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RESEARCH ARTICLE

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Giant cell-rich osteosarcoma: A match pair analysis of 11 new cases and literature review of 56 patients

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Abstract

Background: Limited remains known on giant cell-rich osteosarcoma (GCRO) with current studies being case reports or smaller series. This investigation compared GCRO and conventional osteoblastic osteosarcoma (OOS) with regard to demographics and survival.

Methods: An institutional tumor registry was used to identify 11 patients (six males) treated for GCRO. Mean age was 43 years. Staging showed American Joint Committee on Cancer (AJCC) stages IIA in four and IIB in seven patients. Mean follow-up was 14 years. Study initiatives were: (1) Comparison of demographics between GCRO and 167 OOS from our institutional registry, (2) Differences in survival between GCRO and 33 OOS case controls (based on sex and AJCC stage), as well as 10 OOS using an age-based propensity match, and (3) Summary of all GCRO cases reported in the literature.

Results: (1) Sex ($p = 0.53$), grading ($p = 0.56$), AJCC stage ($p = 0.42$), and chemotherapeutic response rate ($p = 0.67$) did not differ between groups. Age was significantly increased in GCRO ($p = 0.001$). (2) Case–control and propensity-matched groups revealed no difference in disease-free survival, local recurrence, and distant disease-free survival at 2 years ($p > 0.05$). (3) Mean age of 56 patients (50% males) reported in the literature was 26 years. After merging with our 11 cases, the 2-year disease-free survival was 66%.

Conclusions: GCRO remains a rare disease with high short-term mortality. Although affecting older patients more than conventional osteosarcoma, GCRO should not be viewed as a predictor of survival compared to OOS.

KEYWORDS

atypical osteosarcoma, cancer survival, osteoclast-type giant cells, osteosarcoma demographics, survival predictors

1 | INTRODUCTION

Osteosarcoma is the most common malignant primary bone tumor with an estimated incidence of five patients in one million affected per year.[1,2] Osteoblastic, fibroblastic, and chondroblastic histopathology form the group of intramedullary-conventional osteosarcoma, and represent around 80% of all cases.[3,4] Knowledge of the histopathological subtype of osteosarcoma is important as it directly impacts the selection of an adequate treatment regimen with certain subtypes being more susceptible to chemotherapy than others.[5,6]

Despite the impact of histopathology on treatment strategy and possible implications on long-term prognosis, little remains known on

osteosarcomas of atypical histopathology.[7] Giant cell-rich osteosarcoma (GCRO) represents an estimated 1%–3% of all osteosarcoma cases.[8,9] It was first described by Bathurst et al. in 1986.[10] Although a number of case reports have been published over the last decades, no study has reported outcomes of more than 10 patients. Moreover, the limited case series of four to nine patients did not include any comparison groups, limiting knowledge of baseline demographics and survival among GCRO.[10–12] This limitation is even more critical as nationwide databases such as the Surveillance, Epidemiology, and End Results program do not differentiate for GCRO.[3]

For that reason, this study aimed to (1) Compare baseline demographics between GCRO and conventional osteoblastic osteosarcoma (OOS), (2) Analyze survival differences between GCRO and OOS, and (3) Summarize all cases of GCRO reported in the literature to date.

2 | PATIENTS AND METHODS

After obtaining ethical approval, a registry-based search was used to identify all patients treated for GCRO between 1990 and 2020 at three metropolitan, tertiary-care university-based cancer centers. A GCRO was defined as a primary bone tumor with malignant cells producing lace-like primitive bone matrix coexisting with non-neoplastic osteoclast-type giant cells scattered through the entirety of the tumor.[10–12] Using these criteria, 11 patients (six males) at a mean age of 43 years (range, 15–83 years), diagnosed with GCRO between 1993 and 2012, were included (Table 1). The mean follow-up was 14 years (range, 5 days to 29 years).

Three GCROs were located in the distal femur, proximal humerus, and proximal tibia, as well as one in the proximal femur and one in the vertebral body of T1. Preoperative staging, according to the American Joint Committee on Cancer 8th edition (AJCC)[13] demonstrated stages IIA in four and IIB in seven patients. Grading revealed G2 in two, G2 to G3 in two, and G3 in seven patients; all cases were considered high grade according to their histopathology. Clinically, nine patients presented with Enneking classification[14] stages IIA and IIB in two cases. The largest tumor dimension was 10 cm on average (range, 2–17 cm). Elevated alkaline phosphatase was noted in three patients (27%).

One 83-year-old female refused surgery and chemotherapy. One patient underwent an above-knee amputation. Reconstruction strategies among the remaining nine patients included allograft prosthetic composite in three cases, tumor megaprosthesis in three patients, osteoarticular allograft in two cases, and spinal instrumentation with en bloc resection and cage reconstruction in one case. Mean resection margin was 5 cm (range, 0.1–11 cm). Eight patients received preoperative chemotherapy for a mean of 3 months. Postoperative chemotherapy was conducted in six patients for a mean of 5 months. MAP chemotherapy protocol (methotrexate, adriamycin, cisplatin) was used in seven patients. Chemotherapeutic response rate was measured as percentage of necrotic area of the primary tumor.[15]

Study outcomes were defined as: (1) Differences in baseline demographics and treatment approaches between GCRO and OOS, (2) Differences in disease-free survival, local recurrence-free survival, and distant disease-free survival between GCRO and OOS, and (3) Comprehensive analysis of all GCRO cases and case series published to date. Our tumor registry was used to include 167 OOS patients undergoing treatment of osteosarcoma during the same period (1993–2012). Baseline demographics and outcome were compared between the 11 GCRO cases and (1) all 167 OOS cases, (2) through a one to three case–control analysis based on AJCC stage and sex, and (3) through an age-based propensity match.

Comparisons between baseline demographics were performed with a Pearson's chi-squared test for categorical variables, as well as with a Wilcoxon rank-sum test for continuous variables. Kaplan–Meier curves were performed to determine survivorship.[16] A log-rank test was used to determine differences in survival.[17] Calculations were performed with R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria, 2019).

3 | RESULTS

3.1 | Differences in demographics and treatment approaches between GCRO and OOS

While GCRO patients were significantly older than the 167 OOS patients (mean age 43 vs. 21 years, median age 38 vs. 14 years; $p < 0.01$), both groups were otherwise comparable concerning demographics, tumor characteristics, treatment approaches, and chemotherapeutic response rate. Likewise, matched-pair analysis and age-adjusted propensity match showed no statistically significant difference, except for age in the matched-pair group (Table 2).

3.2 | Differences in survival between GCRO and OOS

No statistically significant difference was noted in overall events of local recurrence, any death, and any death by disease between OOS and GCRO (Table 2). Development of distant disease was significantly increased in OOS ($p = 0.02$), although this effect was not significant when comparing the matched cohorts ($p = 0.48$, 0.21).

The 2-year overall survival was 80% (95% confidence interval [CI]: 41%–95%) in GCRO, 84% (95% CI: 77%–89%) for all 167 OOS patients ($p = 0.08$; Figure 1). Similarly, the 2-year overall survival for the 33 OOS patients in the matched cohort was 84% (95% CI: 66%–93%; Figure 2). The disease-free survival was 90% (95% CI: 80%–100%) in 33 case–control OOS ($p = 0.18$), and 80% (95% CI: 55%–100%) in the propensity match group ($p = 0.40$). With one additional disease-related death in the GCRO group at 12 years, the final disease-free survival was 67% (95% CI: 35%–98%). The 2-year local recurrence-free survival was 100%

TABLE 1 Baseline demographics and treatment outcomes of 11 cases of GCRO in our institution.

Localization	Year of diagnosis	Age	Sex	Enneking stages	AJCC stages	Chemotherapy (index treatment)	Radiotherapy (index treatment)	Index surgery	Follow-up after initial diagnosis	Local recurrence/ metastasis	First revision/final limb status	Final status
Femur, distal	1993	25	Male	2A	2B	Preoperative (3 months, MAP), postoperative (6 months, Ifosfamide-Carboplatin-Etoposide)	No	Osteoarticular allograft	360 months	No	120 months to hinged TKA for wear and arthritis/limb salvage	NED
Tibia, proximal	1994	17	Male	2A	2B	Preoperative (3 months), postoperative (8 months); MAP-Ifosfamide each	No	Osteoarticular allograft	329 months	No	Bone grafting for nonunion at 15 months/total knee arthroplasty at 69 months	NED
Tibia, proximal	1995	76	Female	2B	2B	No	Preoperative (external, unspecified)	Above knee amputation	0.2 months	No	No revisions/primary amputation	NED
Femur, proximal	1998	72	Male	2A	2B	No	No	Proximal femoral replacement	1 month	No	Irrigation for infection at 1 month/limb salvage	DWD (perioperative complications)
Humerus, proximal	2001	15	Female	2B	2B	Preoperative (1 month), postoperative (1 month); MAP each	No	Composite allograft prosthesis	270 months	No	Revision at 27 months for fractured allograft/reverse shoulder arthroplasty at 122 months	NED
Femur, distal	2001	83	Female	2A	2A	No	No	None (refused treatment; symptomatic therapy only)	8 months	No	No revision/limb salvage	DWD (complete involvement of femur, multiple fractures)
Humerus, proximal	2001	16	Female	2A	2B	Preoperative (1 month), postoperative (8 months); MAP each	No	Composite allograft prosthesis	266 months	No	Hemiarthroplasty for fracture at 27 months/limb salvage	NED

(Continues)

TABLE 1 (Continued)

Localization	Year of diagnosis	Age	Sex	Enneking stages	AJCC stages	Chemotherapy (index treatment)	Radiotherapy (index treatment)	Index surgery	Follow-up after initial diagnosis	Local recurrence/ metastasis	First revision/final limb status	Final status
Femur, distal	2003	37	Male	2A	2A	Preoperative (4 months, MAP)	No	Distal femoral replacement	301 months	Local recurrence at 24 months	Revision TKA for patellar arthritis and arthrofibrosis at 50 months/limb salvage	NED
Tibia, proximal	2006	49	Female	2A	2A	Preoperative (4 months; MAP), postoperative (3 months; Bleomycin-Cytoxan-Dactinomycin)	No	Composite allograft prosthesis	148 months	Frontal calvarium metastasis at 77 months; lung metastasis at 92 months	Conversion to hinged prosthesis at 13 months for instability/above knee amputation for failed infection control at 120 months	DWD
T1 vertebral body	2011	38	Female	2A	2A	Preoperative (5 months; MAP); postoperative (1 month; Etoposide/ Ifosfamide)	Preoperative (19.8 Gy external), postoperative (3 months)	Staged procedure with (1) posterior fusion, and (2) corpectomy, allograft, and cage C7-T2	20 months	No	No revision/no spinal cord injury	NED
Humerus, proximal	2012	48	Male	2A	2B	Preoperative (external documents missing)	No	Hemiarthroplasty	114 months	No	No revisions/limb salvage	NED

Abbreviations: AJCC, American Joint Committee on Cancer; DWD, death with disease; GCRO, giant cell-rich osteosarcoma; MAP, methotrexate, adriamycin, cisplatin; NED, no evidence of disease.

TABLE 2 Baseline and outcome characteristics of GCRO and OOS.

	GCRO	All OOS comparison		Propensity match comparison		3:1 match pair comparison	
	GCRO	OOS	p**	OOS	p**	OOS	p**
Patients†	11	167	–	10		33	–
Age at diagnosis*	43 (15, 83)	21 (6, 93)	**<0.01**	38 (17, 71)	0.92	26 (6, 93)	**<0.01**
Males†	5 (46)	92 (55)	0.53	4 (40)	0.80	15 (45)	0.99
Localization†			0.09		0.67		0.05
Femur	4 (36)	105 (63)		6 (60)		22 (67)	
Tibia	3 (27)	40 (24)		1 (10)		8 (24)	
Humerus	3 (27)	12 (7)		2 (20)		2 (6)	
Other	1 (9)	10 (6)		1 (10)		1 (3)	
Tumor maximum in cm*^	10 (2, 17)	11 (1, 32)	0.38	11 (9, 12)	0.51	11 (1, 32)	0.33
Tumor grade†			0.56		0.25		0.30
2	2 (22)	19 (15)		0		2 (9)	
3	7 (78)	108 (85)		5 (100)		21 (91)	
AJCC stage†			0.42		0.86		0.99
IIA	4 (36)	57 (34.1)		4 (40)		12 (36)	
IIB	7 (64)	69 (41.3)		6 (60)		21 (64)	
III	0	9 (5.4)		0		0	
IVA	0	25 (15)		0		0	
IVB	0	7 (4.2)		0		0	
Metastasis at presentation†	0	32 (19)	0.11	0	–	0	–
Negative resection margin†^	10 (100)	160 (96)	0.51	9 (10)	0.30	32 (97)	0.57
Chemotherapeutic response rate*	67 (5, 100)	73 (10, 100)	0.67	40 (38, 49)	0.18	70 (10, 100)	0.97
Primary limb salvage†	10 (90)	147 (88)	0.85	9 (90)	0.94	32 (97)	0.43
Local recurrence†	1 (9)	26 (16)	0.56	2 (20)	0.48	4 (12)	0.78
Distant disease†	1 (9)	75 (45)	**0.02**	2 (20)	0.48	8 (24)	0.21
Any death†	3 (27)	46 (28)	0.98	5 (50)	0.28	7 (21)	0.67
Death by disease†	3 (100)	40 (93)	0.64	3 (30)	0.21	4 (12)	0.23

Abbreviations: GCRO, giant cell-rich osteosarcoma; OOS, osteoblastic osteosarcoma.

*Values are given as mean with ranges.

**All p values compared to GCRO.

†Numbers and percentages—(*n* (%)).

^Based on 10 cases undergoing surgery only.

in GCRO, 88% (95% CI: 82%–93%) for all 167 OOS ($p = 0.09$; Figure 3), 94% (95% CI: 85%–100%) in case controls ($p = 0.91$), and 89% (95% CI: 68%–100%) in the propensity-matched cohort ($p = 0.96$). One case of local recurrence was noted in GCRO at 72 months. The 2-year distant disease-free survival was 100% in GCRO, 78% (95% CI: 64%–93%) in case controls ($p = 0.21$), and 78% (95% CI: 51%–100%) in propensity-matched patients ($p = 0.40$). Only one metastasis was noted in GCROs at 6 years, resulting in a distant disease-free survival of 86% (95% CI: 60%–100%).

3.3 | Literature summary of GCRO

Literature search revealed 56 cases of GCRO published between 1986 and 2022 in a total of 34 studies, with 36 cases reported from Asia (64%; Table 3).[10–12,18–50] Mean age was 26 years (range, 5–73 years) and 28 were males (50%). Localizations were reported as follows: Femur (38%; $n = 21$; 10 times distal, 8 times diaphyseal, 2 times proximal, 1 time unspecified), tibia (27%; $n = 15$; 14 times proximal, 1 time diaphyseal), mandible ($n = 5$), vertebrae C6 to T6 ($n = 4$), maxilla ($n = 2$), proximal fibula ($n = 2$), proximal ulna ($n = 2$), foot

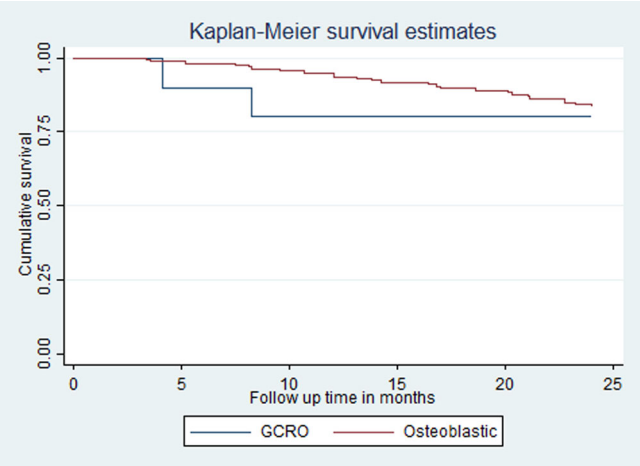

FIGURE 1 Kaplan–Meier overall survival estimated for the overall cohort of patients, GCRO versus OOS. GCRO, giant cell rich osteosarcoma; OOS, osteoblastic osteosarcoma.

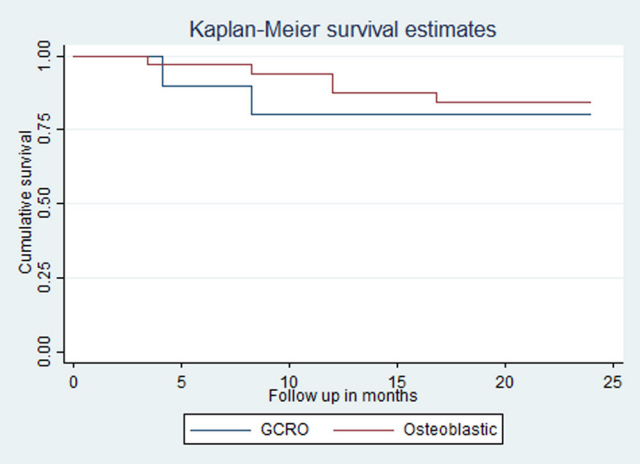

FIGURE 2 Kaplan–Meier overall survival estimated for the propensity-matched patients, 11 GCRO versus 33 OOS. GCRO, giant cell rich osteosarcoma; OOS, osteoblastic osteosarcoma.

($n = 2$; first metatarsal, medial cuneiform), 11th rib ($n = 1$), skull base ($n = 1$), and distal radius ($n = 1$). All but two patients underwent surgical treatment for osteosarcoma, 34 additional chemotherapy, and 11 radiation therapy. Primary limb salvage was performed in all but 11 patients (26% of 43 osteosarcomas located in the extremities). Twenty-nine patients had no evidence of local recurrence or metastasis (52%), 7 suffered from metastasis at diagnosis (13%; including 2 skip metastases), 11 had local recurrence (20%), and 15 developed new distant disease after surgery (27%).

Nine patients had no follow-up report or were lost to follow-up. The mean follow-up of the remaining 47 patients was 45 months (range, 0.2–240 months; median 33 months). Among these patients, 28 (60%) had no evidence of disease at a mean of 54 months (range, 1–192 months; median 45 months), 17 patients (36%) died due to the disease at a mean of 34 months (range, 0.2–240 months; median 20 months), and 2 (4%) were alive with disease at 5 and 45 months. Following a merged analysis of the 11 cases of GCRO reported in this investigation and 47 literature cases with a follow-up, the 2-year disease-free survival was 66% (95% CI: 53%–78%). As only one further patient died due to osteosarcoma, more than 2 years after diagnosis, at 12 years, the final disease-free survival was 57% (95% CI: 39%–76%).

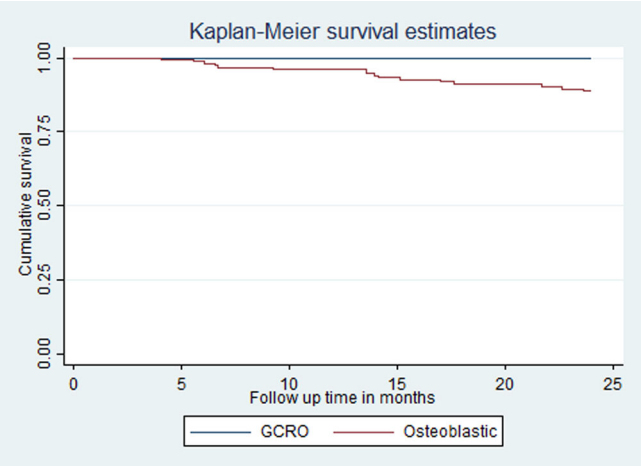

FIGURE 3 Kaplan–Meier local recurrence-free survival estimated for the overall cohort of patients, GCRO versus OOS. GCRO, giant cell rich osteosarcoma; OOS, osteoblastic osteosarcoma.

4 | DISCUSSION

GCRO is a rare osteosarcoma subtype with undetermined short-term survival in the existing literature. As such, we analyzed 11 cases of GCRO at a mean follow-up of 14 years. Not only do we present the largest GCRO series to date but, to the best of our knowledge, this is also the first study to compare GCRO and OOS in the course of a match pair analysis. While patients affected by GCRO were significantly older, survival did not differ compared to OOS.

Estimations on the prevalence of GCRO vary between 1% and 3%.[51,52] We identified a total of 11 patients over 30 years at a total of three university-based tertiary hospitals, representing an estimated 1% of all osteosarcoma treated during this period. Importantly, patients affected by GCRO were significantly older than those treated for OOS. Of note, these results were also confirmed by the literature analysis in which the mean age was nearly 10 years higher than previously reported for the general osteosarcoma population.[53] Moreover, half of all GCRO cases reported to date affected females, contrasting findings on conventional osteosarcomas with male–female ratios of 1.2–1 or higher.[1–3,9]

Surgical approaches in this study reflected well-established strategies for osteosarcoma treatment, including an increased trend toward limb salvage.[54,55] In fact, our primary limb salvage rate (90%) reflects outcomes published in recent trials.[56] Likewise, patients received chemotherapy for a mean of 12 weeks, falling in line with

TABLE 3 Literature overview of 56 GCRO reported to date.

Study	Year	Country	Localization	Age	Sex	Local recurrence/ metastasis	Surgery (index treatment)	Radiotherapy (index treatment)	Chemo (index treatment)	Follow-up after initial diagnosis	Final status
Bathurst et al.[10]	1986	Bristol, UK	Femur, diaphysis	41	Female	Local recurrence at 14 months, postoperative lung metastasis	Curettage, bone graft	No	No	36 months	DWD
			Tibia, diaphysis	13	Female	No	Curettage, bone graft	Postoperative	No	192 months	NED
			Femur, diaphysis	21	Male	Local recurrence	Curettage	Postoperative	No	108 months	NED
			Femur, diaphysis	12	Male	Sacrum at 2 years	Disarticulation	No	No	36 months	DWD
			Tibia, proximal, metaphysis	6	Female	No	Curettage	No	Postoperative	84 months	NED
			Femur, diaphysis	16	Female	Local recurrence, postoperative lung metastasis	Resection, prosthesis	No	Postoperative	24 months	DWD
			Tibia, proximal, metaphysis	12	Male	Local recurrence, lung metastasis at 2 years	Curettage, bone graft	No	No	24 months	DWD
			Femur, condyle	20	Male	No	Curettage	No	Postoperative	24 months	NED
			Femur, diaphysis	8	Male	No	Amputation	No	Postoperative	12 months	NED
Sciot et al.[18]	1995	Leuven, Belgium	Femur, distal	26	Male	No	Transarticular resection, osteoarticular distal femoral allograft	No	No	Unreported	Unreported
Sato et al.[19]	1996	Nagoya, Japan	Femur, metadia-physeal	19	Male	No	Resection, autogenous autoclaved bone graft, vascularized fibular graft	No	Preoperative	72 months	NED
Shuhaibar et al.[20]	1998	Ontario, Canada	Femur, distal	32	Female	Local recurrence, lung metastasis at 14 months	Resection, en bloc	No	Postoperative, 3 cycles Adriamycin-Cisplatinum	45 months	NED
Sundaram et al.[21]	2001	St. Louis, USA	Femoral neck, lateral aspect of the femoral head	34	Female	Local recurrence at 4 months, bilateral lung metastasis at 4 months	Resection, prosthesis	No	No	17 months	DWD
Bertoni et al.[22]	2003	Bologna, Italy	Femur, diaphysis	19	Male	Local recurrence at 13 months, metastasis at 17 years	Resection, metal prosthesis, fibular graft	No	No	240 months	DWD

(Continues)

TABLE 3 (Continued)

Study	Year	Country	Localization	Age	Sex	Local recurrence/ metastasis	Surgery (index treatment)	Radiotherapy (index treatment)	Chemo (index treatment)	Follow-up after initial diagnosis	Final status
Shinozaki et al.[23]	2004	Maebashi, Japan	Radius, distal	17	Male	Local recurrence, metastasis to lung, posterior thoracic walls, thoracic, lumbar spines, sacral bone, lumbar spinal cord, skull at 16 months	Curettage, vascular fibular graft	No	No	41 months	DWD
Hong et al.[24]	2004	Seoul, South Korea	Tibia, proximal, metaphysis	29	Female	No	Resection	No	No	11 months	NED
Nagata et al.[25]	2006	Kurume, Japan	Femur, distal, metaepi-physeal	32	Male	No	Curettage, cement filling	No	No	20 months	NED
Kinoshita et al.[26]	2006	Kohama, Japan	11th rip	16	Male	No	En bloc resection, Marlex mesh	No	Preoperative, 3 cycles Carboplatin-Doxorubicin; postoperative Methotrexate-Carboplatin-Doxorubicin-Ifosphamide	60 months	NED
Shetty et al.[27]	2009	Ghaziabad, India	Mandible	16	Male	Lymph node metastasis at diagnosis	Segmental mandibulectomy, plate	Article no longer archived on journal website and not accessible			
Fu et al.[28]	2011	Shanghai, China	Mandible	67	Female	No	Segmental mandibulectomy, free fibula myocutaneous flap	Postoperative	Postoperative	12 months	NED
Verma et al.[29]	2011	Chandigarh, India	Maxilla	56	Female	No	Total maxillectomy	Postoperative, 60 Gy	Postoperative, 5 cycles	>1 month	NED
Gambarotti et al.[30]	2011	Bologna, Italy	Femur, distal, metaphysis	29	Male	No	Curettage	No	Preoperative adjuvant	Unreported	NED
Imran et al.[31]	2012	Muzaffarabad, Pakistan	Tibia, proximal, metaphysis	16	Female	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported

TABLE 3 (Continued)

Study	Year	Country	Localization	Age	Sex	Local recurrence/ metastasis	Surgery (index treatment)	Radiotherapy (index treatment)	Chemo (index treatment)	Follow-up after initial diagnosis	Final status
Kinra et al.[32]	2012	Pune, India	Femur, shaft, diaphysis	21	Male	Skip metastasis distal at diagnosis	Resection	No	Preoperative, neoadjuvant, 3 cycles Ifosfamide-Cisplatin-Adriamycin	Unreported	Unreported
Mariano et al.[33]	2013	Campinas, Brazil	Fibula, metaepi-physeal	55	Male	Metastasis to labial mucosa at 2 months; scalp, ring finger, lungs, index finger, thigh, cervical nodes later on	Above knee amputation	No	No	11 months	DWD
Wang et al.[11]	2013	Shanghai, China	Femur, proximal	51	Male	Local recurrence, postoperative lung metastasis	Resection, prosthesis	No	Yes, unspecified	18 months	DWD
			Tibia, proximal	18	Male	No	Amputation	No	Yes, unspecified	92 months	NED
			Tibia, proximal	36	Female	Local recurrence	Curettage, cement filling	No	No	90 months	NED
			Tibia, proximal	13	Male	Postoperative lung metastasis	Curettage, allograft	No	No	13 months	DWD
			Femur, distal	19	Female	No	Amputation	No	Yes, unspecified	74 months	NED
			Tibia, proximal	33	Female	No	Amputation	No	Postoperative	111 months	NED
			Tibia, proximal	16	Male	Lung metastasis; time unspecified	Amputation	No	Postoperative	20 months	DWD
			Tibia, proximal	15	Female	No	Amputation	No	Yes, unspecified	114 months	NED
			Tibia, proximal	32	Male	No	None	No	Preoperative	5 months	AWD
Ahrari et al.[34]	2015	Ontario, Canada	Skull base	18	Female	No	Resection, two-stage endoscopic endonasal approach	Postoperative	Postoperative	3 months	NED
Sun LM et al.[35]	2015	Shenyang, China	Mandible	28	Female	Metastasis to sternum and first thoracic vertebra at 45 months	Resection	Postoperative	Postoperative	45 months	AWD

(Continues)

TABLE 3 (Continued)

Study	Year	Country	Localization	Age	Sex	Local recurrence/ metastasis	Surgery (index treatment)	Radiotherapy (index treatment)	Chemo (index treatment)	Follow-up after initial diagnosis	Final status
Vijayan et al.[36]	2015	Karnataka, India	Foot, medial and intermediate cuneiform	19	Female	No	Curettage, fibular strut grafting	No	Preoperative, neoadjuvant, 3 cycles; postoperative, 3 cycles, Doxorubicin-Cisplatin	36 months	NED
Choo et al.[37]	2016	Seoul, South Korea	Femur, unspecified	42	Male	Metastasis to lungs and mandible at diagnosis; 6 months later to skin	Unreported	No	Ifosfamide-Adriamycin, high-dose Methotrexate, later Gemcitabine-Docetaxel, then Cyclophosphamide-Etoposide	15 months	DWD
Chow et al.[12,38,39]	2016	Hong Kong, China	Tibia, proximal, metaepi-physeal	16	Male	Skip metastasis to femur at diagnosis	Above knee amputation	No	Postoperative	110 months	NED
			Fibula, proximal, metaphysis	12	Male	Local recurrence, Metastasis to thigh and groin lymph node at diagnosis	Resection	No	Postoperative, Denosumab	21 months	DWD
			Femur, distal, metaepi-physeal	33	Female	No	Resection	No	Preoperative, neoadjuvant	48 months	NED
			Tibia, proximal, metaepi-physeal	15	Female	No	Resection	No	Preoperative, neoadjuvant	38 months	NED
			Foot, first metatarsal	31	Female	Solitary iliac metastasis after 1 year	Ray amputation of big toe and first metatarsal	No	Postoperative, Denosumab	30 months	NED
			Femur, distal	15	Male	No	Resection	No	Preoperative	12 months	NED
			Femur, distal	26	Male	Skip metastasis to femoral neck at 9 months, generalized metastasis at 9 months	Curettage, cementation	No	No	14 months	DWD

TABLE 3 (Continued)

Study	Year	Country	Localization	Age	Sex	Local recurrence/ metastasis	Surgery (index treatment)	Radiotherapy (index treatment)	Chemo (index treatment)	Follow-up after initial diagnosis	Final status
Hirose et al.[40]	2017	Osaka, Japan	Maxilla	64	Male	Unreported	Segmental maxillectomy	Unreported	Unreported	Unreported	Unreported
Ito et al.[41]	2018	Sapporo, Japan	T6 vertebra	73	Female	No	Posterior decompression and fixation	Postoperative, 2 months	Preoperative, Denosumab for 17 months	Unreported	Unreported
Cahayadi et al.[42]	2019	Jakarta, Indonesia	Ulnar, proximal	46	Female	Possibly lungs at diagnosis	Resection, elbow arthroplasty, latissimus dorsi flap	No	No	Unreported	Unreported
Mallick et al.[43]	2020	Kolkata, India	Mandible	52	Male	No	Hemi-mandibulectomy	Preoperative, adjuvant	No	Lost to FU	Lost to FU
Mosquera-Salas et al.[44]	2020	Cali, Colombia.	T1/2 vertebrae	25	Female	Expansive growth into mediastinum	None, palliative	No	No	0.2 months	DWD
Erwin et al.[45]	2021	Jakarta, Indonesia	Tibia, proximal	5	Female	No	Cryosurgery, vascularized fibular graft, recycled proximal tibia segment	No	Preoperative, neoadjuvant, 3 cycles Cisplatin-Ifosfamide-Adriamycin	12 months	NED
Palmerini et al.[45]	2021	Bologna, Italy	Femur, distal	20	Unreported	Unreported	Amputation	No	Postoperative, Denosumab	12 months	DWD
Jot et al.[46]	2022	New Delhi, India	Mandible	14	Female	No	Hemimandibulectomy	Postoperative	Preoperative, neoadjuvant	12 months	NED
Egea-Gámez et al.[47]	2022	Madrid, Spain	C6, C7, T1 vertebrae	12	Male	No	Anterior fusion, titanium mesh, bone graft/ anterior plate, posterior fixation	Postoperative	Preoperative, neoadjuvant; postoperative 10 cycles	36 months	NED
Santana et al.[48]	2022	Aracaju, Brazil	Ulna, proximal	16	Female	Mandible, forearm, femur, lung metastasis at 3 years	Resection	No	No	36 months	DWD
Tseng et al.[49]	2022	Tainan, Taiwan	T2 vertebra	17	Female	No	T2 costotransversectomy, hypervascular soft tissues	Preoperative, adjuvant	Preoperative, neoadjuvant	48 months	NED

Abbreviations: DWD, death with disease; Lost to FU, lost to follow-up; NED, no evidence of disease.

current guidelines of the American Cancer Society recommending a 10-week course of neoadjuvant chemotherapy in most osteosarcomas.[57] Importantly, the chemotherapeutic response rate, a well-established predictor of survival in osteosarcoma,[58] was similar between GCRO and OOS.

The 2-year disease-free survival among GCRO was 80% (our cohort) and 66% (merged cohort of 47 GCRO). These rates were similar to both the OOS comparison group in this investigation, as well as in line with previous results on the overall osteosarcoma population.[9,59,60] Likewise, the 2-year local recurrence rate (14%) in GCRO was similar to both the OOS comparison group and current studies on conventional osteosarcoma.[61,62] Although only one patient in our cohort developed distant disease at 12 years, metastasis was common in GCRO literature with nearly one in three patients developing metastasis after surgery.

Our study had limitations. Foremost, this retrospective investigation analyzed a heterogenous cohort treated over a period of two decades at three different hospitals. Moreover, we acknowledge small patient numbers as a limit to generalization. We also recognize a short follow-up time as the study was conducted at a single institution and due to the rarity of the disease. Regarding the pathological aspect, the histone immunohistochemistry (IHC) for the internal cases was not able to be assessed, given the historic nature of most of the cases (older than 20 years). Another important point that should be considered is the missing tumor grades of the review patients. The vast majority of the case reports did not mention the tumor grades of the patients. Due to this shortage of information, the pooled survival data lacks validity. Finally, no IHC results were available in existing retrospective records. This might be of importance for future studies, as the latest investigations suggested a further differentiation between GCRO and malignant giant cell tumors of the bone based on H3F3A (Histone 3.3) G34W expression.[63] Despite that, the current study design remained the only way to analyze this unique population, as current nationwide registries do not filter for GCRO histopathology.[3]

In conclusion, this investigation reported the largest GCRO series to date, and was the first to include both a matched comparison group as well as a comprehensive literature review. Our results indicate that patients affected by GCRO were older than in conventional osteosarcoma, whereas chemotherapeutic response rate and survival remained comparable between groups. These findings might help physicians in identifying populations at risk and in providing a prognosis in GCRO.

AUTHOR CONTRIBUTIONS

Conceptualization: Daniel Karczewski and Santiago A. Lozano-Calderon. *Data curation*: Daniel Karczewski, Marcos R. Gonzalez, and Angad Bedi. *Formal Analysis*: All authors. *Funding acquisition*: Santiago A. Lozano-Calderon. *Investigation*: All authors. *Methodology*: All authors. *Project administration*: Daniel Karczewski and Santiago A. Lozano-Calderon. *Resources*: Santiago A. Lozano-Calderon, John E. Ready, and Megan E. Anderson. *Software*: Daniel Karczewski, Marcos R. Gonzalez, and Santiago A. Lozano-Calderon. *Supervision*: Santiago A. Lozano-Calderon, John E. Ready, and Megan E. Anderson. *Validation*: Santiago A. Lozano-Calderon, John E. Ready, and Megan E. Anderson. *Visualization*: Daniel Karczewski and Angad Bedi. *Writing—original draft*: Daniel Karczewski. *Writing—review and editing*: All authors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

This study was approved by Institutional Review Board.

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