Journal of Bone Oncology 6 (2017) 22–26

Contents lists available at ScienceDirect

Journal of Bone Oncology

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

Research paper

# Marrow signal mimicking tumor on MRI T1-weighted imaging after neoadjuvant chemotherapy in extremity osteosarcomas

Zhiping Deng[a], Yi Ding[b], Lin Hao[a], Qing Zhang[a], Yongbin Su[c], Xiaohui Niu[a,*]

[a] Department of Orthopaedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Peking University, Number 31, Xinjiekou East Street, Xicheng District, Beijing 100035, China
[b] Department of Pathology, Beijing Ji Shui Tan Hospital, Peking University, Number 31, Xinjiekou East Street, Xicheng District, Beijing 100035, China
[c] Department of Radiology, Beijing Ji Shui Tan Hospital, Peking University, Number 31, Xinjiekou East Street, Xicheng District, Beijing 100035, China

ARTICLE INFO

*Keywords:*
Osteosarcoma
MRI
Limb salvage surgery
Neoadjuvant chemotherapy
Tumor

ABSTRACT

*Purpose:* Many studies had demonstrated that MRI T1-weighted imaging was the most accurate method to evaluate the intramedullary extent of extremity osteosarcoma. However, we found that after neoadjuvant chemotherapy new low signal of MRI T1 imaging was detected near tumor, which mimicked the tumor progression. The aim of this study was to describe the incidence and type of this new signal, to reveal the pathological correlation with this imaging change.

*Methods:* We included 74 extremity osteosarcomas managed between June 2011 and November 2012 in this retrospective study. The T1-weighted MRI images of the affected extremity before and after neoadjuvant chemotherapy were reviewed and compared. The subjects were then classified according to the appearance of the border between the area involved by osteosarcoma and the normal marrow with attention paid to whether the border was continuous and the width of the zone of transition. The study population was classified into one of four classifications: 'clear', 'continuous diffuse', 'discontinuous island-like' and 'discontinuous diffuse'. 11 patients underwent MRI of bilateral extremities, and for these patients we assessed the appearance of the uninvolved extremity with that with osteosarcoma. Following surgical resection of the tumor, the pathologic appearance was compared with the pre-operative MRI findings.

*Results:* According to our classification system, all 74 subjects were 'clear' before neoadjuvant chemotherapy. After neoadjuvant chemotherapy, 30 subjects (40.5%) were still clear. Of the 44 subjects (59.5%) not classified as 'clear', 22 (29.7%) were classified as 'continuous diffuse', 4 (5.4%) as 'discontinuous island-like', and 18 (24.3%) as 'discontinuous diffuse'. Of the subjects with MRI of bilateral femurs, no radiologic difference was noted in the normal marrow bilaterally. No significant difference in overall survival and relapse free survival was noted between patients grouped according to the subtypes of MRI noted.

*Conclusions:* Neoadjuvant chemotherapy for extremity osteosarcoma can result in a variety of changes of the MRI appearance of tumor and adjacent bone and marrow. Areas of signal change beyond the tumor that represent marrow conversion and not tumor progression appear on T1 weighted imaging to be lower in signal than subcutaneous fat and higher in signal than muscle. Recognizing the existence of the effect of neoadjuvant chemotherapy on the MR appearance of the tumor and surrounding bone and myeloid elements is important so as to plan for oncological sound tumor resections while avoiding resecting more normal bone than necessary.

## 1. Introduction

Many studies had demonstrated that magnetic resonance imaging (MRI) T1-weighted imaging is the most accurate method to evaluate the intramedullary extent of extremity osteosarcoma [1–4]. However, we have found that after neoadjuvant chemotherapy, an area of low signal intensity on T1-weighted MRI was detected near tumor, the radiologic appearance of this suggested tumor progression, but on subsequent pathologic examination showed no involvement by tumor. The aim of this study was to describe, and classify the different types of these signal changes and to report their incidence. Correlation of these imaging findings with pathological findings was also performed.

## 2. Materials and methods

The prospectively collected sarcoma database of the Orthopaedic

* Corresponding author.
*E-mail addresses:* dengzhiping2000@126.com (Z. Deng), niuxiaohui@263.net (X. Niu).

http://dx.doi.org/10.1016/j.jbo.2016.09.001
Received 12 May 2016; Received in revised form 3 August 2016; Accepted 1 September 2016
Available online 15 September 2016

**Fig. 1.** 'Clear' type with distinct boundary between tumor and the normal marrow.

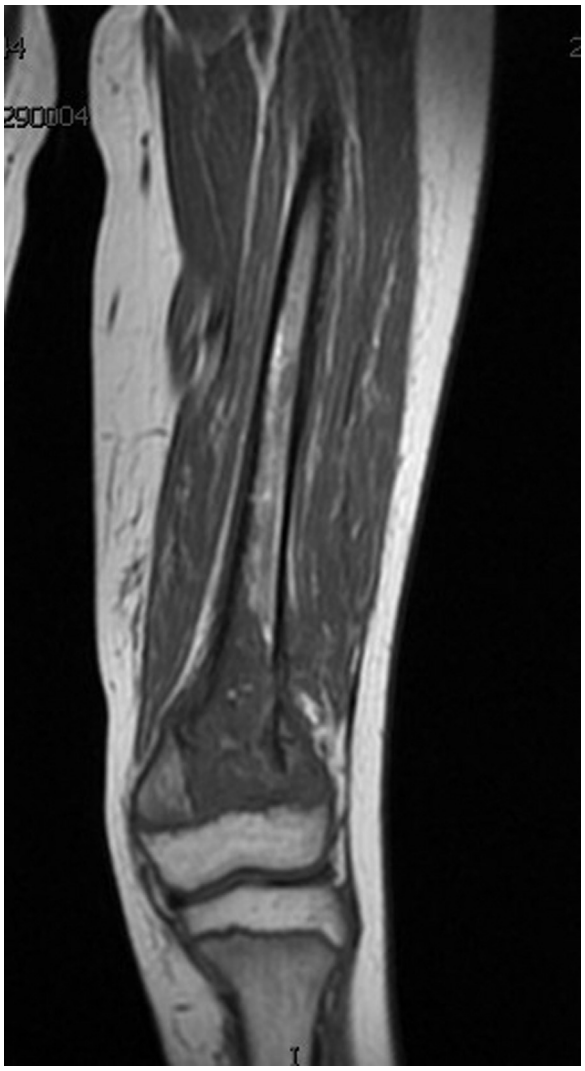

**Fig. 2.** 'Continuous diffuse' type with area of intermediate signal contiguous with the area of tumor.

Oncology Department of Beijing Jishuitan Hospital was searched to identify all patients treated for osteosarcoma.

Of extremities between June 2011 and November 2012. Among these patients, we included patients with two or more pre-operative MRI scans available in the electronic picture archiving and communications system (PACS), including one pre-chemotherapy and one post-chemotherapy scan. All the patients were biopsied for the diagnosis of osteosarcoma. Patients with pathological fracture and who had previously undergone surgery at the site of the tumor were excluded. Patients with osteosarcoma of the fibula were excluded because the marrow space was too narrow to evaluate on MRI.

The study group thus consisted of 74 patients [male, 45; female, 29; median age: 15 years (range, 9–25 years)]. The tumor was located in distal femur in 39 patients, proximal tibia in 26 patients, proximal humerus in 7 patients, proximal femur and distal tibia in 1 patient each.

Neoadjuvant chemotherapy was given following histologic confirmation of the diagnosis. The chemotherapy regimen included high-dose Methotrexate, Ifosfamide Cisplatin and Doxorubicin. The leukopenia was found in all patients during chemotherapy and the G-CSF was given to stimulate the marrow hyperplasia. Staging studies included plain radiographs, computed tomography (CT) and MRI of the limb, CT scans of the chest and total body scintigraphy. MRI of the affected extremity was the most important imaging modality for evaluation of the local extent of the tumor. All these patients received limb salvage surgery and the planning of the bony resection level was done by the operating orthopaedic oncologist and a radiologist.

MRI examinations, performed at our institution, were included in the study if they contained at least pre-chemo and post-chemo T1-weighted imaging. The imaging was analyzed on our PACS for this study. The coronal section was reviewed by one senior surgeon and one radiologist independently. After neoadjuvant chemotherapy, the signal change types were recorded. Eleven patients received the bilateral limb MRI examination and the normal side imaging was compared with the side affected by osteosarcoma.

Following surgical resection, specimens underwent pathological examination with the specimen prepared in a coronal section with a band saw. Areas noted on MRI with specific imaging characteristics were correlated with the pathologic findings in the specimen. A separate biopsy was performed at the time of surgery in the areas of intermediate signal intensity area when this area was not within the resection specimen.

All the patients were followed up according to our protocol, which included follow up every 3 months for the first 2 years, every 4 months for the third and fourth years, and every 6 months for the fifth year. Their oncological outcomes were recorded from a review of their case notes.

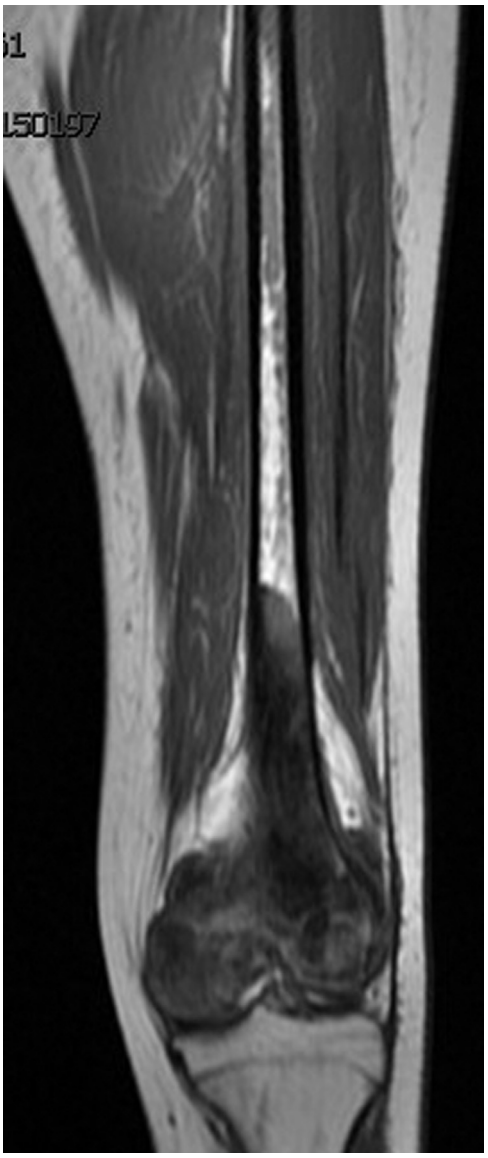

**Fig. 3.** 'Discontinuous diffuse' type with patchy appearance of the area of intermediate signal.

## 3. Results

### 3.1. Type of signal

The shape of MRI T1-weighted imaging was classified into four groups: 'clear', 'continuous diffuse', 'discontinuous island-like' and 'discontinuous diffuse'.

1. Clear: The area with tumor has low signal intensity and normal fatty marrow has high signal intensity with distinct margin between the two areas (Fig. 1).
2. Continuous diffuse: There is an area with signal intensity higher than skeletal muscle and lower than fat between the tumor and normal fatty marrow. This area with intermediate signal was contiguous with the tumor, and was not patchy in appearance (Fig. 2).
3. Discontinuous diffuse: The area with intermediate signal intensity was patchy and diffuse in appearance, not contiguous with the tumor, and intermingled with areas with the normal fat signal (Fig. 3).

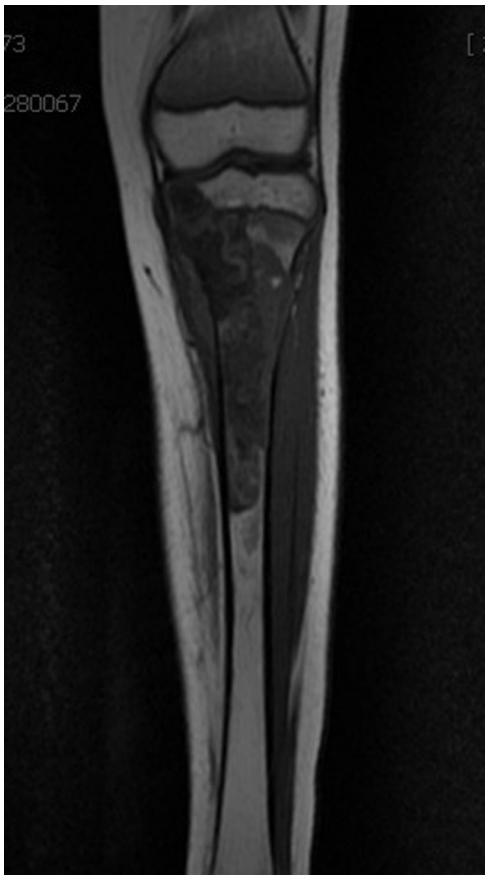

**Fig. 4.** 'Discontinuous island-like' with an area of intermediate signal not contiguous with the tumor signal beyond the tumor.

4. Discontinuous island-like: The area of intermediate signal was beyond the tumor and the normal fat signal could be seen between them. (Fig. 4)

### 3.2. The incidence of signal change

Before neoadjuvant chemotherapy all 74 cases were 'clear'. After neoadjuvant chemotherapy, 30 cases (40.5%) were still classified as clear. Signal change from clear to another classification occurred in 44 cases (59.5%), including 22 'continuous diffuse' (29.7%), 4 'discontinuous island-like' (5.4%), 18 'discontinuous diffuse' (24.3%).

The post-chemotherapy MRI showed bilateral extremities in 11 cases, with all of these being femurs. The marrow signal in the normal femur was the same as the normal marrow in the osteosarcoma femur (Fig. 5). The histological studies showed no tumor cells but the hematopoietic cells.

#### 3.2.1. Pathological correlation

In no patient was tumor were seen in the area of intermediate signal intensity. Histologically, only hematopoietic cell proliferation (Fig. 6a and b) was noted.

#### 3.2.2. Follow-up

The duration of follow-up was 1 month to 57 months. The median follow up was 37 months. The follow up duration for patients who were alive at last follow up was from 18 months to 57 months. Only one patient developed local recurrence and died of metastasis later. Sixteen patients developed metastasis. At the end of follow-up, Seventeen patients died of the disease. The overall survival of patient in this study is shown in the Fig. 7. There was no significant difference between

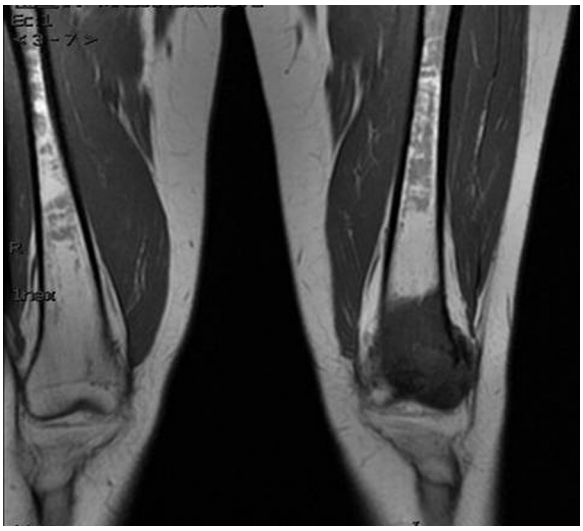

**Fig. 5.** T1 – weighted image of patient with osteosarcoma of the left femur showing similar changes in the shafts of the femurs bilaterally.

patients with the four types of MRI findings in both overall survival and relapse free survival (Fig. 8 and 9).

## 4. Discussion

The results of our study show that, after neoadjuvant chemotherapy of osteosarcoma, signal changes are common at MRI in the marrow of long bones, including 29.7% 'continuous diffuse', 5.4% 'discontinuous island-like', 24.3% 'discontinuous diffuse'.

The survival of osteosarcoma patients has increased dramatically due to the chemotherapy [5,6]. MRI has been widely used to evaluate the extent of tumor during neoadjuvant chemotherapy of osteosarcoma. Because of regenerating red marrow, signal intensity decreases on T1-weighted images. We can see the new signal in MRI which is haematopoietic marrow mimicking tumor. These haematopoietic cells are generally bilateral and symmetric, which is demonstrated in our study.

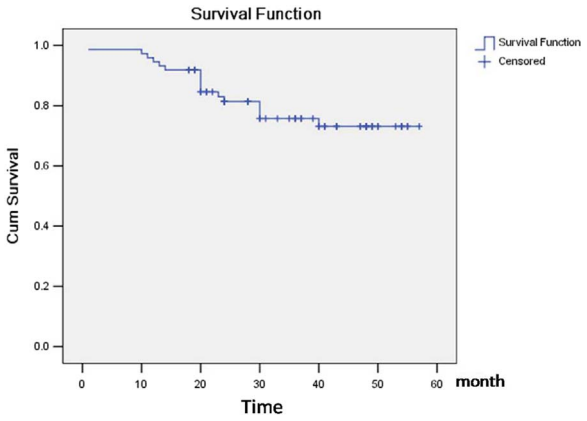


**Fig. 7.** Kaplan–Meier survival curve showing overall survival for all patients in the study.

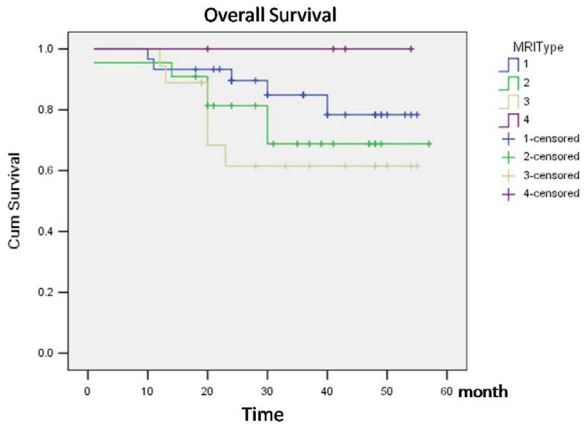


**Fig. 8.** Kaplan–Meier survival curve showing overall survival for subjects classified according to the four imaging subtypes: Type 1, clear. Type 2, continuous diffuse. Type 3, discontinuous diffuse. Type 4, discontinuous island-like.

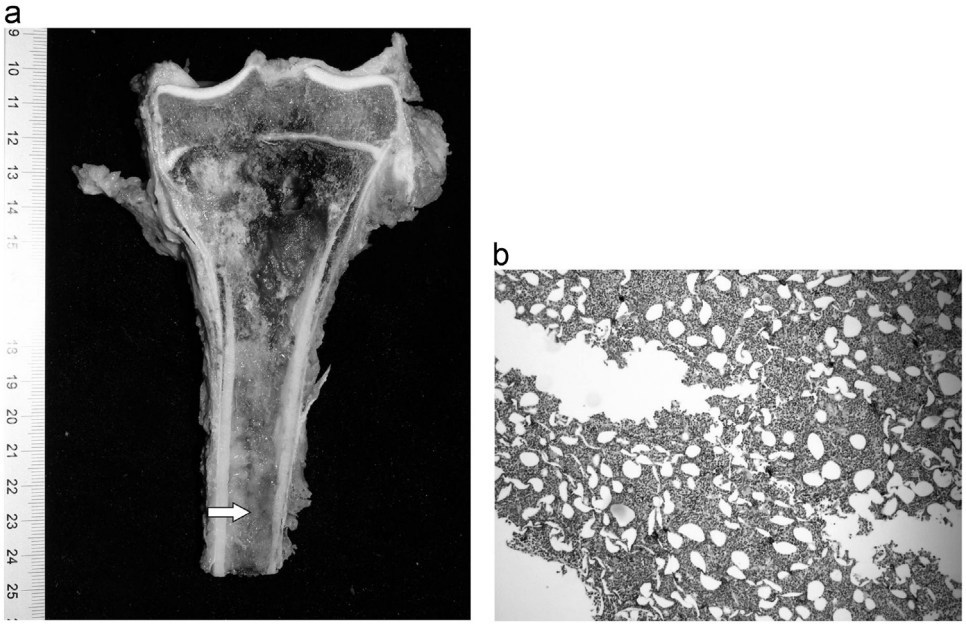


**Fig. 6.** a: Coronal section of a resection specimen. The site of intermediate signal intensity is marked by the arrow. b: Photomicrograph of specimen in a: showing no tumor cells, and only hematopoietic cell proliferation.

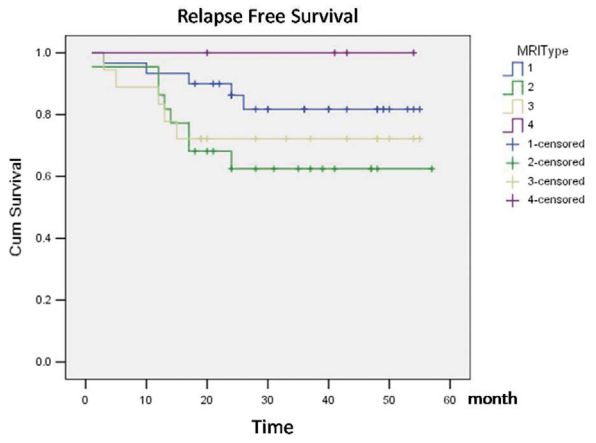


**Fig. 9.** Kaplan-Meier survival curve showing relapse free survival classified according to the four imaging subtypes: I. Type 1, clear. Type 2, continuous diffuse. Type 3, discontinuous diffuse. Type 4, discontinuous island-like.

Granulocyte colony-stimulating factor (GCSF) is used to stimulate myeloid cell production in osteosarcoma patients undergoing chemotherapy. Some studies have described the MRI signal changes noted in patients after the use of GCSF [7–9]. The signal changes may be homogeneously diffuse, mimicking tumor progress or metastases. These changes may also be noted symmetrically and bilaterally, or asymmetrically. Awareness of the occurrence of these changes is important to avoid an incorrect diagnosis of tumor progression or metastases. Our study shows how commonly this phenomenon of marrow reconversion can be noted on MRI when GCSF was administered to patients with osteosarcoma. The oncological results show that there is no significant difference patients with the four subtypes of this finding of MRI. The use of GCSF can stimulate the signal change in the marrow but this change is not related to the oncological results.

In conclusion, we have described the types and incidence of the signal changes that can be noted after neoadjuvant chemotherapy in patients with extremity osteosarcoma. These areas intermediate in signal intensity to subcutaneous fat and normal muscle on T1-weighted MRI imaging signals represent marrow conversion and not tumor progression. Recognition of this type of change can avoid resecting more normal bone in limb salvage surgery.

## Acknowledgments

The authors thank Chung Ming Chan MBBS for his assistance in the preparation of this manuscript.

## References

[1] E. Onikul, B.D. Fletcher, D.M. Parham, Accuracy of MR imaging for estimating intraosseous extent of osteosarcoma, AJR Am. J. Roentgenol. 167 (1996) 1211–1215.
[2] T. Gillespy 3rd, M. Manfrini, P. Ruggieri, Staging of intraosseous extent of osteosarcoma: correlation of preoperative CT and MR imaging with pathologic macroslides, Radiology 167 (3) (1988) 765–767.
[3] A. Saifuddin, The accuracy of imaging in the local staging of appendicular osteosarcoma, Skelet. Radiol. 31 (2002) 191–201.
[4] M.S. Meyer, S.S. Spanier, M. Moser, Evaluating marrow margins for resection of osteosarcoma. A modern approach, Clin. Orthop. Relat. Res. 363 (1999) 170–175.
[5] R.J. Grimer, A.M. Taminiau, S.R. Cannon, et al., Surgical outcomes in osteosarcoma, J. Bone Jt. Surg. (Br.) 84 (2002) 395–400.
[6] S. Ferrari, P. Ruggieri, G. Cefalo, et al., Neoadjuvant chemotherapy with methotrexate, cisplatin, and doxorubicin with or without ifosfamide in nonmetastatic osteosarcoma of the extremity: an Italian sarcoma group trial ISG/OS-1, J. Clin. Oncol. 30 (17) (2012) 2112–2118.
[7] S. Hwang, D.M. Panicek, Magnetic resonance imaging of bone marrow in oncology, Skelet. Radiol. 36 (11) (2007) 1017–1027.
[8] B.D. Fletcher, J.E. Wall, S.L. Hanna, Effect of hematopoietic growth factors on MR images of bone marrow in children undergoing chemotherapy, Radiology 189 (1993) 745–751.
[9] S.P. Ryan, E. Weinberger, K.S. White, MR imaging of bone marrow in children with osteosarcoma effect of granulocyte colony-stimulating factor, Am. J. Roentgenol. 165 (4) (1995) 915–920.