Malignancy in Giant Cell Tumor of Bone: A Review of the Literature

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Abstract

Background: Primary and recurrent giant cell tumor of bone is typically benign; however, rarely giant cell tumor of bone can undergo malignant transformation. Malignancy in giant cell tumor of bone may be primary (adjacent to benign giant cell tumor of bone at first diagnosis) or secondary (at the site of previously treated giant cell tumor of bone). Malignant giant cell tumor of bone has a poor prognosis; it is important to distinguish malignant from benign lesions to facilitate appropriate management. The true incidence of malignant giant cell tumor of bone is not known, probably owing to inaccurate diagnosis and inconsistent nomenclature. We have analyzed current data to provide a robust estimate of the incidence of malignancy in giant cell tumor of bone. **Methods:** A literature search was performed to source published reports of primary and secondary cases of malignant giant cell tumor of bone. Studies that reported a denominator were used to estimate the incidence of malignancy. **Results:** We identified 4 large series of patients with malignant giant cell tumor of bone that provided data on 2315 patients with giant cell tumor of bone. Across these studies, the cumulative incidence of malignancy was 4.0%; the cumulative incidence of primary malignancy was 1.6% compared with 2.4% for secondary malignancy. Our analyses confirmed that most malignant giant cell tumor of bone is secondary and occurs following radiation. In addition, data from 8 small series showed that 4.8% of patients with giant cell tumor of bone who received radiation therapy developed secondary malignancy. **Conclusions:** Malignant giant cell tumor of bone is rare, and its identification is hindered by a lack of clear diagnostic criteria. For optimal care of patients with giant cell tumor of bone, we recommend: comprehensive histologic sampling to ensure accurate diagnoses; watchful follow-up, particularly for patients treated with radiation; and timely treatment of local recurrence.

Keywords

bone tumors, clinical features, diagnosis, incidence, prognosis, rare disease

Abbreviations

CT, computerized tomography; MRI, magnetic resonance imaging; MSKCC, Memorial Sloan Kettering Cancer Center.

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Introduction

Giant cell tumor of bone (GCTB) accounts for approximately 5% to 6% of primary bone tumors.[1,2] It usually occurs in the meta-epiphyseal region of long bones but may also occur in the axial skeleton or small bones of the hands and feet.[3] Giant cell tumor of bone is typically benign but can be locally aggressive; bone disruption can be particularly problematic around joints, compromising joint function and mobility.[2] Local benign GCTB recurrence occurs in approximately 25% of patients,[4,5] with the highest rates reported (up to 50%) following curettage.[5] Synchronous occurrence of benign GCTB at multiple sites is rare.[6] Approximately 1% to 6% of benign tumors will

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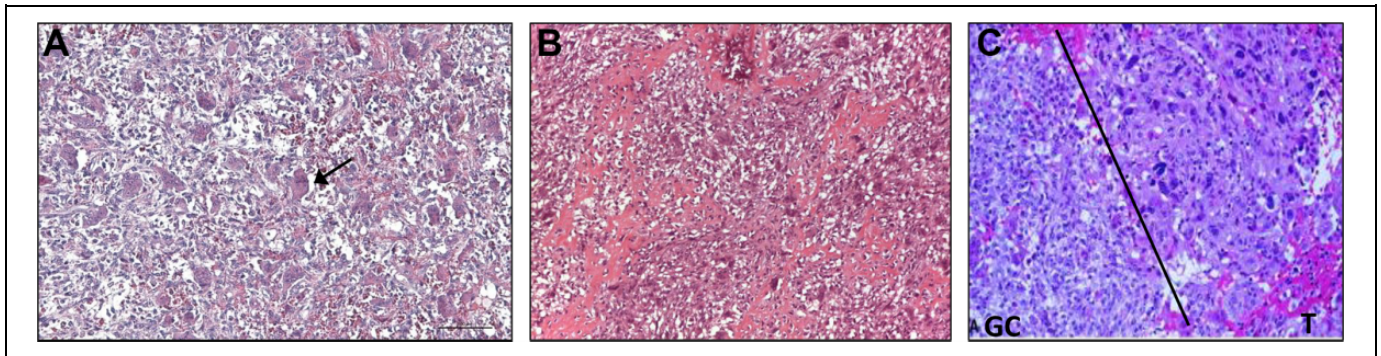Email: emanuela.palmerini3@unibo.it

Figure 1. Histologic differences between benign giant cell tumor of bone (GCTB), giant cell-rich osteosarcoma, and malignant GCTB. (A) Benign GCTB consists of two cell types: stromal mononuclear spindle cells and multinucleated giant cells (GCs). Arrow shows a GC. (B) Giant cell-rich osteosarcoma consists of GCs, oval or spindle mononuclear cells with atypical nuclei, fibrovascular stroma, and new woven bone. (C) Malignant GCTB consists of a GC tumor component with mononuclear cells with typical nuclei, side by side with a pleomorphic malignant spindle cell component (T). Panels A and B are reproduced with permission from Dr Palmerini. Panel C has been adapted with permission from Bertoni et al.[14]

metastasize, most commonly to lung.[1] Although normally indolent, benign metastases can compromise pulmonary function and occasionally be lethal.[1,3,7]

Rarely, GCTB undergoes sarcomatous transformation into a malignant tumor, which may be an osteosarcoma, fibrosarcoma, or undifferentiated pleomorphic sarcoma (historically known as malignant fibrous histiocytoma).[8] Malignant tissue can be considered as either primary or secondary malignant GCTB. Primary malignant GCTBs are evident at first diagnosis of GCTB and contain an area or a nodule of highly pleomorphic mononuclear cells present within an otherwise conventional GCTB. Secondary malignancy GCTBs occur at the site of previously treated GCTB, and the preexisting GCBT may or may not be evident.[9-12] Most malignant GCTB is secondary and typically follows radiotherapy,[13] but it can follow surgery without adjuvant radiotherapy.[7] Primary malignant GCTB is considered to be very rare;[14] differential diagnoses include giant cell-rich sarcomas (eg, osteosarcoma, undifferentiated pleomorphic sarcoma, and leiomyosarcoma) and benign GCTB. A detailed histologic examination is required to confirm malignant tissue and initiate appropriate treatment (Figure 1).

Malignant GCTB was first described nearly 80 years ago;[15] however, estimates of malignant GCTB frequency have been confounded by lack of consensus on definition and diagnosis such that terminology has been inconsistently used in the literature.[16] Furthermore, owing to the juxtaposition of benign and malignant tissue in primary malignant GCTB, failure to comprehensively sample tumors may lead to misdiagnoses of benign GCTB. If malignant tissue is detected during later sampling, primary malignant GCTB could be misdiagnosed as secondary malignancy.[17]

To evaluate the impact of treatments on the risk of GCTB malignant transformation, accurate data on its incidence are needed. This review summarizes published clinical experience of primary and secondary malignant GCTB, with consideration of the challenges associated with its diagnosis.

Classification of GCTB

Historically, GCTB was classified as grade I (benign; no appreciable stromal cell abnormality), grade II (intermediate; slight or more marked stromal cell abnormality), or grade III (malignant; obvious signs of malignancy).[8] This classification system is of limited clinical value and is no longer used.[8]

Radiographically, benign GCTB comprises an eccentric lytic lesion with nonsclerotic and sharply defined margins.[18] It can show aggressive features including a wide zone of transition, cortical thinning and remodeling, and cortical bone destruction with an associated soft tissue mass.[18] Histologically, GCTB comprises neoplastic cells (osteoclast precursor and spindle-shaped stromal cells) and reactive cells, including large, multinucleated, osteoclast-like giant cells (Figure 1).[3]

Malignant GCTB is a high-grade sarcoma.[8] Primary malignant GCTB comprises sarcomatous growth juxtaposed to benign GCTB, whereas secondary malignant GCTB comprises sarcomatous growth at the site of previously documented benign GCTB.[9-11]

Methodology Used to Identify Published Evidence on Malignant GCTB

A structured literature search was performed to identify studies of interest for the review that reported the numbers of nonmalignant and malignant GCTB cases. Reports were selected for inclusion if they (1) reported the total number of patients (denominator for incidence calculation), (2) categorized the malignancy as primary or secondary, and (3) provided the previous treatment for secondary malignancy cases. Case reports of malignant GCTB were also considered. Reports were included irrespective of the diagnostic criteria for GCTB used in each study.

The literature search identified 32 publications that met the predefined criteria. The results included 8 publications from 4 centers reporting data from large patient series; 2 of these centers (the IRCCS Istituto Ortopedico Rizzoli Italy[14,19] and

Mayo Clinic, Rochester, Minnesota, USA[2,11,20,21]) were responsible for multiple publications, and, to avoid duplication, only the most recent reports from each center, with supporting information gleaned from the older publications as appropriate, were included in the review (Table 1).[2,11,14,19-23] There were 8 publications that reported data from smaller series of patients who had received radiotherapy (Table 2).[24-31] Eleven publications were identified that reported data on patients who had undergone curettage and grafting (without radiotherapy; Table 3).[32-42] Finally, there were 5 additional publications that reported cases of secondary malignancy that were unrelated to treatment (Table 4).[8,16,43-45]

Frequency of Primary and Secondary Malignant GCTB: Pooled Analysis

The most recent data from the 4 large GCTB patient series showed that the frequency of malignancy was 1.1% to 11.3% (Table 1).[2,14,22,23] The 4 series comprised 2315 patients, 92 diagnosed with primary or secondary malignant GCTB giving a cumulative incidence of 4.0%. Primary malignant GCTB was rare, with 36 cases reported among the 2315 patients (incidence of 1.6%). At the Rizzoli Institute, Bertoni and colleagues reported 5 cases of primary malignancy among 924 patients with GCTB (0.5%);[14] four had osteosarcomas, and 1 had malignant fibrous histiocytoma.[14] At the Mayo Clinic, of 671 patients with GCTB, only 5 (0.7%) had primary malignancies.[2] The Cancer Hospital, Kolkata, reported the lowest primary malignancy incidence with no cases among the 445 patients with GCTB, despite a follow-up of up to 21 years. The highest rate of primary malignancy was reported at the Memorial Sloan Kettering Cancer Center (MSKCC) with 26 (9.5%) cases among 275 patients after a follow-up of up to 31 years.[22,23] The design of the latter study differed from the others in that it retrospectively applied well-defined diagnostic criteria.[23,46] This may, in part, explain the higher primary malignancy incidence reported from the MSKCC.

The data reported from these large patient series are consistent with most malignant GCTB being secondary; among the 92 malignant cases reported, 56 were secondary. Therefore, among the population of 2315 patients with GCTB, the cumulative incidence of secondary malignancy was 2.4%. In the Mayo Clinic series of 671 patients, 34 of the 39 malignant cases were secondary (5.1%), approximately three-quarters (26 cases) of which were treated with radiation and a quarter (8 cases) with surgery.[2] In the series from the Rizzoli Institute, 12 (71%) of the 17 malignancies among the 924 patients were secondary; equal numbers were treated with radiation and surgery. There were 5 cases each of secondary malignancy at the Cancer Hospital, Kolkata (445 patients with GCTB) and the MSKCC (275 patients with GCTB); all cases were treated with radiation.[22,23]

These data also support that most secondary malignant GCTBs occur several years after radiotherapy and are considered to be radiation induced.[16] Across the large patient series, only a quarter (14/56) of secondary malignancies followed

bone graft/surgery without radiotherapy (cumulative incidence 0.6%; from 2315 GCTB cases), but it is unclear whether the use of surgical adjuvants (such as phenol or cement) in these cases may have influenced the course of the disease. Furthermore, the first of the 2 reports from the Rizzoli Institute showed a clear association between secondary malignancy and prior radiation dose: over a quarter of patients who received 4000 to 6000 rads adjuvant to surgery developed sarcoma, compared with none who received 3000 rads or less.[19] The authors proposed that secondary malignancy cases with short latent periods may be a result of radiation-induced enhancement of the propensity for GCTB to malignant transformation. In secondary malignancy occurring after curettage and bone grafting, it has been postulated that reparative proliferation occurring at the border of dead bone could serve as the source of malignant transformation.[17,32]

When considering data from the pooled analysis of the large patient series, it should be noted that 1 population-based study from the Swedish Cancer Registry, which reported primary malignant GCTB incidences of 56.5% between 1958 and 1982 and 8% between 1983 and 2011, was excluded from our analyses.[47] These high estimates likely arise because the Swedish Cancer Registry receives data from all Swedish clinics; thus, the diagnosis of primary GCTB may not have been verified by an expert. It is probable that many of these cases were giant cell-rich osteosarcomas.[47]

Although data from individual studies suggest that the mean time from GCTB diagnosis to malignant transformation is shorter in patients who receive radiotherapy than in those who receive surgical treatment alone, data from the 4 large patient series do not support a clear relationship. At the Rizzoli Institute, the mean latency following radiotherapy was 9 years compared with 19 years following bone grafts.[14] Early analyses of data from the Mayo Clinic showed latencies of 4 to 38 years following radiotherapy, compared to 1.5 to 22 years following bone grafts.[9,11] At the Cancer Hospital, Kolkata, all cases of secondary malignancy followed radiotherapy, and the average latency was 11 years.[22]

Finally, pooled data were derived from the small patient series comprising 206 patients with GCTB who had received radiotherapy, 12 (4.8%) of who developed secondary malignancy (Table 2).[24-31] In total, 23 cases of secondary malignancy were identified in patients who underwent curettage and grafting without radiotherapy (Table 3).[32-42] Malignant transformation without previous radiotherapy or surgery is considered to be rare: We identified 22 cases of secondary malignancy with no relation to treatment (combined with 14 cases identified in the large series, there were 36 in total; Table 4).[8,16,43-45]

A summary of the different incidences and causes, and other characteristics, of primary versus secondary malignant GCTB are summarized in Table 5.

Comparing Clinical Features of Primary Versus Secondary Malignant GCTB

The retrospective long-term study reported by Domovitov and Healey compared benign and primary malignant GCTB.[23] Of

Table 1. Results of Literature Review: Large Series.[a]

Center	Reference	Patients	Mean (Range) Follow-Up	Malignancies, n (%)	Primary	Secondary	Mean (Range) Time to Secondary Malignancy	Prior Radiotherapy in Secondary Malignant Cases[b]	Prior Surgery Alone in Secondary Malignant Cases[c]
IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy	Bertoni et al[14]	924 cases	NR	17 (1.8%)	5 (4 OS, 1 MFH)	12 (9 OS, 2 FS, 1 MFH)	9 (3-15 years) (postradiation)	6 (50.0%)	6 (50.0%)
	Campanacci et al[19]	293 patients	NR (<2 to 44 years)	10 (3.4%)	–	10 (5 MFH, 3 FS, 2 OS)	NR (2.5-15 years postradiotherapy, 1.5-2 years postsurgery)	8 (80.0%)	2 (20.0%)
Cancer Hospital, Kolkata, India	Mondal et al[22]	445 cases (39 prior radiotherapy)	NR (≤21 years)	5 (1.1%)	–	5 (3 FS, 1 MFH, 1 OS)	11 years	5 (100.0%)	–
Mayo Clinic, USA	Unmi and Inwards[2]	671 cases	NR	39 (5.8%)	5	34	NR	26 (76.5%)	8 (23.5%)
	McDonald et al[20]	221 patients	7 years (2-21 years)	5 (2.3%)	2	3	NR	2 (66.7%)	–
	Rock et al[11]	407 patients	NR	26 (6.4%)	7	19 (14 FS, 5 OS)	12.3 years	18 (94.7%)	1 (5.3%)
	Dahlin[21]	407 patients	NR	24 (5.9%)	5	23	>13 years (postradiation)	21 (91.3%)	2 (8.7%)
Memorial Sloan Kettering Cancer Center, New York, NY, USA	Domovitov and Healey[23]	275 patients	147 months (9-377 months for 26 primary malignancy cases)	31 (11.3%)	26	5 (2 OS, 3 MFH)	2 years (3 months-4 years)	5 (19%)	–

Abbreviations: FS, fibrosarcoma; MFH, malignant fibrous histiocytoma; NR, not reported; OS, osteosarcoma.
[a]Bertoni et al[14] and Campanacci et al[19] reported overlapping series from the same institution. Unmi and Inwards,[2] McDonald et al,[20] Rock et al[11], and Dahlin[21] reported overlapping series from the same institution.
[b]Percentage represents patients who received radiotherapy and developed a secondary malignancy as a proportion of all secondary malignancy cases.
[c]Percentage represents patients who received surgery alone and developed a secondary malignancy as a proportion of all secondary malignancy cases.

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Table 2. Results of Literature Review: Small Series, Following Radiation Therapy.

Reference	Patients	Mean (Range) Follow-Up	Malignancies, n (%)	Primary	Secondary	Mean (Range) Time to Malignancy	Prior Radiotherapy, n (%)	Prior Surgery, n (%)
Boriani et al[24]	327	NR (7 months-10 years)	10 (3%)		10 (5 MFH, 3 FS, OS)	NR (2.5-15 years postradiation; 1-2 years postsurgery)	8 (80%; 29% for dose >40 Gy)	8 (80%)
Ruka et al[25]	77	NR	2 (2.6%)	–	2	NR	77 (100%)	NR
Feigenberg et al[26]	24	12 years (2.5-26 years)	1 (4.2%)	–	1 (UPS)	22 years	1 (4%)	NR
Shi et al[27]	34	16.8 years (1.4-33.7 years)	1 (3%)	–	1 (OS)	52 months	34 (100%)	13 (38%)
Chakravarti et al[28]	20	9.3 years (3-19 years)	(0%)	–	–	NA	20 (100%)	NR
Nair and Jyothirmayi 1999[29]	20	48 months	0 (0%)	–	–	NA	20 (100%)	NR
Caudell et al[30]	25	8.8 years (0.67-34 years)	0 (0%)	–	–	NA	25 (100%)	NR
Malone et al[31]	21	15.4 years (2-35 years)	0 (0%)	–	–	NA	21 (100%)	NR

Abbreviations: FS, fibrosarcoma; MFH, malignant fibrous histiocytoma; NA, not applicable; NR, not reported; OS, osteosarcoma; UPS, undifferentiated pleomorphic sarcoma.

Table 3. Results of Literature Review: Small Series, Following Curettage and Grafting.

Reference	Patients	Mean (Range) Follow-Up	Malignancies, n	Primary	Secondary	Mean (Range) Time to Malignancy	Prior Surgery, n (%)
Picci et al[32]	12	19 years (6.5-28 years)	12	–	12 (8 OS, 3 MFH, 1 FS)	NR	12 (100%)
Takesako et al[33]	1	40 years	1	–	1 (OS)	40 years	1 (100%)
Kadowaki et al[34]	1	41 years	1	–	1 (OS)	41 years	1 (100%)
Li et al[35]	1	15 years	1	–	1 (FS)	15 years	1 (100%)
Marui et al[36]	2	16.5 years	2	–	2 (1 MFH, 1 OS)	14 years	2 (100%)
Saito et al[37]	1	6 months	1	–	1	6 months	1 (100%)
Mori et al[38]	1	29 years	1	–	1 (MFH)	25 years	1 (100%)
Muramatsu et al[39]	1	38 years	1	–	1 (MFH)	38 years	1 (100%)
Miller et al[40]	1	4 years	1	–	1 (OS)	4 years	1 (100%)
Hashimoto et al[41]	1	10 years	1	–	1 (OS)	10 years	1 (100%)
Machinami et al[42]	1	25 years	1	–	1 (OS, SCC)	25 years	1 (100%)

Abbreviations: FS, fibrosarcoma; MFH, malignant fibrous histiocytoma; NR, not reported; OS, osteosarcoma; SCC, squamous cell carcinoma; UPS, undifferentiated pleomorphic sarcoma.

Table 4. Results of Literature Review: Case Studies of Secondary Malignancy in GCTB.

Reference	Cases of Secondary Malignancy in GCTB	GCTB History
Brien et al[43]	1	Lung metastases after 6 years
Wojcik et al[44]	6	All after local recurrence, 2 with radiotherapy
Gong et al[8]	12	All after local recurrence, none with radiotherapy
Grote et al[16]	1	10 years with no treatment
Oda et al[45]	2	All after local recurrence, none with radiotherapy

Abbreviation: GCTB, giant cell tumor of bone.

Table 5. Summary of the Characteristics of Primary and Secondary Malignant GCTB.

	Incidence	Histological Presentation	Differential Diagnosis	Causes	Prognosis
Primary malignant GCTB	1.6% (range 0%-9.5%)[a]	Sarcomatous growth next to benign GCTB	Giant cell-rich sarcomas (osteosarcoma, undifferentiated pleomorphic sarcoma, leiomyosarcoma) and benign GCTB	Sarcomatous/malignant transformation	Better than for secondary malignant GCTB, eg, 5-year survival 87%[23]
Secondary malignant GCTB	2.4% (range 1.1%-5.1%)[a]	Sarcomatous growth at the site of previously documented GCTB	Giant cell-rich sarcomas (osteosarcoma, undifferentiated pleomorphic sarcoma, leiomyosarcoma)	Typically follows radiotherapy (75%); effect is related to dose of radiation used Follows bone graft/ surgery without radiotherapy (~25%)	Worse than for primary malignant GCTB, eg, 5-year disease-free survival 32%[11]

Abbreviation: GCTB, giant cell tumor of bone.
[a]Data are from the 4 large patient series reported, comprising 2315 patients.[2,14,22,23]

the 31 malignant cases identified from 275 patients with GCTB, 5 cases of postradiation malignancy were excluded from the subsequent analysis. The resulting 26 primary malignant cases were compared to 244 benign cases. The data suggested that lesions described as Campanacci stage 1 (associated with a well-defined margin and a thin rim of mature bone[48]) may predict a low hazard of malignancy. The skeletal distribution and epidemiological characteristics of malignant and benign tumors were similar. The recurrence rate was higher for malignant than for benign GCTB (20% vs 9%) although this was not statistically significant. The 5-year survival rate for malignant GCTB was 87%, with a total mortality of 16%; this was interpreted to reflect the low grade of the malignancies that grow and metastasize at a slow rate. Only 1 death was recorded in the benign group (undetermined cause).[23]

Challenges Associated With Diagnosis of Malignant GCTB

Estimates of malignant GCTB frequency have been confounded by a lack of consensus on definition and diagnosis such that terminology has been inconsistently used in the literature.[16] The challenges in the accurate diagnosis of malignant GCTB have been highlighted here by virtue of the range of definitions applied in the reviewed studies (Table 6).[2,11,14,19-23,46] The radiologic features of primary malignant GCTB are similar to those of the benign tumor, making it difficult to diagnose using conventional imaging (Table 5).[49] Histologic analyses are complicated because the high-grade sarcoma of primary malignant GCTB often exists next to histologically benign GCTB.[8] Errors in sampling larger tumors owing to biopsies missing coexistent sarcoma have been well documented.[14,17,50] Primary malignancy may be detected only retrospectively when specimens are reevaluated.[17,51] Therefore, multiple biopsy specimens should be analyzed before excluding primary malignancy[17] to avoid misdiagnoses of secondary malignancy later on; cases of secondary malignancy with short

latencies may indicate missed primary malignancy.[14] There is also a need to standardize diagnostic criteria for malignant GCTB. The studies we examined often did not report details on the criteria used to diagnose GCTB, and the criteria that were reported were inconsistent across studies. Notably, no studies reviewed here reported misdiagnosis of primary malignant GTCB. Given that misdiagnosis is a recognized challenge in primary malignant GCTB,[8,52] this may suggest that there are limitations to the relevance of these data to real-world practice. Alternatively, it could reflect another challenge known to be associated with primary malignant GCTB, in that many diagnoses are missed.[8,52] Complementary to pathologic evaluation in GCTB diagnosis is radiology. Bertoni and colleagues reported that primary malignant cases (and certain secondary malignant cases) were impossible to distinguish from benign lesions on plain films, and computerized tomography (CT)/magnetic resonance imaging (MRI) data were often unavailable.[14] Domovitov and Healey noted that radiologic diagnosis was complicated by the lack of specific malignant features; aggressive features could be seen in benign lesions. Furthermore, these authors reported that CT/MRI also failed to provide specific signs.[23] Upon imaging, secondary malignant GCTB usually presents as an aggressive osteolytic tumor with cortical destruction and soft-tissue extension.[16] Postsurgical and radiotherapy-induced secondary malignancy are believed to have different etiologies but cannot be distinguished by radiographic and histologic presentation.[14]

Giant cell-rich osteosarcoma is characterized by an abundance of osteoclast-like giant cells and lack of tumor osteoid, which can be misdiagnosed as GCTB;[52] similar to GCTB, it also occurs at epiphyses.[52] Bertoni and colleagues suggested that the clinical importance of differentiating primary malignant GCTB from giant cell-rich osteosarcoma may be limited, but the need to differentiate both diseases from benign GCTB is complicated by the subtlety of pathologic evidence of malignancy (Table 5).[14] Malignant GCTB is also confused with other

Table 6. Definition and Diagnostic Criteria for GCTB and Malignant GCTB Used in 4 Large Case Series.

Center and References	Diagnosis of Benign GCTB	Definition of Malignant GCTB
IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy Bertoni et al[14] Campanacci et al[19]	Based on clinical data, radiographs, and histologic slides	GCTB was classified as primary or secondary according to Hutter et al[10] and Dahlin et al[9] Primary malignant GCTB is a high-grade sarcoma that arises side by side with giant cell tumors of bone. Secondary malignant GCTB is a high-grade sarcoma that occurs at the site where a giant cell tumor was previously treated either by radiotherapy (radiation-induced form) or one of various types of surgery (evolutionary form)
Cancer Hospital, Kolkata, India Mondal et al[22]	NAC followed by open biopsy was performed for all patients as part of the diagnostic process. Computerized tomography-guided NAC was used for deep-seated lesions such as those occurring in the vertebrae and pelvic bones. The histopathologic diagnosis of GCTB was verified in three separate orthopedic centers by three separate histopathologists after a clinical meeting with orthopedic surgeons and radiologists	A primary malignant GCTB is composed of sarcomatous growth juxtaposed to zones of typical benign GCTB. A secondary malignant GCTB is a sarcomatous growth that occurs at the site of previously documented benign giant cell tumor of bone. Histopathologic examination, verified by three separate histopathologists, was performed for all suspected cases of malignant GCTB
Mayo Clinic, Rochester, Minnesota, USA Unni and Inwards[2] McDonald et al[20] Rock et al[11] Dahlin[21]	The diagnosis of benign GCTB was confirmed by a review of histologic sections	GCTB was classified as primary or secondary according to Hutter et al[10] and Dahlin et al.[9] Primary malignant GCTB is a malignant tumor of bone that is composed of sarcomatous growth juxtaposed to zones of typical benign GCTB tumor, and a secondary malignant GCTB is a sarcomatous growth that occurs at the site of a previously documented benign GCTB. For cases designated as malignant GCTB, the pathologic, radiographic, and clinical aspects were reviewed
Memorial Sloan Kettering Cancer Center, New York, NY, USA Domovitov[23]	GCTB was confirmed histologically	Malignancy in GCTB was defined according to Huvos:[46] "primary malignant GCTB shows a characteristic pattern of giant cells and stromal cells in which the appearance of the stromal cells in many microscopic fields gives the tissue a clearly sarcomatous picture." Large areas of collagenous deposits within the lesion and mitotic figures alone were insufficient to make the diagnosis of malignant GCTB Diagnosis of malignancy of GCTBs was established by means of an open biopsy for most tumors; a needle biopsy was used for spinal tumors. Some cases of malignancy were identified from curettage specimens after treatment of what was suspected to be benign GCTB. All cases were reviewed and confirmed in a weekly tumor board meeting by clinical, radiologic, and histologic correlation

Abbreviations: GCTB, giant cell tumor of bone, NAC, needle aspiration cytology.

giant cell-containing tumors, such as angiosarcoma, fibrosarcoma, and chondrosarcoma.[14]

A problem with the definition of malignant GCTB is the occurrence of benign metastasizing GCTB; pulmonary metastases are the most common.[3] Of the 671 patients with GCTB at the Mayo Clinic, 20 developed benign pulmonary metastases and 2 had tumor-related deaths (4 died from other causes).[2] Of the 293 patients at the Rizzoli Institute, only 3 developed confirmed benign pulmonary metastases, and none died from their disease.[19] While GCTB pulmonary metastases tend to be indolent and can be treated with surgery,[3,7] sarcomatous pulmonary metastases are often fatal.[7]

Mutational testing is under evaluation as an approach to assist in the diagnosis of GCTB, with recent research suggesting a potential role for histone 3.3 gene mutations.[53] In particular, *H3F3A* mutations may help to differentiate GCTB from giant cell-rich sarcomas. In a recent study, 24 of the 25 GCTBs evaluated had an *H3F3A* mutation compared with 5 of 35 giant cell-rich sarcomas; all of the sarcomas with the mutation were secondary malignant GCTB.[53] Research is ongoing to further evaluate the potential use of mutational analysis in GCTB diagnosis and to understand whether specific mutations are retained or lost when GCTBs undergo malignant transformation.

Prognosis

The prognosis of malignant GCTB is not fully understood owing to the lack of long-term follow-up data.[8] In the large case series, the prognosis was better among patients with primary than secondary malignancy. At the Rizzoli Institute, 1 patient with primary malignancy died at 8 months, another was alive at 40 months, and the remaining 3 had no sign of disease at 2, 15, and 161 months.[14] At the MSKCC, 5-year survival with primary malignancy was 87%.[23] At the Rizzoli Institute, however, all patients with secondary malignancy following radiotherapy died (after 5-148 months), and half of those with secondary malignancy following bone graft died.[14] At the Mayo Clinic, 5-year disease-free survival in patients with secondary malignancy was 32%.[11] At the Cancer Hospital, Kolkata, all patients who developed postradiation sarcoma died within a few months, owing to sarcomatous lung metastasis.[22]

It is generally accepted that malignant GCTB is a high-grade sarcoma;[1,14] however, data from the MSKCC show that malignant GCTB behaves like a low- or intermediate-grade sarcoma. The difference in GCTB grades reported in this study may reflect that most malignant cases at this center were primary rather than secondary. As discussed, primary malignancies appear to be associated with better prognoses than secondary malignancies (Table 5).

Conclusions

Malignant GCTB is rare; among 2315 patients with GCTB, our analysis identified an incidence of 1.6% for primary malignancy and 2.4% for secondary malignancy. Although current data appear to confirm that most secondary malignancies follow radiation, some large series do not provide complete treatment data, making it difficult to determine secondary malignancy risk associated with specific previous GCTB treatment. Additional studies on treatment patterns and malignancy incidence would help to clarify malignancy risk associated with each treatment. To ensure optimal care of patients with GCTB, we recommend comprehensive histologic sampling to establish an accurate diagnosis; watchful follow-up, particularly for patients treated with radiation; and timely treatment of local recurrence.

Declaration of Conflicting Interests

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