Giant cell tumour (GCT) is still one of the most obscure and intensively examined tumours of bone. Its histogenesis is uncertain. The histology does not predict the clinical outcome; and there are still many unanswered questions with regard to both its treatment and prognosis.

The World Health Organisation has classified GCT as "an aggressive, potentially malignant lesion",1 which means that its evolution based on its histological features is unpredictable. Statistically, 80% of GCTs have a benign course, with a local rate of recurrence of 20% to 50%. About 10% undergo malignant transformation at recurrence and 1% to 4% give pulmonary metastases even in cases of benign histology.

Pathogenesis

GCT is a true neoplastic process originating from the undifferentiated mesenchymal cells of the bone marrow. Multi-nucleated giant cells and mononuclear stromal cells can be distinguished by light microscopy. These giant cells are derived from stromal cells, either by the fusion of mononuclear cells or, less probably, by amitotic division or nuclear segmentation of the stromal cells without the corresponding cytoplasmic division.2 These multinucleated giant cells resemble osteoclasts in their phenotype and function: their size is approximately 60 µm; their numerous nucleoli are centrally located in the cytoplasm. They stain positive for tartrate-resistant acid phosphatase and naphthyl alpha esterase enzymes,3 and possess receptor sites for calcitonin, a phenotypic marker for osteoclasts.

Further histochemical, immunohistochemical, cytogenetic, and molecular-genetic studies in cell cultures derived from GCTs have confirmed that there are two different cell lines within the mononuclear stromal cells. One population consists of mononuclear round cells, which are non-neoplastic and express monocyte-macrophage markers (tartrate-sensitive acid phosphatase, naphthyl alpha esterase) and react with monoclonal antibodies to CD 13 and CD 68 which suggests that these cells have a monocytic-macrophage origin.4-6

The second cell line which appears as mononuclear spindle-shaped (fibro-osteoblast-like) stromal cells is considered to be responsible for the neoplastic character of the GCT. It produces type-I and type-II collagens and alkaline phosphatase, has receptor sites for parathormone and proliferates extensively. This cell line is genetically unstable, as has been found in recent molecular genetic studies. It shows chromosomal abnormalities, a higher incidence of expression of p53 protein and alterations in different oncogenes (C-myc, C-fos, N-myc) which are also found in frankly malignant osteosarcomas.7,8 These spindle-shaped stromal cells secrete a variety of cytokines and differentiation factors (macrophage colony stimulating factor (M-CSF), interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha)), which have chemotactic, differentiation-inducing and activating effects on mononocytes-macrophages and are essential for the differentiation of osteoclasts.

These features support the hypothesis that the genetically unstable spindle-shaped neoplastic mononuclear stromal cells stimulate the immigration of blood monocytes into the tumour tissue and promote the formation of the osteoclast-like giant cells. The characteristic cell types, the monocytes and osteoclast-like giant cells, are therefore simply reactive components of the GCT, while the spindle-shaped stromal cells represent the neoplastic component of the tumour.4,9-11

Clinical appearance

The typical clinical and pathological appearance of GCT has been discussed in detail in various articles12-18 and monographs.2,19-21 It represents 15% of benign and 3% to 8% of all bone tumours and is more common in China and India where it constitutes approximately 20% of all bone tumours.22 Nearly 50% of cases occur in the region of the knee, but other frequent sites are the distal part of the radius, the proximal humerus and fibula, and the pelvic bones. It is usually situated in the epiphysis, grows eccentrically, and
THE JOURNAL OF BONE AND JOINT SURGERY

The Journal of Bone and Joint Surgery

May later also affect the metaphysis. A GCT starting from the metaphysis has been described in skeletally immature patients at an open growth plate.\textsuperscript{23} It appears most often in the second to fourth decades of life (60\% to 75\% of all cases) and the male:female ratio is 1:1.5. The main clinical symptoms are non-specific, local swelling, warmth, and pain radiating independently of weight-bearing. Pathological fracture is the first sign in approximately 15\% of cases.\textsuperscript{24} The duration of symptoms varies between two to six months and by then, in one-third of cases, the size of the tumour exceeds 50\% of the diameter of the affected bone, it has destroyed the cortical bone and reached the subchondral region.

GCT appears as a pure lytic cystic lesion, growing often but not exclusively eccentrically in the epimetaphyseal region of the bone. The affected part of the bone may be expanded and the cortical bone thinned. In an advanced stage, the GCT breaks through the cortex (Fig. 1), and there is a lack of periosteal reaction with formation of spicules around the tumour. According to the radiological classification of Lodwick, Wilson and Farrel,\textsuperscript{25} GCT belongs, depending on its stage, to group IA to IB or IC. GCT is commonly hypervascularised. With modern MRI, the need for angiography has been reduced.

CT is useful in the evaluation of the cortical bone. The density of GCT tissue as measured by CT is between 20 and 70 Housefield units. Below these values a cyst is more likely those of an aneurysmal bone cyst as has been demonstrated both by CT and MRI. The MR signs of GCT are a high-signal intensity in T2-weighted images, high contrast media enhancement and signs referring to tissue haemorrhages.\textsuperscript{26} Dynamic contrast-enhanced MRI shows a characteristic perfusion pattern with a steep slope and maximum intensity value followed by an early and rapid washout phase.\textsuperscript{27}

Tumours and tumour-like lesions containing giant cells with a similar radiographic appearance such as juvenile solitary or aneurysmal bone cysts, chondroblastoma, chondromyxoid fibroma, giant-cell reparative granuloma, non-ossifying fibroma, eosinophilic granuloma, high-grade central osteosarcoma should be considered in the differential diagnosis.

There is a high rate of recurrence, especially after intralesional curettage (Table I), in most cases within the first 12 to 36 months,\textsuperscript{28,29} and rarely after five to six years. The first symptoms of recurrence are pain and enhanced isotope uptake by bone scanning.

### Grading and staging systems for GCT

Based on the degree of histological appearance of the stromal cells and the number of giant cells and mitoses, Jaffe et al.\textsuperscript{18} classified GCT as benign, aggressive and malignant. Dahlin\textsuperscript{19} distinguished only benign and malignant forms of GCT. The grade-3 malignant GCTs should be treated as high-grade bone sarcomas otherwise the practical value of grading is limited. The prediction of the clinical behaviour of GCT based on its histological features is impossible.\textsuperscript{2,30}

Enneking\textsuperscript{20} and Campanacci et al.\textsuperscript{12} developed a similar classification for GCT based on their clinical, radiographic and histological features. Enneking’s surgical stages 1, 2

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### Table I. The rate of recurrence after different intralesional treatments of primary GCT of bone (minimum follow-up ≥ 2 years)

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Number of patients</th>
<th>Adjuvant treatment</th>
<th>Rate of local recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldenberg et al\textsuperscript{17} (multicentre)</td>
<td>120</td>
<td>None</td>
<td>43</td>
</tr>
<tr>
<td>Campanacci et al\textsuperscript{12}</td>
<td>128</td>
<td>None</td>
<td>30</td>
</tr>
<tr>
<td>Capanna et al\textsuperscript{52} (multicentre)</td>
<td>490</td>
<td>None</td>
<td>45</td>
</tr>
<tr>
<td>Lausten et al\textsuperscript{85}</td>
<td>18</td>
<td>None/radiotherapy</td>
<td>56</td>
</tr>
<tr>
<td>Richardson and Dickinson\textsuperscript{62}</td>
<td>16</td>
<td>(Burr) none</td>
<td>0</td>
</tr>
<tr>
<td>Blackley et al\textsuperscript{51}</td>
<td>59</td>
<td>Burr, none</td>
<td>12</td>
</tr>
<tr>
<td>McDonald et al\textsuperscript{35}</td>
<td>85</td>
<td>Burr, phenol, alcohol</td>
<td>34</td>
</tr>
<tr>
<td>Capanna et al\textsuperscript{52} (multicentre)</td>
<td>187</td>
<td>PMMA, phenol, liquid nitrogen</td>
<td>17</td>
</tr>
<tr>
<td>Szendröi\textsuperscript{29}</td>
<td>11</td>
<td>Phenol, PMMA</td>
<td>9</td>
</tr>
<tr>
<td>Komiy and Inoue\textsuperscript{63}</td>
<td>11</td>
<td>Burr, PMMA</td>
<td>0</td>
</tr>
<tr>
<td>Gitelis et al\textsuperscript{16}</td>
<td>16</td>
<td>Burr, phenol, alcohol, PMMA</td>
<td>0</td>
</tr>
<tr>
<td>O’Donnell et al\textsuperscript{99}</td>
<td>60</td>
<td>PMMA/burr phenol</td>
<td>25</td>
</tr>
<tr>
<td>Bini et al\textsuperscript{57}</td>
<td>38</td>
<td>PMMA</td>
<td>8</td>
</tr>
<tr>
<td>Malawar and Dunham\textsuperscript{59}</td>
<td>102</td>
<td>(Burr)+liquid nitrogen</td>
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<tr>
<td>Labs et al\textsuperscript{48}</td>
<td>15</td>
<td>PMMA</td>
<td>12</td>
</tr>
</tbody>
</table>

* polymethylmethacrylate

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Fig. 1

Photograph showing the gross pathology of a GCT. The defect in the proximal tibia is filled by extensive soft fleshy tissue and the cortex is destroyed (surface of transsected specimen).
and 3 represent the clinically latent, active and aggressive forms of GCT. The radiographic grade-1 of Campanacci et al.\textsuperscript{12} represents a quiescent form, in which the cortical involvement is minimal, if at all. Only 10% to 15% of GCTs belong to this rare stage which can even be asymptomatic. The most common active grade-2 lesions show extensive cortical thinning and bulging. The aggressive grade-3 lesions break through the cortical bone and have a soft-tissue component covered by a pseudocapsule and periostheum. On rare occasions, the tumour extends its barrier, the articular cartilage, and enters the joint.

Although Campanacci nominates this latter group of GCT as malignant, the term ‘aggressive’ is more justified because in most cases this tumour has a benign histology and can be cured by conservative surgery, namely curettage. This final stage has, however, a greater risk of local recurrence.

Special forms of GCT

GCT is typically a monostotic process, but multicentric (polyostotic) forms have been described occasionally.\textsuperscript{31,32} This rare condition can appear simultaneously or metachronal\textsuperscript{33} with an interval of more than ten years. A direct, continuous extension of GCT from one bone to the next (Fig. 2), which occurs mostly in the short bones of the hand and feet,\textsuperscript{34} should be excluded.

A rare form is the malignant GCT, which can be divided into primary and secondary groups. The primary form (1% to 3% of all GCTs)\textsuperscript{16,35} is malignant from the onset. Frankly sarcomatous stroma is juxtaposed to areas of typical GCT.\textsuperscript{15} Secondary malignant GCT (5% to 10% of all GCTs)\textsuperscript{36} may develop during recurrence of a benign GCT, or undergo a malignant transformation after radiotherapy. On very rare occasions, the development of a bone sarcoma has been seen after a very long period (18 to 25 years) after the treatment of a primary GCT.\textsuperscript{37}

Benign metastasing GCTs have been described in 1% to 3% of all and 6% of the recurrent GCTs.\textsuperscript{38-40} In these cases the histology of the nodules found in the lung is identical to that of the benign tumour of the primary site. Some authors explain this as secondary to the tumour emboli often seen in the peripheral vessels of GCTs and regard the nodules found in the lung as implants and not as true metastases.\textsuperscript{41,42} Others\textsuperscript{30,43} have not found any correlation between the frequency of finding tumour emboli in vessels and that of pulmonary involvement. Recent basic studies have shown enhanced matrix metalloproteinases, expression of p53 protein and overexpression of the C-myc oncogene in metastasising GCTs.\textsuperscript{7,44} Lung metastases usually appear two to three years after the treatment of the primary tumour.\textsuperscript{38,45} They have also been occasionally observed at the first presentation of a benign GCT. A chest radiograph is therefore justified both at the first presentation and in the course of the follow-up.

Treatment

In most benign aggressive bone tumours control can be achieved by wide surgical excision. Following en-bloc
Resection, the rate of the recurrence is between 0% and 5% in primary lesions.\textsuperscript{46-50} Because it is found in the epiphysis, the GCT often invades the subchondral bone. \textit{En-bloc} resection usually requires sacrifice of the articular surface and a complex reconstruction procedure, which can lead to complications, revision operations, and decreased quality of life in the long term.

Resection is usually performed in GCTs found in the proximal fibula, radius, distal ulna or in the wing of the ilium in which a reconstruction is not necessary, or in malignant types of GCTs. Stage-3 GCTs, which have already destroyed the cortex tend to recur more often and when the defect is large and the joint surface destroyed, resection is indicated. We try to preserve the joint even in a stage-3
lesion, taking into account the higher probability of recurrence. It is also important to know whether it is the first, second or third recurrence. Although repeated recurrences have little influence on the final outcome in most cases and can be treated by curettage as for the primary lesion, it is customary to deal more radically with recurrences.

The treatment of choice in most GCTs is curettage and bone grafting. Historically, however, curettage has been associated with a high rate of recurrence (30% to 50%, Table I) and therefore different adjuvants have been introduced. These presumably remove the tumour cells which remain after curettage because of their thermal (liquid nitrogen, methylmethacrylate) or chemical (phenol, hydrogenperoxide, alcohol) effects.

The use of cement has advantages in that it is cheap, and immediate weight-bearing is allowed. Furthermore, a local recurrence is easily recognised around the cement both by radiographic and MR investigations. Extended curettage and application of bone cement are therefore the most accepted methods in the treatment of GCT.

Rinsing the curetted defect with liquid nitrogen seems to be the most effective treatment for local control of the tumour. Malawer et al observed a rate of recurrence of only 7.9% after cryosurgery in 102 patients with GCT. However, because the depth of the necrotic margin is difficult to control, there is a high risk of bone and skin necrosis and fracture.

Good results have been published recently of the use of high-pressure pulsatile lavage and a high-speed dental burr, which allows the surgeon to remove the contaminated margin up to normal bone. The data summarised in Table I suggest that the use of adjuvants combined with careful curettage may decrease the rates of local recurrence, which were reported in the historical series of Goldenberg et al and Campanacci et al as being from 30% to 43% and 8% to 17%. Some authors found no recurrence either with or without the use of additional adjuvants, but the number of the patients reported was small. It is of interest that Blackley et al using a high-speed burr at the time of curettage and bone grafting achieved a very acceptable rate of recurrence with 12% in 59 patients.

Complete removal of the tumour tissue is more difficult when the tumour is in the distal part of the radius or in the metacarpal bones. There are reports that GCT in the radius is more aggressive and metastasises more often to the lung. En-bloc resection is strongly recommended especially in grade-3 tumours. When the distal part of the radius is removed, an unicortical arthrodesis can be performed, or the defect can be replaced by either non-vascularised (Fig. 3) or vascularised autologous fibula.

Treatment is especially difficult when the GCT has affected the vertebral column, the sacrum or the acetabular region of the pelvis. Marcove et al successfully performed an incomplete curettage of the sacrum with cryosurgery in a patient with GCT. Complications, such as extensive intra-operative bleeding, can be avoided by embolisation of the supplying arteries in huge GCTs of the innominate bone (Fig. 4). Kattapuram et al recommended combined surgery and radiotherapy for GCT located in the pelvis.

Radiotherapy. Three to four decades ago, radiation of aggressive GCT with appendicular, pelvic, sacral and spinal lesions was commonly undertaken. Orthovoltage equipment was used but the bone and tumour dosimetry was poor, since doses below 35 Gy were given. The results were disappointing. The rate of local recurrence was between 50% and 70%. Malignant transformation occurred in 7% to 25% of the irradiated GCT.

According to some reports, the use of modern equipment (supervoltage therapy, Co or linear accelerator), and doses of 40 to 60 Gy (1.8 - 2.0 Gy/fraction, 3 to 5 times/week) can result in local oncological control of 85% to 90%. The risk of secondary radiation-induced malignant tumour is very small (0% to 8%).

In selected cases, therefore, if curettage is only incomplete (pelvis, vertebra, etc) resection will result in significant neurological or functional morbidity (sacral lesions). Radiation is an effective alternative.

Prognosis and final outcome. The evaluation of prognostic factors is difficult for various reasons. GCT is relatively rare, and there are only a few multicentre studies which have described a large number of cases, the indications, treatment philosophy and statistical methods used vary and, there is a lack of prospective, randomised studies. A number of publications deal, however, with potential prognostic factors which may influence or predict the recurrence and malignant transformation of GCT.

The histological grading has little prognostic value. The benign or malignant nature of the tumour can be determined. Benign histology does not necessarily relate to the clinical behaviour of the tumour.

Immunohistological and cytogenetic examinations give additional information which may be useful. There is a relationship, for example, between the increasing rate of proliferation and the probability of recurrence. The value of flow cytometry is disputed. Our results with smear cytometry which allows separate examination of the stromal cell population showed a significant difference in the ploidy of non-recurring and recurring GCTs during follow-up studies. Two-thirds of non-recurring GCTs were characterised by euploidy and most of the recurrence GCTs by aneuploidy.

Bridge et al found that all but one of their recurrent GCTs had some type of chromosomal abnormality, which could also be detected in highly malignant osteosarcomas. Schoedel et al demonstrated an excessive metalloproteinase expression in recurrent or metastasising GCTs, which is also found in the degradation of extracellular matrix and in tissue invasion. An overexpression of c-myc oncogen and p53 was found in GCTs metastasising to the lung.

The clinicoradiological staging systems of Enneking and Campanacci et al and their prognostic significance...
are also disputed. Rock and Wuismann et al observed a sequential increase in local rates of recurrence from stage 1 through to stage 3. However, many authors, including ourselves, do not regard these staging systems as predictive of the prognosis. Most GCTs show a tendency to progress and without treatment they reach stage 3 sooner or later, as we have seen in many cases of retrospective analysis of radiographs of untreated patients (Fig. 2). In Rock’s series, however, the 16 patients with metastases had an equal distribution between stages 2 and 3.

McDonald et al analysing the data of 221 patients with GCT did not find any correlation between the rate of recurrence and the size, localisation, the surgical stage of the tumour and involvement of the subchondral bone. Pathological fracture in itself does not significantly increase the risk of recurrence. The most significant factor is the surgical procedure employed for removal of the tumour i.e., curettage with adjuvant therapy (34% recurrence) versus resection (7% recurrence). This observation has been confirmed by many others authors.

When evaluating the results of the very different surgical methods, there is a lack of prospective randomised studies comparing the effects of the adjuvants with the results of curettage using a high-speed burr and bone grafting alone. In addition, resection and curettage have been performed in different percentages of the material, which may have significantly influenced the rate of recurrence. Gitelis et al performed en-bloc resection in 50% of their patients and curettage with adjuvants in the other 50% without observing any recurrence. In the series of McDonald et al curettage was performed in 80% and the rate of recurrence increased to 34%.

The management of local recurrence of GCT varies. Some authors recommend wide excision for any recurrent lesion, whereas others believe that repeated intralesion surgery with adjuvants for the second or third recurrence is justified.

Malignant transformation or pulmonary metastases of benign GCT have been observed after radiotherapy and after multiple recurrences of a locally aggressive GCT, especially when the tumour has affected the radius and the small tubular bones of the hand or feet. Cheng and Johnston collected about 50 published cases of metastasising GCT from the literature with an overall survival rate of 80% to 85%. Sporadically, spontaneous regression of the nodules in the lung has been reported, but the mortality is about 15% to 20%. The treatment of choice is the surgical excision of the nodules. When this is technically impossible, whole-lung radiotherapy is recommended. The effects of chemotherapy are not convincing. The prognosis of malignant GCT is poor with a five-year
survival of 50%,\(^8\) despite the combination of surgery and chemotherapy.

Malignant transformation occurs, however, only in 5% to 10%, with pulmonary metastases in another 2% to 6%. According to the results of larger series, most authors report a disease-free survival of 96% to 100% as the final outcome of the treatment.\(^3\),\(^4\)

Recurrence of GCT is not fatal in most cases, but can lead to disability and to a poor quality of life as a result of repeated and radical operations, loss of bone stock, and secondary arthritis of the joints. Optimal treatment should include: 1) careful curettage and the use of adjuvants to decrease the rate of recurrence; 2) joint-sparing surgery at revision operations and in stage-3 tumours whenever it is possible; 3) in cases of proven malignancy: resection according to oncological criteria; and 4) comparative histological and molecular biological evaluation of the primary and recurrent tumours. In the future, histochemistry, DNA cytometry, examination of the expression of certain oncogenes, proteins, cytokines and the quantitative-qualitative measurement of molecular genetic instability of the tumour will have a greater influence on the surgical planning.

Because of the relative rarity of the tumour and the special operative techniques involved, it is recommended that GCT be treated in tumour clinics. Inadequate primary intervention by a non-specialist can lead to major technical challenges at an advanced stage of the tumour.

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References