

# Metastatic giant cell tumour of bone: a narrative review of management options and approaches

Ruiwen Xu <sup>†\*</sup> and Peter F. M. Choong<sup>‡§¶</sup>

\*St Vincent's Hospital Clinical School, The University of Melbourne, Melbourne, Victoria, Australia

†Melbourne Medical School, The University of Melbourne, Melbourne, Victoria, Australia

‡Department of Surgery, The University of Melbourne, Melbourne, Victoria, Australia

§Department of Orthopaedics, St. Vincent's Hospital Melbourne, Melbourne, Victoria, Australia and

¶Bone and Soft Tissue Sarcoma Unit, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

## Key words

bone neoplasms, denosumab, diphosphonates, giant cell tumour of bone.

## Correspondence

Dr. Ruiwen Xu, St Vincent's Hospital Clinical School, The University of Melbourne, 23 Regent Street, Fitzroy, Melbourne VIC 3065, Australia.  
Email: ruiwenxu98@gmail.com

**R. Xu** MD, BMedSci; **P. F. M. Choong** MBBS, FRACS.

The corresponding author is not a recipient of a research scholarship.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Accepted for publication 17 January 2022.

doi: 10.1111/ans.17520

## Introduction

Giant cell tumour of bone (GCTB) is a locally aggressive primary bone neoplasm which accounts for 4–8% of all primary bone tumours in Western countries.<sup>1,2</sup> It is a rare disease with an incidence of approximately one per million person years.<sup>3</sup> GCTB primarily affect skeletally mature individuals with a peak incidence in the third and fourth decades of life and a slight female preponderance.<sup>1</sup> Its behaviour is characterized by aggressive local osteolysis and a propensity for recurrence in up to 50% of patients, depending on the initial treatment.<sup>4</sup> GCTB has a rare tendency to metastasise and may also undergo malignant transformation in rare instances.

## Abstract

Giant cell tumour of bone (GCTB) is a locally aggressive bone neoplasm with a rare tendency to metastasise, most commonly to the lungs. The management of metastatic GCTB (metGCTB) is controversial due to its unpredictable behaviour. Asymptomatic patients should be monitored radiologically and undergo treatment only when disease progression occurs. Surgery is recommended for resectable metGCTB. Denosumab, a monoclonal antibody which inhibits receptor activator of nuclear factor- $\kappa$ B ligand, is recommended for unresectable metGCTB with evidence from phase II trials demonstrating its safety and efficacy. Relapse after denosumab withdrawal may occur and prolonged treatment may be associated with serious adverse events, thus further research is warranted to inform a maintenance regimen with reduced dosing and frequency. Combined denosumab and bisphosphonate therapy has the potential to achieve sustained disease control or remission in unresectable metGCTB without requiring long-term treatment and should be evaluated in prospective trials. Various novel agents have demonstrated *in vitro* and anecdotal efficacy and warrant further evaluation.

GCTB comprises three cell types: multinucleated osteoclastic giant cells (GC), mononuclear stromal cells (SC) and monocytes.<sup>5</sup> The GC after which this tumour is named are responsible for the osteolysis whereas the SC are the neoplastic component that drive tumorigenesis.<sup>5</sup> SC proliferate and secrete chemokines that recruit circulating monocytes into the tumour stroma.<sup>5</sup> SC also express high levels of macrophage colony-stimulating factor and receptor activator of nuclear factor- $\kappa$ B (RANK) ligand, which induce monocyte RANK expression and promote monocyte fusion into RANK-positive GC, respectively.<sup>5</sup> The exact cause of SC proliferation and RANK ligand (RANKL) overexpression are unknown. However, a mutation in the H3F3A gene (encodes histone variant H3.3-G34W)

found nearly exclusively in SC was recently discovered to be sufficient to drive tumorigenesis in GCTB.<sup>6</sup>

GCTB can affect any bone, but most arise as unifocal lesions in the epiphysis of long bones.<sup>7</sup> Most patients present with pain but swelling, limited joint motion, neurological deficits or pathological fractures may occur depending on the site and the extent of the tumour.<sup>4,7</sup> Surgery is the mainstay of treatment for primary and recurrent GCTB and intralesional curettage with adjuvants is preferred for most lesions.<sup>7,8</sup> Despite extending the curettage margin with local adjuvant therapy, recurrence rates still remain high at around 30%.<sup>9</sup> Alternatively, en-bloc resection reduces recurrence risks but is associated with significant morbidity.<sup>7</sup> Systemic and locoregional therapies for primary disease include denosumab, bisphosphonates, interferon, radiotherapy and serial arterial embolization.<sup>4,8</sup> Denosumab is preferred for unresectable primary GCTB or utilized neoadjuvantly to facilitate less morbid resections.<sup>7-9</sup>

GCTB most commonly metastasise to the lung parenchyma.<sup>10,11</sup> Metastatic GCTB (metGCTB) is histologically identical to the primary tumour and can present as a solitary lesion or with numerous nodules.<sup>12</sup> Most cases are asymptomatic, but patients may complain of cough, dyspnoea, haemoptysis or chest pain.<sup>11</sup> Metastasis occur in 1–9% of GCTB with large series reporting rates of 2–3%.<sup>13–16</sup> Its natural history is difficult to predict but can be categorized into three groups: spontaneous regression (SR) or growth cessation, indolent growth, or uncontrollable rapid growth.<sup>17,18</sup> The mortality rates of metGCTB range from 0% to 25% but it generally carries a favourable prognosis with a recent study reporting a 5 year survival rate of 94.4%.<sup>12,19,20</sup> There is no validated method to predict metastasis, but several risk factors have been identified: younger age, axial primary disease, initial treatment with curettage, Campanacci or Enneking Stage III disease, and local recurrence (LR).<sup>12,17,20,21</sup> Multiple studies have established LR as an independent risk factor for metastasis.<sup>20,22</sup> As metGCTB is rare and unpredictable, there is significant controversy surrounding its management. This review aims to explore the evidence for the treatment of metGCTB to elucidate treatment options and approaches and identify voids in the literature that require further research.

## Management options

Available treatments for metGCTB depend on the resectability of the lesion and prior treatments (see Table 1). Surgery is the preferred treatment for resectable pulmonary metGCTB and offers good long-term progression-free or disease-free survival.<sup>8,11,13,15,23</sup> Denosumab, bisphosphonates, interferon, radiotherapy, and chemotherapy are available for unresectable metGCTB.

### Denosumab

Denosumab is a monoclonal antibody that inhibits RANKL, thereby eliminating GC and consequent GC-mediated osteolysis.<sup>24</sup> Denosumab has been approved by the Therapeutic Goods Administration for the treatment of GCTB in adults or skeletally mature adolescents that is recurrent, unresectable, or resectable but associated with severe morbidity.<sup>25</sup> It is administered as a single 120 mg subcutaneous injection four-weekly with additional 120 mg loading doses on days eight and 15 of the first cycle.<sup>24</sup>

Thomas *et al.* first assessed the efficacy of denosumab in a multicentre phase II trial involving 37 patients with recurrent or unresectable GCTB (lung metGCTB: nine). Thirty of 35 patients (86%) exhibited tumour response at 25 weeks (definition:  $\geq 90\%$  GC elimination, complete GC elimination if  $< 5\%$  of cells at baseline or no radiologic progression). These outcomes were associated with clinical benefits such as pain reduction and functional improvements.<sup>24</sup> Chawla *et al.* further evaluated the efficacy of denosumab in GCTB in a multicentre phase II trial involving 532 patients divided into three cohorts. Cohort one included 264 patients with unresectable GCTB (lung metGCTB: 52). Cohort two included patients with resectable GCTB where surgery would be associated with severe morbidity and cohort three included patients from another study. Twenty-eight of 262 patients (11%) in cohort one suffered disease progression during treatment (median duration: 44.4 months) but 132 patients (50%) discontinued denosumab without disease progression. Thirty-four patients (26%) then experienced disease progression or recurrence after denosumab discontinuation with a median time to progression of 39 months.<sup>26</sup>

**Table 1** Summary of treatment options for metastatic giant cell tumour of bone

Treatment	Indication	Comment
Metastasectomy	First-line for resectable metGCTB.	Favourable long-term progression-free or disease-free survival from case series.
Denosumab	First-line for unresectable metGCTB.	Level III evidence for safety and efficacy. May require long-term administration for prolonged disease control, complicated by time- and dose-dependent adverse events.
Bisphosphonate	Undefined role in unresectable metGCTB.	Case series showing efficacy and safety. Potential to directly eliminate neoplastic stromal cells and offer prolonged disease control without long-term administration.
Radiotherapy	Undefined role in unresectable metGCTB.	Anecdotal evidence showing good efficacy. May induce malignant transformation.
Interferon $\alpha$	Last-line for unresectable metGCTB that are refractory to other therapies.	Limited evidence, anecdotal only
Chemotherapy	Last-line for unresectable metGCTB that are refractory to other therapies on a case-by-case basis, no routine role in treating metGCTB.	Heterogenous anecdotal evidence with variable efficacy, high risk of toxicity.

Abbreviation: MetGCTB, metastatic giant cell tumour of bone.

Ueda *et al.* in another multicentre phase II trial studied the objective tumour response to denosumab using three radiologic criteria in 17 patients (pulmonary metGCTB: three). Fifteen patients (88%) had an objective tumour response based on best response using any criteria. The median time to an objective response was 3 months, and this response was sustained for at least 24 weeks in 87% of patients.<sup>27</sup>

In terms of safety, Thomas *et al.* reported that 33 of 37 patients experienced an adverse event, with the most frequent being pain in extremity, back pain, and headache. Five patients had grade 3–5 adverse events and only one was possibly treatment related.<sup>24</sup> Chawla *et al.* identified similar adverse event profiles and noted that the commonest treatment-related adverse events were fatigue, headache, and hypophosphatemia. Osteonecrosis of the jaw (ONJ) occurred in 21 of 262 patients (8%) in cohort one. The frequency of ONJ increased with increasing denosumab exposure and the presence of dental comorbidities. Other safety events of interest included four (<1%) atypical femoral fractures (AFF) in cohort one, which all occurred after long-term (> 48 months) denosumab treatment, two cases (<1%) of hypercalcaemia in cohort one after denosumab discontinuation and four cases of malignant GCTB determined to be sarcomatous transformation after denosumab exposure.<sup>26</sup> Other cases of malignancy in GCTB after denosumab exposure have been reported.<sup>28</sup> Although there is no evidence to support a causal relationship between denosumab and malignancy, it is a concerning finding nonetheless and warrants further investigation to understand denosumab's carcinogenic potential.

These multicentre trials provide level III evidence for the safety and efficacy of denosumab in treating metGCTB. However, Chawla *et al.* highlighted that denosumab cessation was associated with a risk of relapse.<sup>26</sup> This is unsurprising because denosumab target GC, which are not the neoplastic cells in GCTB. Although Thomas *et al.* reported that denosumab may have indirect effects on SC through a reciprocally dependent survival relationship between SC and GC,<sup>29</sup> this effect might not be substantial enough to produce a sustained response. Therefore, long-term denosumab therapy might be necessary for some patients. This is complicated by dose-dependent and time-dependent adverse events such as ONJ and AFF, respectively. More research is needed to evaluate maintenance regimens with reduced dose or frequency and to identify patients who are likely to require ongoing treatment. A phase II trial to examine a reduced-dose denosumab maintenance regimen for unresectable GCTB was terminated due to poor accrual (NCT03620149).

## Bisphosphonate

Bisphosphonates (BP) inhibit osteoclast formation, inhibit osteoclast-mediated bone resorption, and stimulate osteoclast apoptosis.<sup>29,30</sup> BP can also induce apoptosis of GCTB SC and GC *in vivo* and *in vitro*.<sup>30,31</sup> It is likely through these mechanisms that adjuvant BP have achieved efficacy in reducing recurrence after surgery for GCTB.<sup>32</sup> However, data on the use of BP in metGCTB is sparse. The only study to evaluate the efficacy and safety of BP in metGCTB was a case series by Balke *et al.* with 12 cases of pulmonary metGCTB. Patients received various BP regimens and exhibited no radiologic evidence of

progression, with one lesion demonstrating partial regression. No patients experienced significant adverse effects during treatment.<sup>29</sup>

Due to the introduction of denosumab, the role of BP in metGCTB has not been well-studied. BP are the only therapy that directly inhibit growth and induce apoptosis of both SC and GC.<sup>29–31</sup> Denosumab directly inhibit GC with an indirect inhibitory action on SC but does not seem to inhibit growth or induce apoptosis of SC without GC.<sup>29,31</sup> Therefore, BP may have an advantage over denosumab in achieving sustained disease control or remission in unresectable metGCTB without long-term treatment. However, BP need to adsorb to bone surfaces to act and the lack of osseous tissue in metGCTB may limit its efficacy.<sup>27</sup> As denosumab can induce bone formation in GCTB, the combination therapy of denosumab followed by BP may have potential to provide sustained disease control.<sup>24,33</sup> Prospective trials should compare BP to denosumab and evaluate the efficacy of combining denosumab and BP to treat metGCTB.

## Radiotherapy

The evidence for radiotherapy in metGCTB is limited to small case series. Feigenberg *et al.* reported three cases of pulmonary metGCTB treated with radiotherapy to the entire lung and to local areas of disease. Two patients with residual disease after surgery and chemotherapy had excellent response with complete resolution of disease and long-term survival of seven and 13 years and the other patient failed to respond to chemotherapy and radiotherapy, and died.<sup>34</sup> Other series have described patients with unresectable metGCTB treated with radiotherapy and most have observed sustained regression or resolution of the metastatic disease.<sup>23,35</sup> The role of radiotherapy in metGCTB is unclear due to limited evidence but it may have potential in treating metGCTB that are unresectable or refractory to other treatment.<sup>34</sup> However, radiotherapy can induce malignant transformation so further evaluation is needed before its role in metGCTB can be safely established.<sup>35,36</sup>

## Interferon

Evidence for the use of interferon  $\alpha$  in metGCTB is anecdotal only. Kaiser *et al.* reported one case of chemotherapy-refractory pulmonary metGCTB treated with interferon  $\alpha$ -2a 9 000 000 IU subcutaneously three-times-weekly for 13 months, which reduced the size of the pulmonary nodules by over 50%. The therapy was well tolerated, and the patient reported no pulmonary symptoms.<sup>37</sup> Wei *et al.* reported further success in treating pulmonary metGCTB with interferon  $\alpha$ -2a 3 000 000 IU/m<sup>2</sup> subcutaneously daily. Continued treatment saw some metastatic lesions shrink and others disappear but was complicated by leukopenia and thrombocytopenia, which were reversible with temporary treatment cessation.<sup>38</sup> Authors have recommended interferon  $\alpha$  as last-line therapy for metGCTB refractory to other treatment.<sup>37,38</sup>

## Chemotherapy

The literature on the use of chemotherapy in metGCTB is highly heterogeneous. Various regimens have been used in diverse contexts (as single therapy for unresectable disease, as adjuvant therapy or with radiotherapy) with variable responses.<sup>11,13,15,17,19,20,23,35,39–42</sup> Death from chemotherapy-related sepsis have occurred.<sup>13,19,35</sup>

Given its toxicity and the lack of evidence for its efficacy, chemotherapy should not have a routine role in the management of metGCTB. However, it may be considered on a case-by-case basis as last-line therapy for aggressive metGCTB that have failed to respond to other treatment.

## Emerging therapy

Novel agents with anecdotal or *in vitro* evidence have been reported. Lau *et al.* found that simvastatin suppressed SC proliferation and induced SC apoptosis *in vitro*.<sup>43</sup> With direct action on the neoplastic SC and a well-established safety profile, simvastatin has potential in treating metGCTB, but human studies are required. Two tyrosine kinase inhibitors, apatinib and sunitinib, have demonstrated efficacy in treating denosumab-resistant metGCTB in case reports, and warrant further evaluation in prospective studies.<sup>44,45</sup> Cabozantinib, another tyrosine kinase inhibitor, and norcantharidin, an anticancer drug derived from Chinese medicine, inhibited SC proliferation in *in vitro* studies.<sup>46,47</sup> These agents also have potential in treating metGCTB and should be evaluated in human studies.

## Management approaches

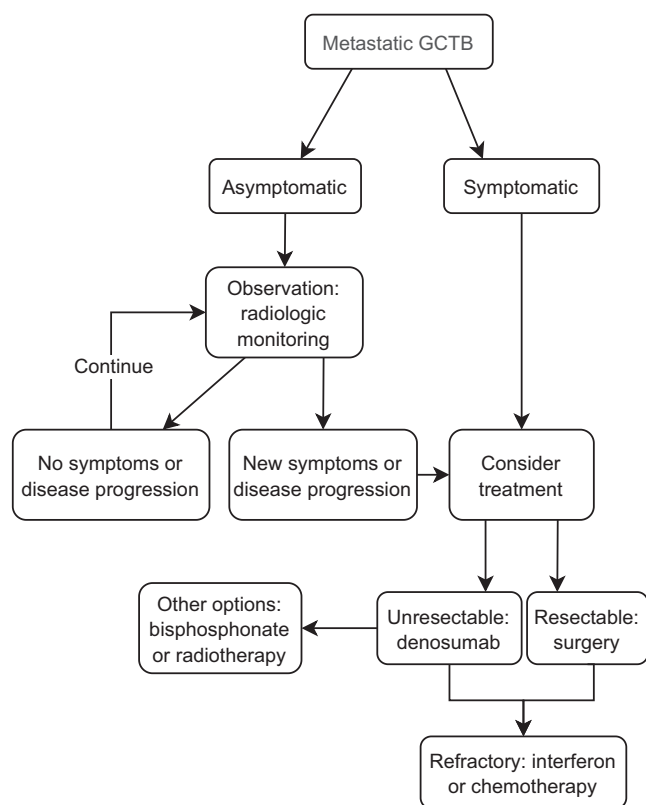
Successful management of metGCTB starts with timely detection of metastases. Metastases have been diagnosed concurrently with primary GCTB, but most develop within three to 4 years after

surgery for the primary tumour. Hence, authors have suggested screening for metGCTB at initial presentation and for at least 3 years after initial surgery.<sup>19,21,22,36</sup> Chest computed tomography (CT) was found to be superior to chest radiography in detecting metGCTB and should be the preferred modality in screening for pulmonary metastases.<sup>22</sup> GCTB has similar metastatic risks as low-grade sarcomas (2–10%), therefore the recommended screening interval of 6 months for low-grade sarcomas may be adequate for GCTB.<sup>22</sup> LR has been identified as an independent risk factor for metastasis and over 80% of metastases occur within three to 4 years after LR, thus intensified screening intervals should be considered for patients with LR for at least 3 years following recurrence.<sup>22</sup> The impact of other risk factors on screening is unclear and should be further evaluated.

MetGCTB exhibits highly unpredictable behaviour. Various series have reported cases of SR and growth cessation, and a recent systematic review has calculated a pooled SR rate of 4.5%.<sup>10,36,41</sup> Though, the true SR rate may be higher as many lesions were treated before SR could occur. Authors have historically recommended immediate treatment after a diagnosis of metGCTB.<sup>17,18,39,42</sup> With an awareness that some metGCTB exhibit self-limiting or dormant behaviours and considering the risks associated with aggressive treatment, authors have recently recommended observation of pulmonary metGCTB with frequent radiologic surveillance as initial management for asymptomatic patients, and consideration of treatment only when symptoms develop or disease progression occurs (increase in number or size of lesions).<sup>19–21,36</sup>

Tsukamoto *et al.* observed 22 patients with pulmonary metGCTB using chest CT and detected disease progression in 12 patients (54.5%) at a median of 8 months after diagnosis. Ten of these patients required treatment for their progressive disease, but none died. Interestingly, the metastases progressed in 5 of 11 patients (45.5%) with lesions of 5 mm or less, whereas progression occurred in all patients with lesions greater than 5 mm. Progression-free survival was significantly poorer in patients with lesions larger than 5 mm ( $p = 0.022$ ), suggesting that more aggressive monitoring may be necessary for patients with pulmonary metGCTB larger than 5 mm.<sup>36</sup>

We propose that instead of immediate treatment after diagnosis, asymptomatic pulmonary metGCTB should be monitored with a regime of imaging to establish the tempo of disease. Surgery should be considered for resectable lesions and denosumab considered as first-line for unresectable lesions only when patients develop symptoms or their disease progresses (see Fig. 1 for algorithm). Based on limited data, most metastases that progress do so within 2 years of diagnosis.<sup>21,36</sup> Hence, it might be prudent to initiate with more aggressive surveillance (such as three-monthly CTs scans) for 2 years, then prolong the surveillance interval if the disease is stable. We acknowledge the limited evidence to guide any approach but believe that an observation first approach is appropriate for this often asymptomatic disease with a self-limiting potential. This approach will also provide an opportunity to collect data on the behaviour of metGCTB, which can be used to determine factors that predict disease progression or regression. These factors can then inform the frequency and duration of an evidence-based surveillance program. As metGCTB is rare, multi-institutional studies should be encouraged.



**Fig. 1.** Approach to the management of metastatic giant cell tumour of bone.

## Conclusion

The approach to managing metGCTB should commence with observation and frequent radiologic surveillance in asymptomatic patients and consideration of treatment only when disease progression occurs. Further studies to understand factors that predict the behaviour of metGCTB is needed to guide surveillance programs. Surgery is recommended for resectable metGCTB. Denosumab should be first-line for unresectable metGCTB as it has demonstrated safety and efficacy in phase II trials. However, denosumab cessation carries a risk of relapse, thus requiring long-term treatment which may be associated with serious adverse effects. Future studies should evaluate denosumab maintenance regimens with reduced dosing and frequency. Combining denosumab and BP may offer sustained disease control or remission in unresectable metGCTB without requiring long-term treatment and should be evaluated in prospective trials. Interferon and chemotherapy may have a role as last-line treatment for refractory unresectable metGCTB. Finally, various novel agents have demonstrated anecdotal or *in vitro* efficacy and should be evaluated in human studies or prospective trials.

## Acknowledgement

Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

## Conflicts of interest

None declared.

## Author contributions

**Ruiwen Xu:** Conceptualization; methodology; writing – original draft; writing – review and editing. **Peter F. M. Choong:** Conceptualization; project administration; supervision; writing – review and editing.

## References

- Rockberg J, Bach BA, Amelio J *et al.* Incidence trends in the diagnosis of giant cell tumor of bone in Sweden since 1958. *J. Bone Joint Surg. Am.* 2015; **97**: 1756–66.
- WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours Series: Soft Tissue and Bone Tumours*, 5th edn. France: International Agency for Research on Cancer, 2020.
- Liede A, Bach BA, Stryker S *et al.* Regional variation and challenges in estimating the incidence of giant cell tumor of bone. *J. Bone Joint Surg. Am.* 2014; **96**: 1999–2007.
- Ng VY, Davidson DJ, Kim EY, Pollack SM, Conrad Iii EU, Jones RL. The multidisciplinary management of giant cell tumor of bone. *Expert Rev. Anticancer Ther.* 2014; **14**: 783–90.
- Cowan RW, Singh G. Giant cell tumor of bone: a basic science perspective. *Bone* 2013; **52**: 238–46.
- Fellenberg J, Sähr H, Mancarella D *et al.* Knock-down of oncohistone H3F3A-G34W counteracts the neoplastic phenotype of giant cell tumor of bone derived stromal cells. *Cancer Lett.* 2019; **448**: 61–9.
- Basu Mallick A, Chawla SP. Giant cell tumor of bone: an update. *Curr. Oncol. Rep.* 2021; **23**: 51.
- National Comprehensive Cancer Network. Bone Cancer (Version 1.2021). Available from URL: [https://www.nccn.org/professionals/physician\\_gls/pdf/bone.pdf](https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf)
- van der Heijden L, Dijkstra S, van de Sande M, Gelderblom H. Current concepts in the treatment of giant cell tumour of bone. *Curr. Opin. Oncol.* 2020; **32**: 332–8.
- Itkin B, Straminsky S, De Ronato G, Lewi D, Marantz A, Bardach A. Prognosis of metastatic giant cell tumor of bone in the pre-denosumab era. A systematic review and a meta-analysis. *Jpn. J. Clin. Oncol.* 2018; **48**: 640–52.
- Kay RM, Eckardt JJ, Seeger LL, Mirra JM, Hak DJ. Pulmonary metastasis of benign giant cell tumor of bone. Six histologically confirmed cases, including one of spontaneous regression. *Clin. Orthop. Relat. Res.* 1994; **302**: 219–30.
- Yang Y, Huang Z, Niu X, Xu H, Li Y, Liu W. Clinical characteristics and risk factors analysis of lung metastasis of benign giant cell tumor of bone. *J. Bone Oncol.* 2017; **7**: 23–8.
- Siebenrock KA, Unni KK, Rock MG. Giant-cell tumour of bone metastasising to the lungs. A long-term follow-up. *J. Bone Joint Surg. Br.* 1998; **80**: 43–7.
- Rock M. Curettage of giant cell tumor of bone. Factors influencing local recurrences and metastasis. *Chir. Organi. Mov.* 1990; **75**(1 Suppl): 204–5.
- Dominkus M, Ruggieri P, Bertoni F *et al.* Histologically verified lung metastases in benign giant cell tumours--14 cases from a single institution. *Int. Orthop.* 2006; **30**: 499–504.
- Niu X, Zhang Q, Hao L *et al.* Giant cell tumor of the extremity: retrospective analysis of 621 Chinese patients from one institution. *J. Bone Joint Surg. Am.* 2012; **94**: 461–7.
- Viswanathan S, Jambhekar NA. Metastatic giant cell tumor of bone: are there associated factors and best treatment modalities? *Clin. Orthop. Relat. Res.* 2010; **468**: 827–33.
- Takanami I, Takeuchi K, Naruke M, Kodaira S. Aggressive surgery for treating a pulmonary metastasis of a benign giant cell tumor of the bone: results in four cases. *J. Thorac. Cardiovasc. Surg.* 1998; **116**: 649–51.
- Chen CC, Liao CT, Chang CH, Hsu YH, Shih HN. Giant cell tumors of the bone with pulmonary metastasis. *Orthopedics* 2016; **39**: e68–73.
- Chan CM, Adler Z, Reith JD, Gibbs CP Jr. Risk factors for pulmonary metastases from giant cell tumor of bone. *J. Bone Joint Surg. Am.* 2015; **97**: 420–8.
- Kito M, Matusmoto S, Ae K *et al.* Pulmonary metastasis from giant cell tumor of bone: clinical outcome prior to the introduction of molecular target therapy. *Jpn. J. Clin. Oncol.* 2017; **47**: 529–34.
- Rosario M, Kim H-S, Yun JY, Han I. Surveillance for lung metastasis from giant cell tumor of bone. *J. Surg. Oncol.* 2017; **116**: 907–13.
- Bertoni F, Present D, Sudanese A, Baldini N, Bacchini P, Campanacci M. Giant-cell tumor of bone with pulmonary metastases. Six case reports and a review of the literature. *Clin. Orthop. Relat. Res.* 1988; **237**: 275–85.
- Thomas D, Henshaw R, Skubit K *et al.* Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol.* 2010; **11**: 275–80.
- Therapeutic Goods Administration. Australian public assessment report for Denosumab. In: Department of Health (ed). Australia: Commonwealth of Australia, 2014.
- Chawla S, Blay J-Y, Rutkowski P *et al.* Denosumab in patients with giant-cell tumour of bone: a multicentre, open-label, phase 2 study. *Lancet Oncol.* 2019; **20**: 1719–29.

27. Ueda T, Morioka H, Nishida Y *et al.* Objective tumor response to denosumab in patients with giant cell tumor of bone: a multicenter phase II trial. *Ann. Oncol.* 2015; **26**: 2149–54.
28. Murphy B, Vodanovich D, Spelman T *et al.* Clinical, radiological and pathological outcomes following treatment of primary giant cell tumour of bone with Denosumab. *ANZ J. Surg.* 2020; **90**: 2553–8.
29. Balke M, Campanacci L, Gebert C *et al.* Bisphosphonate treatment of aggressive primary, recurrent and metastatic giant cell tumour of bone. *BMC Cancer* 2010; **10**: 462.
30. Cheng Y, Huang L, Lee K, Xu J, Zheng M, Kumta S. Bisphosphonates induce apoptosis of stromal tumor cells in giant cell tumor of bone. *Calcif. Tissue Int.* 2004; **75**: 71–7.
31. Lau CP, Huang L, Wong KC, Kumta SM. Comparison of the anti-tumor effects of denosumab and zoledronic acid on the neoplastic stromal cells of giant cell tumor of bone. *Connect. Tissue Res.* 2013; **54**: 439–49.
32. Kaiser P, Compton J, Caldwell J-M, Hickernell T, Lee F. Systemic therapy in patients with resectable and unresectable cases of Giant cell tumor: a systematic review. *J. Cancer Ther.* 2014; **05**: 339–53.
33. Branstetter DG, Nelson SD, Manivel JC *et al.* Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin. Cancer Res.* 2012; **18**: 4415–24.
34. Feigenberg SJ, Marcus RB Jr, Zlotecki RA, Scarborough MT, Enneking WF. Whole-lung radiotherapy for giant cell tumors of bone with pulmonary metastases. *Clin. Orthop. Relat. Res.* 2002; **401**: 202–8.
35. Cheng JC, Johnston JO. Giant cell tumor of bone. Prognosis and treatment of pulmonary metastases. *Clin. Orthop. Relat. Res.* 1997; **338**: 205–14.
36. Tsukamoto S, Ciani G, Mavrogenis AF *et al.* Outcome of lung metastases due to bone giant cell tumor initially managed with observation. *J. Orthopaed. Surg. Res.* 2020; **15**: 510.
37. Kaiser U, Neumann K, Havemann K. Generalised giant-cell tumour of bone: successful treatment of pulmonary metastases with interferon alpha, a case report. *J. Cancer Res. Clin. Oncol.* 1993; **119**: 301–3.
38. Wei F, Liu X, Liu Z *et al.* Interferon alfa-2b for recurrent and metastatic giant cell tumor of the spine: report of two cases. *Spine* 2010; **35**: E1418–22.
39. Rock MG, Pritchard DJ, Unni KK. Metastases from histologically benign giant-cell tumor of bone. *J. Bone Joint Surg. Am.* 1984; **66**: 269–74.
40. Stewart DJ, Belanger R, Benjamin RS. Prolonged disease-free survival following surgical debulking and high-dose cisplatin/doxorubicin in a patient with bulky metastases from giant cell tumor of bone refractory to “standard” chemotherapy. *Am. J. Clin. Oncol.* 1995; **18**: 144–8.
41. Sanjay BK, Kadhi SM. Giant cell tumour of bone with pulmonary metastases. A report of three cases. *Int. Orthop.* 1998; **22**: 200–4.
42. Faisham WI, Zulmi W, Halim AS, Biswal BM, Mutum SS, Ezane AM. Aggressive giant cell tumour of bone. *Singapore Med. J.* 2006; **47**: 679–83.
43. Lau CPY, Fung CSH, Wong KC *et al.* Simvastatin possesses antitumor and differentiation-promoting properties that affect stromal cells in giant cell tumor of bone. *J. Orthop. Res.* 2020; **38**: 297–310.
44. Wang G, Jiang S, Li Z, Dong Y. Denosumab and Sunitinib in the treatment of giant-cell tumor of bone with pulmonary and bone metastases in an adolescent: a case report. *Medicine* 2019; **98**: e17778.
45. Gong T, Luo Y, Wang Y *et al.* Multiple pulmonary metastases of recurrent Giant cell tumor of bone with expression of VEGFR-2 successfully controlled by Denosumab and Apatinib: a case report and literature review. *Cancer Manag. Res.* 2021; **13**: 4447–54.
46. Liu L, Aleksandrowicz E, Fan P *et al.* Enrichment of c-Met+ tumorigenic stromal cells of giant cell tumor of bone and targeting by cabozantinib. *Cell Death Dis.* 2014; **5**: e1471.
47. Chen F, Wang S, Wei Y *et al.* Norcantharidin modulates the miR-30a/Metadherin/AKT signaling axis to suppress proliferation and metastasis of stromal tumor cells in giant cell tumor of bone. *Biomed. Pharmacother.* 2018; **103**: 1092–100.