

Clinical Features of Giant Cell Tumor of Bone in Elderly Patients

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Abstract

Background: Giant cell tumor of the bone (GCTB) occurs most often in younger individuals aged between 20 and 40 years. However, it also occurs in a small proportion of elderly people. Therefore, it is necessary to determine the clinical characteristics of GCTB in elderly people, as only few reports have completely examined the characteristics of GCTB in elderly patients. **Methods:** This retrospective study enrolled 69 patients with benign GCTB. Patients' information on age, sex, anatomical location and size, Campanacci grade, pathological fracture, treatment for primary tumors, local and distant relapse, and outcome was collected. We compared these clinical courses between the younger and older groups. We divided the age groups into three subgroups: ≤ 54 years and ≥ 55 years, ≤ 59 years and ≥ 60 years, and ≤ 64 years and ≥ 65 years. We compared the two groups in each subgroup. In addition, we examined factors affecting local recurrence and distant metastasis. **Results:** Tumor size was significantly larger in the older group between the two subgroups of 55 and 60 years. Kaplan-Meier curves for local recurrence-free survival and distant metastasis-free survival between the two subgroups of 65 years showed significant differences ($p = 0.0183$ and $p = 0.0014$). In the multivariate logistic regression analyses, female sex, curettage-only surgical procedure, and denosumab usage before surgery affected local recurrence. **Conclusion:** Age is unlikely to affect local recurrence and distant metastases in GCTB patients, but local recurrence and distant metastases may be noted in elderly patients aged ≥ 65 years with GCTB.

Keywords

Giant Cell Tumor, Bone, Elderly, Local Recurrence

1. Introduction

Giant cell tumor of the bone (GCTB) is a rare mesenchymal tumor. GCTB is classified as a histologically benign lesion composed of mononuclear stromal cells and multinucleated giant cells, and it exhibits ongoing osteoclastic activity. Primary malignant GCTB is rare, accounting for up to 5% - 10% of all GCTBs, and most GCTBs are primary benign GCTBs [1]. However, even in primary benign GCTB, local recurrence is likely to occur, and distant metastasis to the lung can occur at a low frequency (<5%). Therefore, more attention should be paid to benign GCTB cases.

GCTB occurs most often in younger individuals aged between 20 and 40 years, but it also occurs in middle-aged and older people. Age distribution in GCTB varies across the reports [2]-[8]. Some studies report that there is a rapid decrease in the number of cases among patients aged above the 50s [2] [3] [4], while some studies report that the number of cases among patients aged in the 50s is still relatively large and decreases rapidly from the 60s [5] [6]. In Japan, 1849 GCTB cases have been registered in the registry in 12 years, from 2006 to 2017, and the proportion of patients is reported to be 11.8% in those over 50 years old, 8.7% in those over 55 years old, 6.3% in those over 60 years old, and 4.5% in those over 65 years old. Therefore, GCTB occurs at a small but constant rate in middle-aged and elderly people. Thus far, few reports have fully examined the characteristics of GCTB in middle-aged and elderly patients.

The proportion of the elderly population is rapidly increasing in developed countries. According to the United Nations, the most marked increase is expected to occur in Japan [9]. Although 26% of Japanese citizens were more than 65 years old in 2015, it is said that this will increase to 32% by 2050 [10]. Although 22% of the population was over the age of 65 years in Tokyo, Japan in 2015, Akita and Hokkaido, northern regional prefectures, have already shown high rate of the elderly population, at 34% and 31%, respectively. Therefore, there is a need to fully unravel the clinical characteristics of GCTB in the elderly.

This study aimed to analyze the clinical features of GCTB in elderly patients and identify the age group that is particularly characteristic of this condition.

2. Materials and Methods

2.1. Subjects

We retrospectively reviewed the medical records of 78 patients with GCTB involving the extremities or trunk and who visited our two institutions between January 1994 and November 2019. We enrolled patients with GCTB who underwent adequate follow-up for GCTB. Patients with malignant GCTB detected at the initial pathological diagnosis and patients with malignancy were excluded from the present study. Finally, 69 consecutive patients with GCTB (35 males and 34 females, with a mean age of 38.0 years, range: 12 - 78 years) were included in this study. Patients' information on age, sex, anatomical location and size of the tumor, Campanacci grade [5], presence of pain, pathological fracture,

treatment for primary tumors, local and distant relapse, follow-up period, and outcome was collected. We also obtained information about surgical methods such as curettage only, curettage and adjuvant therapies (phenol, absolute ethanol, hot water, and bone cement), and excision. We also investigated the use of denosumab before surgery, which may affect outcomes. In the absence of any events, the date of the last follow-up was considered as the end-point. Local recurrence-free survival was defined as the time during which the patient remained free of local recurrence after resection of the primary tumor. Distant metastasis-free survival was defined as the time during which the patient remained free of metastases after the first consultation. As there were no deaths due to postoperative complications in this study, we defined deaths from GCTB as “died of disease”.

In our series, we compared these clinical courses and results between the younger and older groups. We divided the age groups into three subgroups: ≤ 54 years and ≥ 55 years, ≤ 59 years and ≥ 60 years, and ≤ 64 years and ≥ 65 years. We compared the two groups in each subgroup. In addition, we examined factors affecting local recurrence and distant metastasis.

This study was approved by the Institutional Review Board for Clinical Research at Akita University and Sapporo Medical University (approval number: 2477), and informed consent was obtained from all patients.

2.2. Statistical Analysis

We compared the clinical courses and results between the younger and older groups and analyzed the factors affecting local recurrence and distant metastasis.

Date of continuous variables was expressed as mean \pm standard deviation. Student's *t*-tests, Welch *t*-tests, and chi-square (χ^2) tests were used to compare patients' characteristics between the two groups. The curves for local recurrence-free survival and distant metastasis-free survival were constructed using the Kaplan-Meier method, and differences were analyzed using the generalized Wilcoxon test. A Cox proportional hazards model was used to identify the factors associated with local recurrence and distant metastasis. Probability (*p*) values less than 0.05 were considered significant.

3. Results

The mean follow-up period for all patients was 82.3 ± 77.1 months (range: 2 - 486 months). The sites of the primary lesions were the extremities in 63 patients (91.3%) and axial sites in 6 patients (8.7%): distal femur in 20 patients, proximal tibia in 18, proximal fibula in 6, proximal femur in 4, distal radius in 4, distal ulna in 3, proximal humerus in 2, distal tibia in 2, ischium in 2, sternum in 1, proximal ulna in 1, lumbar spine in 1, proximal phalanges of finger in 1, cuboid bone in 1, and metatarsal bone in 1. The mean tumor size of the primary lesion was 53.0 ± 17.3 mm (range: 11 - 96 mm). The Campanacci grade was grade I in 12 patients, grade II in 28, grade III in 16, and unknown in 13. Pain was con-

firmed in 64 patients (92.8%), and pathological fractures occurred in 14 patients (20.3%). Surgical treatment was performed in 64 patients: curettage only in 9 patients, curettage and adjuvant therapies in 47, and excision in 8. In adjuvant therapies, phenol was used in 5 patients, absolute ethanol in 8, hot water in 3, and bone cement in 36. To treat GCTB, denosumab was administered to 8 patients (12.5%) in the preoperative period: 1 patient who underwent curettage only, 5 who underwent curettage and received adjuvant therapies, and 2 underwent excision. A total of 22 patients (34.4%) developed local recurrence. The mean period until the appearance of local recurrence in patients who underwent surgical treatment was 35.3 ± 52.6 months (range: 4 - 240 months). Six patients (8.7%) developed metastases after the first consultation. The outcomes in all patients were as follows: 59 patients had no evidence of the disease, 7 were alive with the disease, and 3 died owing to the disease. No patients died because of complications during the perioperative period.

Although there were no significant differences in clinical information between the two subgroups of 65 years group, tumor size was significantly larger in elderly patients between the two subgroups of the 55 and 60 years group (**Tables 1-3**). However, no significant difference was found for other clinical information.

Table 1. Comparison of characteristics between patients aged ≤ 54 years and those aged ≥ 55 years.

Characteristics	≤ 54	≥ 55	<i>p</i> -Value
Number	57	12	
Age (years)	32.4 ± 10.6	64.6 ± 5.6	-
Sex: Male/Female	30/27	5/7	0.7092
Location: Extremity/Axial	52/5	11/1	0.6068
Size (mm)	50.2 ± 15.2	66.3 ± 21.2	0.0027
Campanacci grade			
Grade I/II/III/Unknown	11/26/12/8	1/2/4/5	0.2008
Pain: Present/None	54/3	10/2	0.4399
Pathological fracture: Present/None	11/46	3/9	0.9589
Surgical treatment: Present/None	54/3	10/2	0.4399
Surgical methods			0.8747
-Curettage and adjuvant therapy	39	8	
-Excision	7	1	
-Curettage only	8	1	
Denosumab before surgery: Present/None	5/49	3/7	0.1932
Local recurrence: Present/None	19/35	3/7	0.9639
Time to local recurrence (months)	38.5 ± 56.0	15.0 ± 12.2	0.4860
Distant metastasis - Present/None	4/53	2/10	0.6068
Follow-up period (months)	81.1 ± 78.7	88.1 ± 71.8	0.7774
Outcome at the last follow-up			
Alive without disease/Alive with disease/Dead	50/4/3	9/3/0	0.1368

Values are expressed as the number and proportion of patients or mean \pm standard deviation (SD) with range.

Table 2. Comparison of characteristics between patients aged ≤ 59 years and those aged ≥ 60 years.

Characteristics	≤ 59 years	≥ 60 years	<i>p</i> -Value
Number	59	10	
Age (years)	33.3 \pm 11.4	66.1 \pm 4.7	-
Sex: Male/Female	30/29	5/5	0.7699
Location: Extremity/Axial	53/6	10/0	0.5823
Size (mm)	51.1 \pm 16.1	64.4 \pm 20.8	0.0236
Campanacci grade			
Grade I/II/III/Unknown	11/27/12/9	1/1/4/4	0.0830
Pain: Present/None	56/3	8/2	0.3064
Pathological fracture: Present/None	11/48	3/7	0.6888
Surgical treatment: Present/None	55/4	9/1	0.7670
Surgical methods			0.9475
-Curettage and adjuvant therapy	40	7	
-Excision	7	1	
-Curettage only	8	1	
Denosumab before surgery: Present/None	5/50	3/6	0.1349
Local recurrence: Present/None	19/36	3/6	0.7584
Time to local recurrence (months)	38.5 \pm 56.0	15.0 \pm 12.2	0.4860
Distant metastasis: Present/None	4/55	2/8	0.4442
Follow-up period (months)	83.1 \pm 78.2	77.8 \pm 73.7	0.8443
Outcome at the last follow-up			
Alive without disease/Alive with disease/Dead	51/5/3	8/2/0	0.4340

Values are expressed as the number and proportion of patients or mean \pm standard deviation (SD) with range.

Although there were no significant differences in Kaplan-Meier curves for local recurrence-free survival between the two subgroups of 55 and 60 years, Kaplan-Meier curves for local recurrence-free survival between the two subgroup of the 65 years group showed significant difference ($p = 0.0183$), and local recurrence was likely to occur in elderly patients (**Figure 1**). Similarly, Kaplan-Meier curves for distant metastasis-free survival showed significantly poor prognosis in elderly patients between the two subgroups of the 65 years group ($p = 0.0014$) (**Figure 2**). In the univariate and multivariate Cox regression analyses, female sex, curettage-only surgical procedure, and denosumab usage before surgery affected local recurrence (**Table 4**). However, there were no evident factors affecting distant metastasis.

4. Discussion

In our analysis, age was not an apparent poor prognostic factor for local recurrence and distant metastases in multivariate analysis. However, Kaplan-Meier curves showed a significantly higher risk of local recurrence and distant metastasis

Table 3. Comparison of characteristics between patients aged ≤ 64 years and those aged ≥ 65 years.

Characteristics	≤ 64 years	≥ 65 years	<i>p</i> -Value
Number	63	6	
Age (years)	35.1 \pm 13.1	68.5 \pm 4.8	-
Sex: Male/Female	32/31	3/3	0.6964
Location: Extremity/Axial	57/6	6/0	1.0000
Size (mm)	52.8 \pm 17.2	55.8 \pm 20.7	0.6815
Campanacci grade			
Grade I/II/III/Unknown	11/28/14/10	1/0/2/3	0.1823
Pain: Present/None	59/4	5/1	0.9144
Pathological fracture: Present/None	13/50	1/5	0.7640
Surgical treatment: Present/None	59/4	5/1	0.9144
Surgical methods			0.6552
-Curettage and adjuvant therapy	43	4	
-Excision	8	0	
-Curettage only	8	1	
Denosumab before surgery: Present/None	7/52	1/4	0.8603
Local recurrence: Present/None	19/40	3/2	0.4436
Time to local recurrence (months)	38.5 \pm 56.0	15.0 \pm 12.2	0.4860
Distant metastasis: Present/None	4/59	2/4	0.1380
Follow-up period (months)	83.6 \pm 68.7	68.7 \pm 76.5	0.6534
Outcome at the last follow-up			
Alive without disease/Alive with disease/Dead	55/5/3	4/2/0	0.1326

Values are expressed as the number and proportion of patients or mean \pm standard deviation (SD) with range.

in GCTB patients aged 65 years and older. However, few previous reports have shown that age affects local recurrence or distant metastases [10]-[18]. Most reports have shown that age is not a risk factor [10]-[15]. Moreover, a study reported a lower risk of local recurrence in GCTB patients aged 51 years and older [16]. However, some reports showed that older age may have adverse effects in patients with GCTB [17] [18]. Amelio *et al.* analyzed 337 GCTB patients and reported a higher mortality rate in older age, especially over 55 years old [17]. Lin *et al.* examined 334 GCTB patients and showed that the Enneking stage was advanced in GCTB patients aged 40 years and older [18]. Although there are various reports on whether age is a risk factor, as described above, the criteria for old age are different in each study. Therefore, in our study, we divided age into three groups, namely, 55, 60, and 65 years old, and we analyzed each of them. Then, it was shown that the course of local recurrence and distant metastasis was rapidly poor when the GCTB patients of the 65 years group were divided into two subgroups, which had never been analyzed in the past. Considering the results of the current study that age was not a risk factor in multivariate analysis, it

Table 4. Results of univariate and multivariate analyses of factors affecting local recurrence-free survival and distant metastasis-free survival.

Variables	Univariate			Multivariate		
	OR	95% CI	<i>p</i> -Value	OR	95% CI	<i>p</i> -Value
Local recurrence						
Age	0.992	0.963 - 1.021	0.5800			
Sex: Female	2.707	1.042 - 7.031	0.0408	2.770	1.036 - 7.406	0.0423
Size	0.990	0.960 - 1.022	0.5542			
Campanacci grade	1.554	0.756 - 3.193	0.2306			
Symptom: Pain	1.056	0.141 - 7.906	0.9575			
Pathological fracture	1.887	0.724 - 4.920	0.1940			
Surgical methods: Curettage only	3.741	1.430 - 9.789	0.0072	3.686	1.322 - 10.277	0.0126
Denosumab before surgery	3.481	1.124 - 10.780	0.0306	5.445	1.639 - 18.084	0.0056
Distant metastasis						
Age	1.022	0.970 - 1.077	0.4054			
Sex: Female	0.952	0.192 - 4.729	0.9524			
Location: axial	4.188	0.720 - 24.352	0.1108			
Size	0.971	0.922 - 1.022	0.2614			
Campanacci grade	1.487	0.371 - 5.961	0.5752			
Pathological fracture	1.065	0.119 - 9.546	0.9549			
Surgical treatment	0.208	0.037 - 1.164	0.0743			
Denosumab before surgery	5.393	0.482 - 60.354	0.1715			
Local recurrence	2.287	0.379 - 13.816	0.3674			

OR: odds ratio, 95% CI: 95% confidence interval.

was considered that the clinical course of local recurrence and distant metastasis did not worsen as the age increased, but the prognosis may suddenly worsen after a certain age.

The most commonly reported risk factors for local recurrence are non-adjuvant curettage surgery and extraosseous tumor progression (high grade of Campanacci classification) [5] [12] [19] [20] [21]. In our study, curettage without adjuvant therapy was cited as one of the risk factors for local recurrence, and the result was similar to those in the past. Various other factors, such as the presence of distant metastases at the first visit and development of the primary tumor in the proximal tibia have been reported in the past as risk factors [22] [23] [24]. In our study, female sex was also observed to be a risk factor for local recurrence. However, some reports show different results for these factors [16] [25] [26], and it is difficult to say that there is sufficient consensus. Distant metastasis has the same recognition as that for local recurrence. It is well reported that the risk of distant metastasis is high when the number of local recurrences is frequent [13] [14] [15]. However, the site, bearing time, and size of the tumor have also been reported as risk factors for distant metastasis [13] [14] [27]. For example, regarding the site of tumor occurrence, while the distal radius is reported to be a risk factor, the bone around the knee is also reported as a risk factor [27] [28], and it is unlikely that there is sufficient consensus on these

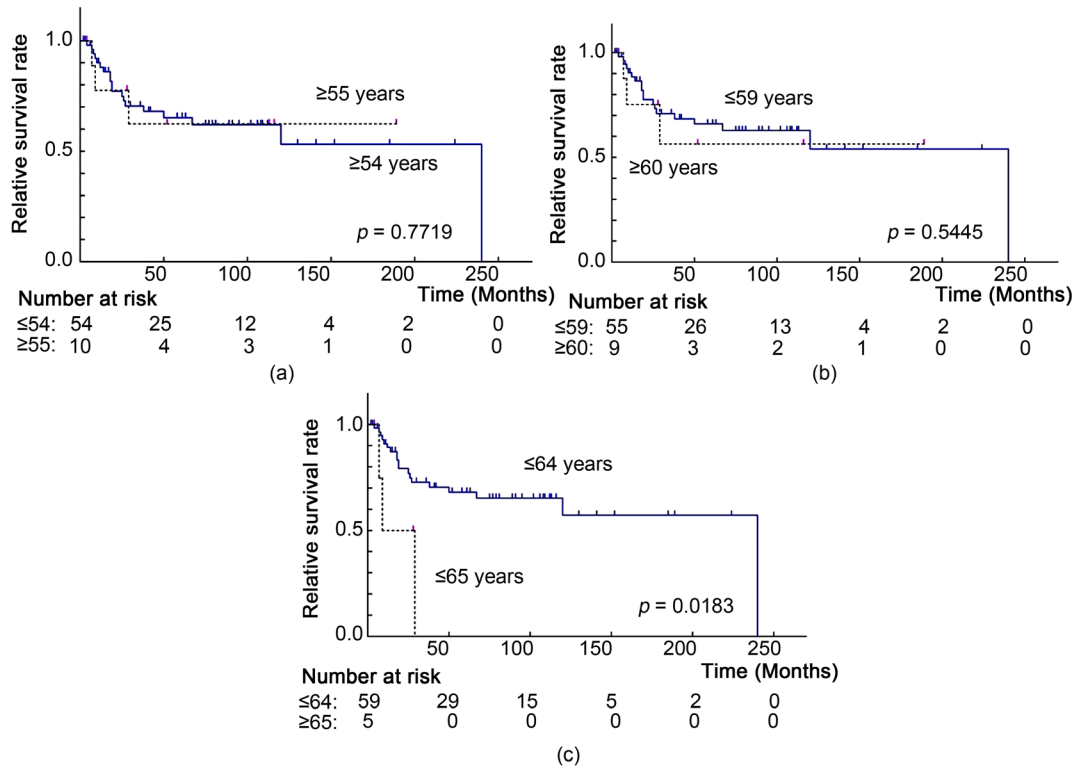


Figure 1. Kaplan-Meier local recurrence-free survival curves between each 2 groups divided into 55 (a), 60 (b), and 65 (c) years. A significant difference was shown between the 2 groups divided into 65 years ($p = 0.0183$).

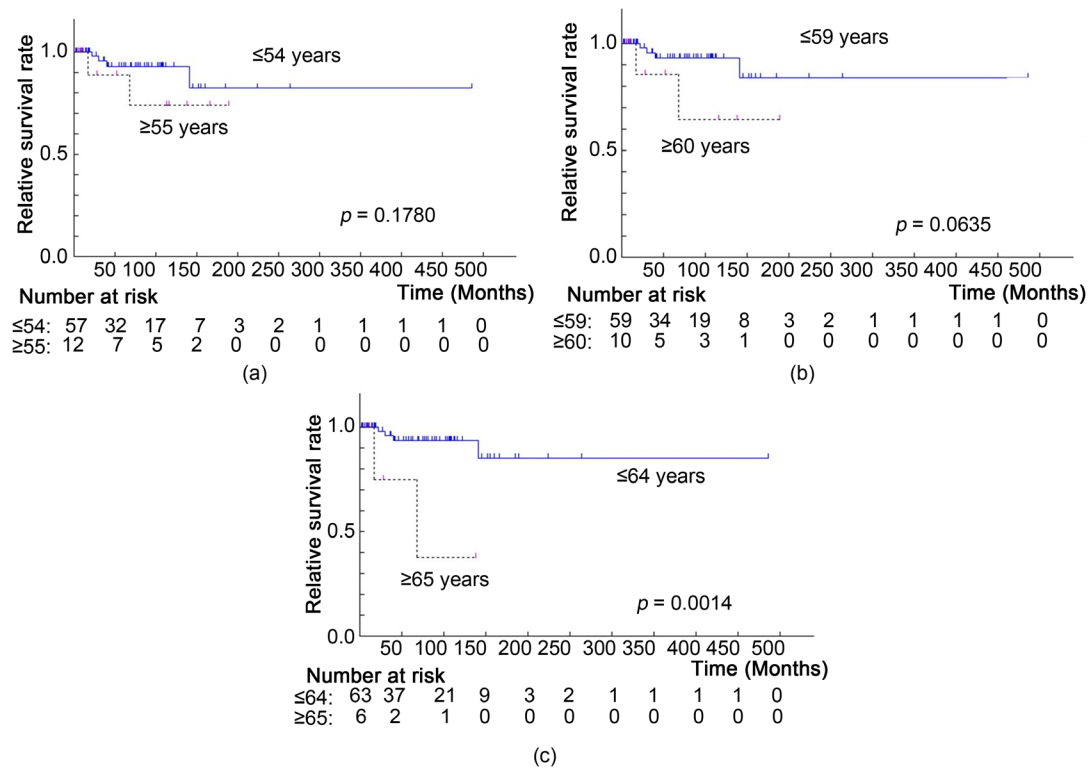


Figure 2. Kaplan-Meier distant metastasis-free survival curves between each 2 groups divided into 55 (a), 60 (b), and 65 (c) years. A significant difference was shown between the 2 groups divided into 65 years ($p = 0.0014$).

proposed risk factors.

Denosumab is a fully human monoclonal antibody that specifically binds to RANK ligand and inhibits its action. Because GCTB produces and is dependent on RANK ligand for growth, denosumab can be expected to suppress the increase of GCTB. However, it has recently been reported that the use of denosumab before curettage surgery increases the local recurrence rate [29] [30], and we also reported the preoperative use of denosumab as a risk factor for local recurrence. Although the use of denosumab in unresectable cases is a good indication for GCTB, it should not be used in patients in whom curettage surgery is assumed.

In this study, the local recurrence rate was 34.4% and the distant metastasis rate was 8.7%, both of which were higher than those reported in recent studies [10] [12]-[19] [24]. In the 64 GCTB patients who received surgical treatment, 8 used denosumab preoperatively, 9 underwent curettage surgery without adjuvant therapy, and a total of 17 patients received treatment with a high risk of local recurrence. This is considered to have greatly affected the high local recurrence rate and the incidence of distant metastasis.

The strength of the present study is that this is the first study to examine in detail the characteristics of GCTB in middle-aged and older patients grouped by age and to show the potential risks in elderly patients with GCTB. However, several limitations of our study should be mentioned. First, the number of GCTB cases is small, especially in elderly patients. There were only 6 GCTB patients over the age of 65 years. Several factors may have led to biases such as Campanacci classification, tumor size, and tumor location. Second, there are various surgical methods, and various adjuvant therapies are combined with curettage surgery. Because it was difficult to compare these contents in detail, we could divide them only into the curettage only group or the curettage with adjuvant therapy and excision group. The number of patients is limited, and it is difficult to strictly comply with the criteria for target patients.

5. Conclusion

In conclusion, the present study showed some clinical features of GCTB in elderly patients. Age is unlikely to affect local recurrence and distant metastases in GCTB patients, but local recurrence and distant metastases may be noted in elderly patients aged 65 years and older.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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