Giant cell tumour of bone: a new evaluating system is necessary

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Abstract Giant cell tumour (GCT) of bone is still one of the most obscure and intensively studied tumours of bone. The histogenesis of GCT remains unclear. The recommended therapy of GCT evolved during the 20th century. The best treatment should ensure local control and maintain function. Curettage has been the preferred treatment for most GCTs. Good results have also been published on the use of high-speed burr and local adjuvants. Local tumour control can be satisfactorily achieved by wide excision. However, treatment options for GCT have remained fairly static over the past 30 years and there is no widely held consensus regarding the standard treatment selection for all patients. This challenge may result from the fact that there are no single clinical, radiographic, histological or morphological aspects that allow surgeons to accurately predict the trend of a single lesion to recur. In this research, a comprehensive review of the previously described radiographic staging systems by Enneking and Campanacci et al. and the shortfalls associated with them are provided, and then the possible risk factors of predicting local recurrence or evaluating functional outcome of GCT are also discussed. A new preoperative evaluating system of GCT may be necessary and feasible, so that surgeons may accurately assess the aggressiveness or severity of GCT in order to reliably guide treatment decisions and predict outcomes.

Introduction

Giant cell tumour (GCT) of bone is classified by the World Health Organisation (WHO) as a benign but locally aggressive tumour that usually involves the end of a long bone [1]. It most frequently occurs in young adults between 20 and 40 years of age with a slight female predominance [2–5]. GCT has a significant incidence, accounting for 5 % of all bone tumours [2]. Higher incidence has been reported for the Chinese population, in which it can be up to 20 % of all bone tumours [6].

Most authors advocate intralesional excision as preferable treatment when feasible with the aim of excising the whole tumour and sparing the native joint [7–12]. Historically, curettage alone has been associated with a high rate of local recurrence, from 25 to 50 % [13–18]. Therefore, various adjuvants and high-speed burr, which were used to “extend” the curettage were employed [12, 13, 19]. However, no clear evidence exists as to whether adjuvant therapies are effective [14, 20]. Local control can be achieved by wide excision of GCTs and various studies suggest wide resection provides the lowest recurrence rate at 0–5 % [2, 21–23]. But wide resection is associated with higher rates of surgical complications [18, 24, 25] and often is accompanied by considerable functional impairment [2, 7, 26]. Decision-making regarding the surgical approach must weigh the morbidity of treatment against the likelihood of recurrence and the conservation of function, particularly in a benign aggressive disease with a variable growth potential [27, 28]. Currently, there is no widely held consensus regarding the ideal treatment selection for all GCT patients (Table 1). This challenge may result from the fact that there are no single clinical, radiographic or histological aspects that allow one to accurately predict the trend of a single lesion to recur. Therefore, the first purpose of this review was to analyse the drawbacks of the existing grading system of GCT and discuss

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Table 1 Literature review of surgical treatment, local recurrence and functional outcome with large sample

Study	Year	Number of cases	Follow-up (range)	Surgical treatment	Recurrence rate	Factors influencing recurrence rate	Factors influencing functional outcome
Niu et al. [2]	2012	621	49 months (18–256)	Wide resection Curettage along Curettage+burr+bone graft Curettage+burr+bone graft+PMMA Curettage+burr+PMMA	1.6 % 56.1 % 11.1 % 3.3 % 10.2 %	Surgical margin Tumour extension	The type of surgery
Klenke et al. [23]	2011	118	108 months (36–233)	Wide resection Curettage+burr Curettage+burr+phenol Curettage+burr+phenol +PMMA	5 % 32 % 34 % 15 %	Surgical margin PMMA Age	Not given
Errani et al. [7]	2010	349	91 months (36–204)	Wide resection Curettage+burr+phenol Curettage+burr+phenol +PMMA	12 % 12.5 % 18 %	Location	The type of surgery
Kivioja et al. [4]	2008	294	5 years (0.2–18)	Wide resection Curettage Curettage+PMMA	12 % 56 % 20 %	Surgical margin PMMA Age	Not given
Knochentumuren et al. [50]	2008	256	64.2 months (0–421)	Wide resection Curettage Curettage+PMMA Curettage+PMMA +phenol Curettage+phenol +toxins	2 % 49 % 22 % 27 % 15 %	Surgical margin Tumour extension PMMA	Not given
Balke et al. [30]	2008	214	59.8 months (8–280)	Wide resection Curettage without adjuvants Curettage+burr Curettage+PMMA Curettage+burr+PMMA Curettage+burr+PMMA +H ₂ O ₂	0 % 30 % 22.2 % 35.6 % 23.8 % 16.0 %	Surgical margin Tumour extension Location Burr PMMA H ₂ O ₂	Not given
Prosser et al. [8]	2005	137	70 months (24–214)	Curettage	19 %	Tumour extension	Not given
Turcotte et al. [9]	2002	186	60 months (24–192)	Wide resection Curettage±burr±PMMA ±phenol	16 % 18 %	None	Not given

whether a new evaluating system that allows surgeons to accurately assess the aggressiveness or severity of GCT should be established and recommended, so that surgeons can predict which patients will need more intensive treatment; and, second, to perform a comprehensive evaluation of the possible prognostic factors of GCT (Fig. 1).

The existing grading system of GCT

The histological system of GCT

The histogenesis of GCT remains unclear [12, 17, 29–31]. Based on the degree of histological appearance of the

stromal cells and the number of giant cells and mitoses, Jaffe et al. [32] classified GCT as benign, aggressive and malignant. The histological staging system of Jaffe and its prognostic value of this grading had been disputed. Sanerkin et al. [33] reviewed 86 cases of GCT with particular attention to the histogenesis changes. No correlation has been found between the aggressiveness of the tumour and the histological grade. Lausten et al. [34] studied the prognostic value of the histological grading of GCT. None of the tumours graded 1 recurred, while five out of 19 grade 2 (26 %) and five out of nine grade 3 tumours (56 %) had local recurrences, but none of these differences were statistically significant. Thus, the prediction of the clinical behaviour of GCT based on its

Fig. 1 The expected function of a new preoperative staging system or scoring system of giant cell tumour (GCT)

histological features is impossible, as found in other reports [35, 36].

In addition, the grade-3 “malignant” GCT should be treated as high-grade bone sarcomas, otherwise the practical value of grading is limited. However, it is agreed to some extent that intralesional curettage rather than wide resection provides adequate tumour eradication for the majority of patients with GCT. Above all, histopathological grading of GCT was of no prognostic value, and as a result, histological grading as a predictor of clinical outcome, aggressiveness or recurrence has been abandoned.

The clinicoradiological system of GCT

Similar classifications of GCT based on their clinical, radiographic features were described by Enneking [37] and later by Campanacci et al. [38]. As well as histopathological grading of GCT, the clinicoradiological staging systems of Enneking and Campanacci et al. and their prognostic significance are

also disputed [2, 7, 23]. Prosser et al. [8] reviewed 193 cases treated during a 27-year period. The recurrence rate of the 137 patients who had curettage alone varied with Campanacci grades, being only 7 % in patients of grade I and II, but 29 % in grade III patients. Rock et al. [39] and Wuisman et al. [40] observed a sequential increase in local rates of recurrence from grade I through grade III. But many authors including Campanacci et al. found no correlation between the risk of recurrence and the radiographic grading of the tumour [7, 23, 38]. Balke et al. [30] reviewed 214 cases of GCT and showed the recurrence rate of grade III tumours was higher than of grade II (31.3 % vs 20 %), without significant difference. Therefore, a good correlation has not been found between radiography and local recurrence of GCT, or in other words its aggressiveness. For this reason, many authors, including ourselves, do not regard these staging systems as predictive of the prognosis [5, 8, 9, 38, 41].

The classifications of Enneking and Campanacci et al. were designed to define the extent of surgery required to completely remove the tumour, which may influence the surgical resection of GCT [42]. GCTs that caused more destruction, such as grade III lesions, were more likely to require aggressive treatment. Ward et al. [43] reported that of the patients who were primarily treated with wide resection, 86 % had grade III tumours; in contrast, of the patients treated initially with curettage and adjuvants, only 50 % had grade III tumours. If the bone destruction is deemed too extensive for a biomechanically sound reconstruction, then wide resection should be performed. Turcotte et al. [9] limited wide resection to patients with severe grade III tumours. However, to our knowledge, there is no clear definition of “more,” “extensive” or “severe” destruction” in grade III GCTs and the reported indications of wide resection for GCT are also heterogeneous [5, 7, 22, 23, 30, 38]. Furthermore, another dilemma of the application of the system of Campanacci et al. is that some authors declared that conservative treatments instead of wide resection should be recommended for grade III GCTs [44, 45]. Therefore, the role of the classifications of Enneking and Campanacci et al. in planning the initial surgical treatment is limited.

We may conclude that although different classifications based on histology and clinical and radiological appearance have been put forward, they were not able to accurately assess the aggressiveness or severity of GCT, provide reliable prognostic significance in terms of recurrence rates or functional results to provide valuable guidelines for decision-making on surgical treatment of GCT [5, 12, 30].

Possible prognostic factors of GCT

Determining the ideal treatment selection of GCT is subjective and will vary with the experience and judgment of the

surgeon. One major reason may be that the surgeons cannot accurately evaluate the severity or aggressiveness of GCT preoperatively by single clinical, radiographic, histological or demographic aspects. Thus, many factors must be considered comprehensively.

Patients' age

The peak incidence of GCTs is between the ages of 20 and 45 years. GCT is rare in skeletally immature patients, especially in children younger than ten years. Klenke et al. [23] reviewed 118 patients with GCT and found age at diagnosis independently predicted recurrence regardless of the status of the disease and the aggressiveness of the chosen treatment—recurrence rate decreased as the patient's age increased. Kivioja et al. [5] reported patient age and surgical margin were prognostic factors of local recurrence. Younger patients had a slightly increased risk of local recurrence with an annual reduction of around 2 %. The greater risk of young patients may be associated with increased bone turnover in young people [5]. This hypothesis is supported by studies showing inhibition of bone turnover with bisphosphonates reduced the risk of recurrence of GCT [46]. However, many authors found that the recurrence rate did not correlate with age [2, 5, 7, 9, 22, 28, 30, 38]. Niu et al. [2] reviewed 621 patients with GCTs in extremities and Cox regression analysis indicated that age was not the variable contributing to recurrence-free survival. To our knowledge, there are few studies showing the predicted recurrence of patients' age [5, 23]. But it is a fact that GCT most frequently occurs in young adults between 20 and 40 years of age, and bisphosphonates which were used to inhibit the bone turnover of GCT really reduce the risk of recurrence [46]. These contradictory phenomena will need further study.

Size of GCT

According to the Mankin's Big Four, "big is bad, small is good" when talking about the size of a tumour [47]. Thus a large tumour size of the GCT may indicate more bone destruction of the lesions. However, few studies have discussed the tumour volume of GCT, and the major reason may be that an objective, accurate, reproducible method of tumour volumetric measurement was not available because of the irregular shape of the GCT. Jeys et al. [4] reported on tumour volume estimated using measuring the largest dimensions of the tumour and assuming the tumour was spherical in shape. Univariate analysis indicated that the difference in tumour volume reached statistical significance between the fracture group and the intact cortex group, and significant differences were also shown between the ratio of tumour volume to distal femoral volume in patients with and without a fracture or cortical breach. Hirn et al. [48] reported

146 patients who underwent curettage without bone substitute filling or bone grafting and found the risk of subsequent fracture or the late development of osteoarthritis was strongly related to the size of the cyst at diagnosis, with a cyst of over 60 cm³ (about 5 cm in diameter) having a much higher incidence of complications. However, Prosser et al. [8] measured the tumour volume by computed tomography (CT) and magnetic resonance imaging (MRI) scans and found the mean volume of recurrent GCT was 142.6 cm³, which was comparable to 166.1 cm³ of non-recurrent GCT without significance.

Besides the correlation between the tumour volume and fracture or subsequent complications, another author tried to find the relationship between tumour size and radiotherapy. Miszczyk et al. [49] found that only tumour size significantly influenced local recurrence in patients treated with radiotherapy. The five year local control rate was 90 % for tumours four centimetres or smaller and decreased approximately 8 % for every one centimetre increase in tumour size over four centimetres. In all, we thought the tumour volume may be a useful factor in representing the severity of GCT, thus influencing the treatment decision-making process. However, there was no further study on this aspect.

Cortical bone destruction and soft tissue involvement

GCT grows in a penetrating fashion, entering every fold and protrusion of a bone, almost breaking through to the cortical bone. A bump or a soft tissue mass can even be seen resulting from the cortical destruction and tumour progression outside the bone [12, 17]. The prognostic relevance of cortical bone destruction and soft tissue involvement is controversial [7, 23, 30, 50]. Prosser et al. [8] reported local recurrence rate varied with cortical destruction, being only 7 % in patients with intraosseous tumours, but 29 % in patients with tumours with extraosseous extension. Balke et al. [30] found that soft-tissue extension has been proven to be a prognostic marker concerning local recurrence which could be reproduced by the data with a likelihood four times higher when a soft-tissue component was present. However, Errani et al. [7] reviewed 349 cases and found no significant statistical effect on local recurrence rate could be identified for the cortical bone destruction and soft tissue expansion. Although the risk of recurrence is dubious, the cortical bone destruction and soft tissue involvement influenced the selection of the optimal surgical procedure. Many authors agreed that tumours with extensive bone destruction and large soft tissue mass or without the possibility to save the adjacent joint as a result of loss of the articular continuity should be treated preferentially with wide resection [7, 11, 21, 23, 43]. But the key problem of choosing a surgical procedure based on cortical destruction and soft tissue involvement is that there is no exact definition of "extensive" or "large" destruction and the single factor of cortical

destruction and soft tissue involvement is not adequate for selecting an optimal treatment protocol. Therefore, a clearer recognition of cortical destruction and soft tissue involvement based on expert consensus and a comprehensive consideration including other possible prognostic factors are highly recommended.

Pathological fracture

Bigger and more aggressive GCTs may expand into soft tissues and cause pathological fractures. There is an approximately 20–30 % incidence of pathological fracture at presentation [4, 45]. Pathological fractures have been considered to signify a potentially more aggressive subset of GCT, less amenable to joint salvage, with higher local and systemic recurrence rates and inferior functional outcomes compared to patients without pathological fracture [51, 52]. But is this an accurate interpretation? Dehesi et al. [45] attempted to perform joint salvage in lesions of the distal femur or proximal tibia. They found joint salvage was performed in more patients without pathological fracture than patients with pathological fracture (96 % vs 84 %, $P=0.035$). A more aggressive approach is undertaken in the setting of pathological fractures. However, Dreinhofer et al. [52] underlined that pathological fracture is not a contraindication for intralesional excision and cement. Their results suggested that the treatment of pathological fractures in GCT by curettage and cementing gave a result as good as en bloc resection and reconstruction, both with respect to the local recurrence rate and joint function. Thus, the appropriate treatment of GCT patients with pathological fractures is still controversial.

The correlation of pathological fractures and local recurrence should be considered when selecting the treatment procedure. There are limited data in the literature comparing local recurrence rates between patients with and without pathological fracture [4, 7, 8]. Dehesi et al. [45] found no difference in local recurrence after curettage between patients with or without pathological fracture. However, in a Canadian multicentre study by Turcotte et al. involving 186 patients, displaced fracture was shown to be a prognostic factor for local recurrence [28].

Patients with pathological fracture were also thought to have a worse functional outcome [9, 19, 38, 45]. Turcotte et al. [28] reported that functional scores were reduced significantly in patients with a fracture with statistical analysis showing that this difference was related to the existence of a displaced fracture. Subset analysis revealed that SF-36 scores were significantly lower in the bodily pain section when patients had sustained a fracture. Dehesi et al. [45] did not find a difference in functional scores after joint salvage between patients with and without a pathological fracture through weight-bearing long bones, and they also did not detect a difference in functional outcome between

the patients with or without articular involvement of the fracture.

From imaging, we could classify pathological fracture patients based on articular extension, articular defects, displacement, and comminution of the fracture. There might also be a difference among various types of pathological fractures as the aggressiveness of the GCT, the ideal treatment, the local recurrence or functional results were concerned, which is a valuable topic for further study.

Involvement of the subchondral bone

Because the knee is a weight-bearing joint, the integrity of the subchondral bone is essential. Chen et al. [53] defined the subchondral bone to be affected when there was less than three millimetres distance to the tumour. Chen et al. [53] found the mean area of the affected subchondral bone was 18.6 % for patients initially treated with curettage and bone grafting and the mean MSTS score was 88 %. There was a linear trend showing that the larger the area of affected subchondral bone, the worse the functional score. While among patients initially treated with wide resection, the mean area of affected subchondral bone was 68.2 % and there was, however, no significant association between affected subchondral bone area and functional score. Therefore, the involvement of the subchondral bone may be a good factor to predict the functional results postoperatively. By this method that indirectly reflects the extent of subchondral bone involvement, Chen et al. identify patients who are at risk of complications from curettage and bone grafting, especially for those exceeding 40 % [53]. However, Ward and Li [43] recommended taking a wide resection of the knee joint with approximately 50 % of articular surface compromised. For all we know, the involvement of the subchondral bone may be a practical factor of predicting the functional outcome or complications postoperatively, and a more precise definition of the articular surface compromised is thought to be helpful in treatment decision-making.

Other possible prognostic factors

There are many other factors that should be taken into account when evaluating the aggressiveness or severity of GCT, such as the distance from articular surface to the tumour, the percentage of bone occupied by tumour and the anteroposterior and mediolateral diameter.

Ninety percent of GCT exhibits the typical metaphyseoepiphyseal location. Tumour often extends to the articular subchondral bone or even abuts the cartilage [12]. Therefore, the distance from articular surface to the tumour is also an essential evaluation variable and may play an important role in determining the resection or reconstruction methods of GCT. Another factor may be the percentage of bone

occupied by tumour, which was calculated as the proportion of the cross-sectional area of the bone at the widest dimension of the tumour. Prosser et al. [8] measured the distance from the articular surface which was divided into three groups (less than one millimetre, one to five millimetres, more than five millimetres), the percentage of bone occupied by tumour and the anteroposterior and mediolateral diameter of the tumour using CT and MRI scans. However, they found that there was no significant association between different groups and the local recurrence. The mean proportion of bone occupied by the tumour was 82 %. And the mean anteroposterior and mediolateral diameter for local recurrence tumour was 82.2 % and 91.5 %, respectively, without significant difference with non-recurrence tumour. Though, we believe that these factors are worth further study on their influence on the decision-making process of the resection technique and reconstruction technique.

Summary

Giant cell tumour of bone, although one of the most common primary musculoskeletal tumours, continues to be one of the most controversial and discussed bone tumours. The recommended therapy of GCT evolved during the 20th century, however, treatment options for GCT have remained fairly static over the past 30 years and there is no widely held consensus regarding the ideal treatment algorithm for all patients. The histological grading of GCT as a predictor of clinical outcome has been abandoned and the radiological staging systems of GCT by Campanacci et al. do not provide reliable prognostic significance in terms of recurrence rates or functional results nor valuable guidelines for decision-making on surgical treatment of GCT. After comprehensively evaluating the possible risk factors, we have exposed the necessity and feasibility for a full preoperative evaluation system including various possible risk factors for tumour recurrence or functional compromise that allows surgeons to accurately assess the aggressiveness and/or severity of GCT and helps surgeons to decide the ideal treatment of GCT.

Conflict of interest The authors declare that they have no conflict of interest.

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