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Research Paper

The epidemiological and clinical features of primary giant cell tumor around the knee: A report from the multicenter retrospective study in china

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ABSTRACT

Objectives: We aimed to determine the demographic characteristics of giant cell tumor around the knee in China.
Methods: Between March 2000 and June 2014, patients with primary giant cell tumor around the knee were recruited from 6 institutions located in different regions of China, and were reviewed retrospectively the clinical features according to gender and age.
Results: 334 qualified patients were included in this study. The sex ratio was 1.14:1 (178/156), with mean ages of 36.9 years in men and 33.1 years in women, constituting a significant difference ($P=0.007$). The prevalence of pathological fracture was 32.9% overall (28.7% in men and 37.8% in women). The prevalence of simple fracture was significantly higher in women (26.3%) than in men (15.2%), $P=0.042$. Tumor location and staging did not differ significantly according to sex ($P>0.05$). However, comparing with >40 years old, those patients aged ≤ 40 were more likely to have a right knee tumor (56.7% vs. 44.7%, $P=0.042$), less likely to have Enneking stage 3 disease (18.6% vs. 35.0%, $P=0.005$), and less likely to have both soft-tissue extension and a mass (18.6% vs. 34.0%, $P=0.009$).
Conclusions: Giant cell tumor around the knee was more common in men than in women, although female patients were younger on average. Further, cases among patients ≤ 40 years old were observed to be milder than cases among older patients. The results suggest that efficient treatment and preservation of function should both be valued for young patients with giant cell tumor around the knee.
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1. Introduction

Giant cell tumor (GCT) is a primary intramedullary bone tumor that is composed of mononuclear and giant mononuclear cells, resembling osteoclasts [1]. It usually involves the end of a long bone. The World Health Organization has classified GCT as an aggressive, potentially malignant lesion [2]. GCT accounts for 3–8% of primary bone tumors in Western nations, but it is more common in Asia, accounting for 20% of primary bone tumors [3–8]. GCT is most commonly diagnosed among 20–40 year olds, more likely to locate many sites of body, but half of GCTs occur around the knee [3,4,9–12]. About 10% of GCTs undergo malignant transformation, and pulmonary metastases occur in 1% to 4% of cases [13]. It has been reported that the postoperative recurrence rate is 10%–65% [5,6,14–16]. Therefore, GCT is one of the most controversial and widely discussed bone tumors [1,17,18].

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Previous, large retrospective studies from a single institution have indicated that GCTs predominantly occur among women, with a male-to-female gender ratio of 0.8:1 [5,19,20]. However, some studies have not shown this predominance [1,17,18]. Further, other studies have shown that most cases in Asia occur in men, with a gender ratio of 1.27–1.77 [21–24].

Recently, several studies from one institution have documented the characteristics of GCT in China. However, there has been an absence of large, multicenters, and representative studies of patients with GCT in China. In this study, we recruited the GCT patients from The Giant cell tumor Team of China, a multicenter nationwide GCT registry system, to explore the epidemiological characteristics of primary GCT around the knee, focusing on improving its diagnosis and treatment in China.

2. Materials and methods

2.1. Patients' selection

Between March 2000 and July 2014, patients with primary GCT around the knee were recruited from this multicenter nationwide GCT registry system, which included 6 centers of Orthopedic Oncology from different regions in China: Tianjin, Shandong, Shanxi, Zhejiang, Jiangsu, and Inner Mongolia. All patients had received their first histologically confirmed diagnoses of benign GCT and underwent surgical treatment. We excluded all patients with a preoperative diagnosis of GCT that was postoperatively determined to have been incorrect (i.e., patients with a non-GCT postoperative diagnosis). We further excluded all cases of GCT recurrence and all patients who were not treated surgically. Clinical and imaging data of the primary GCTs around the knee were reviewed retrospectively.

The ethics committee of Tianjin Hospital approved the study, and written informed consent was obtained from all patients during recruitment.

2.2. Tumor location

The patients with primary GCT around the knee were classified in three ways, according to the locations of their tumors. The first method of classifying location included the distal femur, proximal tibia, and other sites (the fibula and patella). The second method of classifying the tumor provided information on laterality (whether the tumor was located in the left or right knee). In the third method of grouping the tumors, tumors were classified as having grown centrically or eccentrically.

2.3. Staging

GCT is staged according to the Enneking staging system for benign bone tumors [25]. Under this system, stage 1(T_0) includes latent lesions that are biologically static; stage 2(T_1) includes active, slow-growing lesions that are confined within the bone; and stage 3(T_2) includes locally aggressive lesions with soft-tissue extension. GCTs can also be stratified according to the Campanacci system, which is based on plain radiography [26]. Under the Campanacci system grade I are the least common, and show features of latent or slow-growing tumors. The lesion is small, with a mild amount of sclerosis delineating the tumor. Bone contour is not affected, although the cortex can be thinned. The tumor does not extend to the articular cartilage. Symptoms are absent or minimal and of long duration. Grade II show features of an active lesion with ill-defined borders and without sclerosis. The cortex is thinned, if not breached and deformed with expansion, and the periosteum is elevated. The tumor often extends to the articular cartilage from within the marrow. Grade III show features of extreme aggressiveness, with a tumor that has a large volume, destroys bone, and invades the surrounding soft tissues.

2.4. Soft-tissue extension and mass

Depending upon whether soft-tissue extension and/or mass were present, all patients were divided into 3 groups: patients with neither soft-tissue extension nor mass, patients with soft-tissue extension alone, and patients with both soft-tissue extension and mass.

2.5. Pathologic fracture

Pathologic fracture was confirmed based on radiological and surgical data. The types of pathologic fracture included (i) the absence of any pathological fracture, (ii) simple pathological fracture, and (iii) complex pathological fracture. Simple pathological fracture was defined as the presence of pathological fractures located extra-articular, or the presence of intra-articular fracture with a complete articular surface, no or mild shifting, a gross tumor volume $< 200\ cm^3$, a distance of > 3 mm between the tumor and subchondral bone, and no soft-tissue extension or mass. Complex pathological fracture was defined as the presence of pathological fractures located in the intra-articular with a destructive articular surface, obvious shifting, a gross tumor volume $> 200\ cm^3$, a distance of < 4 mm between the tumor and subchondral bone, and soft-tissue extension and mass.

2.6. Surgical treatment

Surgical techniques were based on the severity of the tumor and included intralesional curettage, curettage combined with resection, and en bloc marginal resection [27].

Intralesional curettage was indicated for patients with a localized lesion. With this procedure, a window in the cortical bone is made, followed by resection of the mass using a series of curettes of various sizes; the residual tumor cavity is then polished with a high-speed burr until the normal cortical bone is reached and is filled with allogeneic particle bone graft to fill the window.

Curettage combined with resection was performed in patients with an extensive lesion. With this procedure, the cortical bone and soft tissue mass impossible reserved are removed, and the tumor cavity is disposed using curettes and a high-speed burr; cavitary bone defects are then filled with allogeneic particle bone graft, and an anatomical bone plate is used for internal fixation.

En bloc marginal resection was indicated for patients with severe involvement lesions. With this procedure, an osteotomy plane is confirmed based on preoperative magnetic resonance imaging, and the tumor is resected en bloc; an articulated prosthesis is used to reconstruct the knee.

2.7. Follow-up and outcome

The patients were followed-up every 3 months for the first 2 years post-operation, every 6 months until 5 years post-operation, and every 12 months until 10 years post-operation. Telephone interviews were allowed only after 5 years of follow-up. Information of local recurrence and metastases was obtained by face-to-face interview or telephone follow-up.

2.8. Statistical methods

All patient data were analyzed according to gender and age group. Because cases of GCT most commonly occur among patients 20–40 years old, age was categorized to two groups: ≤ 40 years

and >40 years. Continuous variables were summarized in terms of means (standard deviations) and categorical variables were summarized in terms of case numbers (percentages). The chi-square test was used to assess differences between the clinical and radiological characteristics of different gender and age groups. Differences in age were compared using the *t*-test. Statistical significance was defined as $P<0.05$.

3. Results

3.1. Demographic characteristics

Of the 334 patients with primary GCT around the knee, 178 were men and 156 were women, amounting to a sex ratio of 1.14:1. The mean ages of first diagnosis with GCT were 35.1 years overall, there was a significantly younger mean age of diagnosis in women than in men (33.1 vs. 36.9 years), $P=0.007$ (Table 1).

3.2. Location

Tables 2 and 3 showed than there were no significant gender differences in tumor location ($P>0.05$). But there was more lesions located in the right knee in ≤ 40-years-old patients than in >40-year-old patients (56.7% vs. 44.7%, $P=0.042$). (Table 3).

3.3. Tumor staging

There were no remarkable gender differences in Campanacci grades and Enneking stages (Table 2). However, patients ≤ 40-year-olds were less likely to have Enneking T_2, as compared with patients >40-year-olds (18.6% vs. 35.0%), $P=0.005$ (Table 3).

3.4. The style of soft-tissue extension and mass

Table 2 presented that there was not significant gender difference in the style of soft-tissue extension and mass. The proportion of patients with both soft-tissue extension and mass was higher among >40-year-olds than among ≤ 40-year-olds (34.0% vs. 18.6%), $P=0.009$ (Table 3).

3.5. Pathological fracture

The prevalence of pathological fracture in patients with primary GCT around the knee was 32.9% overall. The prevalence of simple pathological fracture was significantly lower in men than in women (15.2% vs. 26.3%), $P=0.042$ (Tables 2 and 3).

Table 1
The demographical characteristics of primary GCT around the knee in China.

Categories	Male	Female	Total	*P*
Number, *n* (%)	178 (53.3)	158 (46.7)	334 (100)	–
Age, year, means(SD)	36.9 (13.5)	33.1 (12.1)	35.1 (13.0)	0.007
Age group, *n* (%)				0.118
<20	10 (5.6)	13 (8.3)	23 (6.9)	
20∼	53 (29.8)	65 (41.7)	118 (35.3)	
30∼	48 (27.0)	31 (19.9)	79 (23.7)	
40∼	37 (20.8)	26 (16.7)	63 (18.9)	
≥ 50	30 (16.9)	21 (13.5)	51 (15.3)	
Center, *n* (%)				0.831
Tianjin	34 (51.5)	32 (48.5)	66 (19.8)	
Shandong	34 (61.8)	21 (46.6)	55 (16.5)	
Xian	47 (53.4)	41 (46.6)	88 (26.3)	
Jiangsu	18 (51.4)	17 (48.6)	35 (10.5)	
Zhejiang	36 (50.0)	36 (50.0)	72 (21.6)	
Inner Mongu	9 (50.0)	9 (50.0)	18 (5.4)	

Table 2
The clinical characteristics of primary GCT around the knee by gender in China.

Categories	Male	Female	Total	P
Location 1, *n* (%)				0.369
Distal femur	93 (52.2)	82 (52.6)	175 (52.4)	
Proximal tibia	75 (42.1)	70 (44.9)	145 (43.4)	
Others	10 (5.6)	4 (2.6)	14 (4.2)	
Location 2, *n* (%)				0.770
Left knee	85 (47.8)	72 (46.2)	157 (47.0)	
Right knee	93 (52.2)	84 (53.8)	177 (53.0)	
Location 3, *n* (%)				0.544
Non-centricity growth	136 (81.0)	127 (83.6)	273 (82.2)	
Centricity growth	32 (19.0)	25 (16.4)	57 (17.8)	
Campanacci grade, *n* (%)				0.496
I	23 (12.9)	14 (9.0)	37 (11.1)	
II	77 (43.3)	73 (46.8)	150 (44.9)	
III	78 (43.8)	69 (44.2)	147 (44.0)	
Ennecking stage, *n* (%)				0.741
T_0	77 (43.3)	61 (39.1)	138 (41.3)	
T_1	60 (33.7)	57 (36.5)	117 (35.0)	
T_2	41 (23.0)	38 (24.4)	79 (23.7)	
Soft tissue extension and mass			0.437	
None of them	63 (35.4)	55 (35.3)	118 (35.3)	
Soft tissue extension without mass	78 (43.8)	60 (38.5)	138 (41.3)	
Both of them	37 (20.8)	41 (26.3)	78 (23.4)	
Type of pathologic fracture, *n* (%)				0.042
No	127 (71.3)	97 (62.2)	224 (67.1)	
Simple	27 (15.2)	41 (26.3)	68 (20.4)	
Complex	24 (13.5)	18 (11.5)	42 (12.6)	
Surgical treatment, *n* (%)				0.616
Intralesional curettage	40 (22.6)	37 (23.7)	77 (23.1)	
Curettage combined with resection	93 (52.6)	75 (47.5)	168 (50.3)	
En bloc marginal resection	44 (24.9)	45 (28.8)	89 (26.6)	

Table 3
The clinical characteristics of primary GCT around the knee by age in China.

Categories	≤ 40 years	>40 years	Total	P
Location 1, *n* (%)				0.086
Distal femur	115 (49.8)	60 (58.3)	175 (52.4)	
Proximal tibia	103 (44.6)	42 (40.8)	145 (43.4)	
Others	13 (5.6)	1 (1.0)	14 (4.2)	
Location 2, *n* (%)				0.042
Left knee	100 (43.3)	57 (55.3)	157 (47.0)	
Right knee	131 (56.7)	46 (44.7)	177 (53.0)	
Location 3, *n* (%)				0.067
Non-centricity growth	184 (84.4)	79 (77.5)	263 (82.2)	
Centricity growth	34 (15.6)	23 (22.5)	57 (17.8)	
Campanacci grade, *n* (%)				0.923
I	26 (11.3)	11 (10.7)	37 (11.1)	
II	105 (45.5)	45 (43.7)	150 (44.9)	
III	100 (43.3)	47 (45.6)	147 (44.0)	
Ennecking stage, *n* (%)				0.005
T_0	103 (44.6)	35 (34.0)	138 (41.3)	
T_1	85 (36.8)	32 (31.1)	117 (35.0)	
T_2	43 (18.6)	36 (35.0)	79 (23.7)	
Soft tissue extension and mass			0.009	
None of them	86 (37.2)	32 (31.1)	118 (35.3)	
Soft tissue extension without mass	102 (44.2)	36 (35.0)	138 (41.3)	
Both of them	43 (18.6)	35 (34.0)	78 (23.4)	
Pathologic fracture, *n* (%)				0.756
No	157 (68.0)	67 (65.0)	224 (67.1)	
Simple	47 (20.3)	21 (20.4)	68 (20.4)	
Complex	27 (11.7)	15 (14.6)	42 (12.6)	
Surgical treatment, *n* (%)				0.021
Intralesional curettage	60 (26.1)	17 (16.5)	77 (23.1)	
Curettage combined with resection	118 (22.6)	50 (47.6)	168 (50.3)	
En bloc marginal resection	52 (22.6)	37 (35.9)	89 (26.6)	

3.6. Surgical treatment

There were higher frequency of En bloc marginal resection in patients aged 40 years and older than in patients aged <40 years, with the rate of 35.9% and 22.6% ($P=0.013$), respectively (Table 3).

3.7. Outcomes

Total 268 were qualified for follow-up, with a median follow-up time of 55 months (range, 12–188 months). Of these patients, 215 patients completed ≥ 12 months of follow-up, with a responding rate of 80.2% in this study. The local recurrence rate was 21.4% overall, 24.3% in men, and 18.3% in women; no significant difference in local recurrence rate was found between genders ($P=0.279$). Similar trends were observed for age group, with a local recurrence rate of 24.5% in those aged ≤ 40-year-olds and 14.7% in those aged >40-year-olds ($P=0.104$).

Among the patients with at least 12 months of follow-up, there were 3 patients with metastasis, including two cases of pulmonary metastasis and one case of thoracic vertebra metastasis. The pulmonary metastasis rate of GCTs around the knee was 0.9%, while the overall metastasis rate of GCTs around the knee was 1.4%.

4. Discussion

The incidence rates and gender distributions of GCT have become issues of contention for researchers around the world. In a study in the US city of Philadelphia, it was determined that GCT accounts for 5–7% of all primary bone tumors, yet it has also been reported that GCT accounts for 30% of primary bone tumors in south India [22]. In Western nations, GCT is more likely to occur in women than in men; one study has reported that 48.5% of cases occur in men and 51.5% occur in women [20], while another study has reported that 44% of cases occur in men and 56% occur in women [28]. However, several studies have reported that GCT predominately occurs in men, with a male-to-female gender ratio of 1.27–1.77 [7,21–23]. Consistent with these studies, we also found that first GCT around the knee predominantly occurred in men, with a gender ratio of 1.14:1 in the present study.

Most studies have indicated that GCT usually occurs in young adults aged 20–40 years, accounting for 70–80% of all cases, and that few cases occur after epiphysis clogging [20,28]. In the present study, 77.8% patients with primary GCT around the knee were diagnosed at the age between 20–40 years. Moreover, we found that first GCT around the knee was diagnosed at a younger average age in women than in men; this may be explained by earlier epiphysis clogging in women.

Studies of the laterality of GCTs of the knee are rare, though all studies have confirmed that the knee is the joint that is the most common site for this disease, accounting for 50–70% of cases [6,7]. In this study, a higher prevalence of first GCT was observed for the right knee in the group of patients ≤ 40 years of age. This may partly be explained by dextrality and heavy load bearing in young adults. The prevalence of eccentric growth was dominant in this study, a finding that is consistent with previous studies [7].

Campanacci et al. reported that only 10–15% of GCTs belong to grade I [29]. The most common grades were II and III, accounting for 70–80% and 20% of cases, respectively [28]. In contrast with these previous studies, we found similar prevalence rates of grade II (44.9%) and grade III (44.0%) disease in the present study. In several studies, it has been reported that grade III has a high recurrence rate [6,26,30]. However, results from China suggest higher recurrence of GCT with Campanacci grade II [7]. Thus, treatment of GCT should simultaneously focus on local control and the maintenance of function. We found a greater prevalence of Enneking stage T_2 stage in patients aged >40 years (35.0%) than in patients aged ≤ 40 years (18.6%).

The GCT usually involves a cladding that consisted of reactive bone and fibrosis, with a distinct boundary surrounded by soft tissue. Nevertheless, the active cladding is very thin among patients with severe invasiveness, including tumors that extend directly in into the muscle and fat, or other signs. Moreover, the tumor can be involved in synovial tissue, joint capsules, ligaments, and muscle tendons. It can even extend the contralateral bone along with soft tissue. Therefore, the assessment of soft-tissue extension is very important to guide clinical treatment. Moreover, soft-tissue extension has been found to increase the risk of local recurrence [2].

We found that more than one-third of patients aged >40 years at their first GCT diagnosis had both tumor and soft-tissue extension.

GCT is an osteolytic lesion. The bone cortex tends to attenuate because it has been invaded by tumor, rupture because of stress or an exogenous process, and then form a pathological fracture. Pathological fracture is found in 9–30% of patients with GCT [30]. It has been reported that 15% of GCT patients have the first symptoms of pathological fracture [3,31]. A previous study reported that pathologic fractures were associated with increased recurrence rates [26].

The prevalence of pathological fracture was 32.9% in this study, and a significantly higher prevalence of simple fracture was observed in women (26.3%) than in men (15.2%). This sex difference may be partly explained by the lower weights of bones in women than in men. Indeed, we observed that the female patients were more likely to have thin cortex of bone, lower bone mineral density, and few bone trabeculae. Moreover, the pulmonary metastasis rate of GCTs around the knee was 0.7%, while the overall metastasis rate was 1.3%, lower than rates reported previously [6,7].

There are limitations to this study. Most notably, this is a multicenter retrospective study, and there may have been differences between the identification standards in radiological data and the clinical staging at different institutions. However, this could be overcome by training the investigators from the 6 centers. Moreover, all patients were recruited from 2000 to 2014; new techniques were not developed during this 15-year period, and the standard of diagnosis did not change.

5. Conclusion

This is the first report of the epidemiological characteristics primary GCT on clinical and radiological features around the knee in China, as analyzed according to gender and age group, and as based on a large, multicenter, and nationwide sample. Our results validate previous findings, including the male preponderance of GCT, its more frequent occurrence at ages 20–40, the overall frequency of its occurrence around the knee. Moreover, we have provided several new discoveries: women are diagnosed at younger average ages and have a greater prevalence of simple pathological fracture than do men. Further, young patients have a tendency towards right knee preponderance. However, the disease is generally milder among young patients. These results suggest that surgeons should emphasize both the risk of local recurrence and the preservation of joint function for young and female patients.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional

and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Disclosure

The authors declare that they have no conflict of interest regarding the publication of this paper.

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