

Secondary Malignancy in Giant Cell Tumor: A Single-Center Study

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Abstract

Giant cell tumor of bone (GCTB) uncommonly undergoes sarcomatous transformation. Secondary malignancy in giant cell tumor (MGCT) develops at the prior treatment site, and is associated with radiotherapy and dismal prognosis. The objective of this study is to investigate the clinicopathological characteristics of MGCT patients.

We reviewed medical records of patients with secondary MGCT. Twelve patients were analyzed including six females and six males, with a median age of 42.5 years. Benign recurrence occurred in five GCTB patients, who were not treated with radiotherapy. No pulmonary implants were observed. The median latency was 63 months. Nine patients were AJCC stage IIB, and three were stage IVA. The median follow-up period after malignant transformation was 62.5 months. Five patients developed local recurrence and six had metastasis. Five-year overall, recurrence- and metastasis-free survivals were 61.9%, 66.7% and 58.3%. The local recurrence of GCTB was a potential factor for metastasis-free survival. Difference in overall survival according to benign local recurrence was almost significant.

In our series, the occurrence of secondary MGCT did not follow radiotherapy, contrary to the Western literature. The prognosis was better than the findings reported in previous studies. The local recurrence of benign GCTB could reflect the prognosis of MGCT.

Introduction

Giant cell tumor of bone (GCTB) is a benign, locally aggressive neoplasm, with an incidence that varies according to the geographic region. Although it is a benign lesion, pulmonary metastasis can develop, which is called pulmonary implants¹. GCTB may uncommonly undergo sarcomatous transformation².

The term "malignant giant cell tumor" first appeared in the 1930s³ and was used to describe sarcoma arising from a giant cell tumor⁴. However, the term frequently led to confusion, resulting in the inclusion of many giant cell-rich sarcomas in this category, which were not associated with GCTB^{4,5}. To resolve the confusion, the term "malignancy in giant cell tumor (MGCT)" was used first in 2001⁶. MGCT is categorized into two subtypes based on the World Health Organization (WHO) classification⁷. Recent studies referred to primary MGCT as a type of tumor where high-grade sarcoma components histologically appeared synchronously beside benign GCTB components at the initial diagnosis and secondary MGCT referred to high-grade sarcoma components that developed in previously treated GCTB^{4,5,8,9}. That is, a previous history of GCTB and the local recurrence information were the main differentiating points between secondary MGCT and different malignancies^{5,10}.

Previous studies reported that most MGCT was secondary and developed normally after radiotherapy, but it can follow surgery without adjuvant radiation therapy^{6,10,11}. It was suggested that irradiation affected malignant transformation and decreased the latency interval⁴. Most studies reported the dismal prognosis of patients with MGCT^{4,5,9}. However, there currently is no consensus on the appropriate treatment⁸.

Unfortunately, most published studies involving a relatively large number of cases failed to collect patient data based on a consistent definition and sub-classification of MGCT¹², so it is not easy to analyze or compare the previous studies with each other. Therefore, we investigated the clinicopathological characteristics and prognostic factors of patients with secondary MGCT based on the recent diagnostic criteria.

Results

A total of 12 cases were reviewed and the details are presented in Tables 1 and 2. One hundred and forty-three patients with GCTB were managed in our institution during the study period. The study included six males and six females, with a median age of 42.5 years (range, 36–66 years) at the initial diagnosis of MGCT. Six lesions were located in the distal femur, three in the proximal tibia, two in the proximal femur, and one in the distal radius. Six patients with benign GCTB were assigned Campanacci grade 2 radiologically, and six were grade 3. Surgical treatment for such lesions entailed intralesional tumor removal in 11 patients. In addition, bone grafting and cementation were performed in six and three patients, respectively. The second patient listed in Table 1 had tumor resection and arthroplasty using an implant. Benign recurrent GCTB occurred in five cases. Among them, the seventh case in Table 1 relapsed three times. No patient had radiotherapy for benign GCTB and recurrent lesions. No pulmonary implants were observed.

Table 1
Patient characteristics

Location	Primary benign giant cell tumor			Latent period (month)	Malignancy in giant cell tumor					
	Campanacci grade	Surgical method	Local recurrence		Patient No./Gender/Age (years)	Size (cm)	Radiologic feature	Stage (AJCC/Enneking)	Surgery type	Histology/subtype
PT	3	Cu & Ce	0	90	1/M/53	10.3 x 10.3 x 3	osteolytic	IIB/IIA	LS	OSA/conventior
PF	2	Re & AP	1	180	2/M/41	10.5 x 10 x 4	osteolytic	IVA/III	LS	OSA
PT	3	Cu & Ce	0	123	3/M/41	10.8 x 10.5 x 8.3	osteolytic	IIB/IIA	LS	UPS
DF	2	Cu & BG	0	150	4/M/41	8.5 x 6 x 4	osteoblastic	IIB/IIA	LS	OSA/osteoblast
DF	2	Cu & Ce	1	25	5/F/40	5 x 5 x 2	osteolytic	IIB/IIA	LS	OSA
DF	3	Cu	0	7	6/F/62	11.1 x 7.4 x 3.7	osteolytic	IIB/IIA	LS	OSA
PT	3	Cu & BG	3	240	7/F/66	9.0 x 6.5 x 4.3	osteolytic ABC change	IIB/IIA	LS	OSA
DF	2	Cu	0	36	8/F/50	5.8 x 6.5 x 3.3	osteoblastic	IVA/III	Amp	OSA/osteoblast
DR	3	Cu & BG	1	24	9/F/40	4.5 x 4.0 x 3.0	osteolytic	IIB/IIA	LS	OSA/fibroblastic
DF	3	Cu	0	126	10/F/36	5.1 x 3 x 4	osteolytic	IIB/IIA	LS	OSA/fibroblastic
PF	2	Cu & BG	1	27	11/M/44	8.2 x 6.4 x 3.7	osteoblastic	IVA/III	LS	OSA/osteoblast
DF	2	Cu & BG	0	33	12/M/59	6.0 x 5.5 x 4.3	osteolytic	IIB/IIA	LS	OSA/mixed type

PT, proximal tibia; PF, proximal femur; DF, distal femur; DR, distal radius; Cu, curettage; Ce, cementation; Re, resection; AP, arthroplasty; BG, bone graft; LS, limb salvage; Amp, amputation; OSA, osteosarcoma; UPS, undifferentiated pleomorphic sarcoma

Table 2
Prognosis after malignant transformation of giant cell tumor

Patient No./Gender/Age (years)	Local recurrence		Distant metastasis			Follow-up period	Oncologic outcome
		Interval from diagnosis (months)		Site	Interval from diagnosis (months)		
1/M/53	Yes	38	Yes	Lung	38	91	DOD
2/M/41	Yes	7	Yes	Lung	0	81	DOD
3/M/41	No	-	No	-	-	28	CDF
4/M/41	No	-	No	-	-	72	CDF
5/F/40	Yes	202	Yes	Lung	74	294	NED
6/F/62	No	-	No	-	-	94	CDF
7/F/66	No	-	No	-	-	6	DOAD
8/F/50	Yes	5	Yes	Lung	0	14	DOD
9/F/40	Yes	5	Yes	Lung	13	21	DOD
10/F/36	No	-	No	-	-	53	CDF
11/M/44	No	-	Yes	Lung	0	12	DOD
12/M/59	No	-	No	-	-	26	CDF

DOD, died of disease; CDF, continuous disease free; NED, no evidence of disease; DOAD, died of other disease

The patients were diagnosed with MGCT and underwent surgical treatment in our tertiary center from 1995 to 2018. All patients presented with pain and the sixth patient in Table 1 visited our center following a pathologic fracture. The median latent period was 63 months (range, 7–240 months). The median main length of the MGCT lesions at presentation was 8.35 cm (range, 4.5–11.1 cm) and the volume was 199.1 cm³ (range, 50–968.11 cm³). Nine patients were AJCC stage IIB and Enneking stage IIA, and three were AJCC stage IVA and Enneking stage III. Nine patients demonstrated osteolytic lesions, and three showed osteoblastic lesions in plain radiographs. Magnetic resonance imaging revealed extraosseous extension in all patients. The seventh case in Table 1 carried a secondary aneurysmal bone cyst. Eleven patients underwent wide resection and limb reconstruction with endoprostheses while the eighth case had an amputation. Curative surgical margins were achieved in all patients. Ten patients underwent postoperative chemotherapy, among whom two also had preoperative chemotherapy. No patients underwent radiation treatment for MGCT. The prognoses after the diagnosis of MGCT are summarized in Table 2. Local recurrences occurred in five patients and the median local recurrence-free survival interval was 7 months (range, 5–202 months). Six patients had distant metastasis and the median distant metastasis-free survival interval was 6.5 months (range, 0–38 months). The median follow-up period was 62.5 months (range, 6–294 months). Regarding the oncologic outcomes at the last follow-up, five patients were continuously disease-free, one had no evidence of disease, five died of disease, and one died of other disease.

The 5-year overall survival rate (OSR), local recurrence-free survival rate (RFSR), and distant metastasis-free survival rate (MFSR) was 61.9%, 66.7%, and 58.3%, respectively. The analysis of potential risk factors for OSR, RFSR, and MFSR are presented in Tables 3, 4, and 5, respectively. The difference in OSR according to initial metastasis (yes versus no) showed statistical significance ($p = 0.021$) and, depending upon the local recurrence of GCTB (yes versus no), was almost significant ($p = 0.056$). None of the potential factors had any impact on the RFSR. The difference in MFSR depending upon benign local recurrence (yes versus no) was significant ($p = 0.035$) (Fig. 1).

Table 3
Statistical analysis of prognostic factors for overall survival

Factors	Univariate analysis			
		N (%)	5-year OSR (%)	P value
Gender	Male	6 (50%)	83.3	0.888
	Female	6 (50%)	50	
Age	≥ 50 years	5 (41.7%)	60	0.641
	< 50 years	7 (58.3%)	71.4	
Campanacci grade	2	6 (50%)	67.7	0.837
	3	6 (50%)	67.7	
Benign local recurrence	No	7 (58.3%)	85.7	0.056
	Yes	5 (41.7%)	40	
Latent period	≥ 10 years	5 (41.7%)	80	0.746
	< 10 years	7 (58.3%)	57.1	
Main length	≥ 8 cm	7 (58.3%)	71.4	0.541
	< 8 cm	5 (41.7%)	60	
Volume	≥ 250 cm ³	5 (41.7%)	80	0.801
	< 250 cm ³	7 (58.3%)	57.1	
MGCT local recurrence	No	7 (41.7%)	71.4	0.238
	Yes	5 (58.3%)	60	
Initial metastasis	No	9 (75%)	77.8	0.021*
	Yes	3 (25%)	33.3	
Chemotherapy	No	2 (16.7%)	100	0.174
	Yes	10 (83.3%)	60	
MGCT, malignancy in giant cell tumor; OSR, overall survival rate				
*Statistically significant				

Table 4
Statistical analysis of prognostic factors for local recurrence-free survival

Factors		Univariate analysis		
		N (%)	5-year RFSR (%)	P value
Gender	Male	6 (50%)	100	0.574
	Female	6 (50%)	60	
Age	≥ 50 years	5 (41.7%)	75	0.934
	< 50 years	7 (58.3%)	83.3	
Campanacci grade	2	6 (50%)	80	0.471
	3	6 (50%)	80	
Benign local recurrence	No	7 (58.3%)	85.7	0.09
	Yes	5 (41.7%)	66.7	
Latent period	≥ 10 years	5 (58.3%)	100	0.313
	< 10 years	7 (41.7%)	66.7	
Main length	≥ 8 cm	7 (41.7%)	66.7	0.271
	< 8 cm	5 (58.3%)	100	
Volume	≥ 250 cm ³	5 (58.3%)	100	0.888
	< 250 cm ³	7 (41.7%)	66.7	
Chemotherapy	No	2 (16.7%)	100	0.125
	Yes	10 (83.3%)	75	
RFSR, local recurrence-free survival rate				

Table 5
Statistical analysis of prognostic factors for distant metastasis-free survival

Factors		Univariate analysis		
		N (%)	5-year MFSR (%)	P value
Gender	Male	6 (50%)	83.3	0.888
	Female	6 (50%)	60	
Age	≥ 50 years	5 (41.7%)	75	0.814
	< 50 years	7 (58.3%)	71.4	
Campanacci grade	2	6 (50%)	67.7	0.302
	3	6 (50%)	80	
Benign local recurrence	No	7 (58.3%)	85.7	0.035*
	Yes	5 (41.7%)	50	
Latent period	≥ 10 years	5 (58.3%)	100	0.22
	< 10 years	7 (41.7%)	57.1	
Main length	≥ 8 cm	7 (58.3%)	57.1	0.663
	< 8 cm	5 (41.7%)	60	
Volume	≥ 250 cm ³	5 (58.3%)	60	0.590
	< 250 cm ³	7 (41.7%)	57.1	
Chemotherapy	No	2 (16.7%)	100	0.109
	Yes	10 (83.3%)	66.7	
MGCT, malignancy in giant cell tumor; MFSR, distant metastasis-free survival rate				
*Statistically significant				

While it is generally known that GCTB constitutes 5–7% of all primary bone tumors and 20% of benign skeletal tumors^{13,14}, the incidence differs by regional groups. Overall, it seemed higher in Asian countries than in the Western population. GCTB represents 20% of all primary bone tumors and the incidence was estimated at around 14% in China^{15,16}. Interestingly, a Japanese cohort showed a low incidence of about 2–7%^{17,18}. Although Sweden is a European country, the GCTB incidence was reported to be about 11%¹⁹. The incidence was reportedly greater than 30% in South India²⁰, whereas it was around 6% in West India²¹.

Although radiotherapy is known to induce malignant tumors^{22,23} and most secondary MGCT cases developed after radiation treatment in previous studies¹⁰, none of the cases in this study were associated with radiation treatment. Currently, limited radiotherapy data are available for benign GCTB¹¹ because the treatment is indicated for locations where curative surgery is unfeasible, such as the spine or sacrum, or for aggressive or recurrent tumors²³. However, several studies^{22–27} demonstrated clinical results. According to the Western literature^{23–25}, radiotherapy was often performed for GCTB²⁸ and resulted in favorable local control rates, whereas the risk of post-radiation malignancies was a concern^{22–25}. In a retrospective review, 26 lesions, 9% of the total cases, with a high risk of local recurrence treated at an institution from 1972 to 1996 reported a 77% local control rate (LCR) and the development of one post-radiation sarcoma 22 years after radiotherapy²³. Another study investigating 122 consecutive patients with unresectable GCTB between 1985 and 2007 showed an 85% LCR and the occurrence of two malignant transformations during a median follow-up of 58 months²⁴. In another study involving 34 patients from 1973 to 2008, an LCR of 81% was reported 15 years after radiation treatment and one secondary malignancy developed 52 months after radiotherapy²⁵.

Previous studies with a large case series revealed that most secondary MGCTs were not associated with radiotherapy in an Asian population²⁹ even though most of the cases were post-radiation sarcoma in a Western population¹⁰. Radiotherapy appears to be rarely used for benign GCTB in Asian countries. We searched the MEDLINE, Embase, and Cochrane databases in May 2020 using the terms “giant cell tumor” AND (“radiation” OR “radiotherapy”) and found only two relevant studies published in Asian countries. Radiation treatment was used for five of 35 patients with extremity disease in one study²⁶ and for 18 of 22 cases with GCTB in the axial skeleton in another²⁷. In contrast, two relatively large case series from China reported that radiation treatment was not applied for 621 patients with GCTB in extremities¹⁵ and 208 other cases¹⁶.

Pulmonary implants were observed in 2% of the patients with GCTB at a mean duration of three to four years after the initial diagnosis³⁰. In general, such lung metastasis developed in benign GCTB of unusual sites and rarely occurred at the initial presentation³¹. As local recurrence is a known risk factor for pulmonary implants¹, the biologic activity of GCTB may be related to lung metastasis. However, no pulmonary implants were observed although some local recurrences were diagnosed in the current study. Therefore, whether pulmonary implant is a risk factor for malignant transformation is unclear.

Although the numbers of GCTB and secondary MGCT patients treated in our institution during the study period were 143 and 12, respectively, the incidence of malignant transformation of GCTB cannot be simply estimated at 8.4% because 11 out of all 12 MGCT patients were referred from other primary or general hospitals. As only one patient was diagnosed with secondary MGCT after GCTB treatment at our institution, we believe that an incidence of < 0.7% could be more reliable. Previous studies reported that the incidence of non-post-radiation secondary MGCT was below 0.7%^{4,12,13,29,32}.

In our study, MGCT developed at a median interval of seven years and four months after the first treatment for benign GCTB. Several previous studies reported latent periods of 1.8 to 36 years for the malignant transformation of a benign lesion after surgery alone^{4,29,33,34} and 4 to 42 years after radiation treatment^{4,33,35}, which suggests no significant difference in the latency interval depending upon radiotherapy. Nevertheless, a recent Western study⁴ demonstrated that the mean latent period was nine years in patients who underwent radiation therapy and 18 years in those who did not, and proposed that irradiation would have an impact on sarcomatous change and shorten its latent period. However, an Asian study reported a short mean latent interval of 42 months in three patients out of 110 with GCTB. Among them, one developed MGCT nine months after surgery without previous exposure to irradiation, and one case developed seven months postoperatively in the current study (Fig. 2)²⁹. To exclude the possibility of malignancy involving the original lesion, pathologic slides were repetitively reviewed by two experienced pathologists in the current study. As the lesions were diagnosed with entire specimens obtained by extended curettage, the histologic confirmations were unlikely to be inaccurate. Several recent studies demonstrated that H3.3 p.Gly34 mutations might contribute to distinguishing GCTB-related tumors from giant cell-rich sarcomas^{10,36–38}. Nevertheless, further studies are required to assess the potential use of mutational analysis for the diagnosis of GCTB or MGCT^{10,36,39}.

Although the resection margins were regarded as sufficient in all 12 MGCT patients in the current study, five patients developed local relapses. Four of them underwent limb-salvage operations. A previous study⁴⁰ demonstrated no local recurrence after surgical treatment in two non-post-radiation secondary MGCT cases. Another study reported one local relapse among six patients⁴. The local recurrence rate seems relatively high in our study. However, it would be difficult to directly compare the rates from different studies because the number of non-post-radiation secondary MGCT cases in the studies was small, the surgical methods might differ, and the individual patients showed different survival periods^{4,40}.

Due to the rarity of the disease, and the unclear definition and sub-classification of MGCT, the prognosis has yet to be established. Most studies reported a dismal prognosis regardless of primary or secondary MGCT^{5,9}. The prognosis for secondary MGCT was unfavorable compared with primary MGCT in previous studies from the West^{4,33,41}. Exceptionally, a study⁹ reported a 5-year survival rate of 50% in both the primary and secondary MGCT groups. Another study demonstrated that the 5-year survival rate of patients with primary malignancy was 87% and implied that MGCT behaved like a low- to intermediate-grade sarcoma¹², which was contrary to other studies. However, the distinction between primary and secondary MGCT was practically vague¹² although the study was regarded to be a relatively well-designed study compared to previous ones¹⁰.

The poor prognosis of secondary MGCT following radiotherapy has been thought to be attributed to the unfavorable tumor location where radiation treatment is a unique option⁴. Lymphatic destruction, vascular deficiency, or fibrosis after radiotherapy could also cover malignant cells from the immune system⁴²,

which may result in more aggressive and poorly differentiated secondary lesions⁴³. As no patient in the current study received radiotherapy, their oncologic outcome may have been relatively favorable. Nonetheless, a 5-year survival rate of 61.9% is unlikely to be explained by the influence of radiation alone. Given the differences in the incidence of GCTB according to regions, latency depending upon ethnicity, and prognosis reported in previous studies, ethnic factors may play an important role in the development of MGCT and its prognosis.

An analysis of the Surveillance, Epidemiology, and End Results (SEER) database of patients with MGCT reported that the age at diagnosis, tumor size and extension, and radiation treatment were prognostic factors for overall survival⁸. The age at diagnosis and tumor size were not significant prognostic factors and tumor extension was not evaluated in the current study. Local recurrence of benign GCTB was a significant prognostic factor for MFSR. In addition, the difference in the OSR depending upon the benign recurrence of GCTB was almost significant.

There is currently no comprehensive agreement on MGCT management⁸. Curative surgery is generally considered when it is feasible⁴. The efficacy of chemotherapy in MGCT is unclear⁴, while several studies^{33,41,44} reported that the use of chemotherapy offered some benefit. A previous report⁹ demonstrated that the difference in 5-year survival rates was statistically insignificant between the groups that were treated by surgery alone and the combination of surgery and chemotherapy. Another study showed that adjuvant chemotherapy as a salvage procedure following surgery with an inadequate margin did not result in any obvious advantage³³. In this study, chemotherapy was also not a statistically significant prognostic factor. Another recent study reported that resected tumors in three patients out of four who were administered preoperative chemotherapy based on an osteosarcoma protocol showed excellent necrosis rates⁹. Radiation treatment was frequently employed to treat MGCT in the past^{33,45}. However, the preference has declined lately⁸. In contrast to findings from the Western countries, radiotherapy does not appear to be readily used for managing post-radiation sarcomas in Asian populations²².

There were several limitations in this study. Inevitably, this retrospective analysis could not exclude inclusion bias. Its statistical power, especially for prognostic factor analysis, was limited by the small number of cases as the incidence of secondary MGCT was extremely low, with approximately 1 to 5% of the patients with GCTB undergoing sarcomatous transformation to secondary MGCT in four large case series¹⁰.

In our series, the occurrence of secondary MGCT did not follow radiotherapy, contrary to the Western literature. The prognosis was better than the findings reported in previous studies. The local recurrence of benign GCTB before malignant transformation could reflect the prognosis of MGCT. Further studies with a large number of cases are required, especially to elucidate the ethnic differences in the development and prognosis of MGCT.

Methods

This study was a retrospective medical record review of patients with histologically confirmed secondary MGCT who were surgically treated at our tertiary center from 1995 to 2018. The enrollment criterion was histologically proven high-grade spindle cell sarcoma, which developed at the previous treatment site in patients with benign GCTB, reflecting the definitions in the two latest editions of the WHO classification of tumors^{4,9,10,32-34,46-48}.

This study (VC20RIS10093) was approved by the Catholic University of Korea St. Vincent's Hospital Institutional Review Board, which dispensed with the need of informed consent as this study was a retrospective and minimal risk one, and any personal identifiable information was not collected. All methods and research were performed in accordance with the relevant guidelines and regulations of the ethical commission.

Clinical and radiological information was obtained. Data regarding gender, age, location, the Campanacci grade of primary GCTB, initial treatment of the primary lesion, local recurrence or pulmonary implants of GCTB, latency to malignant transformation, lesion size of the MGCT at the initial presentation, the American Joint Cancer Committee (AJCC)^{49,50} and Enneking stage⁵⁰ of MGCT, MGCT treatment, local recurrence or distant metastasis of the malignancy, the follow-up period, and oncologic outcomes were reviewed. Lesion volume was calculated as $\pi/6 \times (\text{length axis}) \times (\text{width axis}) \times (\text{height axis})$. In addition, the number of GCTB patients who were treated in our hospital during the same study period was investigated.

In patients with a latent interval of fewer than three years, the existing histopathologic slides and new ones made using paraffin blocks were reviewed again by two experienced pathologists because secondary malignancies usually occur at least three years after the initial GCTB⁵¹. The latent period was defined as the period from the date of the first surgery for GCTB to the diagnosis of malignant transformation. In MGCT, local recurrence-free survival, distant metastasis-free survival, and overall survival were evaluated based on the intervals from the time of initial surgery for the malignant lesion to the time of the first local recurrence, the first distant metastasis, and death or final follow-up, respectively. The follow-up period was defined as the interval from the date of diagnosis of malignant transformation to the last follow-up.

The 5-year survival rates for MGCT were analyzed using the Kaplan-Meier method, and the log-rank test was used to compare the survival curves for univariate analysis. The impact of potential prognostic factors was assessed using the log-rank test by univariate analysis. A p-value of < 0.05 was considered significant. All statistical analyses were performed using SPSS 21.0 for Windows (SPSS Corporation, Chicago, IL, USA).

Declarations

Author contributions

MWJ and YGC conceptualized and designed the work. MWJ and YSL collected clinical data. MWJ, HSP and CY developed the methodology and performed collection and analysis on radiologic and pathologic data. MWJ, YSL and HSP interpreted the data and drafted the work. MWJ reviewed and supervised the work. All the authors approved the manuscript.

Competing interests

Authors declare that they have no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this published article.

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Figures

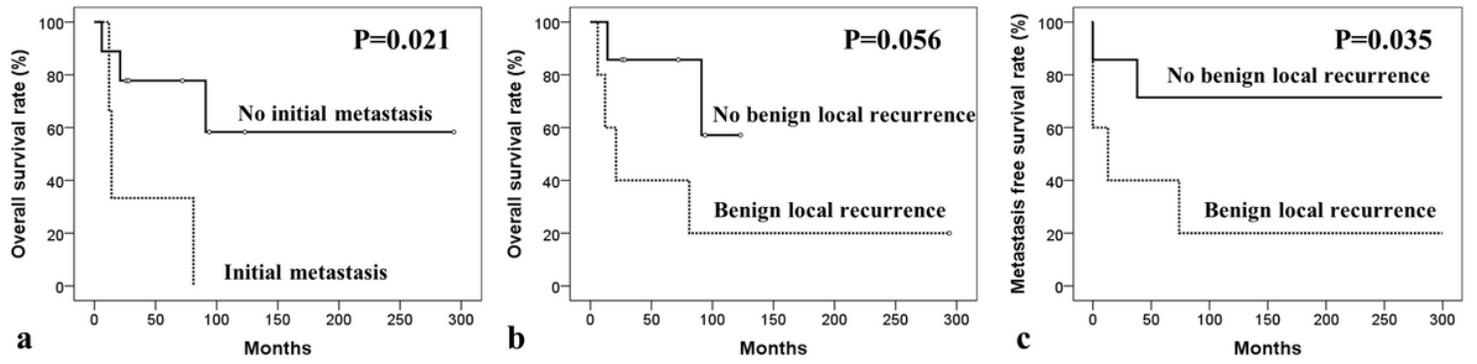


Figure 1

Kaplan-Meier survival curves of univariate analyses for secondary malignancy in giant cell tumor. Kaplan-Meier curves for overall survivals according to (a) initial metastasis and (b) benign recurrence of giant cell tumor of bone, and for (c) metastasis-free survival depending on benign local recurrence.

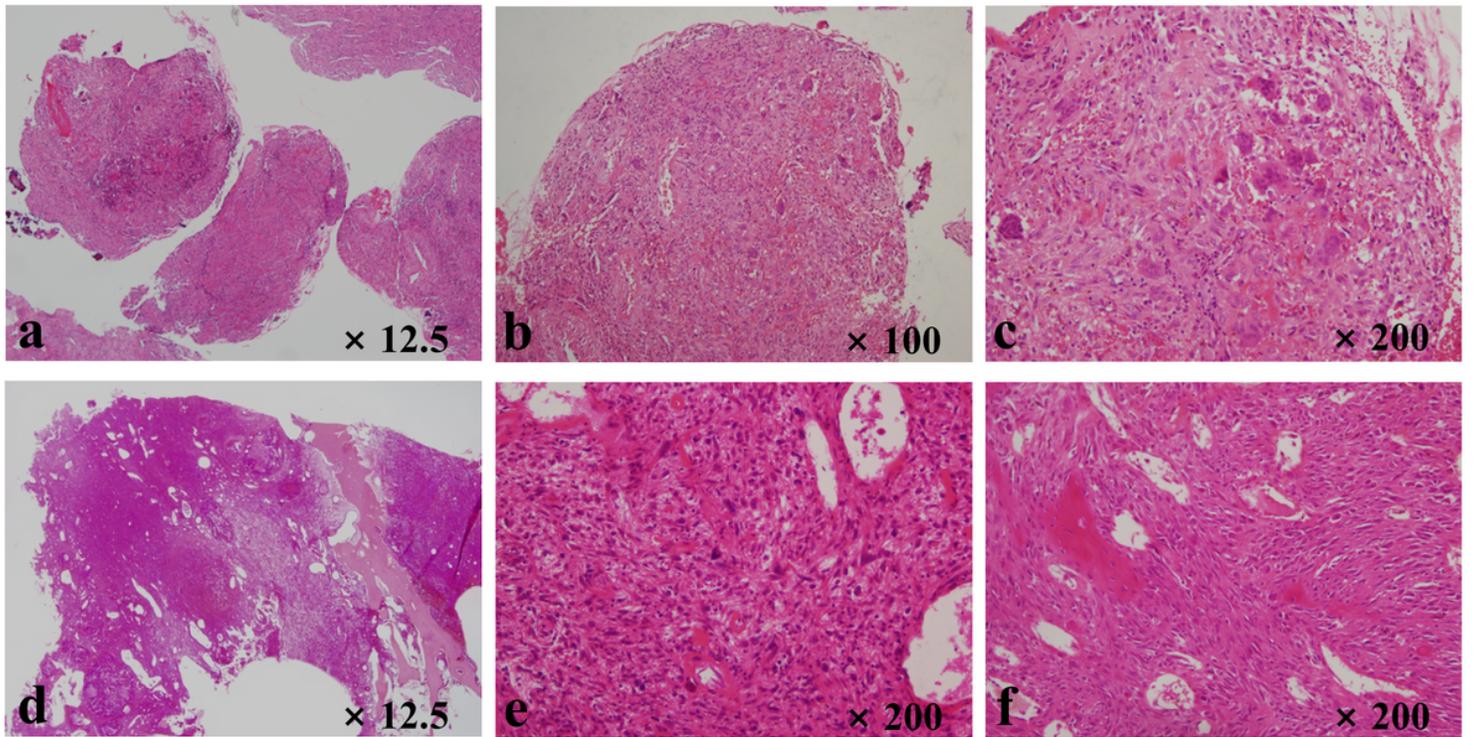


Figure 2

Histopathologic evaluation of the sixth case listed in Table 1. The slides of benign giant cell tumor of bone show (a) fibrous tissues with giant cells, (b) giant cells and histiocytes, and (c) spindle-cell lesion with giant cells and histiocytes. Slides related to secondary malignancy in giant cell tumor demonstrate (d) lesion filling most of the intramedullary space in the distal femur, (e) malignant spindle cells with a few giant cells, and (f) malignant osteoids.