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Accuracy of CT and MRI to assess resection margins in primary malignant bone tumours having histology as the reference standard

L. Cannavò [a,1], D. Albano [b,c,*,1], C. Messina [c,d], A. Corazza [c], S. Rapisarda [c], G. Pozzi [c], A. Di Bernardo [e], A. Parafioriti [e], G. Scotto [a], G. Perrucchini [f], A. Luzzati [a], L.M. Sconfienza [c,d]

[a] *IRCCS Istituto Ortopedico Galeazzi, Centro di Chirurgia Ortopedica Oncologica e Ricostruttiva del Rachide, 20161 Milano, Italy*
[b] *Sezione di Scienze Radiologiche, Dipartimento di Biomedicina, Neuroscienze e Diagnostica Avanzata, Università degli Studi di Palermo, Via del Vespro 127, 90127 Palermo, Italy*
[c] *IRCCS Istituto Ortopedico Galeazzi, Unità Operativa di Radiologia Diagnostica ed Interventistica, 20161 Milano, Italy*
[d] *Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, 20122 Milano, Italy*
[e] *Anatomia Patologica, Azienda Sociosanitaria Territoriale PINI-CTO, 20122 Milano, Italy*
[f] *Ortopedia Oncologica, Fondazione Istituto G. Giglio, Contrada Pietrapollastra – Pisciotto, 90015 Cefalù, Italy*

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AIM: To evaluate the accuracy of magnetic resonance imaging (MRI) and computed tomography (CT) in assessing the resection margins of primary malignant bone tumours.

MATERIALS AND METHODS: Resected primary malignant bone tumour specimens removed from 46 patients (27 male; mean age: 48±22 years) were imaged using MRI (fat-saturated proton density-weighted and three-dimensional fat-suppressed T1-weighted gradient-recalled-echo) and CT immediately after surgery. A radiologist and an orthopaedist evaluated bone and soft-tissue margins of the specimens on both examinations. Histological evaluation was performed by a senior orthopaedic oncology pathologist. Margins were classified as R0 (safe margins), R1 (residuals between 0 and 1 mm), and R2 (macroscopic residuals). Cohen's k, chi-square, and McNemar's statistics were used.

RESULTS: Having histology as the reference standard, reproducibility of the radiologist ranged from moderate (k=0.544) to substantial (k=0.741) for bone and soft-tissue margins on CT, respectively, while that of the orthopaedist ranged from fair (k=0.316) to moderate (k=0.548). When comparing R2 and R0+R1 scores, reproducibility of readers' evaluation of bone margins increased ranging from substantial (k=0.655) to perfect (k=1.000). Inter-reader agreement ranged from fair (k=0.308) to substantial (k=0.633). Accuracy of the radiologist and orthopaedist ranged from 76% to 83% and from 68% to 72%, respectively. When comparing R2 and R0+R1 scores, the accuracy of both readers ranged from 83% to 100%. There was no association between local recurrence and margin scores of histology, MRI, and CT ($p \geq 0.058$).

* Guarantor and correspondent: D. Albano, Sezione di Scienze Radiologiche, Dipartimento di Biomedicina, Neuroscienze e Diagnostica Avanzata, Università degli Studi di Palermo, Via del Vespro 127, 90127 Palermo, Italy. Tel.: +39 02/66214497; fax: +39 02/66214004.
E-mail address: albanodomenico@me.com (D. Albano).
[1] These authors share the first authorship as they equally significantly contributed to the present work.

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CONCLUSIONS: MRI and CT may be useful for extemporaneous analysis of resection margins of primary malignant bone tumours, although wide accuracy variability between the different imaging methods was observed.

Introduction

Bone tumours are relatively uncommon entities, representing approximately 0.2% of all tumours.[1] Although some may benefit from chemotherapy or radiation therapy, surgery generally represents the standard of care.[2] The main goal of surgery is the resection *en bloc* of the lesion with wide margins of safety.[2,3] Postoperative histopathological analysis of surgical specimens is the reference standard to assess the involvement of the margins after surgery,[3] while magnetic resonance imaging (MRI) and computed tomography (CT) are widely used for preoperative planning,[4] being able to evaluate tumour features, extent, and relationships with surrounding organs.[5,6]

In oncological surgery, careful resection of the tumour margins is always required to reduce the possibility of local recurrence. The analysis of resection margins is generally done by a pathologist postoperatively, but it can also be done with intra-operative frozen-section pathological consultation to assess doubtful margins. This has the purpose of the possibility to further extend the surgical margins while the patient is still in the operating room if residual tumour is detected; however, for bony lesions this procedure is not feasible, as the assessment of bone margins requires a long procedure which includes tissue decalcification for histological processing.[7] This represents the critical issue in intra-operative evaluation of bone tumour margins. Therefore, the present study was undertaken to test whether intra-operative CT and MRI evaluation of the resected tumour specimens might be of help to detect pathological involvement of the margins. Thus, in the case of positive involvement, resection boundaries could immediately undergo extension while the patient is still in the operating room.

Very little is known on this topic: a single paper used MRI to evaluate margins in specimens of soft-tissue sarcomas resected in rats,[8] while another used MRI to evaluate resection margins of bone sarcomas,[9] both with good reproducibility between the pathology and imaging evaluation. In the former study, the authors used a 1.5 T MRI machine to perform a feasibility study on seven rats reporting a strict correlation between MRI and histological results[8]; the latter was performed on 12 patients with bone sarcomas of the limbs or pelvis, again with excellent accuracy of the radiologist[9]; however, those studies[8,9] have limited sample size, in the study on the rats >80% of the margins were safe and both studies did not include tumours in complex anatomical structures such as the spine. Moreover, no data have been published about the use of CT in this setting.

Thus, the aim of the present study was to assess the accuracy of MRI and CT in the evaluation of resection margins of surgical specimens of primary malignant bone tumours with histology as the reference standard.

Materials and methods

Study population

At our Institution (IRCCS Istituto Ortopedico Galeazzi, Milan, Italy), resected specimens of bone tumours almost routinely undergo CT and/or MRI. Institutional review board approval for this retrospective study was obtained and patients' informed consent was waived.

Newly diagnosed primary malignant bone tumours, with available pre- and post-operative MRI and CT performed at our institution, with specimen assessed by a senior orthopaedic oncology pathologist, and a minimum of 6 months follow-up were included in the analysis. The entire database of the orthopaedic oncology surgery department was cross-referenced with the picture archive and communication system of the radiology unit to include patients with bone tumours surgically resected and imaged between February 2010 and November 2017. The resected specimens of the primary malignant bone tumours of 46 patients (27 males, 19 females; mean age±standard deviation = 48±22 years; range = 5–79 years) were imaged using MRI and/or CT immediately after surgery. All patients underwent preoperative contrast-enhanced MRI and CT a maximum of 3 days before surgery. MRI examination of the specimen was available in 41 cases, whereas CT was available in 40 cases. In one case, after adjuvant therapies, there was no vital tissue within the bone, but only in the adjacent soft tissue. In five cases, the tumour was confined to the bone, with no soft tissue involved.

The mean maximum diameter of tumours measured by a senior radiologist on the preoperative MRI examination was 11.7±6.7 cm and range was 3–26.5 cm. After a mean follow-up of 21 months (range: 8–86 months), 7/46 (15.2 %) patients showed local recurrence of disease.

MRI examination

MRI examinations were performed with one of two 1.5 T MRI systems (Avanto, gradient strength 45 mt/m, slew rate 200 t/m/ms; or Espree, gradient strength 33 mt/m, slew rate 170 t/m/ms; Siemens Medical Solutions, Erlangen, Germany). According to the body segment under investigation, the table-integrated coil, or the abdominal coil, or their

combination was used. The preoperative imaging protocol included T1-weighted turbo spin-echo, T2-weighted turbo spin-echo, short tau inversion recovery, axial spin-echo echo-planar diffusion-weighted imaging (DWI) with b-values of 0 and 1,000 s/mm^2 before intravenous contrast agent injection, and three-dimensional fat-suppressed T1-weighted gradient-recalled-echo after the administration of 0.2 ml/kg body weight gadolinium-diethylenetriamine pentaacetic acid (Magnevist; Bayer Schering, Berlin, Germany).[10] The postoperative imaging protocol included axial fat-saturated proton density-weighted (2,090 ms repetition time [TR], 33 ms echo time [TE], number of excitations [NEX]=3, 3 mm slice thickness, 20% distance factor, 0.7×0.5×3 mm voxel size) and three-dimensional fat-suppressed T1-weighted gradient-recalled-echo (15.6 ms TR, 6.55 ms TE, NEX=1, 1 mm slice thickness, 20% distance factor, 1×1×1 mm voxel size).

CT protocol

CT examinations were performed using a 64-section CT system (Somatom Emotion, Siemens Medical Solutions, Erlangen, Germany). Preoperative CT examinations were acquired before and after the intravenous injection of iodinated contrast agent according to standard protocols designed to investigate the relevant anatomical region. A bolus of 100–120 ml of non-ionic iodinated contrast agent (iomeprol; Iomeron 400, Bracco, Milan, Italy) followed by a saline flush of 20–30 ml was administered intravenously at an injection rate of 3–4 ml/s. For dynamic phase imaging, a portal phase was performed following a scanning delay of 80 seconds after contrast agent administration. Postoperative examination was performed on the tumour specimen with the same CT system.

Image interpretation

A radiologist with 7 years of experience in musculoskeletal imaging and an orthopaedist with 8 years of experience in bone tumour surgery, independently evaluated the bone and soft-tissue margins of the specimens on both the MRI and CT images, blinded to the histopathological results. MRI and CT images were evaluated in random order and in different sessions. Margins were classified according to the standardised classification, created by the Union for International Cancer Control (UICC),[11] as: R0 (safe margins); R1 (possible microscopic residuals between 0 and 1 mm); or R2 (macroscopic residual disease). The readers compared specimens' images with the preoperative MRI and CT images, which were available in all cases.

Pathologic evaluation

Histological margin evaluation was performed by a senior orthopaedic oncology pathologist with 25 years of experience in bone tumour pathology. At gross examination, the specimens' surface was macroscopically assessed to identify the most critical margins, such as area of the tumour covered only by pseudocapsule. The surface of the surgical resection was marked with Indian ink and the specimen was fixed with neutral buffered formalin 10% for at least 24 hours. After fixation, bone specimens underwent decalcification. Serial sections were then performed and tissues were taken for histology, paying particular attention to the inked margins closest to the tumour. These samples were embedded in paraffin and 5 μm-thick sections were cut from paraffin blocks and stained with haematoxylin–eosin. Then, the pathologist evaluated the excision margins microscopically by measuring the distance in millimetres between the tumour edge and the closest inked surface on the haematoxylin–eosin sections, thereby providing a grade (R0, R1, or R2) according to the UICC classification.[11] The pathologist was blinded to the MRI and CT margin results.

Statistical analysis

Reproducibility of margin scores between histology and MRI or CT as assessed by the radiologist or the orthopaedic surgeon was evaluated using Cohen's k. The same test was used to assess interobserver reproducibility between the radiologist and the orthopaedic surgeon. The same analysis was also repeated grouping together the scores R0 and R1 and comparing them with R2 scores. Agreement was considered as absent (values $\leq$0), poor (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or almost perfect (0.81–1.00). Accuracy of radiologist and orthopaedic surgeon in correctly evaluating true-positive and true-negative margins was calculated as ([number of true-positive cases + number of true-negative cases]/total number of cases × 100) and accuracies were compared using the McNemar test. The association between local recurrence and margin scores of histology, MRI, or CT was assessed using the chi-square test. Bonferroni correction for multiple comparisons was applied and a p-value $<$0.002 was considered to indicate statistical significance. Statistical analysis was performed using the SPSS software (v. 24, IBM, Armonk, NY, USA).

Results

Histotypes and anatomical sites of 46 bone tumours with pathological results of margins' assessment and raw data of radiologist's and orthopaedist's evaluations of resected margins on MRI and CT are reported in Tables 1 and 2, respectively.

MRI

Using pathology as the reference standard, the reproducibility of the radiologist's evaluations was moderate for bone margins (k=0.605) and moderate for soft-tissue margins (k=0.615); when considering R0+R1 versus R2 the reproducibility was substantial for bone margins (k=0.787) and moderate for soft-tissue margins (k=0.561). The reproducibility of the orthopaedist's evaluations was moderate for both bone and soft-tissue margins (k=0.410 and k=0.470), becoming almost perfect for bone margins

Table 1
Histotypes and anatomical sites of 46 bone tumours with raw data regarding the radiologist's evaluations of resected margins on magnetic resonance imaging (MRI) and computed tomography (CT) and pathological assessment of the margin.

Sex	Location	Type	Histo bone	Histo soft	MRI bone	MRI soft	CT bone	CT Soft
M	Spine	Pleomorphic sarcoma	1	1	0	1	0	1
M	Spine	Chordoma	1	1	1	1	0	1
F	Sacrum	G2 CSA	2	2	2	2	NA	NA
M	Spine	Ewing sarcoma	0	0	0	0	0	0
M	Spine	Pleomorphic rhabdomyosarcoma	[a]	1	[a]	1	[a]	1
M	Pelvis	G2 central CSA	0	1	NA	NA	0	1
M	Spine	G2 CSA	1	\	1	\	NA	NA
F	Spine	Ewing sarcoma	0	\	NA	NA	0	\
F	Spine	Osteogenic osteosarcoma	1	1	1	1	1	1
M	Spine	Chordoma	0	0	0	2	0	2
M	Spine	Pleomorphic sarcoma	1	0	1	1	1	1
M	Femur	Osteosarcoma	0	1	0	1	NA	NA
M	Pelvis	Dedifferentiated CSA	0	1	0	0	0	0
M	Pelvis	G3 central CSA	0	0	0	0	NA	NA
M	Pelvis	G3 central CSA	0	1	0	1	0	1
M	Spine	Chordoma	1	1	0	1	0	1
F	Spine	Chordoma	0	1	0	1	0	1
M	Spine	G2/G3 CSA	2	2	2	2	2	2
M	Spine	Ewing sarcoma	0	0	0	0	0	0
M	Femur	Ewing sarcoma	0	0	0	0	0	0
M	Femur	G3 CSA	0	1	NA	NA	0	1
F	Femur	G2 CSA	0	1	0	1	NA	NA
M	Spine	Chordoma	1	2	1	2	1	2
M	Spine	G2 CSA	1	2	0	2	0	2
M	Tibia	Dedifferentiated CSA	0	1	0	1	0	1
F	Spine	Ewing sarcoma	0	0	NA	NA	0	0
M	Femur	G2 CSA	0	1	0	1	NA	NA
F	Spine	G2 CSA	0	1	0	2	0	2
F	Spine	Sarcoma n.o.s.	0	2	0	1	0	1
M	Humerus	Spindle cell sarcoma	0	\	0	\	0	\
F	Spine	Osteosarcoma	0	0	0	0	0	0
F	Spine	Mesenchymal CSA	0	1	0	1	0	1
F	Spine	High-grade leiomyosarcoma	1	2	0	2	0	2
F	Pelvis	Ewing sarcoma	0	1	0	0	0	1
M	Spine	Chordoma	1	\	1	\	1	\
F	Spine	Mesenchymal CSA	1	1	0	1	0	1
F	Spine	G2 CSA	1	1	0	1	0	1
M	Spine	Chordoma	1	2	1	2	1	2
M	Femur	Ewing sarcoma	0	0	NA	NA	0	0
M	Spine	Chordoma	2	2	1	1	1	1
F	Femur	Osteosarcoma	1	2	0	1	0	1
M	Spine	Chordoma	0	\	0	\	0	\
F	Pelvis	Spindle cell sarcoma	0	2	1	1	1	1
F	Femur	Dedifferentiated CSA	0	0	0	0	0	0
F	Femur	Dedifferentiated CSA	0	0	0	0	0	0
F	Femur	High-grade osteosarcoma	0	0	0	0	0	0

NA, not available perioperative examination on the specimen; \, the tumour was confined to the bone, with soft tissues being not involved; 0, R0 (safe margins); 1, R1 (possible microscopic residuals between 0 and 1 mm); 2, R2 (macroscopic residual disease). CSA, chondrosarcoma; Histo, histology; bone, bone margins; soft, soft tissue margins. M, male; F, female; G2/G3, grading of the tumor.
[a] Absence of vital tissue on the specimen after neoadjuvant therapy.

(k=0.844) and moderate for soft-tissue margins (k=0.593) when grouping R0+R. Full data are reported in Table 3.

The accuracy of the radiologist's evaluations was 80% and 76% for bone and soft-tissue margins, respectively, becoming 98% and 84% when grouping R0+R1; while the accuracy of the orthopaedist's evaluations was 70% and 68%, becoming 98% and 86% when considering R0+R1 versus R2, with no statistically significant differences ($p \geq 0.264$). Full data are reported in Table 4.

Interobserver agreement between the radiologist's and orthopaedist's evaluations was moderate for bone margins (k=0.538) and fair for soft-tissue margins (k=0.308), becoming substantial (k=0.643) and poor (k=0.170), respectively, when grouping R0+R1. Full data are reported in Table 5.

CT

Using histology as the reference standard, the reproducibility of the radiologist's evaluations was moderate for bone margins (k=0.544) and substantial for soft-tissue margins (k=0.741); when grouping R0 and R1 margins

Table 2
Histotypes and anatomical sites of 46 bone tumours with raw data of orthopaedist's evaluations of resected margins on magnetic resonance imaging (MRI) and computed tomography (CT) and pathological results of margins' assessment.

Sex	Location	Type	Histo bone	Histo soft	MRI bone	MRI soft	CT bone	CT Soft
M	Spine	Pleomorphic sarcoma	1	1	0	1	0	1
M	Spine	Chordoma	1	1	1	1	1	1
F	Sacrum	G2 CSA	2	2	2	2	NA	NA
M	Spine	Ewing sarcoma	0	0	1	0	1	0
M	Spine	Pleomorphic rhabdomyosarcoma	[a]	1	[a]	1	[a]	1
M	Pelvis	G2 central CSA	0	1	NA	NA	0	1
M	Spine	G2 CSA	1	\	1	1	NA	NA
F	Spine	Ewing sarcoma	0	\	NA	NA	0	0
F	Spine	Osteogenic osteosarcoma	1	1	2	1	1	1
M	Spine	Chordoma	0	0	0	1	0	1
M	Spine	Pleomorphic sarcoma	1	0	1	1	1	1
M	Femur	Osteosarcoma	0	1	0	1	NA	NA
M	Pelvis	Dedifferentiated CSA	0	1	0	1	1	1
M	Pelvis	G3 central CSA	0	0	0	1	NA	NA
M	Pelvis	G3 central CSA	0	1	0	0	0	0
M	Spine	Chordoma	1	1	0	1	0	1
F	Spine	Chordoma	0	1	0	1	0	1
M	Spine	G2/G3 CSA	2	2	2	2	2	2
M	Spine	Ewing sarcoma	0	0	0	0	0	0
M	Femur	Ewing sarcoma	0	0	0	1	0	0
M	Femur	G3 CSA	0	1	NA	NA	0	1
F	Femur	G2 CSA	0	1	0	0	NA	NA
M	Spine	Chordoma	1	2	1	1	0	1
M	Spine	G2 CSA	1	2	0	1	0	1
M	Tibia	Dedifferentiated CSA	0	1	1	1	1	1
F	Spine	Ewing sarcoma	0	0	NA	NA	0	0
M	Femur	G2 CSA	0	1	0	1	NA	NA
F	Spine	G2 CSA	0	1	0	0	0	0
F	Spine	Sarcoma n.o.s.	0	2	0	1	0	1
M	Humerus	Spindle cell sarcoma	0	\	0	\	0	\
F	Spine	Osteosarcoma	0	0	0	0	0	0
F	Spine	Mesenchymal CSA	0	1	0	1	0	1
F	Spine	High-grade leiomyosarcoma	1	2	0	1	0	1
F	Pelvis	Ewing sarcoma	0	1	0	1	0	1
M	Spine	Chordoma	1	\	0	\	0	\
F	Spine	Mesenchymal CSA	1	1	0	1	0	1
F	Spine	G2 CSA	1	1	0	1	0	1
M	Spine	Chordoma	1	2	0	1	0	1
M	Femur	Ewing sarcoma	0	0	NA	NA	0	0
M	Spine	Chordoma	2	2	2	2	2	2
F	Femur	Osteosarcoma	1	2	0	2	0	1
M	Spine	Chordoma	0	\	0	\	0	\
F	Pelvis	Spindle cell sarcoma	0	2	0	2	0	2
F	Femur	Dedifferentiated CSA	0	0	0	0	0	0
F	Femur	Dedifferentiated CSA	0	0	0	0	0	0
F	Femur	High-grade osteosarcoma	0	0	0	0	0	0

NA, not available perioperative examination on the specimen; \, the tumour was confined to the bone, with soft tissues being not involved; 0, R0 (safe margins); 1, R1 (possible microscopic residuals between 0 and 1 mm); 2, R2 (macroscopic residual disease). CSA, chondrosarcoma; Histo, histology; bone, bone margins; soft, soft tissue margins. M, male; F, female; G2/G3, grading of the tumor.

[a] Absence of vital tissue on the specimen after neoadjuvant therapy.

scores, the reproducibility was substantial for both bone (k=0.655) and soft-tissue margins (k=0.704). The reproducibility of the orthopaedist's evaluations was fair for bone margins (k=0.316) and moderate for soft-tissue margins (k=0.548), becoming perfect for bone margins (k=1.000) and remaining moderate for soft-tissue margins (k=0.429) when considering R0+R1 versus R2 (see Table 3).

Accuracy of the radiologist's evaluations was 79% and 83% for bone and soft-tissue margins, respectively, becoming 97% and 89% when grouping R0+R1; while the accuracy of the orthopaedist's evaluations was 69% and 72%, increasing to 100% and 83% when considering R0+R1 versus R2, with no statistically significant differences ($p \geq 0.031$; see Table 4).

Interobserver agreement between the radiologist's and orthopaedist's evaluations was fair for bone margins (k=0.312) and substantial for soft-tissue margins (k=0.633), becoming substantial (k=0.655) and moderate (k=0.429), respectively, when grouping R0+R1 (see Table 5).

No significant association between local recurrence and bone and soft-tissue margin scores were found for histology ($p \geq 0.430$), MRI ($p \geq 0.058$), and CT ($p \geq 0.058$) of both the

Table 3
Reproducibility of margin scores of radiologist's and orthopaedic surgeon's evaluations of 46 bone tumours whose specimens underwent peri-operative magnetic resonance imaging (MRI) and computed tomography (CT) margins assessment compared to histology.

Margins	Reader	MRI		CT	
		Bone	Soft tissues	Bone	Soft tissues
R0 versus R1 versus R2	Radiologist	0.605±0.121	0.615±0.112	0.544±0.129	0.741±0.097
	Orthopaedic surgeon	0.410±0.133	0.470±0.124	0.316±0.149	0.548±0.116
R0+R1 versus R2	Radiologist	0.787±0.205	0.561±0.178	0.655±0.320	0.704±0.138
	Orthopaedic surgeon	0.844±0.152	0.593±0.154	1.000±0.000	0.429±0.165

Numerical data are Cohen's k values ± standard deviation. Margins were classified according to the standardised classification, created by the Union for International Cancer Control as: R0 (safe margins); R1 (possible microscopic residuals between 0 and 1 mm); or R2 (macroscopic residual disease); bone, bone margins; soft tissues, soft tissue margins.

radiologist's and orthopaedic surgeon's evaluations. Full data are reported in Table 6.

One case of vertebral epithelioid leiomyosarcoma and one case of femoral Ewing's sarcoma are shown in Figs 1 and 2, respectively.

Discussion

The main finding of the present study was that both the radiologist and orthopaedic surgeon had good accuracy when reading CT and MRI to assess specimen margins of resected bone tumours with histology as the reference standard. As expected, the accuracy was higher when comparing R2 versus R0+R1, especially for the assessment of the bone margins; however, inter-rater reproducibility ranged from fair to substantial and no significant association was found between local recurrence and bone and soft-tissue margin scores of histology, MRI, and CT.

Pathology is the reference standard to assess surgical margins of bone and soft-tissue tumours.[3] The "R" classification is widely used in the literature with a proven correlation between histological margin scores and clinical outcome.[2,11,12] Kawaguchi *et al.* underlined the relationship between histological surgical margins in bone and soft-tissue sarcomas and local recurrence.[3] Bacci *et al.* showed that intralesional or marginal resection, particularly combined with a poor response to chemotherapy, is related to higher risk of local and systemic recurrences.[12] In the present study, this association was not statistically significant, as well as between local recurrence and both CT and MRI margin scores. This may be due to the low number of patients with local recurrence included in the present series, which in turn may be due to the short follow-up of the most recent patients.

Preoperative MRI has shown to be an excellent tool to plan bone resection in sarcomas. In a retrospective study on 25 patients affected by Ewing sarcoma, Thèvenin-Lemoine *et al.* found excellent correlation between MRI and histological assessment of tumour limits both pre-chemotherapy and post-chemotherapy.[13] Thompson *et al.* evaluated the role of MRI in the assessment of osseous extension of primary bone tumours on 55 patients.[14] The authors concluded that T1-weighted MRI images are accurate for this purpose, especially after neoadjuvant chemotherapy, considering a potential difference of up to 1 cm between MRI and histological margins of bone tumours[14]; however, the role of MRI for peri-operative evaluation of surgical margins has been scarcely investigated while the role of CT has never been tested. Bellanova *et al.* analysed 14 resected specimens of sarcoma in rats both histologically and with

Table 4
Accuracy of margin scores of radiologist's and orthopaedic surgeon's evaluations of 46 bone tumours whose specimens underwent peri-operative magnetic resonance imaging (MRI) and computed tomography (CT) margins assessment compared to histology.

Margins	Reader	MRI		CT	
		Bone	Soft tissues	Bone	Soft tissues
R0 versus R1 versus R2	Radiologist	32/40; 80%	28/37; 76%	31/39; 79%	30/36; 83%
	Orthopaedic surgeon	28/40; 70%	25/37; 68%	27/39; 69%	26/36; 72%
	p-Value	0.264	0.539	0.565	0.112
R0+R1 versus R2	Radiologist	39/40; 98%	31/37; 84%	38/39; 97%	32/36; 89%
	Orthopaedic surgeon	39/40; 98%	32/37; 86%	39/39; 100%	30/36; 83%
	p-Value	0.500	0.508	>0.999	0.031

Numerical data are accuracies, calculated as ([number of true positive cases + number of true negative cases]/total number of cases) and percentages in parentheses. *p*-Values were calculated using the McNemar test. Bonferroni correction for multiple comparisons was applied and a *p*-value <0.002 was considered as statistically significant.
Margins were classified according to the standardised classification, created by the Union for International Cancer Control as: R0 (safe margins); R1 (possible microscopic residuals between 0 and 1 mm); or R2 (macroscopic residual disease. bone, bone margins; soft tissues, soft tissue margins.

Table 5
Interobserver agreement of margin scores of radiologist's and orthopaedic surgeon's evaluations of 46 bone tumours whose specimens underwent peri-operative magnetic resonance imaging (MRI) and computed tomography (CT) margins assessment.

Margins	MRI		CT	
	Bone	Soft tissues	Bone	Soft tissues
R0 versus R1 versus R2	0.538±0.132	0.308±0.132	0.312±0.154	0.633±0.108
R0+R1 versus R2	0.643±0.230	0.170±0.185	0.655±0.320	0.429±0.175

Numerical data are Cohen's k values ± standard deviation. Margins were classified according to the standardised classification, created by the Union for International Cancer Control as: R0 (safe margins); R1 (possible microscopic residuals between 0 and 1 mm); or R2 (macroscopic residual disease); bone, bone margins; soft tissues, soft tissue margins.

Table 6
Association between local recurrence and bone and soft-tissues margin scores at histology and radiologist's and orthopaedic surgeon's evaluations of 46 bone tumours whose specimens underwent peri-operative magnetic resonance imaging (MRI) and computed tomography (CT) evaluation.

	Score	R0 versus R1 versus R2	R0+R1 versus R2
Histology	Bone	0.729	0.430
	Soft tissues	0.555	0.976
Orthopaedic surgeon	MRI - bone	0.590	0.325
	MRI - soft tissues	0.058	0.247
	CT - bone	0.711	0.430
	CT - soft tissues	0.058	0.325
Radiologist	MRI - bone	0.520	0.583
	MRI - soft tissues	0.110	0.145
	CT - bone	0.694	0.583
	CT - soft tissues	0.200	0.360

Numerical data are *p*-values calculated using the chi-square test. Margins were classified according to the standardised classification, created by the Union for International Cancer Control as: R0 (safe margins); R1 (possible microscopic residuals between 0 and 1 mm); or R2 (macroscopic residual disease); bone, bone margins; soft tissues, soft tissue margins. Bonferroni correction for multiple comparisons was applied and a *p*-value <0.002 was considered as statistically significant.

MRI.[8] Using the UICC classification, the authors found a strong correlation (k=0.84, $p<0.05$), between MRI and histological margin scores; however, that work was not a clinical study and the accuracy of assessment of bone and soft-tissue margins was not evaluated.[8] Furthermore, rat specimens are small, while human tumour specimens are larger and more complex to evaluate; the average size of specimens in the present series was approximately 12 cm. Vandergugten *et al.* compared the accuracy of MRI and histology in the evaluation of resection margins of 12 fresh specimens of patients affected by bone sarcoma. As in the present study, the authors used the UICC classification and compared the results of histological evaluations performed by a pathologist with the margin scores obtained by an experienced radiologist, an experienced orthopaedic surgeon, and an unexperienced orthopaedic surgeon. They found perfect agreement for margin evaluation between the pathologist and the radiologist (k=1) and substantial agreement between the radiologist and the experienced orthopaedic surgeon.[9]

In the present study, a much larger series of patients was investigated, achieving different results. When comparing R2 versus R0+R1 margin scores, both radiologist and orthopaedic surgeon evaluation had good accuracy. The accuracies of the orthopaedist's and radiologist's evaluation of bone margins when evaluating R2 versus R0+R1 was not significantly different, but the radiologist was more accurate than the orthopaedist (79% versus 69%) in the differentiation of R0 versus R1 versus R2. The accuracy of both readers' evaluations grouping R0 and R1 was assessed because the evaluation of microscopic infiltrations (residuals between 0 and 1 mm) of resected margins would

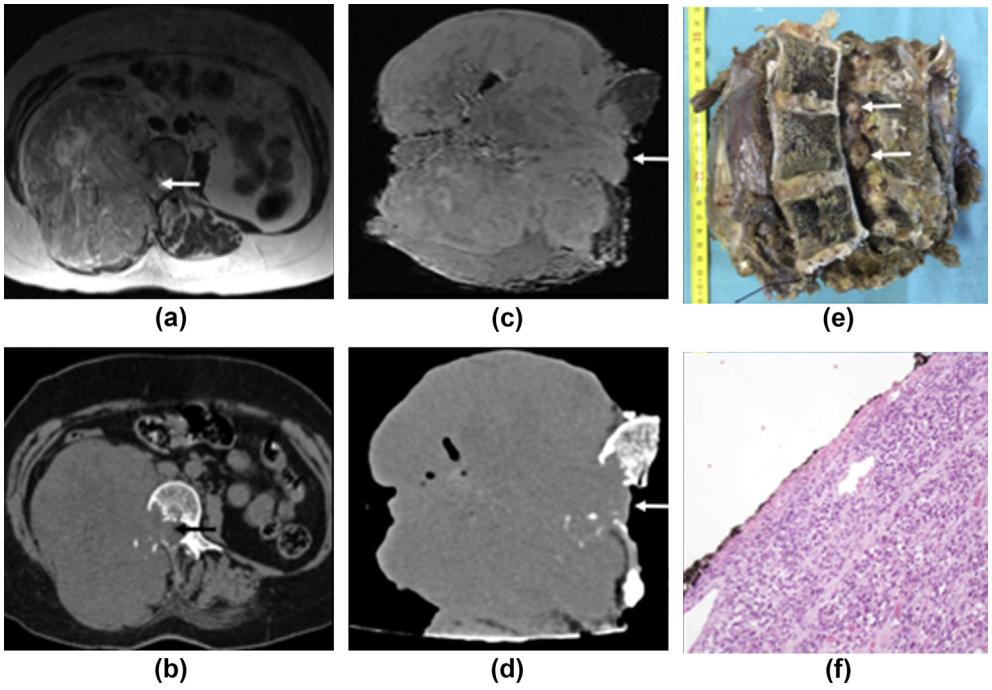

Figure 1 A 55-year-old woman with epithelioid leiomyosarcoma. Preoperative T2-weighted MRI (a) and CT (b) images and peri-operative MRI three-dimensional fat-suppressed T1-weighted gradient-recalled-echo (c) and CT (d) images of the resected specimens, show a large lumbar spine tumour extending into the spinal canal (arrows) and to the right paravertebral tissues. Macroscopic examination of the resected specimen (e) shows right multilevel vertebrectomy L2–L3–L4 with voluminous paravertebral mass. Microscopic examination with haematoxylin–eosin stain (f) revealed spindle cells arranged in alternating fascicles having pleomorphic nuclei, indistinct margin, eosinophilic cytoplasm, and foci of haemorrhage and necrosis, with neoplastic foci being present at margin inked surface. Bone and soft-tissue margins were considered as R1 and R2, respectively, at histology, MRI, and CT examinations.

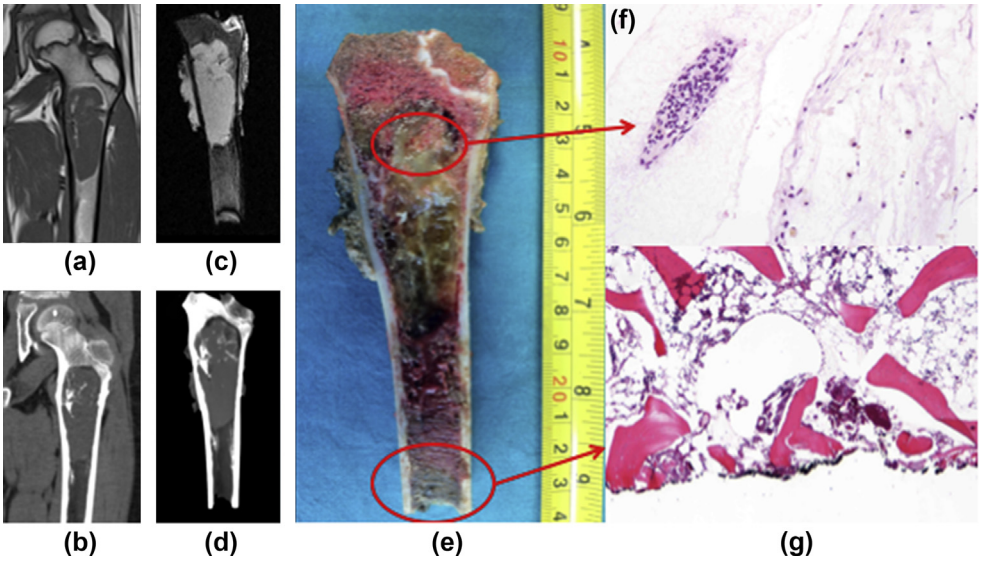

Figure 2 A 13-year-old male patient with Ewing's sarcoma of the left femur. Preoperative T1-weighted MRI (a) and CT (b) images and perioperative MRI three-dimensional fat-suppressed T1-weighted gradient-recalled-echo (c) and CT (d) images of the resected specimen show a bone lesion of the proximal metadiaphyseal femur. Macroscopic examination (e) shows diffuse infiltration of the diaphyseal canal and the metadiaphyseal region by friable necrotic yellowish tissue with haemorrhagic foci. (f) Microscopic examination with haematoxylin–eosin stain revealed microscopic residual foci of tumour in medullary cavity in the proximal femur (circle and arrow). (g) At the distal portion of the femur, microscopic examination shows the inked surface on the lamellar bone without tumour (circle and arrow). At histology, as well as the MRI and CT images of the specimen, the resection margins were considered as R1.

have been challenging using imaging. Indeed, in daily clinical practice, imaging examination of the resected specimens is used to search for macroscopic residuals which require further resection. It is important to underline that the choice to further extend the resection cannot rely only on the status of the specimens' margins, as it also depends on the anatomical structures involved. This evaluation requires evaluation from a surgical point of view, which can be obtained only after image interpretation in consensus with the orthopaedist. In some doubtful cases, the orthopaedists further extended resection margins: however, when important structures are involved, surgical resection cannot be extended, as in some cases of dural involvement.

Thus, imaging might potentially help the surgeon to quickly detect macroscopic tumour residuals while the patient is still in the operating room. This allows for further extension of the surgical margins on the patient if residual tumour is detected at CT or MRI on margins of the resected specimen; however, it should be noted that the presence of small residuals might be underestimated. Moreover, imaging could be useful especially for the extemporaneous assessment of cortical bone and bone marrow margins when dealing with primary bone tumours. Indeed, only an extemporaneous evaluation of marrow can be performed by the pathologist while both MRI and CT appear to be accurate in detecting macroscopic residuals in resected margins. The reproducibility of the scores of the radiologist's and orthopaedic surgeon's evaluations versus histology and interobserver reproducibility were highly variable. Indeed, an optimal assessment of resection margins with "R" evaluation according to UICC classification through imaging techniques is still challenging, as it requires differentiation of bone and soft-tissue involvement under 1 mm. Another consideration is that more than half of the tumours were spine tumours in the present series. Compared to other locations (e.g., long bones), the spine has greater anatomical complexity, which further complicates evaluation. Conversely, Vandergugten *et al.* included eight patients in their study with long bone sarcoma of the limbs and four primary tumours of the pelvis.[9] This difference could partly justify the lower accuracy of the present evaluations.

Another important point is that imaging examinations of resected specimens may also provide the distance between safe margins and tumour tissue, which is crucial when dealing with tumours such as Ewing's sarcoma and osteosarcoma. This is particularly important as limb preservation is more and more preferred over amputation. Nevertheless, the correlation between safe margin width and local recurrence rate is still unclear. Some authors proposed 2 cm as an adequate margin in osteosarcoma with good response to neoadjuvant therapies[3,15] while others reported that margins >2 mm can be considered safe when > 90% necrosis has been observed after neoadjuvant chemotherapy.[16] Further, the actual impact of resection margins on local recurrence is controversial too. Some studies did not show significant differences between patients with adequate and those with inadequate margins, whereas others confirmed that the intralesional margin (R2) is associated with the highest rate of recurrence and safe margins (R0) with the lowest.[17] In the present study, imaging assessment of resection margins has achieved similar

results in the evaluation of soft-tissue and bone margins. Nevertheless, higher accuracy was found on bone margins when grouping R0 and R1 evaluations. These data would be related to the fact that the evaluation of soft-tissue resected margins can be challenging due to the pseudocapsule and reactive changes of adjacent tissues related to the tumour and surgery; however, to the authors' knowledge, variation of recurrence rate of primary bone tumours according to resection margins involvement in the soft tissues or in the bone has not been reported before.

The present retrospective MRI protocol included just two sequences, thereby limiting the accuracy of the examination itself by not including a three-dimensional T2-weighted gradient-recalled-echo, which can be helpful in this setting. This is something that is being systematically undertaken in a prospective protocol currently in preparation. Indeed, the accuracy of MRI can be increased by improving imaging protocols, in addition to acquiring images on 3 T systems, which could be a further interesting point for future research. Some additional limitations should be highlighted. First, margin scores on histological evaluation of surgical specimens were obtained by only one pathologist. Then, several histological tumour subtypes were included, with some histotypes being underrepresented in this series. Moreover, primary tumours of several bone segments were included without comparing the accuracy of imaging margin scores at the different sites.

In conclusion, both the radiologist and orthopaedic surgeon had good accuracy when reading CT and MRI to assess specimen margins of resected bone tumours with histology as the reference standard, with even higher accuracy when comparing R2 versus R0+R1. Extemporaneous imaging examinations of resected specimens might be useful to detect macroscopic residuals thereby guiding further extension of tumour resection, but relatively low inter-rater reproducibility may still limit the use of this method in clinical practice. Further prospective studies with optimised MRI protocols are warranted.

Conflict of interest

The authors declare that they have no conflict of interest.

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