Could Routine Magnetic Resonance Imaging Detect Local Recurrence of Musculoskeletal Sarcomas Earlier? A Cost-effectiveness Study

Abstract

Background: Current practice in our unit is to perform clinical assessment and plain film radiographs at regular intervals following treatment of a bone or soft tissue sarcoma (STS). Cross-sectional imaging is used in cases with a clinical suspicion of recurrence. We aimed to investigate the effectiveness of this protocol to determine if earlier detection may have been possible had more intensive imaging been undertaken, and whether this may have affected outcome. **Materials and Methods:** We reviewed clinical records and imaging of all patients with diagnosed local recurrence (LR) in the previous 5 years to investigate: how it was diagnosed, the site and size of recurrence, and management. A value judgment was then made as to whether earlier diagnosis may have altered treatment and/or outcome. **Results:** 161 patients with LR were identified: 87 with a STS and 74 with bone sarcoma. Median time from diagnosis to LR was 17.8 months for STS and 20.1 months for bone sarcoma. One hundred and fifteen cases (71%) were identified by the patient, 28 by routine imaging (17%), 13 by a doctor (8%), and five diagnosed by other methods. Median size of LR was 5.5 cm for STS and 5 cm for bone sarcomas. Seventy nine of the patients (49%) could have had their LR diagnosed earlier with routine imaging. Of these, 53 would have received the same treatment, but 26 (33%) could have had different treatment. **Conclusion:** Earlier diagnosis could have led to altered management in one-third of those patients with the potential to have their LR diagnosed earlier. If all patients had regular magnetic resonance imaging, it would cost £6987 per recurrence where management was altered in imaging costs alone. We suggest a stratified approach whereby patients at highest risk of LR and those in whom early detection of LR may be easily treatable are prioritised for more intensive followup.

Keywords: *Sarcoma, musculoskeletal, local recurrence, magnetic resonance imaging, surveillance. cost analysis*

MeSH terms: *Magnetic resonance imaging, recurrence, tumours, sarcoma*

**Andrew George,
Robert J Grimer,
Steven L J James**

Department of Orthopaedic Oncology, Royal Orthopaedic Hospital, Birmingham, UK

Introduction

Sarcomas are a rare type of malignant tumor arising from the connective tissues and bone accounting for approximately 1% of all cancer diagnoses in the UK.[1] The mainstay of treatment is by surgical excision and adjuvant radiotherapy or chemotherapy. One of the major concerns in the management of such tumors is the development of local recurrence (LR). LR for soft tissue sarcomas (STS) is reported to be as high as 10%–20% within the first 2–3 years following treatment.[2] Prognostic factors for the development of LR in STS are well documented and, most notably, are known to include: histological grade, size of the tumor, depth in relation to the deep fascia, and surgical resection margins.[3-6] The main prognostic factors for the recurrence of bone sarcomas are the adequacy of surgical resection margins and the response to neoadjuvant chemotherapy.[7]

One of the main aims of followup for patients following initial treatment of any sarcoma is to detect recurrent disease at a time when it can be successfully managed, offering a chance of further disease remission. There is, however, a dearth of studies investigating the optimum followup regimen with most guidance being consensus rather than evidence based.[8,9] UK studies have shown that a wide variation exists between clinicians in their followup protocols; some using far more frequent imaging to detect recurrence than others.[6] While this may in part relate to cost or availability of imaging services; in the majority is probably due to clinician preference and lack of clear evidence for the benefit of one regimen over another. LR has been shown to lead to significantly

Address for correspondence:
Mr. Andrew George,
Royal Orthopaedic Hospital,
Bristol Rd S, Birmingham,
B31 2AP, UK.
E-mail: andrew.george@doctors.
org.uk

poorer outcomes and prognosis and may also increase the risk of future distant metastasis.[10-12] More importantly, therefore, this potentially translates into disparity of clinical care experienced by patients. One notable exception is the TOSS trial carried out by Puri *et al*. which compared low and high-intensity followup (3-monthly and 6-monthly) along with enhanced versus standard imaging (computed tomography [CT] vs. chest X-ray [CXR]) in a 2 × 2 factorial study. While this showed that metastasis could be identified earlier with CT scans, as compared with CXR, this did not result in improved survival.[13] This does, however, contrast with a retrospective study by Paioli *et al*., who did find better survival in those whose metastasis were identified by CT compared with CXR.[14]

Current practice in our center is to perform clinical followup and chest radiographs for patients following treatment of sarcoma with the use of cross-sectional imaging reserved if there is a high clinical suspicion of recurrence. Clinical followup typically takes place every 3 months for the first 2 years after primary treatment has ended and then 6 monthly up to 5 years, with annual visits thereafter. Routine MRI imaging is generally advocated only in those patients with either pelvic or sacral tumors due to the relative difficulty in detecting signs of LR clinically. This is supported by the findings of Cipriano *et al*. who investigated their followup regimen for bone sarcomas.[15] Currently, there is no risk stratified method available to identify patients at greatest risk of LR and who would particularly benefit from earlier detection.

This study aimed to assess the effectiveness of this policy by investigating those patients who developed recurrence following definitive treatment of a bone sarcoma or STS. We intended to identify: how LR was detected and treated; the size of LR at diagnosis; if LR could have been identified earlier had routine imaging with MRI been used; and whether earlier detection would likely have altered subsequent management and/or outcome for patients. We also assessed the economic impact of implementing regular cross-sectional imaging for the detection of LR in all patients and evaluated the possible cost-benefit ratio of this.

Materials and Methods

A total of 161 patients (of approximately 4000 patients under review during this period) were diagnosed with LR of a bone sarcoma or STS over a 5.5-year period, between January 1, 2005, and July 1, 2010. A retrospective review of clinical records and appropriate radiological imaging was undertaken to include: how the LR was diagnosed; the site and size of the recurrence, and its subsequent management. Time to LR was taken from the date of first definitive treatment to the date of diagnosis of the first LR.

A value judgment was then made by the senior authors (RG and SJ) to determine whether earlier diagnosis would have been possible had routine cross-sectional imaging

with MRI been carried out at each outpatient visit, up to 5 years. The decision was reached in consensus by looking at the time to LR, the size of LR at the time of detection and its location. We identified whether MRI carried out at the previous routine visit would have likely detected the LR, and whether this might have affected the subsequent management.

Statistical analysis

Analyses of data were carried out using StatView® version 5.0.1 (SAS® Institute Inc., Cary, NC, US). Median values were used due to the nonparametric nature of the data. *P* <0.05 was considered statistically significant.

Results

Bone sarcoma

Of 161 patients developing LR, 74 were bone sarcomas. Forty-one patients were male. Median age at first diagnosis was 44 years (interquartile range [IQR]: 37–71) with a median age of 46.8 years (IQR: 39.5–75.2) at diagnosis of LR. The median time from definitive treatment to development of LR was 27 months (IQR: 10.0–36.9).

The most common site for LR of bone tumors was the femur (*n* = 22), pelvis (*n* = 21), and proximal tibia (*n* = 9). Thirty of the 74 patients with bone sarcomas developing LR had a chondrosarcoma, for which the pelvis (*n* = 13) was the most common site followed by proximal femur (*n* = 5). Twelve patients with osteosarcoma developed LR; the most common sites being the distal femur (*n* = 5), proximal tibia (*n* = 2), and pelvis (*n* = 2). Seven patients with Ewing's sarcoma developed LR.

Median tumor size was 5 cm for bone sarcomas (IQR: 1–28 cm) [Figure 1], while median size of LR detected by patients was 6 cm (IQR: 2.5–11 cm). Symptoms reported by those patients with patient-identified LR are outlined in Table 1. Of the 74 patients with bone sarcoma, we determined 33 patients could have been diagnosed earlier with routine cross-sectional imaging. Eleven of these 33 patients were pelvic sarcomas.
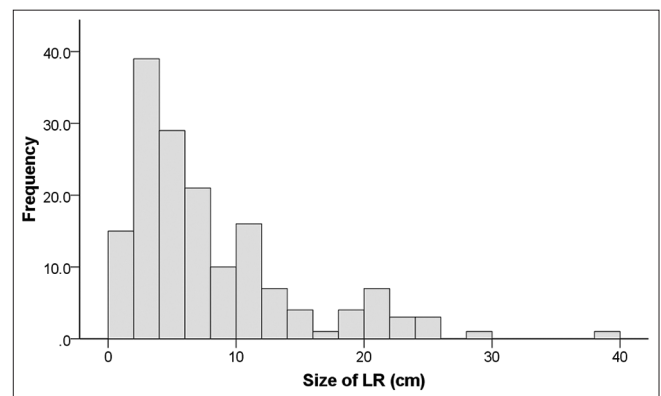

Figure 1: Histogram showing size of local recurrence at time of diagnosis for all cases in this series

Soft tissue sarcoma

Of 161 patients developing LR, 87 were STS. Fifty patients were male. Median age at first diagnosis was 64 years (IQR: 53–71.5 years) with a median age of 67.5 years (IQR: 55.2–75.2) at diagnosis of LR. The median time from definitive treatment to development of LR was 26.5 months (IQR 8.8–37.6).

Of the 87 patients with STS who developed LR, 35 were in the thigh or knee region with a wide range of diagnoses. Median tumor size at the time of LR was 5.5 cm for STS (IQR: 3–10.5 cm) [Figure 1] and 5.5 cm for LR detected by patients (IQR 3–10 cm). Median size of LR for STS was 5 cm for superficial tumors (IQR 2–8 cm) and 5.5 cm for deep tumors (IQR: 3.3–12 cm). Symptoms reported by those patients with patient-identified LR are outlined in Table 1. Median size of LR for patients presenting with a painless lump was 5.3 cm (IQR: 3.3–10 cm); 3 cm for patients presenting with pain alone (IQR 2.5–4 cm) and 8 cm for those presenting with a painful lump (IQR: 4–16.5 cm). Of the 87 patients with STS, we determined 46 patients could have been diagnosed earlier with routine cross-sectional imaging. Only one of these 46 patients was a pelvic sarcoma.

All cases

Median time to LR for all cases in this series is illustrated in Table 2 and Figure 2. In general, this was shorter for higher grade tumors for both bone sarcoma and STS. Twenty-one patients overall had LR detected after 5 years and seven diagnosed after 10 years. Twenty-three per cent of low-grade tumors which developed LR were diagnosed after 5 years, compared to 8% of all LR in those with high-grade or intermediate tumors.

One hundred and fifteen cases of LR were initially identified by the patient, 28 detected by routine imaging
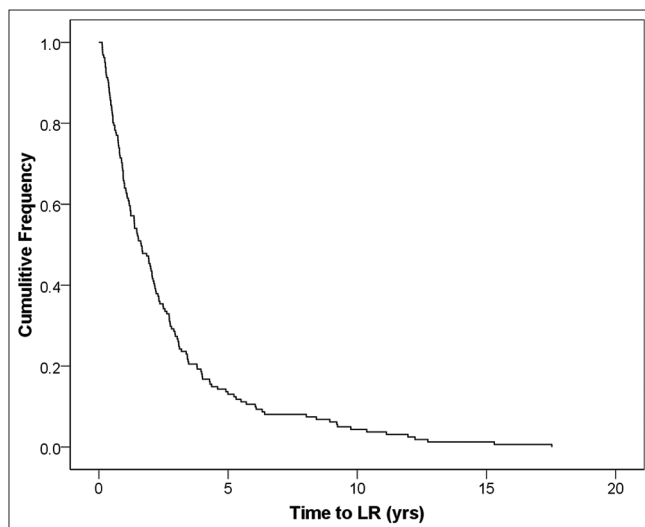
used at followup, 13 by a doctor during routine clinical examination at followup visits, and 5 diagnosed by other means. This included: by district nurse, positron emission tomography (PET) scan, and as an unexpected finding at the time of surgery [Table 3 for bone sarcoma and STS]. Of those detected on routine imaging, 24 patients had LR detected by MRI but only 4 patients had their LR initially identified on plain radiographs (three chondrosarcomas and one parosteal osteosarcoma). Of the 13 pelvic tumor recurrences, eight were detected by routine imaging (MRI), only four by the patient, and one was discovered during outpatient review. There was no significant difference between the time to detection of LR and the method of diagnosis used. There was no significant difference in size by gender, age, diagnosis, or time to LR.

We determined that 79 cases would likely have had their LR diagnosed earlier with routine imaging using MRI. However, 17 of the 79 developed their LR after 5 years and thus may not have had imaging continued that long in any event. Of those, 53 would have received the same treatment if diagnosed at an earlier stage (as assessed by the senior authors). The remaining 26 (33% of this group or 16% of the total group) would have received different management. Of those, 18 would have had a smaller operation: eight avoiding amputation and ten receiving less extensive

Table 1: Presenting symptoms of patient-identified locally recurrent disease for bone and soft tissue sarcomas

Symptoms	STS (%)	Bone sarcoma (%)
Painless lump	54 (62)	21 (28)
Painful lump	7 (9)	12 (16)
Pain only	5 (6)	11 (15)
Other	3 (3)	2 (3)
Total	69 (80)	46 (62)

STS=Soft tissue sarcoma

Table 2: Median time to local recurrence for bone and soft tissue sarcoma by grade of sarcomas

Grade	Median time to LR (months)	
	STS	Bone sarcoma
High	11.2	17.5
Intermediate	36.6	18.2
Low	35.2	25.2

STS=Soft tissue sarcoma, LR=Local recurrence

Table 3: Route by which local recurrence was initially detected for soft tissue sarcoma and bone sarcomas

Route diagnosed	STS (n=87)	Bone sarcoma (n=74)	Total (%)
Patient identified	69	46	115 (71)
Routine imaging	7	21	28 (17)
Routine clinic	8	5	13 (8)
Other	3	2	5 (3)

STS=Soft tissue sarcoma

Figure 2: Kaplan-Meier graph showing time from first definitive treatment to development of local recurrence for all cases in this series

surgery. A further five patients would potentially have been operable with earlier diagnosis; however, the LR was too extensive by the time of diagnosis. Finally, three patients would have undergone amputation had their LR been diagnosed earlier. All three, however, had metastasis by the time the LR was eventually diagnosed and thus received palliative treatment. As these patients would probably have developed metastasis in any event, the delay in diagnosis of LR led to them avoiding amputation [Figure 3]. The subsequent management patients actually received following diagnosis of LR is outlined in Table 4.

Of the 161 patients with diagnosed LR, 52 patients developed metastatic disease within the time frame of this study. Of those, 38 developed metastasis after LR had been diagnosed with 14 developing metastasis before the diagnosis of LR. The remaining 109 cases had not developed any metastatic disease at the time of review.

Economic evaluation

The current national average unit cost to the NHS of an MRI scan is £175.[16] A patient followed-up for 5 years, receiving MRI at every followup visit, would receive 14 MRI scans at a cost of £2,450 (four a year for the first 2 years then twice a year for the subsequent 3 years). Had all the 161 patients in this study received MRI at each regular followup, a total of 1038 scans would have been carried out before the time of diagnosis of LR. This relates to a cost of £181,650, detecting 79 of the LR earlier at a cost of £2299 per earlier diagnosed case. However,

this would only have made a difference in 26 patients, thus altering management at a cost of £6987 per patient. Furthermore, nine of the 26 cases were diagnosed after 5 years, with the above calculation assuming ongoing regular annual scans even after 5 years.

This data can now be extrapolated to a population of sarcoma patients. Approximately 60% of patients survive to 5 years (including those developing LR) with the median survival in those not surviving being 2 years (data from our own unit). If an overall LR rate of 10% is assumed, for every 100 patients:

40% will die of metastasis at a mean of 2 years (average of 6 scans), 10% will develop LR at a mean of 2.3 years (average 6.5 scans), 50% will not develop LR or metastasis (receive 14 scans).

The total number of scans carried out in this group would be (40 × 6) + (10 × 6.5) + (50 × 14) = 1005. This would cost £175,875 to detect the ten patients developing LR. Of these, half (five) would be detected earlier by MRI but in only 1.6 would treatment be altered. The cost would thus be £35,175 per LR detected earlier but would be £109,921 for each case in which management was altered. If the LR rate was 20% then there would be 930 scans to detect 20 LR, of which 3.2 would have management altered. The cost would thus be £50,860 per case where management was altered.

Discussion

This paper set out to assess the effectiveness of our current surveillance strategy for the detection of LR following definitive primary treatment for musculoskeletal sarcoma. It is evident that there is a wide variation in posttreatment followup for patients with sarcoma. This has been identified by Gerrand *et al.*,[6] with recent UK and European consensus guidelines also confirming disparity over the optimum followup protocol for patients.[8,9,17] Cool *et al.* demonstrated that the majority of LR (76% of STS and 62% of bone

Table 4: Management of patients following local recurrence for soft tissue sarcoma and bone sarcomas

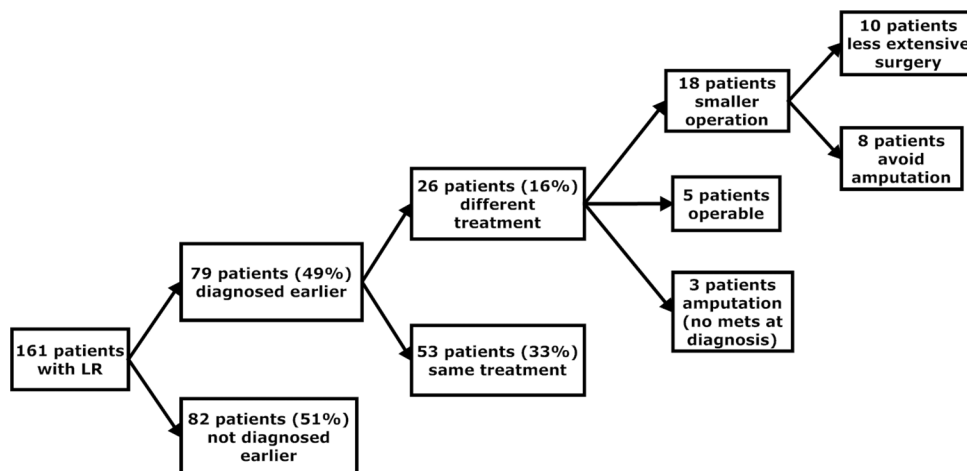| Management	Patients (%)
Local excision	84 (52)
Limb amputation	28 (17)
Palliative care	33 (21)
Radiotherapy or chemotherapy	9 (6)
Other treatment	7 (4)

Figure 3: Flowchart illustrating the differential management of patients if they had undergone regular cross-sectional imaging

sarcomas) are detected by the patient themselves, and in Rothermundt's more recent study, 97% of LRs were detected by the patient.[18,19] This finding is replicated in the current study; 71% of all LRs (79% for STS and 62% for bone sarcoma) being initially identified by patients. If pelvic tumors are excluded, then 77% of all LRs were detected by the patient. A lump, whether painful or not, was the most common presentation seen.

The median size at diagnosis, however, for those LR detected by patients was 6 cm. This is still quite substantial and suggests that patients are in fact relatively poor at detecting LR at an early stage. Even LR for superficial STS detected by patients was as large as 5 cm before it was identified. Thus, better patient education about regularly checking for lumps may have a role in earlier detection of LR. This advice is routinely given to patients with breast cancer but not to sarcoma patients and there is clearly scope for investigating this simple measure as was suggested by Puri *et al*. at the conclusion of their randomized followup study.[13,20]

Only four patients (5%) with bone sarcoma had LR detected through followup with routine plain radiographs. This relates to <1 sarcoma identified through this method each year. This raises a major concern as to whether there is any clinical benefit to continue routine radiographs following definitive treatment for patients with bone sarcomas. We estimate approximately 1000 patients with bone sarcomas are seen for followup each year in our unit, and thus the detection rate for LR from this method is approximately 0.1%. The primary role of radiographs in the postoperative phase is in evaluating complications relating to implanted metalwork rather than in the assessment of LR.

Just under 10% of LR (13 patients) were detected during routine clinical followup. Relative to the number of patients undergoing review during this period, this relates to a <1% chance of identifying LR on clinical grounds alone. In addition, this should be considered against the time, resources, and burden for patients coming to clinic.

Approximately one-third of patients also developed metastatic disease, the majority being detected after the diagnosis of LR. However, there is remarkably little literature relating to the timing of metastatic disease in relation to LR and the potential causative relationship between them.[21] Furthermore, we are not aware of any study correlating the size of LR at the time of detection with outcome although size is an important prognostic factor for primary sarcomas.

A number of imaging techniques have been proposed for the detection of LR in musculoskeletal sarcoma including: radiographs, MRI, CT, ultrasound, PET, and bone scintigraphy. MRI is widely thought to offer the greatest sensitivity, but it is not specific and may lead to over-investigation of benign abnormalities with benefits of regular MRI imaging being unproven to date.[22,23] Although it may be desirable that patients should receive cross-sectional imaging at every followup, this will not alter the rate of LR which is determined by tumor and treatment characteristics. It may, however, bring forward the time of diagnosis leading to easier further local control although it remains uncertain whether this will lead to improved overall survival.

Watts *et al*. evaluated the usefulness of regular MRI imaging as a surveillance strategy for LR, reporting that 9 out of 13 LR were detected by routine surveillance scans.[23] They did not comment how this affected outcome nor the size of the tumors at the time of LR. The fact that these 13 LRs arose in just 57 patients (22%) suggests that they must have been a very high-risk population. They estimate the cost of MRI surveillance to be £4414 per recurrence detected. The estimated figure in this study is approximately ten times that proposed by Watts *et al*. Thus, although routine MRI imaging may have a role in detecting LR at an earlier stage, it appears to be a relatively high-cost, low-yield modality for routine use at every clinical followup. It should be noted that these calculations were made on the basis that MRI was carried out at the same frequency as normal followup until 5 years. Therefore, this would not have detected the 13% of cases where LR arose after 5 years. If imaging were to be continued annually after 5 years, this would increase the cost further still.

The use of ultrasound has been suggested as an alternative to MRI, particularly in patients with STS. However, it is operator dependent and assessment is frequently limited when examining the deep pelvic regions. Furthermore, appearances are often nonspecific requiring confirmatory MRI and biopsy in many cases. These same problems also apply to MRI, added to which is the problem of artifact from metallic prostheses or other implants.[24-26]

It is evident that a number of challenges still exist in detecting LR earlier. Possible strategies for improvement in the detection of LR include better patient education and regular imaging (either MRI or ultrasound). Potentially, most important of all, however, is risk stratification of patients so that those in whom there is a perceived high risk of LR, and where earlier detection may make a difference, could be considered for regular imaging. Nomograms for estimating risk of LR are now available and are likely to be refined further.[27] This should be combined with an assessment of the role of patient education in improving their awareness of the risk of LR.

It is acknowledged that this study has significant limitations. First, this is a retrospective review of cases from just one unit and may not reflect experiences across the UK. Second, the highly subjective nature of the assessment by the senior clinicians, both about the likelihood of earlier detection with regular MRI and the effect of this on treatment, is clearly open to bias. Independent review of the cases may

result in a change in the percentages but is unlikely to have a major impact on overall outcome.

The question as to whether LR leads to a worse prognosis or whether it is merely an indicator of bad disease has not yet been satisfactorily resolved. However, there is no doubt that earlier detection of LR will lead to a better chance of regaining local control without major further surgery in some cases. Furthermore, a more comprehensive cost analysis is required in subsequent studies to determine the true economic impact of implementation of regular cross-sectional imaging for the detection of LR. This should also include the length of time surveillance should be continued. Ideally, a randomized controlled trial should be considered to address whether intensive imaging improves outcomes in any way and/or is cost effective for sarcomas.

In general, however, and certainly in developing countries, there is as yet no evidence that enhanced imaging is either beneficial of cost effective in allowing earlier detection of LR or improving survival.

Conflicts of interest

There are no conflicts of interest.

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