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Inter-rater Variability in the Interpretation of Pre and Post Contrast MRI for Pre-Surgical Evaluation of Osteosarcoma in Long Bones in Pediatric Patients and Young Adults☆

T.T. Pierce[a,*], R. Shailam[b], S. Lozano-Calderon[c], P. Sagar[b]

[a] Massachusetts General Hospital, Department of Radiology, 55 Fruit Street Founders 216, Boston, MA, 02114, USA
[b] Massachusetts General Hospital, Department of Radiology, Division of Pediatric Radiology, 34 Fruit Street Ellison 237, Boston, MA, 02114, USA
[c] Department of Orthopedic Surgery, Massachusetts General Hospital, 55 Fruit Street Yawkey Center for Outpatient Care, Suit 3B, Boston, MA, 02114, USA

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ABSTRACT

Background and Objectives: The value of gadolinium enhanced magnetic resonance imaging (MRI) sequences for extremity osteosarcoma resection planning is unverified. We evaluate the performance of intravenous gadolinium enhanced MRI for identification of neurovascular bundle involvement (NBI) and intraarticular extension (IAE) in patients with osteosarcoma.

Methods: Two pediatric radiologists independently analyzed MRI examinations of patients with pathology proven extremity osteosarcoma for NBI and IAE. Initial evaluation utilized only non-contrast MRI images (PRE) and, after 2 weeks, subsequent evaluation included both the pre and post contrast images (POST). Cohen's Kappa and McNemar's test were calculated to assess agreement between PRE and POST image interpretations of NBI and IAE.

Results: 56 patients with 90 preoperative MRI examinations were analyzed. PRE and POST interpretations were rarely discordant; 4/90 cases for NBI (Kappa 0.91) and 2/90 cases for IAE (Kappa 0.95). McNemar's test did not show a difference between PRE and POST imaging (NBI $p = 0.62$; IAE $p = 0.48$).

Conclusion: No significant difference between PRE and POST image interpretation was found. A high level of agreement between PRE and POST image interpretation suggests that pre-contrast MRI may be sufficient for pre-surgical planning for pediatric patients with long bone osteosarcoma.

Introduction

Osteosarcoma is a primary tumor of bone that most commonly affects long bones around the knee in pediatric and young adult patients. Optimal treatment includes neoadjuvant chemotherapy to treat presumed micro-metastases, which are common at presentation, followed by surgical resection, at which time pathological assessment of primary tumor necrosis, a strong predictor of survival, is assessed [1]. Magnetic resonance imaging (MRI) plays an important role throughout the course of treatment from evaluating disease extent, atypical presentations, and guiding the percutaneous biopsy approach to assessing treatment response and facilitating operative planning [2-7]. In all these scenarios, including at initial diagnosis as well as for pre-surgical planning after chemotherapy, the MRI examinations are typically performed with intravenous gadolinium-based contrast media, with the assumption of providing superior image quality and improved reader confidence. While certain indications benefit from contrast administration, conclusive evidence to support the utility of contrast for pre-surgical planning is lacking [8].

The choice of surgical approach and reconstruction technique rely on clinical variables, surgeon preference, and diagnostic imaging, the most important of which is MRI. The role of intravenous gadolinium in MRI is debated for two imaging parameters, tumoral neurovascular bundle involvement (NBI) and intraarticular extension (IAE), which

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* Corresponding author.
E-mail addresses: ttpierce@partners.org (T.T. Pierce), rshailam@mgh.harvard.edu (R. Shailam), slozanocalderon@mgh.harvard.edu (S. Lozano-Calderon), psagar@mgh.harvard.edu (P. Sagar).

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Table 1
Imaging criteria for intra-articular tumor extension and neurovascular bundle involvement.

	Intraarticular Extension	Neurovascular Bundle Involvement
Pre Contrast Findings	• Intraarticular pathologic fracture • Intramedullary mass eroding through articular cortex • Loss of synovial fat • Intermediate T1 signal, intermediate to high T2 signal mass within the joint or involving the collateral or cruciate ligaments	• Tumor encasing or abutting any portion of the neurovascular bundle (loss of fat plane on pre contrast T1)
Post Contrast Findings	• Enhancing tissue within the joint or involving the collateral or cruciate ligaments	• Enhancing tissue abutting or encasing the neurovascular bundle

each have important surgical implications. Tumor involvement of major neurovascular structures often requires amputation to achieve negative surgical margins and optimize functionality, whereas limb salvage surgery is otherwise preferred [1, 2, 6]. In the event of tumor extending into the adjacent joint space, the optimal surgery requires extra-articular resection of an intact joint capsule, a more extensive surgery resulting in a more complex reconstruction and usually a poorer functional outcome [5, 9, 10]. If imaging findings for intraarticular extension are equivocal, joint fluid obtained by arthrocentesis can be evaluated for malignant cells to definitively assess for tumor involvement, however this is not routinely performed in the absence of suspicious imaging findings.

Reliable and accurate imaging evaluation of NBI and IAE, a must for surgical planning, would ideally be accomplished with non-contrast MRI given the recently published logistic and safety concerns related to gadolinium administration. These include soft tissue deposition of unbound gadolinium in the setting of marked renal dysfunction causing the debilitating skin condition known as nephrogenic systemic fibrosis [11]. Furthermore, gadolinium deposition in the globus pallidus and dentate nucleus has been noted in patients with normal renal function, although this is of uncertain clinical significance [12-15]. Additional considerations for gadolinium enhanced imaging include the requirement for intravenous catheter placement, prolonged examination times, and risk of contrast reaction. These may be routine considerations in adults however, can invoke added stress and anxiety, including the requirement for sedation, when imaging pediatric patients. To justify these risks, we seek to determine the utility of intravenous gadolinium for identification of NBI and IAE by MRI in pediatric and young adult patients with extremity osteosarcoma undergoing evaluation for surgical resection.

Materials and Methods

Case Selection

All procedures performed were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments. A waiver of consent was granted by the institutional review board for our Health Insurance Portability and Accountability Act (HIPAA)-compliant study protocol. Cases of interest were identified by retrospective search of radiology reports between 2000 and 2015 for the key word “osteosarcoma” for patients ages 0-25 inclusive at the time of imaging. Cases from before 2000 were excluded due to significant differences in imaging quality. We identified cases with preoperative MRI exams containing both pre and post gadolinium enhanced imaging sequences. The cases analyzed encompass a variety of imaging parameters and protocols since the exams were performed on MRI scanners from multiple manufacturers, and protocols evolved over the study duration. Nonetheless, all exams included had routine T1 weighted, fluid sensitive T2 weighted or STIR (short tau inversion recovery), and contrast enhanced sequences. For patients who underwent multiple MRI examinations prior to surgery, each exam was analyzed separately.

Pathology

Cases involving the extremity long bones (humerus, radius, ulna, femur, tibia, and fibula) were included while tumors arising from the axial skeleton, clavicles, scapulae, pelvis, hands, and feet were excluded. The medical record for each case was reviewed for documentation of a pathologic diagnosis of osteosarcoma from either percutaneous biopsy or surgical resection. For cases in which biopsy and surgical resection pathology reports were discordant, the final pathology report was used. Synchronous, metachronous, and metastatic osseous lesions were included for analysis provided that clinical evaluation for surgical resection was considered and that pathology was available for each lesion. Surgical operative reports and tumor excision pathology reports were reviewed for each case to identify the presence or absence of NBI and IAE at the time of surgery.

Pre-contrast Image Evaluation

Two board certified pediatric radiologists with 10 and 11 years of experience respectively (RS and PS) independently analyzed each MRI case on a picture archiving and communication system (PACS) workstation without availability of other imaging or clinical information. Initially, only the pre-contrast series were viewed to evaluate for intraarticular extension of tumor and tumor involvement of the neurovascular bundle. Imaging criteria for IAE are noted in table 1. If findings for IAE were equivocal, the absence of a joint effusion excluded the possibility of IAE. For NBI, we assessed the major neurovascular bundle supplying the extremity and considered it involved by evaluating any degree of loss of fat plane between the neurovascular bundle and the mass. We included a wide spectrum of tumor-neurovascular bundle contact ranging from simply abutting (< 25% neurovascular bundle circumference involvement), to frank encasement (Table 1). Representative cases are shown in figures 1-4. Inter-rater discrepancies were resolved by consensus.

Pre and Post-contrast Image Evaluation

After two weeks, the MRI exams were independently reanalyzed (blinded to the results of the pre-contrast only interpretation) with

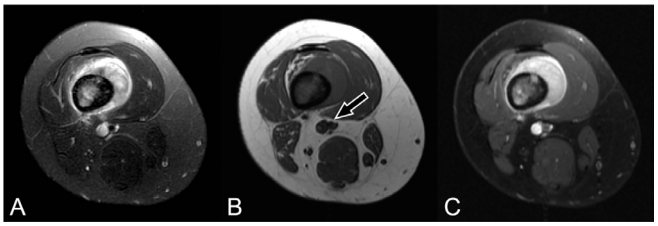

Fig. 1. 22-year-old woman with right femoral osteosarcoma demonstrating absence of neurovascular bundle involvement (NBI). Axial fat suppressed T2 (a), pre-contrast T1 (b), and fat suppressed post contrast T1 (c) images demonstrate a preserved fat plane (arrow), best seen on pre-contrast T1 images, between the enhancing femoral mass and the neurovascular bundle suggesting against NBI.

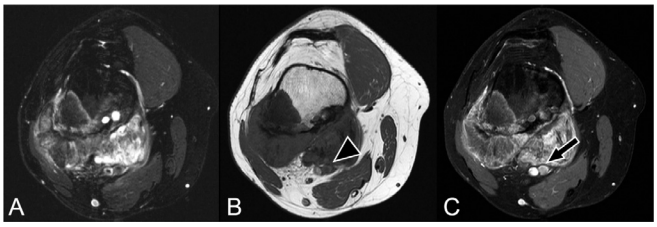

Fig. 2. 18-year-old woman with right femoral osteosarcoma demonstrating presence of neurovascular bundle involvement (NBI). Axial fat suppressed T2 (a), pre-contrast T1 (b), and fat suppressed post contrast T1 (c) images demonstrate obliteration of the fat plane (arrowhead), best seen on the pre-contrast T1 images, between the enhancing femoral mass and the neurovascular bundle suggestive of NBI. On post contrast images (c), the mass abuts the curvilinear hypointense vessel wall (arrow) which could be mistaken for fat on this fat-suppressed image.

Fig. 3. 15-year-old woman with left femoral osteosarcoma demonstrating absence of tumor intra-articular extension (IAE). Sagittal fat suppressed fluid sensitive (FSEIR) (a), pre-contrast T1 (b), and fat suppressed post contrast T1 (c) images demonstrate an enhancing distal femoral diaphyseal mass (arrowhead) remote from the joint space, not involving the anterior cruciate ligament (arrow), and without an associated joint effusion suggestive of absence of IAE.

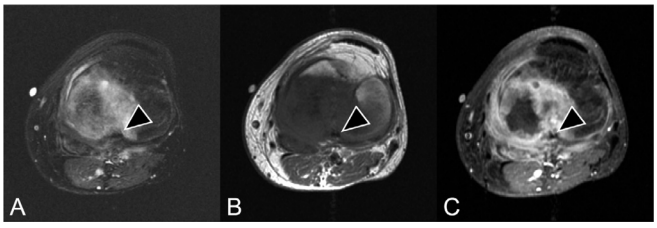

Fig. 4. 24-year-old man with left tibial osteosarcoma demonstrating presence of tumor intra-articular extension (IAE). Axial fat suppressed T2 (a), pre-contrast T1 (b), and fat suppressed post contrast T1 (c) images demonstrate an enhancing proximal tibial plateau mass involving the posterior cruciate ligament (arrow head) suggestive of IAE.

evaluation of the pre-contrast and post-contrast series together. In addition to the previously described non-contrast findings of IAE, enhancing tissue within the joint or involving the cruciate or collateral ligaments defined IAE. NBI included the loss of the adjacent fat plane or enhancing tissue abutting the neurovascular bundle. Inter-rater discrepancies were resolved by consensus following independent review.

Statistical Analysis

Analysis was performed using RStudio, version 0.99.1103. Total agreement and Cohen's Kappa is calculated for each pairwise comparison between the two reviewers prior to arriving at consensus. Agreement between interpretation of pre contrast only and pre and post contrast MRI evaluation of IAE and NBI after consensus was performed with Cohen's Kappa statistic and McNemar's test.

Results

Our search identified 90 preoperative MRI exams from 56 individual patients with pathology confirmed osteosarcoma meeting inclusion criteria. Demographics for our sample are detailed in table 2. The majority of cases analyzed arose from the femur, 52 total cases from 29 individual patients, and the tibia, 26 total cases from 18 individual patients.

Table 2
Clinical characteristics.

Characteristic	Frequency
Age Range, Median (years)	8-25, 16
Gender M/F	55/35 (34/22)
Femur	52 (29)
Tibia	26 (18)
Humerus	6 (5)
Fibula	3 (2)
Ulna	2 (1)
Radius	1 (1)

Total number of cases analyzed are reported with the number of unique patients reported parenthetically. Age range and median age are reported for total cases, not unique patients.

Inter-rater Agreement

Agreement between MRI exam interpretations between the two raters is detailed in table 3. Agreement is reported for NBI and IAE for both pre-contrast only image interpretation and pre/post contrast image interpretation. Total agreement between the two raters varied between 78% and 82% for these four pairwise comparisons while, Cohen's Kappa varied between 0.54 and 0.6.

Pre-contrast Only and Pre/Post-contrast Interpretation Comparison

Evaluation of NBI and IAE by non-contrast MRI was remarkably similar to evaluation by pre and post contrast MRI (table 4). For NBI, there were only 4 discrepant interpretations out of a total of 90 cases. 3 cases suggested NBI on initial evaluation of pre-contrast only sequences, but 2 weeks later were interpreted as negative for NBI on reviewing both pre and post contrast sequences in conjunction. On the contrary, 1 case was interpreted as negative for NBI on pre-contrast only sequences, however the subsequent pre and post contrast images suggested tumor involvement. Two sided McNemar's test did not reach statistical significance $p = 0.62$ ($\alpha = 0.05$). Overall agreement was 96% with a kappa of 0.91 indicating near perfect agreement.

Table 3
Inter-rater agreement for the identification of neurovascular bundle involvement (NBI) and intraarticular extension (IAE). The identification of NBI and IAE are compared between Rater 1 and Rater 2 (before consensus) on pre contrast only exams and pre and post contrast exams. 2x2 table entries reflect number of cases (for example 39 cases were interpreted as positive for NBI by both raters on pre contrast only images). Diagonal terms reflect agreement while off diagonal terms reflect disagreement. Accuracy and agreement (Cohens Kappa) are reported.

	Neurovascular Bundle Involvement				Intraarticular Extension			
	Pre Contrast Only		Pre + Post Contrast		Pre Contrast Only		Pre + Post Contrast	
	Rater 2		Rater 2		Rater 2		Rater 2	
Rater 1	Yes	No	Yes	No	Yes	No	Yes	No
Yes	39	10	38	11	50	17	54	13
No	8	33	9	32	2	21	3	20
Accuracy	80%		78%		79%		82%	
Kappa	0.60		0.55		0.54		0.59	

Table 4
Inter-sequence agreement between pre contrast MRI and pre and post contrast MRI for the evaluation of neurovascular bundle involvement (NBI) and intraarticular extension (IAE).

	Neurovascular Bundle Involvement		Intraarticular Extension	
	Pre + Post Contrast		Pre + Post Contrast	
Pre Contrast Only	Yes	No	Yes	No
Yes	47	3	63	2
No	1	39	0	25
Accuracy	96%		98%	
Kappa	0.91		0.95	
McNemar's Test	p = 0.62		p = 0.48	

The identification of NBI and IAE are compared between pre contrast only exams and pre and post contrast exams. Diagonal terms in the 2x2 tables reflect cases in which post contrast imaging failed to change the diagnosis (both sets of images identified or did not identify NBI/IAE). Off diagonal terms reflect the number of discordant cases. Total accuracy and Agreement (Cohen's Kappa) are reported, indicating near perfect agreement. McNemar's test fails to reach statistical significance ($p > 0.05$).

Similarly, the interpretation of IAE did not differ significantly with the added availability of post contrast MRI images (table 4). Only 2 interpretations were discordant out of 90, where both cases were initially interpreted as positive for intraarticular tumor extension on pre contrast only MRI, while evaluation of pre and post contrast images suggested the absence of intraarticular tumor extension. Two sided McNemar's test did not reach statistical significance $p = 0.48$ ($\alpha = 0.05$). Overall agreement was 98% with a kappa of 0.95 indicating near perfect agreement.

Pathology

Intraoperative surgical and pathologic reports were examined for reliable comparison of image interpretation with pathology, however, several limitations were encountered in these reports including insufficient or missing data which thus precluded confirmation of our results. Given that neoadjuvant chemotherapy could affect tumor size and boundaries, particularly the soft tissue components, only the 56 immediate preoperative MRIs were eligible for analysis. Of these cases, pathology data was absent or insufficient for 25% ($n = 14$) of NBI cases and 14% ($n = 8$) of IAE cases for reasons including: unavailable surgical resection records, NBI/IAE involvement not reported, or positive surgical margins without documented NBI/IAE. Due to the substantial reduction of approximately 50% in available cases to analyze, and the potential to introduce bias through nonrandom censorship, formal analysis of pathology results was omitted. Furthermore, the goal of our study was to examine the added value of intravenous gadolinium by influencing change in radiology interpretation, for which pathological confirmation was not required.

Discussion

When compared with pre-contrast images alone, the addition of gadolinium enhanced MRI sequences did not change the radiologic interpretation of NBI or IAE of tumor in the vast majority of cases, 96 % and 98% respectively. The observed near perfect agreement (Kappa 0.91-0.95) between the imaging interpretations may obviate the need for intravenous gadolinium during MRI examinations performed solely for the purpose of pre-surgical planning given that other key parameters (not assessed here) are well visualized on non-contrast sequences. For example, non-contrast T1 weighted images without fat saturation or STIR images clearly define intramedullary tumor boundaries and violation of the physis [4, 8, 10, 16-21]. Non-contrast T2-weighted images are known to overestimate tumor size, although static post contrast T1 weighted images are also unable to distinguish tumor from peri-tumoral edema [8]. Given that soft tissue extension can be palpated intraoperatively, non-contrast T2 weighted images sufficiently approximate soft tissue mass size [4].

It is well accepted that indications beyond pre-surgical planning benefit from contrast enhanced imaging. Prior to histologic diagnosis, contrast may be helpful for diagnostic evaluation of an indeterminate mass or for percutaneous biopsy target selection, although such a consideration is only relevant for the initial MRI examination [4]. Contrast enhanced MRI may also be helpful to assess tumor response to preoperative chemotherapy including a noninvasive assessment of tumor viability and percentage necrosis, the most important determinant of prognosis. However, pathologic assessment of tumor viability and necrosis, which is routinely available following surgical resection, remains the gold standard. Furthermore, since non-contrast and single phase contrast enhanced images have difficulty distinguishing between viable tumor, nonviable tumor, and peri-tumoral edema, dynamic contrast enhanced MRI has been investigated (although is not routinely used) to more accurately assess tumor boundaries, tumor viability, and treatment response [4-6, 18, 22-24]. Although dynamic contrast enhanced MRI may be able to identify non-responders to treatment, such data may not ultimately impact clinical care since therapy modification solely based on imaging is not currently recommended [25-27]. For these reasons we believe that there is no clear indication for contrast enhanced MRI following the initial diagnostic examination.

We acknowledge that our study has several limitations. These include the long time frame relative to the rapidly evolving field of MRI over which we analyzed cases increasing the heterogeneity of the image acquisition parameters. However, this permitted us to analyze larger sample sizes than many previous studies. Allowing additional reviewers to interpret the pre contrast and pre/post contrast exams may be helpful in the future to validate our results. Our study design of viewing pre contrast images alone followed by pre and post contrast images 2 week later reduces the possibility of recall bias since the reviewers are permitted to view the pre contrast images in both phases. A longer time period between pre contrast only and pre and post contrast image review could be employed in the future to further reduce the potential of this bias. We also understand that a detailed comparison with pathologic findings may improve confidence in our results, however the presence or absence of NBI and IAE was not reliably documented on pathology for a sufficient number of patients in our study. Furthermore, for our purposes we believe that the pathology results are only truly of interest in the cases in which pre contrast only and pre and post contrast image interpretations were found to be discordant. The assessment of pathology results for other cases would address overall MRI performance, however this has been well assessed in the literature by multiple previous authors [9, 16, 17, 19, 22, 28].

We acknowledge that many surgeons and radiologists may prefer utilizing gadolinium, particularly for oncologic purposes, since this has been common practice for decades. Nonetheless, in this era of confirmed and published risks associated with intravenous gadolinium such an approach in our standard protocols needs to be objectively reassessed and questioned, particularly in children, who may need multiple imaging studies for a variety of indications during their lifetime. Our retrospective study, albeit without pathologic confirmation, found that gadolinium enhanced MRI rarely changed the pre contrast imaging interpretation for the key parameters utilized in osteosarcoma resection planning. We suggest that perhaps intravenous gadolinium can be omitted in pre-surgical MRI exams when other indications for intravenous contrast do not apply, as in the case when a tissue diagnosis has already been made.

Conclusion

Our results suggest that the current practice of routine gadolinium administration for the sole purpose of NBI and IAE assessment for

surgical planning prior to extremity osteosarcoma resection may be unnecessary as post contrast MRI images rarely changed the pre contrast assessment of these key pre-surgical parameters. Given that gadolinium administration is not risk free, we hope that similar studies be done in the future to validate our results and further assess the appropriateness of routine gadolinium administration in patients with extremity osteosarcoma.

Conflicts of interest

The authors have no financial conflicts of interest to disclose. A waiver of consent was granted by the institutional review board for our HIPAA-compliant study protocol. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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