Systematic review on the utility of magnetic resonance imaging for operative management and follow-up for primary sarcoma—lessons from extremity sarcomas

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Abstract: Primary sarcomas of the vertebral column affect roughly 5 in every million persons annually, of which half to one-third are malignant. Treatment of these lesions requires multimodal management, often employing attempts at *en bloc* resection of the lesion with negative margins. This may be facilitated using magnetic resonance imaging for preoperative margin planning, but current literature is lacking regarding the use of such imaging to accurately predict planned surgical margins. Here we review prior studies describing the use of magnetic resonance imaging for *en bloc* resection of sarcomas of the extremities to identify learning points for application to the treatment of spinal neoplasms. We conducted a systematic review of the PubMed and EMBASE literature. Included studies described the accuracy of MRI for preoperative evaluation of tumor margins, intraoperative guidance for *en bloc* resection, or post-operative evaluation of residual or recurrent disease. All included studies described patients treated for osseous or soft tissue sarcoma of the limbs. We found 1,705 unique references of which 27 met criteria for inclusion. Seven studies reported MR had an overall diagnostic accuracy of 93.6–96% for preoperative margin evaluation with non-contrast T1 most accurately reflecting true margins. In the nine articles reporting results of MR-guided resection, negative margins were achieved in 88.8–100% of cases with a closest margin of 2–4 mm. Eleven articles combined reported the accuracy of MR for residual disease or local recurrence, with a mean sensitivity and specificity of 71.7% and 79.3%, respectively for residual disease and 87.9% and 85.9%, respectively for local recurrence. The current literature for appendicular musculoskeletal sarcoma suggests that MR is highly accurate for defining tumor margins preoperatively, guiding osteotomy cuts intraoperatively, and documenting recurrence or residual disease. Further evidence is necessary to evaluate the degree to which it can accurately guide osteotomy planning for *en bloc* resection of vertebral primaries.

Keywords: *En bloc* resection; magnetic resonance imaging (MRI); musculoskeletal sarcoma; osteosarcoma; primary vertebral column tumor

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Background

Primary tumors of the vertebral column tumors are a rare clinical entity with a reported incidence of 0.14–0.19 persons per 100,000 population annually, increasing steadily with patient age (1). These lesions can be divided into benign and malignant varieties, of which the latter account for 50–67% of clinical cases (1). While benign lesions are often best initially managed with conservative therapies

Table 1 Search strings and databases employed in literature search

Database	Search string
EMBASE	• osteosarcoma AND 'nuclear magnetic resonance imaging' AND margin
	• sarcoma AND 'nuclear magnetic resonance imaging' AND 'recurrent disease'
PubMed	• "limb salvage"[MeSH Terms] OR ("limb"[All Fields] AND "salvage"[All Fields]) OR "limb salvage"[All Fields]) AND ("osteosarcoma"[MeSH Terms] OR "osteosarcoma"[All Fields]) AND ("Bildgebung"[Journal] OR "imaging"[All Fields]) AND ("recurrence"[MeSH Terms] OR "recurrence"[All Fields]
	• "osteosarcoma"[MeSH Terms] OR "osteosarcoma"[All Fields]) AND ("Bildgebung"[Journal] OR "imaging"[All Fields]) AND ("margins of excision"[MeSH Terms] OR ("margins"[All Fields] AND "excision"[All Fields]) OR "margins of excision"[All Fields] OR "margin"[All Fields]
	• "magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields]) AND ("recurrence"[MeSH Terms] OR "recurrence"[All Fields]) AND ("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields]

addressed at the patient's symptomatology (2), malignancies (including chordoma, chondrosarcoma, Ewing's sarcoma, osteosarcoma, and plasmacytoma) are often treated through surgical management (3).

Pre-operative evaluation of patients being considered for surgical management can be divided into pathology, tumor grading, and tumor location/operative characteristics. Pathology consists of CT-guided needle biopsy (4), which confirms the malignant nature of the tumor and indicates the amenability of the tumor to non-surgical management. In the absence of mechanical instability, plasmacytoma is best managed through a combination of radiation and CyBorD (cyclophosphamide-bortezomib- dexamethasone) chemotherapy and Ewing sarcoma benefits from multimodal management with surgery and chemoradiation (5); all others are treated principally with surgical resection when feasible. Grading—the histological description of tumor differentiation and potential aggressiveness—is then performed using the system presented by Enneking in 1980 and later refined in 1986 (6,7). Lastly, the Weinstein-Boriani-Biagini system is applied to localize the tumor within the spine, identifying the approach, feasibility of *en bloc* resection, and potential need for instrumentation (4,8).

Originally developed for appendicular lesions, the Enneking system has since become a staple of pre-operative planning for primary vertebral malignancies (9). It prescribes proper surgical margins for lesions based upon histologic features. For primary vertebral column malignancies, the goal is negative margins, as this typically decreases local recurrence and may improve mortality (10,11). Consequently, being able to pre-operatively identify dissection planes that will produce negative margins is paramount. Currently magnetic resonance imaging (MRI) with and without contrast is the gold standard due to its high-resolution. Additionally, routine MRI is used to assess residual disease and as a surveillance tool for local recurrence. Despite the accepted superiority of MR, little to no primary literature exists evaluating the diagnostic utility of MR for pre-operative or post-operative evaluation of spinal malignancies. Several studies have been done in patients with primary osseous and soft tissue sarcomas of the periphery however. Here we review this literature as a means of describing the likely accuracy of MR for pre- and post-operative evaluation of primary vertebral malignancy.

Literature search

We performed a systematic review of the existing literature on October 21, 2018 using the PubMed and EMBASE databases and the search strings identified in *Table 1*. Articles were identified based upon their ability to address one of the following questions:

- How accurate is pre-operative MR for assessing tumor margins in primary bone malignancies?
- To what degree can pre-operative MR imaging be used to guide osteotomy formation for *en bloc* resection of primary bone tumors?
- How accurate is post-operative MR imaging for the diagnosis of residual disease following resection of soft tissue sarcoma?
- How accurate is post-operative MR imaging for the diagnosis of disease recurrence following resection of soft tissue sarcoma?

The inclusion and exclusion criteria for the study are

Table 2 Inclusion and exclusion criteria

Inclusion	Exclusion
• Describes accuracy (including sensitivity, specificity, PPV, NPV) of MR for defining pre-operative osteosarcoma margins	• Describes accuracy of another imaging modality (e.g., CT, XR) without independently discussing MR
• Describes accuracy of MR for evaluating local recurrence or residual disease following resection	• Describes indications for MR use during recurrence monitoring only
• Article is a piece of primary literature, including a prospective cohort, retrospective cohort, case series >5 patients, or randomized controlled trial	• Does not describe accuracy/diagnostic ability of MR
• Describes results in humans	• Article format is systematic review, narrative review, perspective/commentary, case series (n ≤5 patients)
• Pathology is a primary bone tumor or soft tissue sarcoma	• Describes *in vitro* results or *in vivo* results of animal model
	• Pathology of tumors is not a primary bone tumor or soft tissue sarcoma
	• Results are mixture of pathologies

outlined in *Table 2*. Only studies involving humans with English full-text translations in peer-reviewed journals were considered for inclusion; conference proceedings and poster presentations without accompanying manuscripts were excluded. Title and abstract screening was performed concurrently by two authors (Z Pennington and AK Ahmed) with discrepancies being resolved by a third author (EM Westbroek). Articles meeting criteria for full-text review underwent the same scrutiny and those meeting inclusion criteria had data abstracted by a single author (Z Pennington) and confirmed by a second author (AK Ahmed).

Results

Search results

Our queries yielded 1,705 unique results, of which 1,619 were excluded as irrelevant based upon title and abstract. Full texts of the remaining 86 studies were then reviewed for inclusion, of which 27 studies met the inclusion criteria (*Figure 1*). The most common reason for exclusion was that the article failed to address one of the four questions used to focus the review. Overall, the results were too heterogenous to perform a meta-analysis.

How accurate is pre-operative MR for assessing tumor margins in primary bone malignancies?

Seven articles published results describing the accuracy of MR for identifying pre-operative margins (*Table 3*) (12-18). Three evaluated the accuracy with which MR was able to assess margins for appendicular osteosarcoma, where the remaining four assessed accuracy across several different primary osseous malignancies of the appendicular skeleton. Of those studies reporting test accuracy characteristics, sensitivity of pre-operative MR for tumor margins was 100% and specificity varied between 50% and 60% (13,16) with an overall diagnostic accuracy of 93.6–96% (13,15). Thompson *et al.* (18) and Jin *et al.* (14) presented two large series of appendicular bone sarcoma with a combined 310 patients. Both groups correlated pre-operative margins on T1-weighted imaging with post-operative histological margins. Thompson and colleagues reported a correlation of 0.846 between the two measures with a mean difference of 5.9 mm. Jin *et al.* reported even greater correlation (r=0.99) with an average discrepancy of 5.0 mm, though the direction of this discrepancy led to underestimation of tumor invasion in 58.4% of cases. The high level of accuracy reported by these newer studies is similar to that reported by the previous work of O'Flanagan (15), Onikul (16) and Gillespy (12), who all reported mean discrepancies between MR and histological findings of less than 1.0 cm. Gillespy *et al.* noted that the discrepancy was reduced roughly three-fold for properly aligned slices, with a mean discrepancy of 1.8 mm (12). Putta *et al.* noted a similarly small discrepancy in their evaluation of 21 patients, finding a mean difference between histological margin and radiological margin of 0.8 mm using non-contrast T1-weighted imaging (17). They found that employing contrast imaging and using STIR sequence imaging both substantially increased

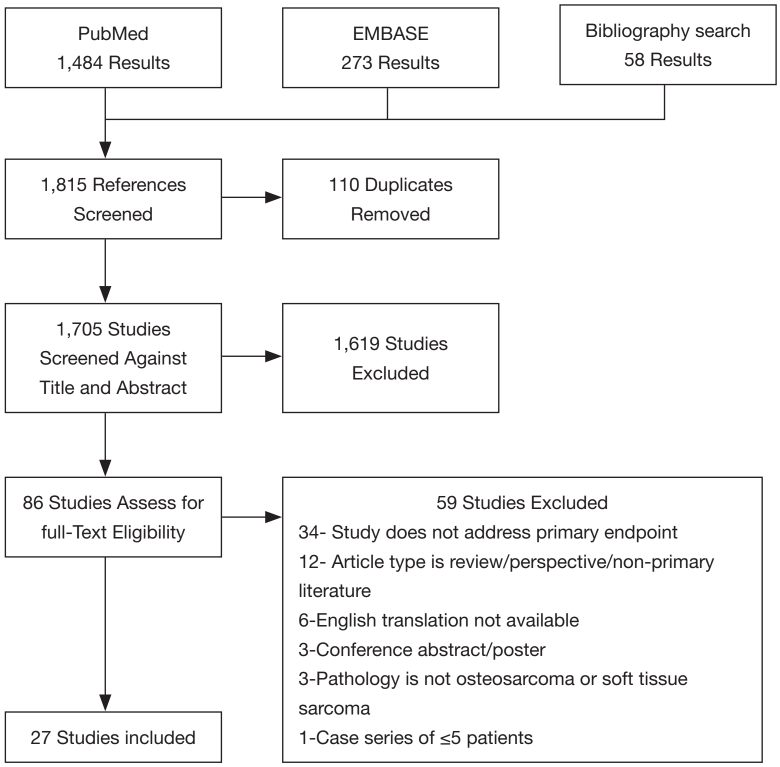

Figure 1 PRISMA diagram for systematic review.

the error in radiological margins, overestimating true tumor size by 1.68 and 1.67 cm, respectively. However, the authors did note that the use of fat-saturated, post-contrast-T1-weighted imaging was useful for identifying involvement of the neurovascular bundle. Combined post-contrast T1 imaging and T2 imaging was able to identify neurovascular bundle involvement with a sensitivity of 100% and specificity of 90%. Aggregated, the studies found non-contrast T1-weighted MR to be an accurate means of determining pre-operative margins for primary osseous malignancies.

To what degree can pre-operative MR imaging be used to guide osteotomy formation for en bloc resection of primary bone tumors?

Nine articles published results describing the utility and accuracy with which MR-guidance can facilitate *en bloc* resection with negative margins (19-27) (*Table 4*). Eight of the articles examined osseous malignancies, three of which focused on appendicular osteosarcoma, while two studies described the results for soft tissue sarcoma, with Hao *et al.*, 2018 (22) reporting a mixed cohort. The articles examining exclusively osseous malignancy reported a total of 205 patients. Overall, the proportion of patients achieving clean margins was high, ranging from 88.8% to 100% of patients. Two studies—Ahmad *et al.* (19) and Iwata *et al.* (23)—compared the accuracy of different imaging sequences for the guidance of resection. Both studies found T1-weighted imaging to mediate better guidance. Ahmad and colleagues reported a stronger correlation of radiological lesion size on T1-weighted imaging with size on gross pathology (r=0.98) as compared to STIR (r=0.89) for primary osseous malignancies. The authors reported that this discrepancy may stem from the visualized peritumoral edema seen on STIR volumes. Iwata *et al.* found that for soft tissue sarcoma, the overall correlation of tumor invasion on imaging and gross histology was much weaker than the correlation of size reported for bony tumor. However, post-contrast fat-saturated T1-weighted imaging was significantly better than STIR at predicting size (r=0.27 for T1 *vs.* r=0.06 for STIR).

Four studies reported local recurrence rates following navigated resection of primary osseous malignancies (20,24,25,27). Of the 23 patients included, all had wide

Table 3 Summary of evidence—accuracy of margin identification using preoperative MRI

Article	N	Pathology	Findings
Gillespy *et al.*, 1988 (12)	17	Appendicular osteosarcoma	• Average discrepancy between histologic and radiological margin was 4.9 mm overall and 1.8 mm for properly aligned slices
Hoffer *et al.*, 2000 (13)	40	Appendicular osteosarcoma	• Mean diagnostic accuracy for T1-weighted imaging was 93.6%; sensitivity =100%, specificity =60% • Mean STIR accuracy was 93.4%; sensitivity =100%; specificity =40%
Jin *et al.*, 2017 (14)	255	1° long bone malignancy	• 87.5% of patients diagnosed with osteosarcoma • Correlation of tumor length on histopathological specimen and pre-operative T1-weighted imaging was r=0.99 • 58.4% of preoperative MR underestimate true tumor invasion • Average histology-imaging discrepancy was 5.0 mm
O'Flanagan *et al.*, 1991 (15)	34	1° long bone malignancy	• MRI successfully determined lesion margins in 96% of cases to margin of error less than 1.0 cm • CT correctly identified lesion margins in only 75% of cases
Onikul *et al.*, 1996 (16)	20	Appendicular osteosarcoma	• Median discrepancy between margins on T1-weighted imaging and histopathological sample was 0.5 cm, equivalent to the margin of error for the histopathological specimen • MRI documented epiphyseal involvement with 100% sensitivity, though specificity was low at 50%
Putta *et al.*, 2016 (17)	21	Appendicular 1° bone malignancy	• Mean difference between margin on non-contrast T1-weighted imaging and histopathological specimen was 0.8 mm • STIR and contrast-enhanced T1 imaging overestimated by 1.67 and 1.68 cm, respectively • Combination of post-contrast T1 and non-contrast T2 diagnosed neurovascular bundle involvement in the tumor with a sensitivity of 100%, specificity of 90%, positive predictive value of 33.3% and negative predictive value of 100%
Thompson *et al.*, 2018 (18)	55	Appendicular 1° bone sarcoma	• Good degree of correlation between radiological margin and histological margin (r=0.846) using post-chemotherapy T1-weighted imaging • Pre-chemotherapy imaging was much less accurate (r=0.516) • Mean discrepancy between histological and radiological margin was 5.9 mm

margin excision, and none experienced local recurrence at a mean of 31.6 months. Though all groups described the importance of including a healthy tissue cuff of at least 2 cm, the overall accuracy of the navigation system was quite high. Across all included studies, the mean registration error between image and actual anatomy was 0.4–0.98 mm. Additionally, both Han *et al.* and Li *et al.* reported the mean discrepancy between osteotomy as planned and osteotomy as executed (21,24). The mean discrepancy across both studies was 4 mm or less, with Li *et al.* reporting a discrepancy of only 2.0 mm, or roughly 26% the width of their closest margin (24). In all studies, the authors concluded that MR was a necessary component for successful navigated resection, including in Hao *et al.*, who employed MR/CT fusion images (22).

How accurate is post-operative MR imaging for the diagnosis of residual disease following resection of soft tissue sarcoma?

Our search yielded 5 studies discussing the utility of MR for diagnosing residual disease (*Table 5*) (28-32). Combined,

Table 4 Summary of evidence—efficacy of MRI as tool for navigated resection of primary bone tumors

Article	N	Pathology	Findings
Ahmad *et al.*, 2014 (19)	34	1° long bone malignancy	• T1-weighted MR able to determine safe tumor margins with 88.8% overall accuracy • STIR imaging able to determine safe osteotomy planes in 85.4% of cases • Correlation between radiological tumor size and tumor size on gross pathology was 0.98 for T1-weighted imaging and 0.89 for STIR
Cho *et al.*, 2011 (20)	6	1° bone tumor of leg or sacrum	• Able to identify safe osteotomy planes in all cases • No patients demonstrated recurrence at mean 28.8 months, consistent with curative resection • Mean registration error of navigation system was 0.98 mm
Han *et al.*, 2012 (21)	17	Appendicular osteosarcoma	• Average discrepancy between margins on gross pathology and T1-weighted imaging was 0.6 cm (6% of mean lesion size)
Hao *et al.*, 2018 (22)	25	Osteosarcoma or soft tissue sarcoma	• Navigation using pre-operative CT angiogram-MRI fusion images allowed wide or curative resection in 96% of patients targeted for curative resection preoperatively
Iwata *et al.*, 2018 (23)	145	High-grade soft tissue sarcoma	• Correlation between histological infiltration of tumor and radiological infiltration of tumor was 0.27 for T1-weighted imaging and 0.06 for STIR imaging • Authors recommend 2–3 cm cuff of healthy tissue due to poor ability of MR to detect lesion edge
Li *et al.*, 2014 (24)	9	1° appendicular bone malignancy	• Wide margin resection achieved in all patients • Mean registration error of navigation software was 0.4 mm • Mean discrepancy between narrowest margin planned on pre-operative imaging and narrowest margin realized on pathology was 2.0 mm (26% of width of the closest planned margin) • No patients had local recurrence at a mean follow-up of 25.2 months
Li *et al.*, 2012 (25)	6	1° bone malignancy of proximal humerus	• Clear surgical margins achieved in all patients • Mean discrepancy between planned and realized margin not given
Meyer *et al.*, 1999 (26)	125	High-grade appendicular osteosarcoma	• Wide margins achieved in 100% of the 92 patients with osteotomies planned using preoperative T1-weighted MR; 94% for patients undergoing resection without guidance by preoperative imaging
Wong *et al.*, 2013 (27)	8	1° appendicular bone malignancy	• Curative margins achieved in all patients with no evidence of local recurrence at a mean follow-up of 41 months • Mean registration error of 0.47 mm

the five studies included 299 patients, all having undergone prior resection of soft tissue sarcoma. Not controlling for differences in MR sequence(s) employed, the mean sensitivity of MR imaging for residual disease was found to be 71.7% (range: 60–86.7%) and specificity was found to be 79.3% (range: 57.9–93%) at a mean of 43.5 days post-resection (30-32). Three studies—those of Davies, Kaste, and Patkar—examined the relative diagnostic utility of contrast and non-contrast images and found no significant difference in diagnostic accuracy between contrast and non-contrast image sets (28,30,31). One study—that of Puhaindran *et al.* —compared the diagnostic utility of MR for residual disease as a function of the size of the residual lesion (32). Blocking tumors into gross residual disease and microscopic residual disease, the authors found that the overall diagnostic utility of MR was significantly improved

Table 5 Summary of evidence—accuracy of MRI for identifying residual disease following soft tissue sarcoma resection

Article	N	Pathology	Findings
Davies *et al.*, 2004 (28)	111	Soft tissue sarcoma	• In 104 patients with definitive findings, overall accuracy of MR for residual disease was 77% • Sn =0.64; Sp =0.93; PPV =0.93; NPV =0.67 • Majority of non-diagnostic MR results were due to acute post-surgical changes • Contrast-enhanced images did not enhance diagnostic accuracy of MR
Gingrich *et al.*, 2017 (29)	76	Soft tissue sarcoma	• MR positive or equivocal for residual disease had an overall accuracy of 78.1% • Sn =86.7%; Sp =57.9%
Kaste *et al.*, 2002 (30)	24	Soft tissue sarcoma	• Non-contrast MR: Sn =77.8%; Sp =85.7%; PPV =78%; NPV =86% • In the subset of 16 patients with contrast-enhanced imaging, the sensitivity and specificity of imaging for residual disease was identical to that of non-contrast imaging
Patkar *et al.*, 2017 (31)	55	Soft tissue sarcoma	• Overall diagnostic utility of MR for residual disease was deemed high • Sn =86.7%; Sp =90.9%; PPV =92.9%; NPV =83.3% • No significant difference noted between diagnostic utility of contrast and non-contrasted-enhanced images
Puhaindran *et al.*, 2010 (32)	33	Soft tissue sarcoma	• Overall Sn =60%; Sp =78%; PPV =69%; NPV =70% • For cases with gross/macroscopic residual tumor: Sn =89%; Sp =79%; PPV =62%; NPV =95% • No consistent MR battery/protocol used across all patients

NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

for cases with gross residual disease, with a sensitivity of 89%, as compared to 60% for the overall cohort. None of the studies quantitatively assessed the ability of MR to distinguish residual disease from surgical bed edema or post-radiation changes, though several of the authors reported that these both may lower the discriminative ability of MR.

How accurate is post-operative MR imaging for the diagnosis of disease recurrence following resection of soft tissue sarcoma?

Six articles published results discussing the utility of MR for demonstrating recurrence following radical resection of soft-tissue sarcoma (*Table 6*) (33-38). Combined, the studies included 341 patients with soft tissue sarcoma. Including all MR sequences, the overall sensitivity of MR for local recurrence was found to be 87.9% (range: 83–100%) and the overall specificity was 85.9% (range: 55.6–100%). Of the included studies, three compared the diagnostic utility of MR to other imaging modalities, with Erfanian *et al.* comparing MR to PET/MR, Park *et al.* comparing MR to PET/CT, and Reuther and Mutschler comparing MR to CT (36-38). Erfanian *et al.* found that the addition of ^{18}F-FDG PET to the follow-up regimen increased diagnostic accuracy from 80.7% to 89.5%, with a noticeable increase in sensitivity from 80.0% to 95.0%, albeit at the cost of a slight decrease in specificity (82.4% *vs.* 76.5%) (36). Park *et al.* by contrast found no significant difference between the diagnostic accuracy of MR (93.9%) and PET-CT (95.5%) for elucidating local recurrence, though the authors noted that MR had the advantages of: (I) no additional irradiation and (II) delineation of local anatomy for surgical planning in the case of recurrence (37). Lastly, Reuther and Mutschler found that MR was noticeably superior to CT for the evaluation of recurrence (92.6% *vs.* 85%), again with the benefit of not exposing patients to additional irradiation (38).

Of the six studies, two evaluated the use of diffusion weighted imaging (DWI) as part of the imaging protocol. Del Grande *et al.* and ElDaly *et al.* both found that the addition of DWI may increase the specificity of MR for local recurrence, with Del Grande *et al.* reporting a specificity

Table 6 Summary of evidence—MRI for identifying recurrent disease following resection of soft tissue sarcoma

Article	N	Pathology	Findings
Choi *et al.*, 1991 (33)	26	Soft tissue sarcoma	• Sn =83%; Sp =93% • Overall correlation of combined T1- and T2-weighted MR findings with histopathologic results was 0.77
Del Grande *et al.*, 2014 (34)	37	Soft Tissue Sarcoma	• T1-weighted MR identified recurrence with Sn =100% and Sp =52% • Arterial-enhanced dynamic contrast enhanced imaging had Sn =100% and Sp =97% • Low ADC on DWI had Sn =60% and Sp =97%
ElDaly *et al.*, 2018 (35)	36	Appendicular soft tissue sarcoma	• Post-contrast T1-weighted imaging had Sn =87% and Sp =55.6% for local recurrence • Concomitant post-contrast T1-weighted imaging and diffusion weighted imaging improved Sp to 100% • Minimum tumor size detectable was 0.6 cm • Using ADC of $\leq 1.4\times10^{-3}$mm²/s as a cutoff gave DWI an Sn of 85.19% an Sp of 100% • Combined sensitivity of T1- and T2-weighted imaging for recurrence =59.3%
Erfanian *et al.*, 2017 (36)	41	Soft tissue sarcoma	• For MRI-alone, overall diagnostic accuracy =80.7%; Sn =80.0%; Sp =82.4%; PPV =91.4%; NPV =63.6% • For combined ^{18}F-FDG PET, overall diagnostic accuracy was 89.5%; Sn =95.0%; Sp =76.5%; PPV =90.5%; NPV =86.7%
Park *et al.*, 2016 (37)	152	Appendicular soft tissue sarcoma	• MR had an overall accuracy of 93.9%; Sn =90%; Sp =97.7%; PPV =85.7%; NPV =98.5% • PET-CT had an overall accuracy of 95.2%; Sn =95.0%; Sp =95.5%; PPV =76.0%; NPV =99.2% • No significant difference in diagnostic utility of MR and PET/CT for local recurrence
Reuther and Mutschler, 1990 (38)	49	1° musculoskeletal sarcoma	• Overall accuracy of MR was 92.6%; Sn =82.5%; Sp =96.3%; PPV =75%; NPV =91.3% • Overall accuracy of CT was 85%; Sn =82.5%; Sp =96.3%; PPV =52.3%; NPV =83.2%

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; NPV, negative predictive value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

of 97% with DWI and ElDaly *et al.* reporting a specificity of 100% with DWI (34,35). Additionally, ElDaly *et al.* reported that using an apparent diffusion coefficient cutoff of $\leq 1.4\times10^{-3}$ mm²/s, overall sensitivity for recurrence was 85.19% and overall specificity was 100% with a minimum detectable tumor size of 0.6 cm in diameter (34). No quantitative evaluations between contrast and non-contrast MR were reported though several authors commented on contrast imaging being a valuable intervention from distinguishing tumor from edema or post-radiation changes.

Discussion

Learning points from the existing literature

As high-grade malignancies, osteosarcoma and soft tissue sarcoma of the extremities are currently best treated by *en bloc* resection with negative margins (39). Soft tissue sarcomas can frequently abut or involve key neurovascular structures. Needless sacrifice of these structures again hinders quality of life, but careless exclusion may prevent local control and therefore negatively impact long-term prognosis. It can be seen then that identifying a means of accurately assessing tumor margin preoperatively and guiding cuts along planned margins could confer significant benefit to existing surgical technologies.

The literature reviewed above supports the notion that magnetic resonance imaging is invaluable to the musculoskeletal surgical oncologist. Overall, the accuracy of MR for pre-operative margin evaluation appears to be exquisite, especially for osseous malignancy, with Jin *et al.* reporting a correlation between histopathologic and radiologic tumor size of 99%. Because of this accuracy, pre-operative MRI is routinely used during surgical planning for determination of osteotomy placement (40). Additionally, several groups have employed MR or MR-CT fusion images (22) for osteotomy formation under intraoperative computer-assisted navigation (20,24,25,27). Of the four groups here that employed intraoperative navigation, wide excision was achieved in 100% of cases. Local control was achieved in all patients, demonstrating that MR-navigated surgery may aid in the performance of Enneking-appropriate interventions. Furthermore, the studies presented indicate that MR accurately demonstrates residual disease, especially in cases of macroscopic disease, and is highly effective at demonstrating disease recurrence, though the addition of ^{18}F-FDG PET may improve diagnostic sensitivity, as well as allow for detection of distant metastases (36).

Though the evidence supports the value of MR, many questions remain to be answered. Three of note are: (I) Which MR sequence should be used for preoperatively planning? (II) What follow-up regimen should be employed to look for local recurrence and residual disease? and (III) Does earlier detection of residual disease improve patient outcomes?

Years of experience have demonstrated that no single MR sequence is best for the evaluation of musculoskeletal sarcoma, and by extension, no single MR will be best for the evaluation of primary tumors of the vertebral column (41). Rather, imaging for primary musculoskeletal sarcoma should include a minimum of two MR sequences—at least one T1-weighted or anatomic scan and at least one T2-weighted scan to evaluate soft tissue margins (42-44). T1-weighted imaging gives the best definition of bone marrow invasion (13,15,16) and accordingly will provide the best evidence for guiding osteotomy cuts (15,19,23). By contrast, T2 or spin-spin sequences are highly responsive to free water protons, which are classically enriched in the pseudocapsule produced by atrophy of tumor-adjacent soft tissues (45). Usage of fat-saturated T2 sequences (46) or short tau inversion recovery (STIR) additionally increase the conspicuity of the soft tissue component by attenuating the signal of the normally T2-hyperintense adipose tissue (46,47). It must be noted though that STIR sequences also boost the signal produced by peritumoral edema, which is seen in nearly 70% of musculoskeletal malignancy (48,49), and therefore may give a falsely increased estimate of lesion size (17,50-52). Additionally, this edema is common to both benign and malignant lesions, reducing the prognostic utility of scans aimed at highlighting it (53). However, STIR and T2-weighted sequences have added utility in vertebral column malignancy in that they provide the best means of evaluating neural compression (41). In the case of sizeable lesions, STIR is more sensitive for assessment of the soft-tissue mass than are fat-suppressed sequences, as suppression is often heterogeneous across the large field of view (41).

The usage of contrast-enhanced sequences is advocated by many authors, as gadolinium contrast agents have the ability to distinguish viable tumor from both necrotic tumor (41,47) and peritumoral edema (54). Post-contrast, fat-suppressed T1 weighted sequences also enhance visualization of associated soft-tissue masses, as the mass enhances relative to the suppressed soft tissue (46) Additionally, some evidence suggests that time to peak of the post-contrast T1-weighted signal can distinguish benign from malignant lesions in ≈80% of cases (47). However, contrast administration is not without risk; between 20 and 330 people of every 100,000 experience immediate hypersensitivity reactions to contrast administration and between 0.7 and 0.97 of every million doses of contrast are lethal (55-57). A recent editorial in JAMA even highlights the potential long-term health dangers associated with retained gadolinium (58).

Currently no universal guidelines exist surrounding monitoring for residual disease or recurrence following excision of primary bony malignancies due to the heterogenous clinical courses of the distinct pathologies and relatively low-quality evidence upon which current paradigms are based. Many providers recommend annual MR imaging of the primary site, which is consistent with the most recent recommendations made by the American

Association of Orthopaedic Surgeons. However, other organizations, such as the British National Health Service officially only recommend routine chest X-ray to evaluate for pulmonary metastatic disease. Avoiding questions of health resource distribution, the proper follow-up regimen should be dictated by the accuracy of the diagnostic methods and the degree to which they may alter clinical management. The evidence presented here suggests that routine MR is capable of diagnosing residual disease and local recurrence with an overall accuracy of 77–94% (28,36-38). Given that: (I) many patients with curative resection die from metastatic disease, and (II) local recurrence has only inconsistently been linked to distant metastases (59,60), it has been questioned as to whether routine imaging for local recurrence leads to changes in patient care. Several studies, including those of Kasalak, Richardson, Cheney, Watts, George, and Rothermundt have evaluated the ability of routine MR to mediate early detection of recurrent musculoskeletal sarcoma (61-65). Kasalak, Rothermundt, and Cheney all reported that radiological recurrence was more often than not accompanied or preceded by clinical/symptomatic recurrence, undermining the value of serial follow-up (62,63,66). By contrast, Richardson *et al.* found that ¼ to ½ of soft tissue sarcoma patients will present with radiological recurrence first and Watts *et al.* found that 70% of musculoskeletal sarcoma patients present with radiological recurrence prior to symptomatic recurrence (61,64). George *et al.* reported an intermediate result, finding that routine MR imaging of the surgical bed could lead to earlier detection of recurrence in 49% of patients (65). Additionally, they reported that of these patients, 33% had an alteration in their treatment regimen as a result. Alternatively expressed, serial MR for local recurrence may lead to a change in management of as many as 1 in every 6 patients.

Application to vertebral column malignancy

Like sarcoma of the periphery, primary osseous malignancy of the vertebral column is best treated with *en bloc* resection. Achieving negative margins in this context is often times far more difficult however, as the close proximity of the spinal cord and exiting nerve roots leave little room for error. Accurately identifying tumor margins preoperatively is therefore paramount.

Given the similarity of treatment goals for tumors of the axial and appendicular skeleton, it is logical that advances in one field may be potentially implemented in the other. As described in this paper, pre-operative magnetic resonance imaging outlines tumor margins with a high degree of accuracy and can be effectively used intraoperatively to guide osteotomy cuts. This holds true in the spine as well, with the understanding that surgeons will be constantly working close to tumor margins given the confines of the spine and spinal cord.

Additionally, the ability of intraoperative image guidance to achieve negative margins in the appendicular literature must be couched by the fact that margins of 2–3 cm are commonplace (23) and planned margins of 5 cm are not entirely uncommon (14). Even in the context of a radiological margin that poorly represents the gross pathological margin—1 cm or more—the planned cuff of healthy tissue is likely to include all local disease, giving the appearance of a fail-proof technology. Such large margins may be unreasonable for vertebral body malignancy, and therefore to conclude the perfect translatability of this technology, it is necessary to demonstrate that curative resection can be consistently achieved with a much smaller margin for error. Sparse evidence exists to suggest that imaging accuracy is sufficient to mediate *en bloc* resection. At present, only 4 cases have been reported that describe the accuracy of using pre-operative MRI for intraoperative navigation and *en bloc* resection of primary vertebral body malignancy. In three of the four cases, negative margins were reported and in none of the cases were local recurrence or permanent deficit noted (67-69).

Assuming that the results of these select case series are generalizable, intraoperative navigation appears to be a viable tool for guiding Enneking-appropriate resection of vertebral body malignancy. The last question that must be answered then is whether MR is an effective means of: (I) looking for residual disease, and (II) monitoring for local recurrence. Based upon the literature from peripheral soft tissue sarcomas, the answer appears to be in the affirmative, but the quality of evidence is too low to make a definitive conclusion. Additionally, the literature examined—that of soft tissue sarcoma—does not consider the efficacy of MR for monitoring of a surgical bed adjacent to ferromagnetic hardware as is the case following vertebral column resection. To this end, it is likely that although routine (6–12 mo) multi-sequence MR imaging of the surgical bed may aid in evaluation for recurrence, local metallic artifact precludes its exclusive use. Instead, it may be necessary to use an adjuvant diagnostic imaging modality that is immune to local metallic artifact, such as ^{18}F-FDG PET, which demonstrably increases diagnostic accuracy for recurrence in the sarcoma literature (36). PET follow-up is not without its own issues however, as the intervention is extremely costly and patients are exposed to additional radiation. It is unlikely that in the current cost-conscious medical system this intervention will be supported without high quality evidence to support its use. Consequently, the need remains for a high-quality means of diagnosing early recurrent disease.

Potential pitfalls

One issue not addressed in the included studies is the presence of micro-skip metastases—small tumor foci that are not observable on current pre-operative imaging modalities. A recent study by Takeyama *et al.* examining patients with pathologically-confirmed chordoma reported that these "micro skip" metastases may be found in over 40% of patients (70). Though 95% of lesions existed less than one centimeter from the lesion border, in two cases these "micro skip" metastases were found nearly 2 cm from the lesion border. Takeyama *et al.* additionally reported that the presence of "micro skip" metastases was related with significantly lower overall survival, local recurrence-free survival, and metastasis-free survival. As these lesions are segregated from the gross tumor border and invisible to conventional imaging, even accurate osteotomy planes (as determined by preoperative imaging) may fail to include them. Though this has not been explicitly investigated, work by researchers at the Massachusetts General Hospital has demonstrated the use of adjuvant or neoadjuvant radiation significantly reduces local recurrence-free survival (71). Interestingly, use of neoadjuvant or adjuvant radiation was the only predictor of increased local recurrence-free survival on multivariable analysis; R0 resection did not produce any difference in local recurrence-free survival. This suggests, that as observed in the Takeyama cohort, occult "micro skip" metastases may exist outside the tumor boundaries, comprising a sort of "neoplastic penumbra". This penumbra is missed with *en bloc* resection alone, yet is doubtlessly included in the radiation field, explaining the superior overall and progression-free survivals in these patients (72). In part, these results may undermine the emphasis on achieving precise osteotomies and *en bloc* resection; however, it should be noted that radiation is not without its own risks, including catastrophic mechanical failure (73), tumor dedifferentiation, and induction of high-grade sarcoma (74). The latter are substantially more difficult to treat. Consequently, surgeons and patients, alike, must weigh the potential costs and benefits of adjuvant radiation, namely improved local control versus higher complication rates. Improved imaging that allows the identification of "micro skip" metastases as well as navigated-osteotomies aimed at including at least 5 mm of healthy tissue may help to alter this discussion by relegating radiation to only those patients with extremely high-risk lesions or evidence of positive margins. On the other hand, as most of the patients in the chordoma series above were treated with R0 resection, there exists the possibility that even patients with histologically-clean resections may benefit from adjuvant radiotherapy (71). These results have not been expanded to other primary malignancies though and therefore may not be generalizable to all primary vertebral column malignancies.

Conclusions

Using the extant soft tissue sarcoma and appendicular osteosarcoma literature as a learning ground for spine, it appears as if surgical margins prescribed by pre-operative magnetic resonance imaging are accurate assessments of true pathological margins. Consequently, pre-operative imaging, notably T1-weighted volumes, can be used to guide intraoperative maneuvers for the achievement of curative margins. By contrast, the extant literature on the accuracy of MR for evaluating recurrent disease undermines its utility and is largely reserved to the soft tissue sarcoma literature. The latter is not directly translatable to primary vertebral column malignancies that are reconstructed with metal instrumentation and thus have significant artifact that precludes high resolution looks at the soft tissue post-operatively. Consequently, though useful for pre-operative planning and potentially for intraoperative guidance, MR imaging may not be an effective means of evaluating local recurrence following *en bloc* resection in patients receiving concomitant instrumentation.

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None.

Footnote

Conflicts of Interest: ML Goodwin: Consultant for ROM3, Augmedics; DM Sciubba: Consultant for Orthofix, Globus, K2M, Medtronic, Stryker, Baxter. Other authors have no conflicts of interest to declare.

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