alive) of patients without and with locally recurrent disease on surveillance MRI (excluding 2 patients without locally recurrent disease on MRI but disease recurrence elsewhere). Patients with locally recurrent disease on surveillance MRI had a significantly worse overall survival than patients without locally recurrent disease on surveillance MRI (log-rank test, $P < 0.0001$).

Discussion

The results of this study show that surveillance MRI detects locally recurrent disease in approximately 15% of patients during follow-up after primary treatment for newly diagnosed Ewing sarcoma. Studies on the frequency of recurrent Ewing sarcoma on surveillance MRI were lacking until now. A second major finding is that patients with a local recurrence on surveillance MRI appear to have a poor outcome, with all patients succumbing to their disease within one year. Thus, it appears that early detection of local recurrence (4 of 5 patients with local recurrence had no symptoms at the time of MRI) did not improve outcome. A third finding is that simultaneous recurrent (metastatic) disease elsewhere is not uncommon, and that recurrent metastatic disease can also occur without local recurrence. Isolated local recurrence without systemic relapse occurred in only 2/32 (6.3%) patients in the present study. In a previous study that included 290 patients with relapsed Ewing sarcoma, only 31 patients (10.7%) had a local recurrence, whereas 217 (74.8%) had a systemic relapse and 42 (14.5%) had both a systemic and local relapse [4]. Overall, these data underline that early detection of isolated local recurrence is infrequent, and that these patients still have a dismal outcome in spite of early detection.

Besides patient outcome, MRI costs and potential side-effects should also be taken into account when considering the utility of surveillance MRI. In this study, an average of 35.4 surveillance MRI scans, which corresponds to about \$10,000 (assuming the costs for one MRI scan to be around \$280 [6]), was necessary to detect one local recurrence. Furthermore, each patient underwent an average of 5.5 intravenous administrations of 0.1 mmol gadoterate meglumine per kg of body weight in this study. The latter is of importance given the recent concerns regarding the observed deposition of gadolinium in the deep nuclei of the brain, particularly after repeated exposure to GBCAs [5]. Although some linear contrast agents appear to cause greater signal changes on unenhanced T1-weighted images (as an indicator of brain gadolinium deposition) than some macrocyclic agents, deposition of gadolinium has also been observed with macrocyclic agents [5]. A recent study that included 50 pediatric patients who underwent an average of 10 ± 2.8 (range: 6-18) administrations of the same macrocyclic GBCA at the same dose as in the present study, and a control group of 59 age-matched GBCA-naïve patients, reported significantly increased globus pallidus-to-thalamus and dentate nucleus-to-pons signal intensity ratios on unenhanced T1-weighted images in the former group [7]. In addition, a significant effect of the number of GBCA injections on signal intensity ratios was demonstrated [7]. However, another

study in 24 pediatric patients reported that multiple intravenous administrations of macrocyclic GBCAs (gadoteridol and gadoterate meglumine) were not associated with a measurable increase in signal intensity on unenhanced T1-weighted images [8]. Main limitations of these two studies are their retrospective designs, their relatively limited sample sizes, and the fact that they only included patients with (treated) brain tumors. Although the number of studies in the pediatric population is still limited, according to the International Society for Magnetic Resonance in Medicine (ISMRM), convincing evidence is available for the deposition of gadolinium in the deep nuclei of the brain, particularly after repeated exposure to GBCAs [5]. Furthermore, although there are no reliable data regarding the clinical or biological significance of gadolinium deposition in the brain (if any), both the ISMRM and the U.S. Food and Drug Association recommend limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary and to reassess the necessity of repetitive GBCA MRIs in established treatment protocols [5].

Given the apparent lack of impact of local surveillance MRI on survival in Ewing sarcoma as demonstrated by the present study, the costs of MRI, and GBCA-related concerns that are of particular importance in this generally young patient population, the routine use of MRI in the surveillance setting should be reconsidered, unless improved treatment strategies for recurrent Ewing sarcoma become available. If surveillance MRI is performed anyways, patients (and/or their guardians) should be informed that early detection of recurrent disease does not necessarily imply an improved outcome. On another note, although theoretically one might consider to perform surveillance MRI without GBCA-enhanced sequences, this may be at the expense of decreased sensitivity and specificity for recurrent disease detection.

This study had several limitations. First, the sample size of this study was relatively small and the retrospective design may have introduced selection bias. Second, various treatment regimens were applied and surveillance MRI was variable with regard to timing and frequency among included patients. The latter was at the discretion of the treating orthopaedic surgeon and/or oncologist, and reflects the lack of evidence and guidelines on the use of surveillance imaging after primary treatment. Third, although surveillance MRI seemed not to affect outcome, this study did not include a randomized control arm of patients who did not undergo surveillance MRI. Fourth, gadolinium deposition in the brain of included patients could not be assessed because brain MRI was not (routinely) performed in these patients.

In conclusion, a limited number of patients has locally recurrent Ewing sarcoma on surveillance MRI. These patients often have simultaneous recurrent (metastatic) disease elsewhere, and their outcome is poor. Moreover, some patients present without locally recurrent disease on MRI but disease recurrence elsewhere. Therefore, surveillance MRI currently seems to have little value and should be reconsidered, also given the costs and the repeated exposure of surviving patients to GBCAs.

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