Accuracy of Various MRI Sequences in Determining the Tumour Margin in Musculoskeletal Tumours

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Summary

Background: It is imperative that bone tumour margin and extent of tumour involvement are accurately assessed pre-operatively in order for the surgeon to attain a safe surgical margin. In this study, we comprehensively assessed each of the findings that influence surgical planning, on various MRI sequences and compared them with the gold standard – pathology.

Material/Methods: In this prospective study including 21 patients with extremity bone tumours, margins as seen on various MRI sequences (T1, T2, STIR, DWI, post-gadolinium T1 FS) were measured and biopsies were obtained from each of these sites during the surgical resection. The resected tumour specimen and individual biopsy samples were studied to assess the true tumour margin. Margins on each of the MRI sequences were then compared with the gold standard – pathology. In addition to the intramedullary tumour margin, we also assessed the extent of soft tissue component, neurovascular bundle involvement, epiphyseal and joint involvement, and the presence or absence of skip lesions.

Results: T1-weighted imaging was the best sequence to measure tumour margin without resulting in clinically significant underestimation or overestimation of the tumour extent (mean difference of 0.8 mm; 95% confidence interval between –0.9 mm to 2.5 mm; inter-class correlation coefficient of 0.998). STIR and T1 FS post-gadolinium imaging grossly overestimated tumour extent by an average of 16.7 mm and 16.8 mm, respectively (P values <0.05). Post-gadolinium imaging was better to assess joint involvement while T1 and STIR were the best to assess epiphyseal involvement.

Conclusions: T1-weighted imaging was the best sequence to assess longitudinal intramedullary tumour extent. We suggest that osteotomy plane 1.5 cm beyond the T1 tumour margin is safe and also limits unwarranted surgical bone loss. However, this needs to be prospectively proven with a larger sample size.

MeSH Keywords: Bone Neoplasms • Magnetic Resonance Imaging • Osteosarcoma

PDF file: http://www.polradiol.com/abstract/index/idArt/898108
Involvement of epiphysis, joint space and neurovascular bundle by the tumour, presence of skip lesions and soft tissue extent of tumour also determine the extent of surgical resection. Overestimating the tumour extent may deter the surgeon from performing a limb salvage surgery and instead opt for an amputation thereby increasing the morbidity and worsening the post-operative quality of life. On the other hand, underestimating tumour extent may result in the resection margin being too close to the tumour thereby increasing the chance of recurrence.

Various studies showed that T1-weighted imaging and STIR (short tau inversion recovery) sequence were the best to determine the longitudinal intramedullary tumour extent [1,3–7]. Through our study, we aimed to determine the MRI sequence that accurately depicts the intramedullary longitudinal tumour extent. In addition, we also aimed to identify the best MRI sequence to assess epiphyseal tumour extension, joint and neurovascular bundle involvement, skip lesions and soft tissue extent of the tumour.

Material and Methods

Institutional review board approval was obtained prior to the commencement of the study. Inclusion criteria – only those children with primary musculoskeletal tumours who presented to Paediatric Orthopaedics Department and gave consent for pre-operative MRI and surgical resection of tumour were included in the study. We excluded those children whose MRI showed very well defined, benign bone lesions (those with no reactive zone) and those children who withdrew consent for surgery after initially being enrolled in the study. We also excluded those children who did not have a post neo-adjuvant chemotherapy MRI (due to time constraints or otherwise) and in whom surgical resection was based on the pre-chemotherapy MRI. Patients were recruited prospectively over a period of 10 months, from January 2012 to October 2012. Informed written consent was obtained from the patient’s parent or guardian prior to the MRI and surgery. Verbal assent of the child (patient) was also obtained.

MRI was performed in a 1.5-Tesla scanner (Avanto, SIEMENS Systems, Germany) using 16-channel body array anterior MRI coils. In all extremity tumours, one joint above and one joint below the tumour were included in the scanning field using a larger Field of View (FOV). The contralateral limb was included in the FOV whenever possible. The MRI protocol included the following sequences – spin echo T1 coronal and axial; turbo spin echo T2 sagittal and axial; T2 STIR coronal and axial; T1 FS coronal and axial – pre- and post-contrast; DWI coronal and axial. The MRI scan parameters are given in detail in Table 1. In all patients who received neoadjuvant chemotherapy, an MRI was performed after completion of the chemotherapy and prior to surgical resection. The time interval between the last imaging and surgery was noted.

The extent of signal abnormality was assessed on each MRI sequence by the primary author and another senior radiologist with more than 10 years of experience in paediatric radiology on Picture Archiving and Communication System (PACS, GE Centricity) software. Intramedullary tumour extent and soft tissue abnormality were measured in millimeters in each of the sequences. The involvement of the epiphysis, adjacent joint space, neurovascular bundle and the presence or absence of skip lesions were recorded separately. Intramedullary tumour margin on each of the available MRI sequences was compared with the gross pathological margin which was considered as the gold standard. When the pathological tumour margin was the same as that of any MRI sequence, it was recorded so. In all the remaining cases where there was a discrepancy between the pathological tumour margin and MRI tumour margin, the distance by which each of the MRI sequences underestimated or overestimated the tumour extent was

### Table 1. Showing the MRI scan parameters.

|        | T1          | T2          | STIR        | T1 FS       | T1 FS gado   | DWI         |
|--------|-------------|-------------|-------------|-------------|--------------|-------------|
| TR     | 465 ms      | 3870 ms (sagittal) | 3580 ms (coronal) | 465 ms (coronal) | 465 ms (coronal) | 4400 ms (coronal) |
|       | 4240 ms (axial) | 8020 ms (coronal) |             | 542 ms (coronal) | 542 ms (coronal) | 9700 ms (axial)   |
| TE     | 12 ms       | 75 ms       | 81 ms (coronal) | 1 ms        | 12 ms        | 79 ms       |
|        |             |             | 53 ms (axial)  |             |              |             |
| FA     | 1500        | 1500        | 1500        | 1500        | 1500         | –           |
| ST     | 3 mm        | 3 mm (sagittal) | 3 mm (coronal) | 3 mm (coronal) | 3 mm (coronal) | 3 mm (coronal)  |
|        |             | 6 mm (axial) | 6 mm (axial)  | 6 mm (axial)  | 6 mm (axial)  | 6 mm (axial)   |
| SG     | 0.3 mm      | 0.3 mm (sagittal) | 0.3 mm (coronal) | 0.3 mm (coronal) | 0.3 mm (coronal) | 0.3 mm (coronal) |
|        |             | 1.2 mm (axial) | 1.2 mm (axial) | 1.2 mm (axial) | 1.2 mm (axial) | 1.2 mm (axial) |
| Matrix | 230×384     | 230×384     | 192×320     | 230×384     | 230×384      | 154×192      |
| Others | –           | –           | –           | –           | –            | –           |

TR – repetition time; TE – time of echo; FA – flip angle; ST – slice thickness; SG – slice gap; TI – time of inversion; EPI – echoplanar imaging.
Biopsies were taken during surgery from each of the bone and soft tissue margins as seen on various MRI sequences. These samples were appropriately labelled and sent to the pathologist in a formalin fixative along with the resected tumour specimen. The resection specimen and histopathology slides were reviewed by a single experienced pathologist with a special interest in skeletal pathology. The pathological tumour margin was recorded on the cut surgical specimen which was considered as the gold standard in our study. Histopathological examination of tissue from areas of abnormal signal other than the actual tumour, helped us identify the cause for altered signal intensity in the peritumoral reactive zone. Sections were checked for normal tissue, viable tumour, necrosis, fibrosis, oedema and any other relevant finding and these were recorded. In addition to the presence of a viable tumour, any necrotic tumour tissue was also considered as positive for tumour. The presence of oedema, muscle atrophy, or osteonecrosis (any of which could have contributed to the abnormal signal on MRI) was also separately recorded.

All study variables were described using descriptive statistical methods. Continuous variables were summarised using mean and standard deviation (SD). Skewed data were summarised using median and interquartile range. Frequency calculations were used along with descriptive analysis to assess the accuracy of various MRI sequences to predict tumour margins. Paired t-test was done to assess the mean difference between each MRI sequence and the gold standard. Inter-class correlation coefficients were calculated for all the sequences. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of various MRI parameters like epiphyseal, joint and neurovascular bundle involvement were calculated.

**Results**

A total of 23 consecutive patients with primary bone tumours of the limbs were enrolled in the study, of which 2 patients refused surgery and therefore were excluded from the final analysis. A total of 21 patients underwent surgery during the study period and were included in the final analysis. The patients were between 5 to 17 years of age (mean – 11.5 years; SD – 3.3 years; 12 male and 10 female). The most common tumour was osteosarcoma (16 out of 21) followed by Ewing sarcoma (4 out of 21). There was one case of aggressive giant cell tumour. The median interval between the MRI and the surgery was 11 days with an interquartile range (IQR) of 6 to 17 days.

**Intramedullary tumour extent**

The results are summarised in Tables 2 and 3. The tumour margins as measured on STIR and T1 FS post-gadolinium imaging were inaccurate compared to the pathological margins and the mean difference was statistically significant as assessed on paired t-tests. Mean difference between tumour margin measurement on pathology and T1-weighted imaging was only 0.8 mm, and that difference was statistically insignificant.

**Epiphyseal involvement**

Epiphyseal involvement was taken as present if there was tumour crossing the physeal plate with an abnormal signal within the epiphysis. Epiphyseal involvement on MRI was seen in 16 out of 21 (76%) patients of which 14 were confirmed on pathology and 2 were false-positive cases. One of the false-positive cases showed an abnormal epiphyseal signal on both T1 and STIR images while the second case showed an abnormal epiphyseal signal only on T1W imaging. Histological examination showed signal abnormality in the two false-positive cases to be due to oedema. T1WI and STIR sequences were the best to assess epiphyseal involvement (Figure 1) with sensitivity and specificity of 92% and 71% (T1WI), and 100% and 85% (STIR), respectively. By using a combination of T1 and STIR sequences, the overall sensitivity, specificity, PPV and NPV of MRI to predict epiphyseal involvement were 100%, 71%, 87%, and 100%, respectively.

**Joint involvement**

Joint involvement was taken as positive on MRI when there was a mass seen within the joint space or when there was a definite breach of articular cartilage by the tumour with or without an actual mass projecting into the joint cavity. Involvement of cruciate ligaments in the knee was also taken as a criterion for joint involvement on MRI. Joint involvement was seen on MRI in 6 out of 21 (28%) patients, of which 5 were confirmed on pathology and 1 case was false positive on MRI. T1 FS post-contrast sequence best depicted joint involvement. The sensitivity, specificity, PPV, and NPV of MRI to assess joint involvement were 100%, 93%, 83%, and 100%, respectively.

**Neurovascular bundle involvement**

Neurovascular bundle involvement was taken as present when tumour completely surrounded it or when at least 50% of the neurovascular bundle was surrounded by tumour with loss of fat plane in at least one axial section. A combination of T2W imaging and T1 FS post-gadolinium imaging was used to get this information. Three out of the 21 (14%) patients had neurovascular bundle involvement on MRI. During surgery, it was found that 2 out of those 3 patients did not have encasement of the neurovascular bundle and that was later confirmed on pathology specimen. The sensitivity, specificity, PPV, and NPV of MRI to predict neurovascular bundle involvement were 100%, 90%, 33.3%, and 100%, respectively.

**Skip lesions**

Only 1 patient in our series had skip lesions on MRI (Figure 2). These lesions extended till 10 cm beyond the gross tumour margin and were best seen on T1, T1 FS, and STIR images. These were confirmed by histopathology.
Soft tissue abnormality

In our study, no single MR sequence accurately differentiated the tumour from the peritumoral reactive zone. The extent of abnormal soft tissue signal was more with T2WI, STIR and T1FS than with the other sequences in most of the cases. Even T1 FS post-gadolinium sequence significantly overestimated the extent of soft tissue involvement (Figure 3). In some cases, signal abnormality in the muscles surrounding the tumour involved the entire length of the muscle – a pattern described earlier as "Massive oedema" [8] (Figure 4). This was noted in 5 patients in our study (4 Osteosarcoma; 1 Ewing sarcoma). Histologically the most common cause of an abnormal signal in the peritumoral zone was found to be oedema in any individual sequence. This was followed by other causes like focal areas of haemorrhage, fibrosis and atrophy of myocytes. In most cases, it was a combination of these findings. We also noted that, in all the cases where the intraosseous tumour component was relatively well-defined, the soft tissue component of the tumour ended within a maximum of 1.1 cm from the bony component.

Discussion

The importance of choosing the best MR sequence to identify the tumour margin is to guide the surgeon in planning the osteotomy plane and the extent of resection. The principle behind this is to identify a sequence that does not underestimate the tumour length which increases the chance of post-operative recurrence. Additionally, the ideal MR sequence should not overestimate tumour length which may result in avoidance of limb salvage surgery or reducing the chances of offering maximum prosthetic rehabilitation after surgery. In our study we assessed intramedullary tumour extent, epiphyseal tumour extension, joint and neurovascular bundle involvement, skip lesions and soft tissue extent of the tumour on each of the MRI sequences. To the best of our knowledge, there was no single prior study that comprehensively evaluated all the above parameters. We acknowledge that the small sample size is a limitation in our study and larger prospective studies on a larger scale are needed before we can generalize the conclusions of this study.

Table 2. Showing accuracy of each of the MRI sequences in assessing intramedullary tumour extent compared to gross pathology margins.

| Sequence   | Same as pathological margin | Overestimated | Underestimated |
|------------|-----------------------------|---------------|---------------|
|            |                             | Frequency     | Up to 1 cm    | >1 cm         | Frequency | Up to 1 cm | >1 cm |
| T1 FS*     | 74% (14/19)                 | 21% (4)       | 2             | 2             | 5% (1)    | –           | 1     |
| T2         | 52% (11/21)                 | 43% (9)       | 6             | 3             | 5% (1)    | –           | 1     |
| STIR       | 9% (2/21)                   | 86% (18)      | 8             | 10            | 5% (1)    | 1           | –     |
| DWI**      | 50% (5/10)                  | 20% (2)       | 1             | 1             | 30% (3)   | –           | 3     |
| T1 FS gado*| 32% (6/19)                  | 68% (13)      | 4             | 9             | 0%        | –           | –     |
| T1 (no FS) | 71% (15/21)                 | 19% (4)       | 3             | 1             | 9% (2)    | 2           | –     |

* T1 FS and T1 FS gadolinium images were not available in 2 out of 21 patients; ** DWI images were not available in 2 patients. Only 10 out of the remaining 19 patients showed diffusion restriction within the tumour.

Table 3. Showing the difference in tumour margin measurement on each MRI sequence vs. the gross pathological specimen.

| MRI sequence | Mean difference (in mm) * | 95% confidence interval of the difference (in mm) * | p value (2 tailed) | Inter-class correlation coefficient |
|--------------|--------------------------|---------------------------------------------------|--------------------|-----------------------------------|
| T1 FS        | 2.7                      | Lower -2.2, Upper 7.7                             | 0.262              | 0.990                             |
| T2           | 4.3                      | Lower -0.7, Upper 9.3                             | 0.088              | 0.988                             |
| STIR         | 16.7                     | Lower 7.1, Upper 26.3                             | 0.002              | 0.940                             |
| T1 FS gado   | 16.8                     | Lower 5.7, Upper 27.8                             | 0.005              | 0.929                             |
| T1           | 0.8                      | Lower -0.9, Upper 2.5                             | 0.331              | 0.998                             |

* The negative values represent underestimation of tumour extent on MRI and the positive values represent overestimation of tumour extent.

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Intramedullary tumour extent

Mean difference in tumour margin measurement between the gross surgical specimen and different MR sequences is given in Table 3. There is no statistically significant difference in tumour margin as seen on T1, T2 and T1 FS sequences when compared with the gold standard. Mean difference was the least with T1 (0.8 mm) followed closely by T1 FS (2.7 mm) and T2 (4.3 mm). 95% confidence interval was the narrowest and the inter-class correlation coefficient was the highest with T1 spin echo sequence (0.998).
Surgical excision in our institution is usually planned such that the osteotomy plane is 1.5 cm beyond the tumour margin. Giving a 5-mm margin for error in measurement, any sequence underestimating or overestimating the tumour margin by more than 1 cm was taken as clinically significant (Table 2). In both cases where T1WI underestimated the tumour extent, it was not clinically significant (<1 cm). T1 FS sequence underestimated the tumour extent.
by >1 cm in one case which was a clinically significant error. Hence, T1WI was thought to be better than T1 FS for assessment of intramedullary tumour extent. Pathological tumour margins were the same as MRI in more than 70% of cases in both T1 and T1 FS sequences. All the other MRI sequences were highly inaccurate to define the longitudinal tumour extent in our study. This is in agreement with several of the previous authors [1,5,9–13]. Red marrow did not pose any difficulty in assessing the tumour margin in our study in contrast to the existing literature [14–17]. When surgical resections were performed using the T1 margin as a reference, none of the resection specimens were margin-positive on pathology in our study.

The low signal intensity of most skeletal tumours on T1-weighted imaging makes them stand out conspicuously in the background of the high-signal-intensity fatty marrow [1,2,5]. Fat signal from the bone marrow is suppressed on T1 FS imaging, which explains the suboptimal contrast between tumour and adjacent normal marrow, when compared to that of non-FS T1-weighted imaging. Poor contrast between the hyperintense tumour and the surrounding hyperintense bone marrow is the main drawback in using T2-weighted imaging to delineate the tumour [2]. While STIR sequence overcomes this issue by highlighting the hyperintense tumour against the fat-suppressed background, the main limitation with this sequence is that even the peritumoral oedema is bright and there is poor subjective delineation between the actual tumour and the surrounding reactive zone [5]. Even post-contrast T1 FS imaging may fail to accurately delineate the tumour margin due to enhancement of the peritumoral reactive marrow [13]. We attribute abnormal enhancement of the peritumoral reactive marrow to leakage of the very molecular-weight gadolinium molecules into the interstitial spaces of the oedematous tissue [18].

Epiphyseal involvement

T1WI and STIR sequences were the best to assess epiphyseal involvement. This finding is consistent with some of the earlier studies [4,5] while a few other studies showed T1WI to be better than STIR for assessing epiphyseal

Figure 3. Axial STIR (A), T1-FS (B) and T1-FS post-gadolinium (C) MR images through the distal femur of a 17-year-old-boy with high-grade osteosarcoma showing tumour within the marrow (star). STIR axial image (A) shows peritumoral soft tissue hyperintensity (arrow) which showed enhancement following gadolinium administration (C) which was suspected to be soft tissue component of the tumour; this was proven to be oedema on histological examination.

Figure 4. Coronal STIR image of an 11-year-old boy with osteosarcoma of the left distal femur showing “massive oedema” extending proximally along the entire length of the muscle (arrow).
involvement [6,7]. Any abnormal epiphyseal signal was assumed to be tumour in our study and the sensitivity and specificity for predicting epiphyseal involvement were 92% and 71% respectively on T1WI, and 100% and 85% respectively on STIR sequence. Onikul et al. [5] determined that abnormal epiphyseal MR signal in false-positive cases is because of focal or diffuse areas of red marrow. In our study, the abnormal epiphyseal signal in the false-positive cases was contributed by marrow oedema. Hoffer et al. [4] reported that if any altered signal in the epiphysis is considered as tumour, the sensitivity for both T1WI and STIR is 100%, with specificities of 60% and 40%, respectively. In their study, specificity was improved to 90% and 70% respectively, and the sensitivity was only marginally reduced if only altered signal equal to that of the metaphyseal tumour was considered as tumour.

Joint involvement

The criteria used to determine joint involvement in our study are similar to those used by Baweja et al. [1]. T1 FS post-contrast best sequence showed joint involvement by highlighting the enhancing intra-articular component against the fat-suppressed background. The sensitivity, specificity, PPV and NPV of MRI to assess joint involvement were 100%, 93%, 83%, and 100%, respectively, thereby confirming the usefulness of gadolinium-enhanced imaging in predicting joint involvement pre-operatively. This finding correlates with those of some of the earlier studies [1,19]. In a slightly older study, Schima et al. [20] used similar criteria for depicting joint involvement on post-gadolinium MRI with a PPV of only 50%.

Neurovascular bundle involvement

Neurovascular bundle involvement was assessed according to the criteria used by Baweja et al. [1]. Literature suggests that post-contrast T1 FS axial images are the best to assess neurovascular bundle involvement, even better than T2 axial images [1,8]. Seeger et al. [18] showed T1 FS post-gadolinium imaging to be better than non-contrast T1 FS imaging for depicting involvement of fat surrounding the neurovascular bundle by the tumour. In our study, both T2 and T1 FS post-gadolinium sequences together were used to get this information. The overall incidence of neurovascular bundle involvement in our study was only 4.76%. The sensitivity, specificity, PPV and NPV of MRI to predict neurovascular bundle involvement were 100%, 90%, 33.3%, and 100%, respectively. However, only one case in our study had pathologically-proven neurovascular bundle involvement and we acknowledge that studies with a larger sample size are required before we can categorically say that a particular sequence is better than the other to assess neurovascular bundle involvement.

Skip lesions

Only 1 patient in our study had skip lesions on MRI, which was confirmed by histopathology. Those were missed on the gross pathology specimen examination. Those lesions extended till 10 cm beyond the gross tumour margin and were best seen on non-contrast T1, T1 FS, and STIR images but their extent was underestimated on T2 and post-gadolinium images. Large FOV images are helpful to pick up skip lesions that may otherwise be missed out. This may, however, compromise the image resolution to some extent. An older study by Golfieri et al. [2] demonstrated STIR sequence to be better than the spin echo sequences by highlighting the hyperintense satellite lesions in the background of the fat-suppressed marrow.

Soft tissue abnormality

Existing literature provides various contradicting recommendations when it comes to the assessment of soft tissue component of bone tumours. While an earlier study by Golfieri et al. [2] showed the STIR sequence to be inaccurate for depicting soft tissue tumour margins (sensitive but less specific), a more recent study by Tokuda at al. [21] compared fast STIR sequence with T1 FS post-contrast imaging and showed that subjective image contrast between the soft tissue tumour and the adjacent normal tissue was higher on fast STIR sequence. In our study, we found that conventional spin echo sequences depicted the soft tissue component of the tumour suboptimally. STIR, T2 and T1 FS non-contrast sequences overestimated the extent of soft tissue involvement. We found that T1 FS post-gadolinium sequence also significantly overestimated the tumour in contradiction to one of the earlier studies [8]. This is probably due to the fact that oedematous/reactive peritumoral zone may also show enhancement (Figure 3) because of the leakage of very-low-molecular-size gadolinium molecules into the interstitial space [18] as mentioned earlier. Finally, we propose the combined use of STIR and T1 sequences to estimate the soft tissue margins of the tumour. After reviewing the histological findings from the areas of abnormal MR signal, we list a few subjective parameters which indicate whether the abnormal soft tissue signal is likely to be the tumour or peritumoral...
reaction, some of which have been described earlier in literature. These are as follows:

1. When abnormal hyperintensity in a muscle is streaky or feather-like, it is likely to represent oedema (Figure 5).
2. When the area of abnormal signal has convex and relatively well-defined margins, it is likely to represent tumour; peritumoral oedema is most often ill-defined with no mass effect [2,3].
3. When the STIR hyperintensity of the tissue adjacent to the intramedullary component of the tumour is similar to that of the intramedullary component, it is likely to represent tumour; peritumoral oedema often tends to be of slightly lower signal intensity than the tumour on STIR images [2].
4. The enhancing tissue is likely to represent tumour when it has a mass-like appearance or convex margins (Figure 6). In cases where the enhancement is more diffuse, it is not possible on static post-contrast MRI to decide where the tumour ends and where the reactive zone begins.

Acknowledgements

We sincerely thank Mr. Nixon for dedicately performing the MRI studies for our study patients. We also thank Dr. Varsha Kiron for providing guidance through the analysis and interpretation of the study results.

Conclusions

We conclude that T1-weighted MRI remains the best sequence to assess intramedullary tumour extent despite several newer and advanced MRI sequences that have been introduced in the last few decades. In all the cases where T1WI underestimated the tumour extent, it did so by less than 1 cm. We suggest that osteotomy plane 1.5 cm beyond the T1 margin is adequate (giving a 5-mm margin for error in measurement) to obtain a safe surgical margin and also allows limb salvage surgeries by limiting unwarranted bone loss. However, this needs to be confirmed on prospective studies with a larger sample size. When determining the extent of soft tissue component of the tumour, T1 and STIR sequences can be used together and the suggested guidelines may be applied to distinguish between tumour and peritumoral signal changes. T1 and STIR sequences are the best to determine epiphyseal involvement and T1 FS post-gadolinium sequence is the best to assess joint involvement. Large FOV images including a joint above and below the tumour are recommended to identify the skip lesions.

Financial support

Institution research board research grant. No external funding.

Conflicts of interest

None.

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