Radiol med (2013) 118:456–464
DOI 10.1007/s11547-012-0860-4

MUSCULOSKELETAL RADIOLOGY
RADIOLOGIA MUSCOLO-SCHELETRICA

Recurrence in giant cell tumour of bone: imaging features and risk factors

Tumore osseo a cellule giganti recidivante: caratteristiche radiologiche e fattori di rischio

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Received: 29 October 2011 / Accepted: 15 December 2011 / Published online: 9 August 2012

Abstract
Purpose. This study was done to investigate X-ray, computed tomography (CT) and magnetic resonance (MR) imaging features of recurrence in giant cell tumour of bone (GCTB) and to evaluate risk factors.
Materials and methods. Medical records and imaging data were reviewed for 55 cases of recurrent GCTB. All images were reviewed retrospectively and independently by two radiologists experienced in skeletal musculature. The common radiological findings; factors related to tumour recurrence such as gender, age, location; pathological fracture, Campanacci grading and surgical procedure were analysed by nonparametric test (Mann–Whitney *U* test for two independent samples test and Kruskal–Wallis *H* test for multiple independent samples test). *p* values <0.05 were considered to indicate a statistically significant difference.
Results. The imaging features of recurrent GCTB were as follows: osteolytic destruction or bone resorption of graft bone or around the polymethylmethacrylate (PMMA), soft tissue mass formation and expansile change. Tumour parenchyma showed markedly heterogeneous enhancement, except for necrotic cystic cavities, on contrast-enhanced MR images. Wide resection had a smaller (p=0.031) risk of local recurrence than did intralesional curettage. There was no statistical significance in gender, age, location, pathological fracture and Campanacci staging (p>0.05).
Conclusions. The risk of recurrence in GCTB was influenced by the type of surgery and adjuvants. Bone

Riassunto
Obiettivo. *Questo studio è stato condotto per valutare le caratteristiche radiografiche, di tomografia computerizzata (TC) e di risonanza magnetica (RM) della recidiva del tumore osseo a cellule giganti (GCTB) e valutarne i fattori di rischio.*
Materiali e metodi. *Sono state riesaminate le cartelle cliniche e le indagini radiologiche di 55 casi di GCTB recidivante. Tutte le immagini sono state valutate retrospettivamente ed in maniera indipendente da due radiologi esperti in radiologia muscolo-scheletrica. I rilievi radiologici ed i fattori correlati alla recidiva tumorale come sesso, età, sede, presenza di frattura patologica, classificazione di Campanacci e procedura chirurgica sono stato analizzate mediante test non parametrici (test U di Mann-Whitney U e test H di Kruskal-Wallis). Valori di p<0,05 sono stati considerati statisticamente significativi.*
Risultati. *Le principali caratteristiche radiologiche del GCTB recidivante sono risultate essere: distruzione osteolitica, riassorbimento dell'innesto osseo o in adiacenza al polimetilmetacrilato (PMMA), insorgenza di massa nei tessuti molli e comparsa di formazione espansiva. All'indagine RM il tessuto tumorale ha mostrato enhancement marcatamente eterogeneo, ad eccezione per le cavità cistiche necrotiche. Le resezioni radicali hanno avuto un minor rischio (p=0.031) di recidiva locale rispetto al curettage intralesionale. Non si è evidenziata differenza statisticamente significativa per quanto concerne sesso, età, sede, presenza di frattura*

resorption, soft tissue mass formation and aggravated expansile change are reliable signs of recurrence on imaging.

Keywords Bone neoplasms · Giant cell tumours · Recurrence · Computed tomography · X-rays · Magnetic resonance imaging

patologica e classificazione di Campanacci (p>0.05). ***Conclusioni****. Il rischio di recidiva del GCTB è influenzato dal tipo di chirurgia e dalla presenza di innesti. Riassorbimento osseo, insorgenza di massa nei tessuti molli e comparsa di formazioni espansive sono segni radiologici affidabili di recidiva.*

Parole chiave *Neoplasie ossee · Tumore a cellule giganti · Recidiva · Tomografia computerizzata · Radiografia · Risonanza magnetica*

Introduction

Giant cell tumour of bone (GCTB) is a benign but locally aggressive neoplasm accounting for approximately 5% of all primary bone tumours [1, 2]. Some GCTB have the characteristics of postoperative local recurrence and pulmonary metastasis, although their histopathology is benign [3–6]. The reported local recurrence rate is 2.5–45%, and most are cases of postoperative recurrence within 24 months [4, 7, 8]. These characteristics are frequently ignored and underestimated in clinical practice. Many studies show that tumour size, location, X-ray grading, pathological fracture and histological grading have no impact on tumour recurrence, invasiveness and distant metastases [9]. Tumour recurrence is closely related to the therapeutic regimen, with recurrence rate being high after curettage and low after resection [3, 9]. The recurrence rate after wide resection is 3–12%, and intralesional curettage shows an overall recurrence rate of 16–18% [8, 10].

Radiological monitoring can be used for early detection of recurrence [3–5, 11]. Balke et al. recommend that MR imaging be performed if the patient presents with newly occurring pain or swelling or the standard X-rays shows any suspicious findings [7]. In this study, we retrospectively analysed radiographic, CT and MR imaging features and clinical data of 55 postoperatively recurrent histologically confirmed GCTB. The purpose was to investigate X-ray, CT and MR imaging features of recurrence in GCTB and evaluate the risk factors.

Materials and methods

Patients

Between June 1990 and September 2011, 316 patients with a histologically proven diagnosis of GCTB were treated surgically at our institution. The patients were retrospectively identified from the hospital database, and their radiological images were reviewed to identify those with recurrence in GCTB. There were 159 men and 157 women, with a mean age at operation of 36.8 (14–75) years. The vast majority of tumours were located in the metaepiphyseal region of the long bones. Sixty-eight primary GCTB were located in the distal femur, followed by proximal tibia (n=57), mobile spine (n=24), sacrum (n=23), distal radius (n=21) and other locations (n=123) (Table 1).

Routine postoperative follow-up examinations were performed at 1, 3 and/or 6 months and thereafter every 6 months for 3 years. After that, no further follow-up examination was routinely scheduled. Patients who did not experience recurrence were censored at the time of the last follow-up, and mean follow-up was 51 (3–180) months. Routine follow-up included clinical examination and conventional radiography of the operative site. CT and MR imaging were used for further investigation when radiography demonstrated a suspected relapse (such as graft or bone resorption, expansile change and local soft tissue swelling/mass formation, etc.) or when clinical symptoms and signs suggested recurrence despite negative radiography. In addition, a plain radiograph or CT of the chest was performed to rule out metastasis at presentation.

Fifty-five patients had recurrence after the initial treatment. The overall recurrence rate was 17.4% (55/316). The mean interval between surgery and recurrence was 22 (range, 3–174) months, of which 65.5% (36/55) occurred within in 3–24 months. The main symptoms of recurrence were local mass and mild pain and/or limitation of activity, of which 24 cases had localised swelling and pain as the initial symptoms. Four patients with lesions located in the mobile spine or sacrum had different degrees of nerve compression symptoms (lower-extremity weakness and numbness, urinary and faecal incontinence, etc.). The remaining 27 cases had no obvious clinical pain or dysfunction. The lesions were graded according to the Campanacci staging system [12]: 11 cases were classified as grade 1, 39 as grade 2 and five as grade 3.

In 55 recurrent cases, four showed malignant transforma-

Table 1 Treatment data and factors related to recurrence in giant cell tumour of bone (GCTB). Gender, pathological fracture and surgery were analysed with the Mann–Whitney U test. Age, location, Campanacci grading and adjuvants were analysed with the Kruskal–Wallis H test

Tabella 1 *Dati relativi al trattamento e fattori correlati alla recidiva del tumore osseo a cellule giganti (GCTB). Sesso, presenza di frattura patologica e tipo di intervento chirurgico sono state analizzati con test U di Mann-Whitney. Età, sede, stadiazione di Campanacci e tipo di innesto sono stati analizzati con test H di Krustal-Wallis*

Variable	Recurrence (n)	No recurrence (n)	Recurrence rate (%)	Z or χ^2	p value
Overall state	55	261	17.4		
Gender					
Male	28	131	17.6	0.097	0.923
Female	27	130	17.2		
Age (years)					
<20	6	13	31.6	3.201	0.202
20–40	34	183	15.7		
>40	15	65	18.8		
Location					
Distal femur	10	58	14.7	5.665	0.340
Proximal tibia	15	42	26.3		
Distal radius	4	17	19		
Sacrum	5	18	21.7		
Mobile spine	5	19	20.8		
Other location	16	107	13		
Pathological fracture					
Yes	8	57	12.3	1.214	0.225
No	47	204	18.7		
Campanacci grading					
1	11	59	15.7	1.841	0.398
2	39	164	19.2		
3	5	40	11.1		
Surgery					
Wide resection	6	63	8.7	2.155	0.031
Intralesional curettage	49	198	19.8		
Adjuvants					
PMMA + phenol	17	110	13.4	7.094	0.029
Bone grafting + phenol	23	67	25.6		
No adjuvants (bone grafting)	9	21	30		

PMMA, polymethylmethacrylate

tion. In two patients, a recurrent lesion in the proximal tibia crossed over the knee joint to involve the distal femur; in one case, the proximal tibia lesion involved the fibular head and destroyed the knee joint. Two patients had intrapulmonary metastasis, one of whom died. Of the eight cases of pathological fracture at preliminary diagnosis, five fractures were located in the lower limb and three in the upper limb.

All 55 recurrent patients underwent plain X-ray, 39 CT, and 29 MR imaging. All 55 surgical specimens were reviewed by a pathologist experienced in musculoskeletal oncology to reconfirm the diagnosis. Patient records were screened for clinical data, operative notes and follow-up records.

Imaging procedures

All patients underwent anterior–posterior and lateral plain radiographs routinely, and exposure factors varied depending on diseased region. CT examination was performed in 39 cases with a 4- or 16-slice multidetector spiral CT scanner (LightSpeed, General Electric Medical Systems, Milwaukee, WI, USA), according to an established protocol. Scanning parameters varied depending on the diseased region. The bone window and soft tissue window and 2D or 3D reconstructions were used for observation.

MR imaging was performed in 29 patients on a 1.5-T Signa HD MR system (General Electric Medical Systems) using our routine protocol for evaluating the extent of bone tumour. A combination of axial, sagittal and coronal images was obtained using a T1-weighted spin-echo (SE) sequence and a T2-weighted fast SE (FSE) sequence with and without fat suppression. Contrast-enhanced images of axial, sagittal and coronal planes were obtained in ten patients using a T1-weighted SE sequence. Field of view, slice thickness and interslice gap varied depending on diseased region and tumour size.

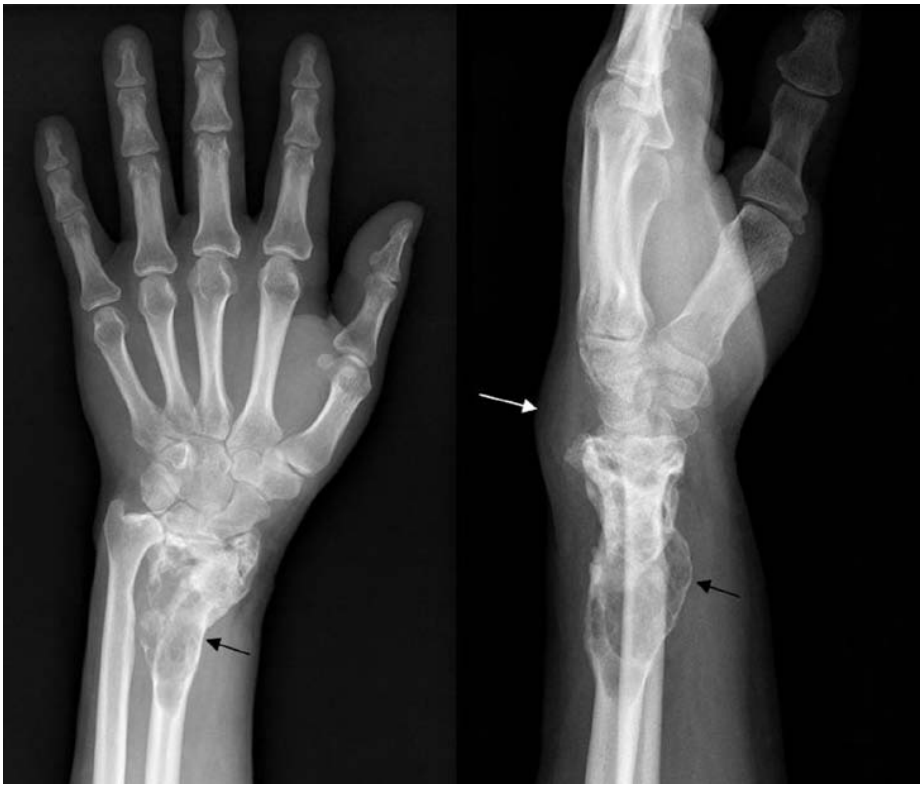

Fig. 1 Recurrent GCTB in the distal radius after intralesional curettage and autogenous bone implantation. Radiography showed graft resorption and expansile destruction of bone (*black arrows*) and surrounding soft tissue (*white arrow*).

Fig. 1 *Recidiva di GCTB a livello della porzione distale del radio dopo curettage intralesionale ed innesto osseo autologo. La radiografia mostra riassorbimento dell'innesto ed osteolisi espansiva dell'osso (frecce nere) e dei tessuti molli circostanti (freccia bianca).*

Imaging interpretation

All images were reviewed retrospectively and independently by two radiologists experienced in skeletal musculature. In the event of disagreement, a consensus was arrived at by discussion.

Statistical analysis

The common radiological findings; factors related to tumour recurrence such as gender, age and location; pathologic fracture, Campanacci grading and surgical procedure were analysed by nonparametric test (Mann–Whitney *U* test for two independent samples test and Kruskal–Wallis *H* test for multiple independent samples test) using SPSS Version 13.0 (SPSS Inc, Chicago, IL, USA). p values<0.05 were considered to indicate a statistically significant difference.

Results

Imaging features

The main presentations on radiography were graft resorption, bone resorption around polymethylmethacrylate (PMMA), anabatic expansile change and local soft tissue mass formation (Figs. 1 and 2a). Twenty-one cases showed different degrees of graft resorption and expansile destruction of bone and surrounding soft tissues (Fig. 1). Sixteen cases after bone cement filling manifested osteolytic destruction and >5 mm irregular radiolucent area (Fig. 2a). Five cases of recurrence in soft tissue showed swelling around the bone graft or prosthesis and soft tissue mass formation. Two cases with recurrence in the proximal tibia manifested graft resorption, and the lesion crossed over the knee joint and resulted in expansile osteolytic bone destruction in the distal femur. One case with recurrence in the proximal tibia demonstrated bone absorption around PMMA and involved expansile destruction in the fibular head, also leading to knee swelling and destruction of articular surface. Eight cases of recurrent lesions in soft tissue were not found due to a lack of obvious change in bone and the smaller mass. Three cases of recurrence in the mobile spine were not detected, other than the condition of the internal fixation, on account of excessive overlapping in the images (Fig. 3a). The common radiographic findings are shown in Table 2. The most common radiographic findings were graft/bone resorption (13.9%), followed by soft tissue swelling/mass formation (9.2%), expansile change (7.6%) and adjacent joint/bone involvement (0.9%). Multiple independent sample nonparametric tests demonstrated a statistical significance (c^2=37.413, p=0.000).

The main CT manifestations were bone graft resorption, osteolytic destruction around PMMA and soft tissue mass

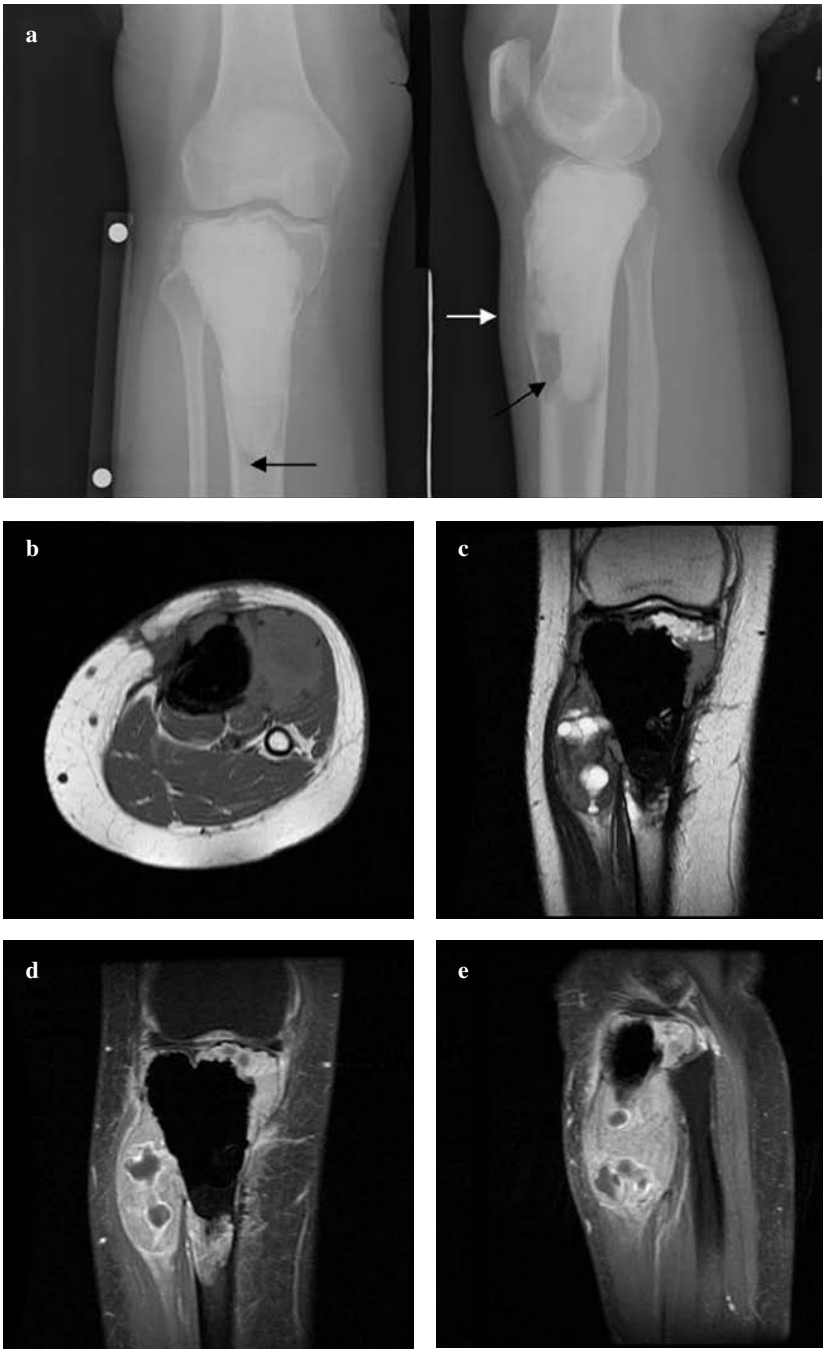

Fig. 2a-e Recurrent GCTB in the proximal tibia after bone-cement filling: **a** osteolytic destruction, >5-mm irregular lucent area (*black arrows*) and soft tissue mass (*white arrow*) in the front of cement were manifested on radiography. **b** Axial T1-weighted image, **c** coronal T2-weighted image, **d** coronal contrast-enhanced scan, **e** sagittal contrast-enhanced scan. The lesion showed a low or moderate signal on T1-weighted images and a moderate or high signal on T2-weighted images. After contrast administration, tumour parenchyma had markedly heterogeneous enhancement, except for necrotic cystic cavities.

Fig. 2a-e *Recidiva di GCTB nella porzione prossimale della tibia dopo riempimento dell'osso con cemento:* ***a*** *alla radiografia si sono evidenziate osteolisi, presenza di area radiotrasparente >5 mm (frecce nere) e di massa nei tessuti molli (freccia bianca) in adiacenza al cemento.* ***b*** *immagine assiale T1-dipendente,* ***c*** *immagine coronale T2-dipendente,* ***d*** *immagine coronale post-contrastografica,* ***e*** *immagine sagittale post-contrastografica. La lesione ha presentato un segnale basso-intermedio nelle immagini T1-dipendenti ed una intensità di segnale intermedia-elevata nelle immagini T2-dipendenti. Dopo somministrazione di mdc, il tessuto tumorale ha presentato enhancement marcatamente eterogeneo, ad eccezione delle aree necrotiche cistiche.*

formation (Figs. 3b and 4). Twenty-nine patients showed new osteolytic bone destruction, 13 of whom showed soft tissue mass (Figs. 3b and 4). Four cases of clinically suspected recurrence in soft tissue were not depicted by radiography, and CT made them clear. Despite beam-hardening artefacts from a metal internal fixation device or PMMA, seven cases of recurrence in the spine or sacrum still displayed soft tissue mass and vertebral canal involvement (Fig. 3b).

MR imaging typically showed the recurrent tumour as a low and/or moderate signal on T1-weighted images and a moderate and/or mixed high signal on T2-weighted images (Figs. 2b,c and 5). Necrotic cystic cavities presented conspicuously low intensity on T1-weighted images and high intensity on T2-weighted images. The extent of lesion and the relationship with surrounding tissues were well displayed in all cases. PMMA appeared as a signal vacuity on all sequences (Figs. 2b–e and 5a–c). Four cases of suspected recurrence predominantly in soft tissue were not depicted by plain radiography and were explicitly demonstrated by MR imaging. Five cases of recurrence in the mobile spine or sacrum displayed the lesion and surrounding soft tissue

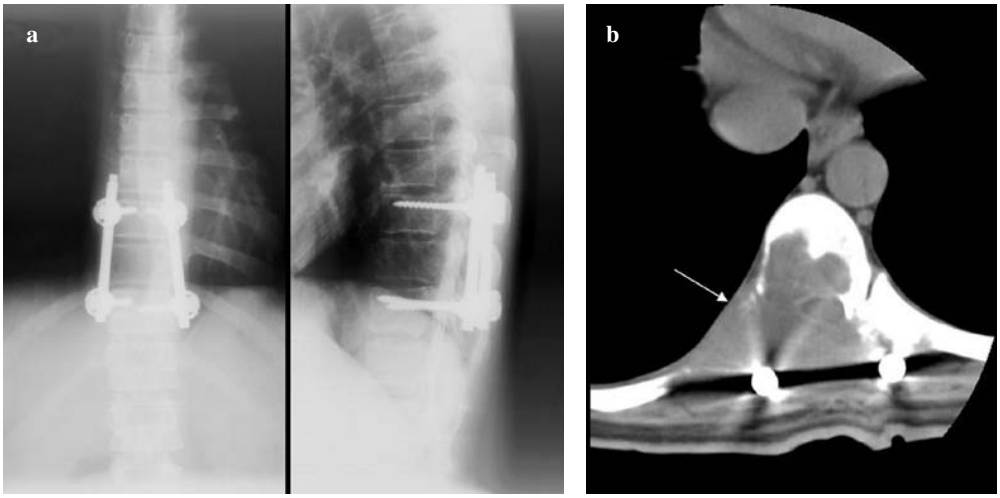

Fig. 3a,b Recurrent GCTB in the 9th to 11th thoracic vertebrae: **a** the lesion was not detected, other than the condition of internal fixation, on account of excessive overlapping on radiographic images. **b** Axial plane scan. The soft tissue mass and vertebral canal involvement were displayed despite beam-hardening artefact from a metal internal fixation device.

Fig. 3a,b *Recidiva di GCTB nella nona-undicesima vertebra toracica:* ***a*** *la lesione non è identificabile, per la presenza di eccessiva sovrapposizione di immagini radiografiche.* ***b*** *Acquisizione sul piano assiale. La massa nei tessuti molli ed il coinvolgimento del canale vertebrale sono evidenziabili nonostante gli artefatti da indurimento del fascio secondari alla presenza di dispositivo di fissazione interna metallico.*

Table 2 Common radiographic findings in recurrent giant cell tumour of bone (GCTB). Radiographic findings were analysed with the Kruskal–Wallis *H* test

Tabella 2 *Aspetti radiografici comuni nella recidiva di tumore osseo a cellule giganti (GCTB). I rilievi radiografici sono stati analizzati con il test H di Kruskal-Wallis*

Radiographic findings	Yes (n)	No (n)	Percentage	χ^2	*p* value
Graft/bone resorption	44	272	13.9	37.413	0.000
Soft tissue swelling/mass formation	29	287	9.2		
Expansile change	24	292	7.6		
Adjacent joint/bone involvement	3	313	0.9		

mass and their relationship with the vertebral canal (Fig. 5). On contrast-enhanced scans, tumour parenchyma had markedly heterogeneous enhancement, except for necrotic cystic cavities, in all ten cases (Fig. 2d,e).

Treatment and factors related to recurrence

The initial surgical procedures performed in these 55 patients included 49 curettage and six wide resections. Patients treated with curettage had a higher recurrence rate than those treated with wide resection (19.8% *vs.* 8.7%). In the curettage group, 23 cases had postoperative relapse after curettage and autologous or allogenic bone grafting, 17 cases after curettage and bone cement filling (PMMA), five cases after vertebral lesion curettage and internal fixation and four cases after simple curettage. In the group treated with wide resection, three cases were relapses after resection of the distal radius and autologous fibula transplantation, and three occurred after resection and artificial prosthetic replacement. The risk of recurrence was influenced by the type of surgery and adjuvants. Wide resection had a smaller (p=0.031) risk of local recurrence than did intralesional curettage. Among patients undergoing intralesional adjuvants, those treated with PMMA plus phenol had a lower (p=0.029) risk of having local recurrence than did patients treated with bone grafting plus phenol and no adjuvants (bone grafting). There was no statistical significance in other factors, including gender, age, location, pathological fracture and Campanacci staging (Table 1).

Discussion

The biological behaviour of GCTB is aggressive. In this study, the recurrence rate was 17.4%, the median relapse time was 22 months and 65.5% of recurrences occurred

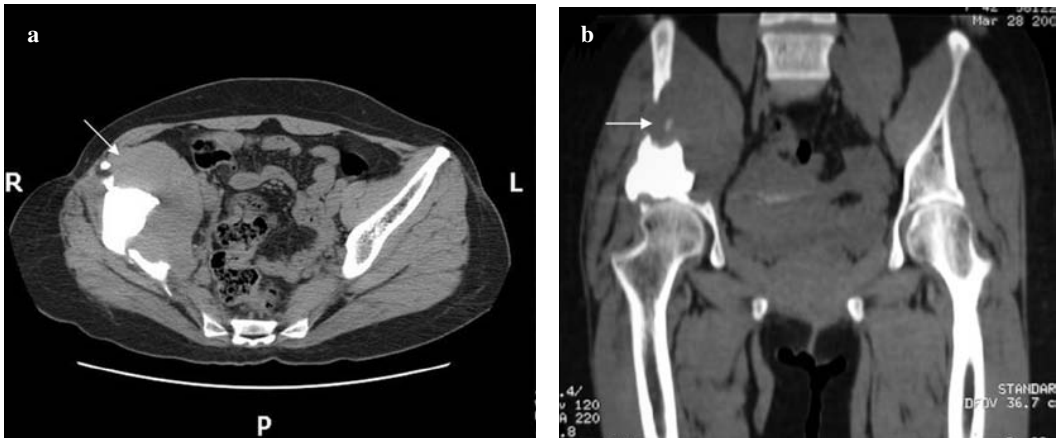

Fig. 4a,b Recurrent GCTB in the right ilium after bone-cement filling: **a** axial plane scan, **b** coronal reconstruction. The main CT features were osteolytic destruction around bone cement and conspicuous soft tissue mass formation.

Fig. 4a,b *Recidiva di GCTB nell'ileo di destra dopo riempimento dell'osso con cemento:* ***a*** *scansione assiale,* ***b*** *ricostruzione coronale. Le principali caratteristiche di TC sono distruzione osteolitica attorno al cemento e formazione di cospicua massa nei tessuti molli.*

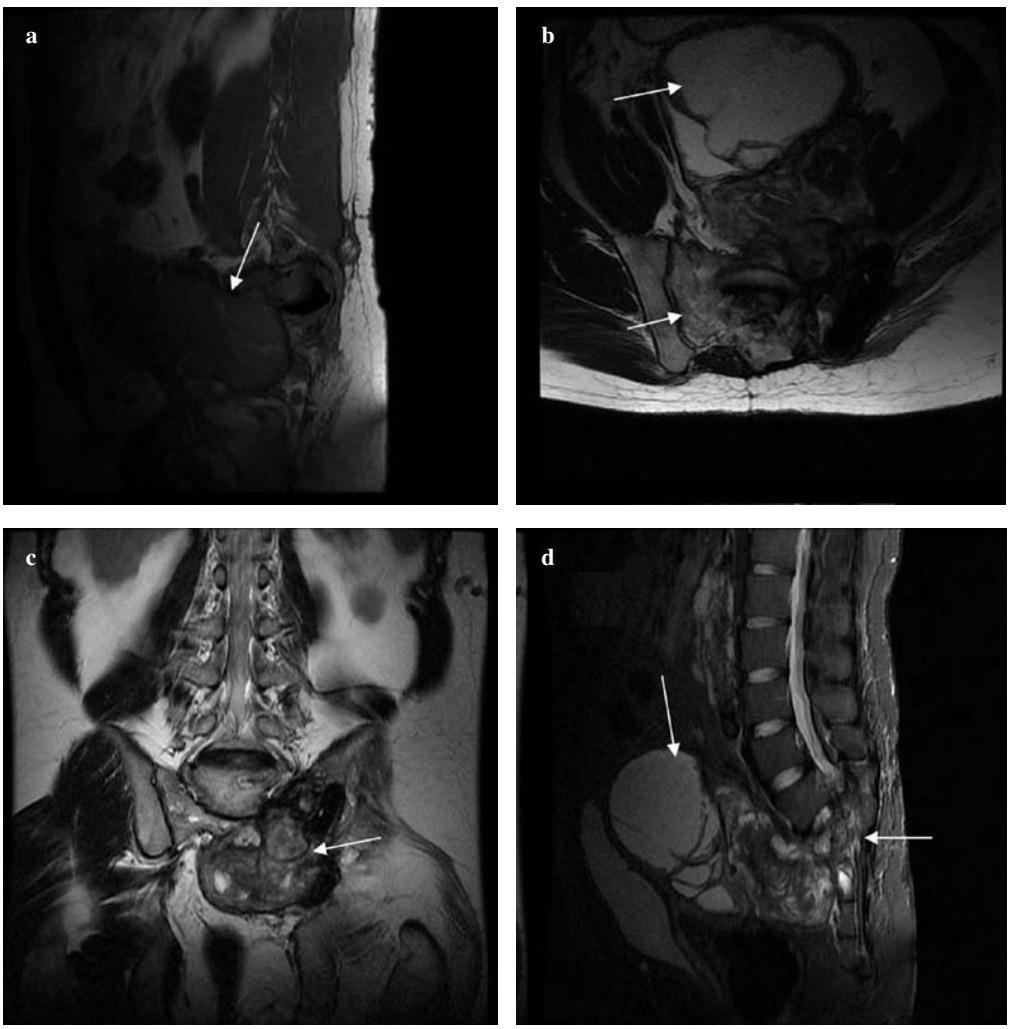

Fig. 5a–d Recurrent GCTB in the sacrum: lesion and surrounding soft tissue mass and their relationships with vertebral canal and pelvic cavity: **a** sagittal T1-weighted image, **b** axial T2-weighted image, **c** coronal T2-weighted image, **d** sagittal fat-suppressed T2-weighted image. The recurrent tumour showed a low or moderate signal on T1-weighted images and a mixed high signal on T2-weighted images.

Fig. 5a-d *Recidiva di GCTB nel sacro: lesione e massa nei tessuti molli circostanti e loro relazione con il canale vertebrale e lo scavo pelvico:* ***a*** *immagine sagittale T1-dipendente,* ***b*** *immagine assiale T2-dipendente,* ***c*** *immagine coronale T2-dipendente,* ***d*** *immagine sagittale T2-dipendente con soppressione del segnale del tessuto adiposo. La recidiva tumorale presenta intensità di segnale bassa-intermedia nelle immagini T1-dipendenti e segnale eterogeneamente elevato nelle immagini T2-dipendenti.*

within 24 months after surgery, consistent with the literature [7]. Therefore, short-term re-examinations and manipulations should be performed within this period, although recurrence in GCTB is usually nonfatal [3–5, 13]. Imaging abnormalities can appear earlier than clinical pain or dysfunction, which may allow further attempts to preserve joint function rather than proceeding to en bloc resection and massive prosthetic replacement [11]. On radiography, local bone absorption or sclerotic rim after implantation of autologous bone or bone allograft and a 2- to 4-mm translucent zone between PMMA and normal bone after PMMA implantation did not represent recurrence at follow-up. New graft or bone resorption, soft tissue mass formation and aggravated expansile change were significant findings for recurrence, although some of these patients had no obvious clinical symptoms. CT and MR imaging had higher costs than X-ray and were used for further examination when radiography suggested a relapse or when clinical symptoms and signs suggested recurrence despite negative radiography. CT has a higher density resolution, and cross-sectional scanning can avoid overlapping interference due to PMMA or metal fixation, which can clearly display the structure within scraped lesions, cortical disruption, surrounding soft tissue mass, bone resorption and destruction. Two- or three-dimensional CT reconstructions can better display the extent of lesion and subchondral bone destruction of the joint. CT reconstructed image can better display lesion extent and relationship with the adjacent joint, which enables further defining of the operative plan. MR imaging has good soft tissue resolution, which can help assess joint involvement [11] and better display the soft tissue masses of recurrent lesions, a particularly obvious advantage after bone-cement filling. PMMA appeared as a signal vacuity on all sequences and did not interfere with MR images as much as it did on CT, where there was substantial beam-hardening artefact. Contrast-enhanced examination helps distinguish tumour recurrence from scar and guide needle biopsy and operative procedure.

Surgical treatment options include intralesional curettage or segmental resection [10]. Intralesional curettage is followed by little patient disability but may be associated with a rather high local recurrence rate [12, 14, 15]. In recent years, many authors have employed intralesional curettage plus adjuvant therapy (high-speed burr, bone-cement filling) to treat Campanacci grade 3 GCTB, and the relapse rate was no different from that of Campanacci grade 2 [13]. Although wide resection minimises tumour recurrence, it is associated with decreased function and usually with higher rates of surgical complications in skeletal reconstruction [16–18]. In our study, 49 patients experienced local recurrence after curettage and only six after tumour-segment resection. In the cases of curettage, the recurrence rate was higher after implantation of autogenous or allogenic bone rather than PMMA [3, 9, 13, 15]. It is possible that PMMA can make the local temperature rise beyond 60° to ablate tumour cells in the process of polymerisation, and the released monomer also has toxicity, which can effectively kill residual tumour cells of the inner wall of the cavity [13, 19]. Another advantage of PMMA is that bone resorption and destruction can easily be found at the junction on radiographs. It is conducive to early detection of recurrent lesions, but it is sometimes difficult to identify nonfusion of transplanted bone and tumour recurrence on radiographs [13].

Since 1969, PMMA has markedly reduced the recurrence rate of GCTB [19]. Local curettage plus adjuvant therapy (bone-cement filling after high-speed burr, chemical cautery, argon knife, laser carbonization, etc.) can effectively reduce recurrence [3, 4, 13, 19], but validation of the efficacy of adjuvant therapy still lacks well-controlled, comparative studies. An important cause of recurrent soft tissue mass formation may be regional perforation of cortical bone into soft tissue or soft tissue contamination during operation [3, 13]. Although there was no statistical significance, more recurrent cases (26.3%) occurred in the proximal tibia. This may be associated with GCTB occurring in the proximal tibial metaphysis, and articular cartilage of knee joints was frequently involved. It was difficult to completely scrape the lesions during the operation.

Conclusions

To conclude, the risk of recurrence in GCTB was influenced by the type of surgery and adjuvants. Wide resection had a lower risk of local recurrence than did intralesional curettage. Bone resorption, soft tissue mass formation and aggravated expansile change are reliable signs of recurrence on imaging. It is useful to detect the recurrent GCTB at an early date, before clinical symptoms develop.

Acknowledgments This study was supported by the National Natural Science Foundation of China (Project Number: 81072188) and a grant-in-aid for scientific research from the Science and Technology Commission of Shanghai Municipality (Project Number: 09411964300)

Conflict of interest None

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