Int J Clin Oncol
DOI 10.1007/s10147-016-0949-1

ORIGINAL ARTICLE

# Atypical and malignant granular cell tumors in Japan: a Japanese Musculoskeletal Oncology Group (JMOG) study

**Jungo Imanishi[1] · Yasuo Yazawa[1] · Tsuyoshi Saito[2] · Michio Shimizu[3] · Hiroyuki Kawashima[4] · Keisuke Ae[5] · Akihiko Matsumine[6] · Tomoaki Torigoe[7] · Hideshi Sugiura[8,9] · Susumu Joyama[10,11]**

Received: 20 June 2015 / Accepted: 4 January 2016


**Abstract**

*Background* Malignant granular cell tumors (MGCTs) are extremely rare neoplasms with only a limited number of studies published to date. The aim of this study is to elucidate the clinicopathological characteristics and prognostic factors of MGCTs.

*Methods* This is a multi-institutional retrospective study of MGCTs with a central pathological review. A total of 18 cases were retrieved. Specimens were blindly reviewed by two pathologists based on the diagnostic criteria by Fanburg-Smith et al. Kaplan–Meier survival probabilities were calculated, and risk factors for poor prognosis were evaluated.

*Results* Three and fifteen cases were diagnosed as atypical GCTs (AGCTs) and mGCTs according to the Fanburg-Smith et al. classification, respectively. Four (one atypical and three malignant) cases had metastasis at the first presentation, including lymph node metastasis. Three out of ten cases treated with wide resection developed local recurrence. Although prolonged static disease periods of $\geq$1 year were observed in four cases receiving chemotherapy, all cases with local recurrence or metastasis, including two atypical cases, eventually died of disease. The 5- and 10-year overall survival rates for localized MGCTs were 69.2 and 34.6 %, respectively. The presence of necrosis was revealed as a risk factor associated with adverse clinical outcomes.

*Conclusions* MGCTs have high rates of recurrence and metastasis including lymph node metastasis. As histologically atypical cases also have metastatic potential, close

✉ Jungo Imanishi
jungo@saitama-med.ac.jp

1 Department of Orthopaedic Oncology and Surgery, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan

2 Department of Human Pathology, Juntendo University School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan

3 Diagnostic Pathology Center, Hakujikai Memorial Hospital, 5-11-1 Shikahama, Adachi-ku, Tokyo 123-0864, Japan

4 Department of Orthopaedic Surgery, Niigata University Medical and Dental Hospital, 754, Ichibancho, Asahimachidori, Chuo-ku, Niigata, Niigata 951-8510, Japan

5 Department of Orthopaedic Surgery, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

6 Department of Orthopedic Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan

7 Department of Orthopaedic Surgery, Juntendo University School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan

8 Department of Orthopaedic Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Nagoya 464-8681, Japan

9 Department of Physical Therapy, Nagoya University School of Health Sciences, 1-1-20 Daiko-minami, Higashi-ku, Nagoya, Aichi 461-8673, Japan

10 Department of Orthopaedic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka, Osaka 537-8511, Japan

11 Department of Orthopaedic Surgery, Kawachi General Hospital, 1-31 Yokomakura, Higashiosaka, Osaka 578-0954, Japan

Published online: 13 January 2016

attention should be paid to AGCTs. The combination of histological evaluation and tumor size may lead to more accurate diagnosis of this rare neoplasm.

**Keywords** Malignant granular cell tumor · Atypical granular cell tumor · Pathological review · Surgery · Chemotherapy · Radiotherapy

## Introduction

Malignant granular cell tumors (MGCTs) are extremely rare sarcomas with Schwannian differentiation [1]. Due to their rarity, this disease has not been well understood. In 1998, Fanburg-Smith et al. reviewed 73 granular cell tumors and proposed a new pathological classification dividing them into malignant, atypical, and benign groups based on six pathological findings. However, nine out of 21 atypical granular cell tumors (AGCTs) with follow-up information diagnosed by the above-mentioned criteria never metastasized or caused tumor-related death [2]. Since then, this classification has been widely used; however, it is still controversial with regard to the criteria that differentiate benign, atypical, and malignant GCTs from each other [3, 4]. Moreover, as atypical GCTs (AGCTs) and MGCTs available for clinical information are fairly limited, further investigation is necessary for better understanding of the biology of GCTs.

This is a multi-institutional retrospective study in Japan with central pathological confirmation. In this study, we reviewed AGCT and MGCT cases based on the classification by Fanburg-Smith et al., and summarized their clinical features. We then statistically analyzed the clinical outcomes according to the clinicopathological factors with a review of the literature.

## Patients and methods

### Patients and blind central pathological review

Twenty-three cases were recruited from 12 hospitals in Japan via the Japanese Musculoskeletal Oncology Group (JMOG). Of these 23 cases, three were excluded because specimens were unavailable or inappropriate for diagnosis. The specimens of the remaining 20 cases were blindly reviewed by two board-certified pathologists (MS and TS) according to the World Health Organization classification and the diagnostic criteria by Fanburg-Smith et al. which includes necrosis, spindling of the tumor cells, vesicular nuclei with large nucleoli, increased mitotic rate of >2 mitoses per 10 high-power fields, a high nuclear-to-cytoplasmic (N/C) ratio, and pleomorphism [1, 2]. At this stage, one case was confirmed as benign, and the diagnosis of mGCT for another case was not reliable and these 2 cases were also excluded from the study. Eventually, eighteen cases from ten hospitals were included in the study. Some of these 18 cases have been published previously [5–9].

### Clinicopathological characteristics and clinical outcomes

First, the clinical history of the 18 cases was collected. Clinical information included the age and sex of the patient; primary location and maximum diameter of the tumor; tumor grade using the Fédération Nationale des Centers de Lutte le Cancer (FNCLCC) grading system [10]; initial stage using the American Joint Committee on Cancer (AJCC) staging version 7 [11]; details of treatment including surgery, radiotherapy and chemotherapy; time of local recurrence and metastasis; the latest follow-up information; and the final oncological status. For staging and follow-up surveillance, local magnetic resonance imaging (MRI) and chest computed tomography (CT) as well as physical examination for the primary lesion and regional lymph nodes was performed in all cases. In addition, contrast CT was used to evaluate initial lymph node metastasis for seven cases (cases 4–8, 13, and 14), and local MRI was available for three cases (cases 2, 12, and 15). Surgical margin status was reported according to the Enneking system [12]. Then, the presence of infiltrative growth and the Ki-67 labeling index (LI) were evaluated, if possible. The Ki-67 LI was calculated on digital data scanned from glass slides using ImageScope (Aperio Technologies, Inc., Vista, CA, USA). Lastly, clinical outcomes were calculated in the form of overall survival (OS), local recurrence-free survival (LRFS), and disease-free survival (DFS). OS was defined as length of time from surgery to the latest follow-up. LRFS was defined for AGCTs and MGCTs with surgery as length of time from surgery to local recurrence. DFS was defined for AGCTs and MGCTs that were localized at the first presentation as length of time from surgery to local recurrence or metastasis.

### Analysis of prognostic factors

The variables examined were age (≤48 vs >48 years), sex, Fanburg-Smith et al. classification (atypical vs malignant), FNCLCC grade (G1 vs G2/3), tumor size (≤6 vs >6 cm), surgical margin status (wide resection vs marginal or intralesional resection, only for LRFS) and each of the six histological criteria by Fanburg-Smith et al. Cut-off values for age and tumor size were determined based on median values among the 14 localized cases. The prognostic impact of these clinicopathological factors in the cohort of 14 cases was analyzed by univariate analyses of OS and LRFS.

### Statistical analysis

All statistical analyses were conducted using JMP® version 10 (SAS Institute, Cary, NC, USA). Survival curves (OS, LRFS, and DFS) were calculated using the Kaplan–Meier method. For univariate analysis of survival, the log-rank test was used. A $p$ value of $\leq 0.05$ was regarded as significant.

## Results

### Pathological review

According to the criteria by Fanburg-Smith et al., three and 15 cases were diagnosed with AGCTs and mGCTs, respectively. Table 1 summarizes the histological findings for all 18 cases. Pleomorphism, high N/C ratio and vesicular nuclei were frequently seen, whereas increased mitotic rate, spindling and necrosis were relatively rare (Fig. 1a). The Ki-67 LI was available for seven cases (two atypical and five malignant cases), and the mean value was 8.1 % (5.0 % in atypical cases and 9.4 % in malignant cases, respectively). Pathological evaluation of the peri-tumor area was possible in two AGCTs and eight mGCTs. Of these ten cases, infiltrative growth pattern was positive in eight (80 %) cases (Fig. 1b).

### Clinical characteristics

Clinical information of the 18 cases is summarized in Table 2. The population was female-predominant in the ratio of 2:1 and age distribution was 29–79 (mean 52.1) years. The most frequent primary site was lower extremity (nine cases, 50 %) followed by upper extremity (four cases, 22 %). The tumor size ranged from 2–17 (mean 8.2) cm in diameter. The FNCLCC grade was low (G1) for seven cases, intermediate (G2) for six cases and high (G3) for only one case. At the time of the diagnosis, four of 18 cases presented with metastases. These initial metastases were lung and lymph node, lung and bone, lung only, and lymph node only (one case each). Surgical margin status was wide (ten cases), marginal (five cases) and intralesional (two cases). Of the five marginal margins, two were microscopically positive. Local recurrence was observed in seven cases (wide margin 3/10, marginal margin 2/5, intralesional margin 2/2), all resulting in tumor-related death (Table 2).

### Radiotherapy and chemotherapy

Radiotherapy was performed in six cases—as post-operative adjuvant therapy for marginal resection (two cases), as palliative therapy for symptomatic local recurrence (three cases), or unresected primary tumor (one case with biopsy

**Table 1** Pathological findings of 18 cases according to the diagnostic criteria by Fanburg-Smith et al.

| Case | Specimen[a] | Necrosis | Spindling | Vesicular nuclei | Mitosis | High N/C ratio | Pleomorphysm | MIB-1 index | Infiltration |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Resection | + | + | + | − | + | + | 10 % | + |
| 2 | CNB | − | − | − | − | + | + | 9 % | ND |
| 3 | Resection | − | − | + | − | + | + | ND | + |
| 4 | Resection | + | − | + | + | + | + | 23 % | ND |
| 5 | Resection | − | − | + | + | + | + | 3 % | ND |
| 6 | Resection | − | − | + | − | − | + | 1 % | + |
| 7 | Resection | − | − | + | − | + | + | 4 % | ND |
| 8 | Resection | − | − | + | − | + | + | 7 % | −[b] |
| 9 | Resection | + | − | + | − | + | + | ND | + |
| 10 | Resection | − | − | + | − | − | + | ND | − |
| 11 | Resection | − | + | + | − | + | − | ND | + |
| 12 | Resection | + | − | + | − | + | + | ND | + |
| 13 | Resection | + | − | + | − | + | + | ND | + |
| 14 | Resection | − | − | + | + | + | + | ND | + |
| 15 | CNB | − | − | + | − | + | + | ND | ND |
| 16 | Resection | − | + | + | − | − | + | ND | ND |
| 17 | Resection | − | + | + | + | + | + | ND | ND |
| 18 | Resection | + | + | + | − | + | + | ND | ND |

*CNB* core needle biopsy, *N/C* nuclear-cytoplasmic, *ND* no data available for evaluation

[a] All specimens for diagnosis were obtained prior to adjuvant therapy or surgery

[b] Intramuscular invasion was noted in the original pathological report; however, no obvious infiltration was observed in the slides sent for central pathological review

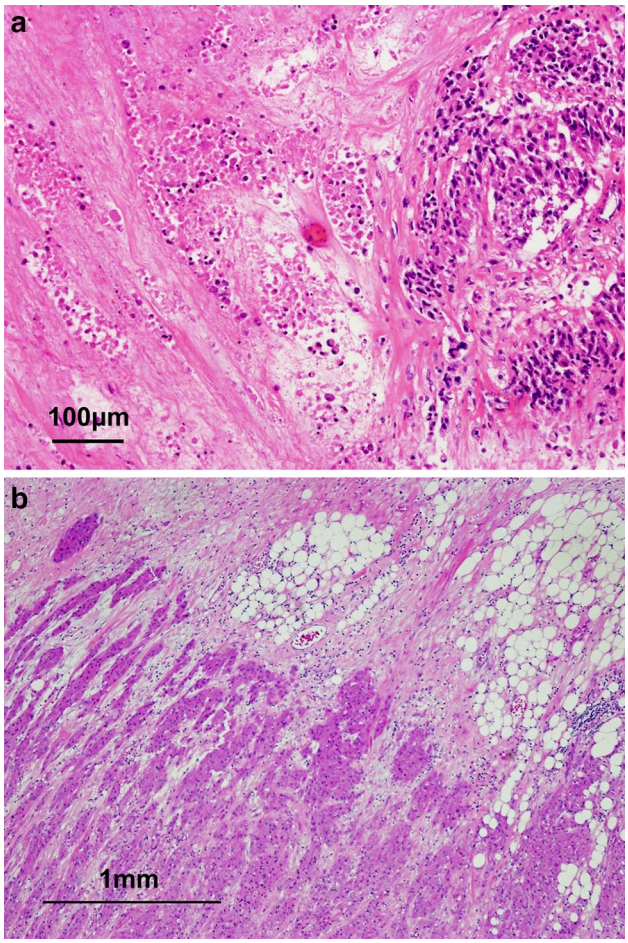


**Fig. 1** Hematoxylin and eosin staining of specimens from case 1 (**a**) and case 6 (**b**) showing necrosis and infiltrative growth of malignant and atypical granular cell tumors, respectively

only). One of the two cases with post-operative adjuvant radiotherapy (case 6) remained local recurrence-free for 79 months until death due to lung metastases. Chemotherapy, including molecular targeted drugs, was conducted in seven advanced cases. Four cases had prolonged stable disease (SD) with duration of at least 1 year, but the final oncological results of all the cases were dead of disease (DOD) (Table 3).

### Survival estimation (OS, LRFS, and DFS)

Five- and 10-year OS rates for all 18 cases were 52.3 and 26.2 %, and for 14 initially localized cases were 69.2 and 34.6 %, respectively (Fig. 2). The 5-year LRFS rate was 68.6 % for patients treated with wide resection (ten cases) and 42.9 % for patients treated with marginal or intralesional resection (seven cases) (Fig. 3). The 5-year DFS rate for 14 initially localized cases was 54.6 % (Fig. 4).

### Prognostic factors

Although the presence of necrosis showed a relatively high tendency for poor OS, there was no prognostic factor with statistical significance (Table 4). Only the presence of necrosis was revealed as significantly associated with lower LRFS ($p = 0.03$) (Table 5).

## Discussion

MGCTs are extremely rare malignant Schwannian tumors, with only a limited number of case reports and studies in the past literature. Biopsy specimens should be carefully examined for precise diagnosis because other types of soft-tissue tumors (benign or malignant) can display granular cell features and mimic MGCTs [2, 13, 14]. Indeed, two out of 20 cases in our study did not fulfill the diagnostic criteria for MGCTs or AGCTs at central pathological review and were excluded from our study.

The clinical presentation of MGCTs still remains uncertain [1]. The study by Fanburg-Smith et al. in 1998, which reported high rates of local recurrence (32 %) and distant metastases (50 %), and short survival for MGCT cases, has been the only study of a large case series to provide constructive information on MGCTs [2], and more investigation is necessary.

The LRFS and OS rates for initially localized MGCT cases in our study were similar to those described in the above study, strongly indicating the aggressiveness and unfavorable prognosis of MGCTs [2]. In particular, the 5-year LRFS rate of 68.6 % after wide resection in our study is unsatisfactory. This high rate of local relapse may be attributed to the high percentage of infiltrative growth pattern seen in MGCTs. Rose et al. reported a high rate of intralesional excision (five out of 11 benign or AGCTs) and macroscopic infiltrative growth margin in one specimen [15]. In our study, microscopic infiltration was observed in eight out of ten AGCT or MGCT cases in which evaluation was possible. Recently, Tsukushi et al. reported that histological invasion is a risk factor of poorer prognosis including higher local recurrence [16]. Furthermore, the lymph node metastasis phenomenon which is rather uncommon among the majority of soft-tissue sarcomas, was observed in four (14 %) out of 28 cases in the Fanburg-Smith et al. study and four (22 %) out of 18 cases in our study. Close attention should be paid to the high potential of MGCTs for local recurrence and lymph node metastasis. Wider resection of tumor and routine sentinel lymph node biopsy possibly followed by lymph node dissection might improve the prognosis of this disease.

The pathological discrimination of MGCTs from benign GCTs is not yet well established. The histological

**Table 2** Summary of three atypical and 15 malignant granular cell tumor cases

| Case | Age/sex | M/A[a] | Location | Size (cm) | FNCLCC grade | AJCC v7 | Surgery[b] | RT | CT | LR | Met[c, d] | Final status[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 57/F | M | Elbow | 7 | G2 | IV | Marginal | − | + | 9 ms | **Lung, LN** | DOD (38) |
| 2 | 66/F | A | Buttock | 17 | G1 | IV | − | + | − | N/A | **Lung, bone** | DOD (10) |
| 3 [5] | 61/F | M | Thigh | 7 | G1 | I | WR | − | − | − | − | CDF (204) |
| 4 [6] | 38/M | M | Neck | 8 | G3 | III | Marginal* | + | + | 3 ms | Lung, LN (4) | DOD (32) |
| 5 | 55/M | M | Thigh | 10 | G2 | IIB | WR | − | − | − | − | CDF (43) |
| 6 [7] | 63/M | A | Thigh | 10 | G1 | I | Intra* | + | + | − | Lung, ST (48) | DOD (79) |
| 7 [7] | 51/F | M | C5 root | 5 | G1 | I | Intra* | + | + | 12 ms | Brain (45) | DOD (52) |
| 8 | 60/F | M | Shoulder | 6 | G1 | I | Marginal | − | − | − | − | CDF (16) |
| 9 | 61/F | M | Thigh | 14 | G2 | IIB | WR | + | + | 38 ms | Lung, LN, bone (40) | DOD (52) |
| 10 [8] | 36/F | A | Calf | 6 | G1 | I | WR | − | − | − | − | CDF (35) |
| 11 [8] | 34/F | M | Thigh | 4 | G1 | I | WR | − | − | − | − | CDF (122) |
| 12 | 29/M | M | Face | 2 | G2 | IIA | Add. WR | − | − | − | − | CDF (55) |
| 13 | 48/M | M | Abd. Wall | 8 | G2 | IIB | WR | + | + | 27 ms | Lung, bone (26) | DOD (87) |
| 14 | 64/F | M | Forearm | 5 | G2 | IIA | WR | − | − | − | − | CDF (61) |
| 15 | 57/M | M | Thigh | 16 | G1 | III | Marginal* | − | + | 1 m | **LN**, lung | DOD (17) |
| 16 | 45/F | M | (Unknown) | 5 | G1 | I | Marginal | − | − | − | − | CDF (34) |
| 17 [9] | 33/F | M | Bilateral elbows | 3, 4 | G2 | IIA | Add. WR | − | − | − | − | CDF (39) |
| 18 | 79/F | M | Thigh | 14 | G2 | IV | WR | − | − | 18 ms | **Lung** | DOD (18) |

*F* female, *M* male, *M/A* malignant/atypical, *Abd.* abdominal, *WR* wide resection, *intra* intralesional, *Add.* additional, *RT* radiotherapy, *CT* chemotherapy, *FNCLCC* Fédération Nationale des Centers de Lutte le Cancer, *AJCC v7* American Joint Committee on Cancer staging system version 7, *N/A* not applicable, *LR* local recurrence, *met* metastasis, *LN* lymph node, *f/u* follow-up, *DOD* dead of disease, *CDF* continuously disease-free

[a] Whether atypical or malignant was decided based on the diagnostic criteria by Fanburg-Smith et al. [2]

[b] Surgical margin was determined according to the Enneking system [11]. Asterisk (*) means microscopically positive margin

[c] Bold metastases were identified at the first presentation

[d] Figures in parentheses show the time of the first metastases from the first presentation (months)

**Table 3** Summary of chemotherapy for seven advanced cases

| Case | Chemotherapy[a] | Target lesions | SD duration | Final status |
|---|---|---|---|---|
| 1 | Pazopanib | LR, lung met, LN met | (PD) | DOD |
| 4 | **IFO, CDDP+ADM** | LR, lung met | >12 months | DOD |
| 6 | GEM+TXT, **cyclophosphamide** | Lung met, ST met | 12 months | DOD |
| 7 | **GEM+TXT**, cyclophosphamide | LR | 12 months | DOD |
| 9 | IFO+ADM, **pazopanib** | Lung met, LN met | 13 months | DOD |
| 13 | IFO+ADM, GEM+TXT | LR | (PD) | DOD |
| 15 | IFO+ADM (neoadjuvant) | Primary tumor, lung met | (PD) | DOD |

*IFO* Ifosfamide, *ADM* adriamycin, *GEM* gemcitabine, *TXT* docetaxel, *LR* local recurrence, *LN* lymph node, *met* metastasis, *SD* stable disease, *PD* progressive disease, *DOD* died of disease

[a] Bold regimens maintained SD for ≥12 months

classification proposed by Fanburg-Smith et al. was based on the clinical outcome of 73 of their cases and 35 past cases. They decided a fulfillment of three out of six pathological criteria as a cut-off for malignancy because cases with two or less criteria had never metastasized or resulted in death [2]. However, they also stated the possibility that this cut-off may not be low enough. Later, Nasser et al. suggested a similar classification by dividing into benign GCTs and GCTs with uncertain malignant potential by examining only necrosis and mitosis [3]. By contrast, Kapur et al. considered only metastatic cases as malignant in their study [4]. In our study, we blindly examined 18 specimens without clinical information, and classified 15 as malignant and three as atypical by the Fanburg-Smith et al. criteria. Of the three AGCTs, one case (case 10) remained continuously disease free, while the two remaining cases

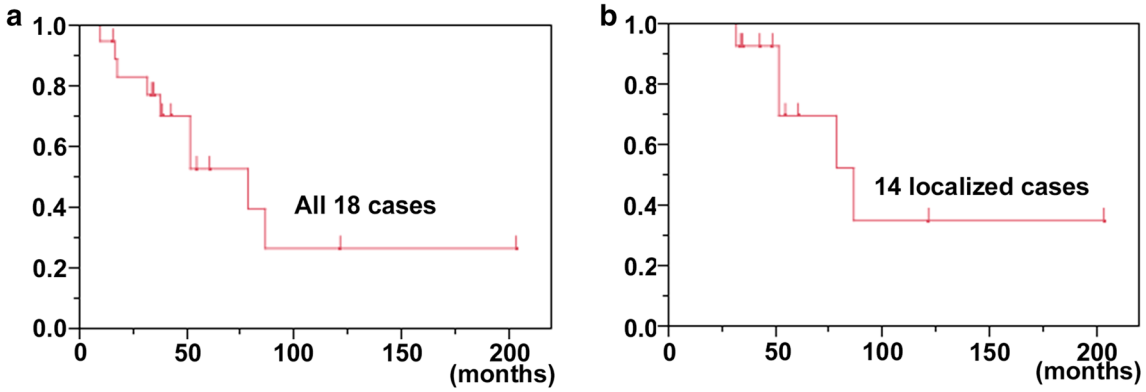


**Fig. 2** Overall survival for all 18 cases (**a**) and 14 localized cases (**b**)

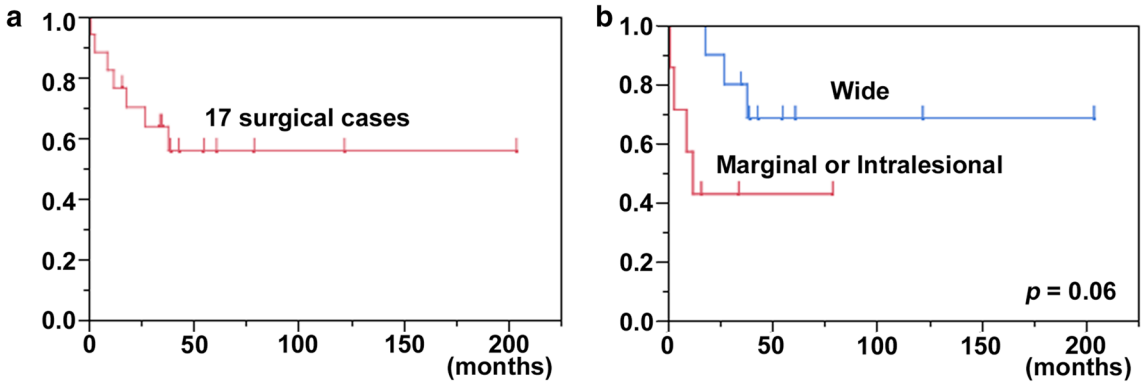


**Fig. 3** **a** Local recurrence-free survival (LRFS) for 17 surgical cases. **b** LRFS for wide resection cases and marginal or intralesional resection cases

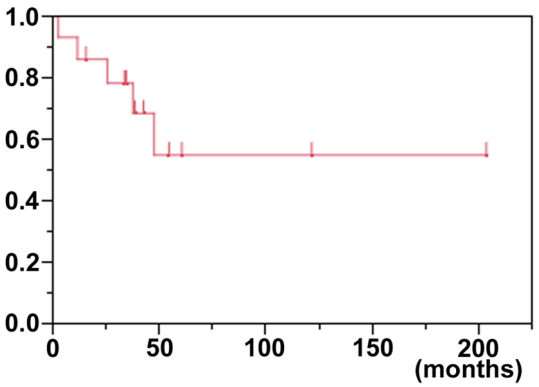


**Fig. 4** Disease-free survival for 14 initially localized cases

followed a malignant course. One atypical case (case 2, size 17 cm) already presented with metastases at the time of diagnosis and could be clinically labeled as malignant. Another atypical case (case 6, size 10 cm) developed soft-tissue and lung metastases 4 years after primary surgery. These two cases would be categorized as histologically benign by the classification of Nasser et al., which includes only necrosis and mitosis as criteria for malignancy [3]. These two cases imply that a GCT histologically classified as benign or atypical by the aforementioned worldwide classifications does have some metastatic potential. The fact that an AGCT according to the Fanburg-Smith et al. classification can cause tumor-related death is important because a malignant clinical course has never been reported for AGCTs. A common feature of the two AGCT cases resulting in tumor-related death was the large tumor size (17 and 10 cm), which may be predictive of aggressive behavior of AGCTs.

The role of Ki-67 staining in predicting adverse prognosis is also uncertain. Some studies have reported a higher Ki-67 LI for MGCTs than for benign or AGCTs [2–4]; however, none of them showed a correlation between Ki-67 LI and definitive clinical outcomes, such as OS and local recurrence. In our study, the Ki-67 LI was informative only in seven cases, with a range of 1–23 % (mean 8.1 %). We did not perform statistical analysis due to the small number of cases available for Ki-67 LI; however, one case with

**Table 4** Univariate and analysis for overall survival (OS) and clinicopathological factors

| Variables | No. of cases | 5-year OS (%) | *p* value |
|---|---|---|---|
| Age | | | |
| >48 years | 7 | 85.7 | 0.67 |
| ≤48 years | 7 | 60.0 | |
| Sex | | | |
| Male | 5 | 80.0 | 0.32 |
| Female | 9 | 60.0 | |
| Size | | | |
| >6 cm | 6 | 62.5 | 0.28 |
| ≤6 cm | 8 | 75.0 | |
| FNCLCC grade | | | |
| G2/3 | 7 | 64.3 | 0.40 |
| G1 | 7 | 75.0 | |
| Fanburg-Smith classification | | | |
| Malignant | 12 | 64.9 | 0.63 |
| Atypical | 2 | 100 | |
| Necrosis | | | |
| + | 4 | 50.0 | 0.18 |
| − | 10 | 80.0 | |
| Spindling | | | |
| + | 3 | 100 | 0.23 |
| − | 11 | 64.3 | |
| Mitosis | | | |
| + | 4 | 75.0 | 0.48 |
| − | 10 | 71.4 | |
| High nuclear-to-cytoplasmic (N/C) ratio | | | |
| + | 11 | 64.3 | 0.72 |
| − | 3 | 100 | |
| Pleomorphysm | | | |
| + | 13 | 65.5 | 0.27 |
| − | 1 | 100 | |

*OS* overall survival, *FNCLCC* Fédération Nationale des Centers de Lutte le Cancer

**Table 5** Univariate analysis for local recurrence-free survival (LRFS) and clinicopathological factors

| Variables | No. of cases | 5-year LRFS (%) | *p* value |
|---|---|---|---|
| Age | | | |
| >48 years | 7 | 68.6 | 0.91 |
| ≤48 years | 7 | 71.4 | |
| Sex | | | |
| Male | 5 | 60.0 | 0.53 |
| Female | 9 | 71.1 | |
| Size | | | |
| >6 cm | 6 | 50.0 | 0.21 |
| ≤6 cm | 8 | 87.5 | |
| FNCLCC grade | | | |
| G2/3 | 7 | 57.1 | 0.38 |
| G1 | 7 | 85.7 | |
| Fanburg-Smith classification | | | |
| Malignant | 12 | 63.5 | 0.40 |
| Atypical | 2 | 100 | |
| Surgical margin | | | |
| Non-wide | 5 | 60.0 | 0.22 |
| Wide | 9 | 76.2 | |
| Necrosis | | | |
| + | 4 | 90.0 | 0.03* |
| − | 10 | 25.0 | |
| Spindling | | | |
| + | 3 | 100 | 0.27 |
| − | 11 | 59.7 | |
| Mitosis | | | |
| + | 4 | 75.0 | 0.86 |
| − | 10 | 63.0 | |
| High nuclear-to-cytoplasmic (N/C) ratio | | | |
| + | 11 | 61.4 | 0.30 |
| − | 3 | 100 | |
| Pleomorphysm | | | |
| + | 13 | 65.3 | 0.53 |
| − | 1 | 100 | |

Asterisk shows a statistically significant difference

*LRFS* local recurrence-free survival, *FNCLCC* Fédération Nationale des Centers de Lutte le Cancer

low Ki-67 expression of 1 % (case 6) eventually resulted in tumor-related death. For a better understanding of the role of Ki-67 staining, further investigation with a larger number of cases is needed.

Several prognostic factors for MGCTs have been identified. Fanburg-Smith et al. analyzed the correlation between clinicopathological factors and clinical outcomes, and found larger size of tumor, older patient age, presence of tumor necrosis, tumor cells with vesicular nuclei and large nucleoli, and increased mitotic activity to be statistically significantly associated with poorer survival [2]. In our study, we could only find the presence of necrosis among the six criteria suggested by Fanburg-Smith et al. was associated with poorer LRFS by univariate analysis, which was probably due to the relatively small number of cases examined. Considering the classification suggested by Nasser et al. [3], necrosis can be a strong indicator of unfavorable prognosis for MGCTs.

While it is apparent that wide resection, irrespective of regional lymph node dissection, is the conventional treatment for MGCTs, the therapeutic effects of radiotherapy and chemotherapy are debatable. In previous literature, radiotherapy and chemotherapy have been applied mainly for advanced cases [17–20]. In our study, all eight patients who received radiotherapy or chemotherapy, including tyrosine kinase inhibitors, eventually died of disease.

However, one of the patients (case 6) who received postoperative radiotherapy due to close margins remained local recurrence-free for 79 months after surgery until death by lung metastases, and four patients who underwent chemotherapy for advanced disease remained static for $\geq$1 year. All things considered, radiotherapy and chemotherapy may not be able to cure MGCTs once the tumor recurs or metastasizes, but they can restrain disease progress and provide prolonged survival to the patient.

Our study has some limitations. First, as it was a multiinstitutional retrospective study, it lacked data consistency and had some selection bias. Patient information was collected at individual hospitals and sent to the primary institution where the study was conducted. As such, some of the data may not be consistent. For example, the intraoperative evaluation of surgical margin status (wide, marginal, or intralesional) and the method of determining microscopic margin (positive or negative) may differ between centers. Furthermore, the number of AGCTs (3 cases, 13 %) in this study was smaller than we expected. The Fanburg-Smith et al. study included 46 MGCTs and 21 AGCTs. We assume that some AGCTs may have been mislabeled as benign because of pathological similarity between AGCTs and benign GCTs even though we recruited both MGCTs and AGCTs for this study. Second, due to the limited examination of specimens, we might have underestimated or overestimated the histological evaluation; if slides containing tumor necrosis were excluded before being sent to the central review, we may have underestimated the extent of necrosis. Lastly, because of the small study scale, we might have overlooked other prognostic factors. However, conducting a prospective study for such a rare tumor is extremely difficult. We have made our best effort to maximize the reliability of our study, and believe our study can help the future treatment and management of MGCTs and AGCTs.

In conclusion, we reviewed 18 atypical and malignant GCT cases. The clinicopathological features of MGCTs in this study were similar to previous reports, with high rates of local recurrence and metastasis, especially lymph node metastasis. Wider resection is recommended for better local control. The two atypical tumor-related deaths suggest that histologically atypical GCTs have certain potential for recurrence and metastasis, and require close attention and long-term follow-up. The combination of tumor size and histological findings may be a clue for more accurate diagnosis and proper management of this tumor.

**Acknowledgments** The authors thank Dr. Akira Kawai, National Cancer Center Hospital; Dr. Kenji Morii, Kyorin University Hospital; Dr. Yoshihiro Nishida and Dr. Eisuke Arai, Nagoya University Hospital; Dr. Akira Ogose, Niigata University Medical & Dental Hospital; Dr. Yosuke Yabuuchi, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Syunsuke Hamada, Aichi Cancer Center Hospital; Dr. Toshitake Yakushiji, Kumamoto University Hospital; Prof. Kyoji Okada, Akita University Hospital; Dr. Hiroaki Kanda, Cancer Institute Hospital of Japanese Foundation for Cancer Research for data collection in this study, and Dr. Takashi Fujino and two cytologists, Mr. Masaru Nakamura and Mr. Atsushi Seyama, Saitama Medical University International Medical Center for calculating Ki-67 labeling index and supporting the central pathological review. The authors also express their sincere appreciation to Dr. Takafumi Ueda, Director in chief of the Japanese Musculoskeletal Oncology Group (JMOG), for his advice and support.

**Compliance with ethical standards**

**Conflicts of interest** No authors has any conflict of interest.

## References

1. Fanburg-Smith JC (2013) Malignant granular cell tumour. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F (eds) WHO classification of tumours of soft tissue and bone, 4th edn. IARC Press, Lyon, p 190
2. Fanburg-Smith JC, Meis-Kindblom JM, Fante R et al (1998) Malignant granular cell tumor of soft tissue: diagnostic criteria and clinicopathologic correlation. Am J Surg Pathol 22:779–794
3. Nasser H, Ahmed Y, Szpunar SM et al (2011) Malignant granular cell tumor: a look into the diagnostic criteria. Pathol Res Pract 207:164–168
4. Kapur P, Rakheja D, Balani JP et al (2007) Phosphorylated histone H3, Ki-67, p21, fatty acid synthase, and cleaved caspase-3 expression in benign and atypical granular cell tumors. Arch Pathol Lab Med 131:57–64
5. Tsuchida T, Okada K, Itoi E et al (1997) Intramuscular malignant granular cell tumor. Skeletal Radiol 26:116–121
6. Saito T, Mitomi H, Torigoe T et al (2012) Malignant granular cell tumor with an unusually long clinical course: an autopsy case with review of literature. J Cancer Sci Ther 4:260–263
7. Imao K, Ogose A, Kawashima H et al (2009) Two cases treated with chemotherapy for malignant granular cell tumor. J East Jpn Orthop Traumatol 21:577–582
8. Arai E, Nishida Y, Tsukushi S et al (2010) Intramuscular granular cell tumor in the lower extremities. Clin Orthop Relat Res 468:1384–1389
9. Sekiya I, Kawaguchi N, Matsumoto S et al (1992) Six cases of granular cell tumor and two cases of malignant granular cell tumor. Clin orthop surg 27:235–240
10. Coindre JM, Terrier P, Bui NB et al (1996) Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 14:869–877
11. Edge S, Byrd D, Compton C et al (2009) American Joint Committee on Cancer Staging Manual. Springer, New York
12. Enneking WF, Spanier SS, Goodman MA (1980) A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res:106–120
13. Nakazato Y, Ishizeki J, Takahashi K et al (1982) Immunohistochemical localization of S-100 protein in granular cell myoblastoma. Cancer 49:1624–1628
14. Nathrath WB, Remberger K (1986) Immunohistochemical study of granular cell tumours. Demonstration of neurone specific enolase, S 100 protein, laminin and alpha-1-antichymotrypsin. Virchows Arch A Pathol Anat Histopathol 408:421–434
15. Rose B, Tamvakopoulos GS, Yeung E et al (2009) Granular cell tumours: a rare entity in the musculoskeletal system. Sarcoma 2009:765927

16. Tsukushi S, Nishida Y, Urakawa H et al (2014) Prognostic significance of histological invasion in high grade soft tissue sarcomas. Springerplus 3:544
17. Rosenthal SA, Livolsi VA, Turrisi AT 3rd (1990) Adjuvant radiotherapy for recurrent granular cell tumor. Cancer 65:897–900
18. Cruz-Mojarrieta J, Navarro S, Gomez-Cabrera E et al (2001) Malignant granular cell tumor of soft tissues: a study of two new cases. Int J Surg Pathol 9:255–259
19. Tawfiq N, Sabri S, Saiss K et al (2013) Granular cell tumor: report of a complicated vulvar localization of pulmonary metastases. Cancer Radiother 17:671–674
20. Khansur T, Balducci L, Tavassoli M (1987) Granular cell tumor. Clinical spectrum of the benign and malignant entity. Cancer 60:220–222