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ORIGINAL PAPER

Denosumab does not decrease the risk of lung metastases from bone giant cell tumour

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Abstract

Purpose There are conflicting reports on the effect of denosumab on lung metastases in patients with giant cell tumor (GCT) of bone. To address these reports, we performed this study to determine if denosumab prevents lung metastasis and to evaluate univariate and multivariate predictors for lung metastases in these patients.

Materials and methods We retrospectively studied 381 GCT patients with surgery alone and 30 GCT patients with surgery and denosumab administration. The median follow-up was 85.2 months (IQR, 54.2–124.4 months). We evaluated lung metastases and local recurrences, univariate and multivariate predictors for lung metastases, response, and adverse events of denosumab administration.

Results The occurrence of lung metastases was similar (surgery alone 4.7%, 18 patients; denosumab administration 3.3%, 1 patient); however, the occurrence of local recurrences was significantly higher in the patients with denosumab administration. Denosumab administration was not an important predictor for lung metastases; Campanacci stage and type of surgery were the only univariate predictors for lung metastases, and type of surgery and local recurrence were the only multivariate predictors for lung metastases. Histology showed viable tumour in all tumor specimens of the patients with denosumab administration.

Conclusion Denosumab does not decrease the risk of lung metastases in patients with bone GCT; the only important predictors for lung metastases in these patients are type of surgery and local recurrence. However, because the number of patients with lung metastases was small for a multivariate analysis, the possibility of denosumab's effect could not be completely eliminated.

Keywords Giant cell tumour of bone · Denosumab · Metastasis · Lungs

Introduction

Giant cell tumour (GCT) of bone is a benign but locally aggressive bone tumour with a wide biological spectrum [1]. Benign metastases may occur, almost exclusively to the lungs, with a range from 2 to 7.5% [2–5]. Growth rate of GCT lung metastases is very low [6]. Previous studies reported that GCT of the distal radius is more commonly associated with lung metastases [7, 8] and a more aggressive behaviour and that resection, if necessary, is associated with worse functional outcomes [9, 10]. The outcome of lung metastases in patients with GCT varies from spontaneous regression to uncontrolled growth, eventually resulting in death [5]; the mortality rate of metastatic GCT ranges widely from 0 to 23% [7, 8, 11]. Therefore, it is vital to prevent lung metastases as no effective medical treatment has been reported to date.

In 2013, the U.S. Food and Drug Administration approved the use of denosumab, a monoclonal antibody that binds to the receptor activator of nuclear factor-kappa β ligand to treat

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adults and skeletally mature adolescents with unresectable GCT or when resection is likely to result in severe morbidity [12, 13]. Previous clinical studies suggested that denosumab is associated with tumour response and reduced surgical morbidity in GCT patients [12, 14, 15]. However, other studies reported conflicting results with minimal inhibitory effect of denosumab on GCT cells [16, 17], persistent tumour cells in the treated specimens [17–19], and increased risk for local recurrences [19, 20]. More important, the literature lacks information regarding the effect of denosumab on lung metastases in these patients.

Therefore, to address these conflicting reports, we performed this study to determine whether (neo-)adjuvant denosumab has any effect on the outcome of patients with GCT. Our primary analysis was to determine if denosumab decreases the risk of lung metastasis, and our secondary analysis was to determine the univariate and multivariate predictors for lung metastases in these patients.

Materials and methods

We reviewed the files of 411 patients with GCT of the extremities without lung metastasis at presentation, as evident in computed tomography (CT) of the chest, admitted and treated at the senior author's institution from January 1990 to December 2013 (Table 1). There were 196 men and 215 women with a median age of 29.3 years (interquartile range [IQR], 23.2 to 40.9 years). All patients gave written informed consent for their data to be included in any possible future scientific study. This study was approved by the Institutional Review Board/Ethics Committee of the senior author's institution.

All patients had histological confirmation of their tumors with pre-operative biopsy, and staging of their tumors with the Campanacci classification on radiographs [21]. The patients were allocated into two groups based on tumours' location in the distal radius (45 patients) or other sites (366 patients), because a distal radius location is considered more aggressive [7, 8]. All patients had surgical treatment including curettage (247 patients), resection and reconstruction for large tumours with soft tissue extension, pathological fractures with joint invasion or an unstable fracture pattern, multiple recurrences, and tumour location in expendable bones [9] (161 patients) or amputation for large tumours involving the neurovascular bundle (three patients). Curettage was performed through a large cortical bone window using curettes of different sizes that enabled removal of all visible tumours. The cavity was then cleaned with a high-speed burr and washed thoroughly with intent to remove all pathological tissues [9]. Phenol alternately with alcohol were applied to the cavity's borders with cotton-tipped swabs as adjuvants, and the bone cavity was filled with polymethylmethacrylate (PMMA) bone cement in 109 patients, bone allografts in 56 patients, combined bone cement and allografts in 78 patients, or left empty in four patients. Reconstruction after resection was done with a modular prosthesis in 57 patients, massive bone allografts in 60 patients, or allograft composite prostheses in 17 patients; a reconstruction was not done in 27 patients with GCT locations in the fibula, distal ulna, proximal radius, scapula, and patella.

From this cohort, 30 patients admitted and treated from 2010 to 2013 at the senior author's institution were assigned to a phase 2 clinical trial protocol (AMG20062004 [ClinicalTrials.gov/; identifier: NCT00680992]) or were administered denosumab off-label. Indications for administration of denosumab were GCT location at the distal radius for down-staging the tumour because tumors at this location are reported more aggressive and their resection

Table 1 Details of the patients included in this series

Variables	All patients ($n = 411$, %)	Denosumab (n, %) Yes	Denosumab (n, %) No	p value[≠]
Age				
< 30 years	207 (50.4%)	7 (23.3%)	200 (52.5%)	0.002*
≥ 30 years	204 (49.6%)	23 (76.7%)	181 (47.5%)	
Sex				
Male	196 (47.7%)	15 (50.0%)	181 (47.5%)	0.792
Female	215 (52.3%)	15 (50.0%)	200 (52.5%)	
Site				
Distal radius	45 (10.9%)	8 (26.7%)	37 (9.7%)	0.010*[,#,a]
Distal femur	137 (33.3%)	5 (16.7%)	132 (34.6%)	
Proximal tibia	99 (24.1%)	6 (20.0%)	93 (24.4%)	
Proximal fibula	16 (3.9%)	0 (0.0%)	16 (4.2%)	
Proximal femur	22 (5.4%)	0 (0.0%)	22 (5.8%)	
Proximal humerus	26 (6.3%)	5 (16.7%)	21 (5.5%)	
Distal tibia	19 (4.6%)	3 (10.0%)	16 (4.2%)	
Distal ulna	13 (3.2%)	1 (3.3%)	12 (3.1%)	
Others	34 (8.3%)	2 (6.7%)	32 (8.4%)	
Campanacci stage				
Stage I	6 (1.5%)	0 (0.0%)	6 (1.6%)	0.579[b]
Stage II	233 (56.7%)	16 (53.3%)	217 (57.0%)	
Stage III	172 (41.8%)	14 (46.7%)	158 (41.5%)	
Previous surgery				
None	342 (83.2%)	25 (83.3%)	317 (83.2%)	0.985
1	69 (16.8%)	5 (16.7%)	64 (16.8%)	
Type of surgery				
Curettage	247 (60.1%)	25 (83.3%)	222 (58.3%)	0.007*[,c]
Resection	161 (39.2%)	5 (16.7%)	156 (40.9%)	
Amputation	3 (0.7%)	0 (0.0%)	3 (0.8%)	
Local recurrence				
None	338 (82.2%)	15 (50.0%)	323 (84.8%)	< 0.0001*
≥ 1	73 (17.8%)	15 (50.0%)	58 (15.2%)	
Pulmonary metastases				
None	392 (95.4%)	29 (96.7%)	363 (95.3%)	0.589
≥ 1	19 (4.6%)	1 (3.3%)	18 (4.7%)	

*Statistically significant

[#] Fisher's exact test

[≠] Statistical significance between the patients who were administered denosumab and those who did not

[a] Comparison between distal radius and other sites

[b] Comparison between Campanacci stages I/II and III

[c] Comparison between curettage and resection/amputation

associated with worse functional outcomes [9, 10], unsalvageable tumours in surgically difficult locations, and salvageable tumours where surgery was considered to be associated with severe morbidity. Pre-operatively, denosumab was administered subcutaneously in a dose of 120 mg once a week for one month and then once a month for six to nine months depending on the recommendation for discontinuation by the treating physician, occurrence of an adverse event, clinical benefit from treatment, planning for surgery, and clinical trial protocol (6 months). Surgical treatment was done one month after the last preoperative dose of denosumab and included curettage in 25 patients and resection in five patients. Post-operatively, denosumab was administered in the same dose as pre-operatively, once a month for three to seven months depending on the recommendation for discontinuation by the treating physician, occurrence of an adverse event, absence of clinical benefit and/or evidence of disease progression, patients' decision to discontinue, and clinical trial protocol (6 months) [22]. In addition to denosumab, the patients were administered calcium (500 mg/day) and vitamin D (≥ 400 IU/day) supplements.

The effect of denosumab treatment was determined by comparing radiographs obtained before denosumab administration vs. those obtained immediately pre-operatively; GCT response was evaluated with the modified inverse Choi criteria (density/size) [23]. Adverse events and laboratory values abnormalities were evaluated with the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [24].

After treatment, the patients were followed every four months for the first two years, every six months for the next three years, and then annually. The median follow-up for all patients was 85.2 months (IQR, 54.2–124.4 months), the minimum follow-up was 24 months, and the median follow-up for the patients who were administered denosumab was 42.4 months (IQR, 37.5–51.9 months); no patient was lost to follow-up. Follow-up evaluation included radiographs of the tumour area and CT of the chest. The occurrence of local recurrence and lung metastases was recorded. Tumour specimens from the diagnostic biopsies, primary tumour, local recurrences, and lung metastases were histologically reviewed. Metastasis-free survival was defined as the interval between surgical treatment and occurrence of nodular, rounded, well-defined opacities suspected to be lung metastases on chest CT (Fig. 1) [11].

The χ^2 test or the Fisher's exact test was used to compare two variables, as appropriate. Metastasis-free survival was evaluated with the Kaplan–Meier survival analysis; survival curves were compared with a log-rank test. Multivariate predictors for lung metastases were determined with a Cox proportional hazards regression analysis. A p value < 0.05 was considered statistically significant. We performed propensity score matching to evaluate matched patients and perform survival analysis; propensity score matching returned 60 matched patients from the overall cohort; the 30 patients with denosumab administration were matched to 30 patients with surgery alone. Analyses were performed with IBM SPSS version 21.0 (IBM Co., Armonk, NY, USA) and JMP® 11 (SAS Institute Inc., Cary, NC, USA).

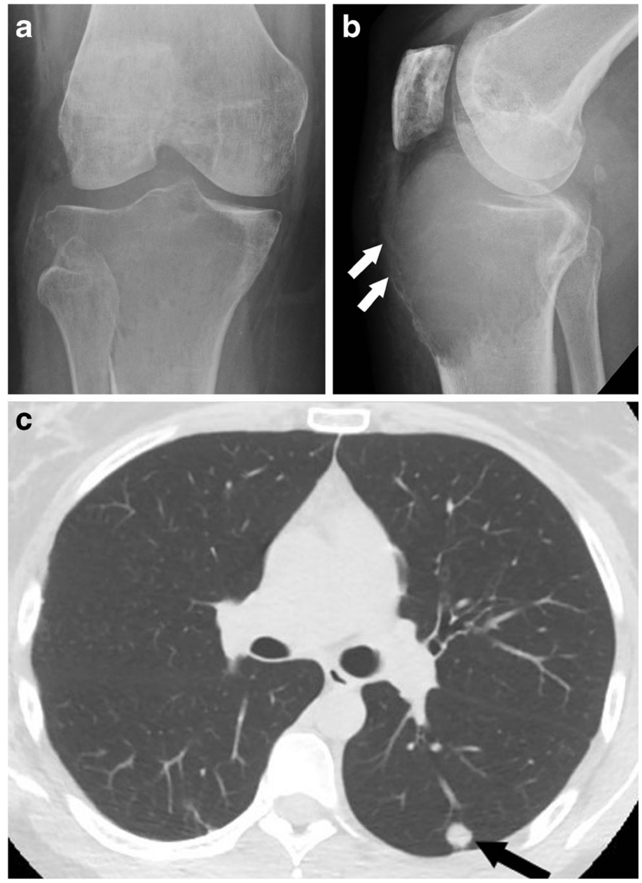

Fig. 1 A 28-year-old patient with a Campanacci stage III GCT of the proximal tibia who later developed lung metastasis. **a** Anteroposterior radiograph shows an osteolytic lesion with thinning of the cortex. **b** Lateral radiograph shows an osteolytic lesion with soft tissue extension (arrows). **c** CT of the chest shows a lung metastasis (arrow)

Results

Overall, 19 patients (4.6%) experienced lung metastases at a median of 68.4 months (IQR, 41–88.7 months), and 73 patients (17.8%) experienced local recurrences at a median of 15 months (IQR, 9.5–29 months) after diagnosis and treatment. There were 18 patients (4.7%) with surgery alone compared to 1 patient (3.3%) with denosumab administration who experienced lung metastases and 58 patients (15.2%) with surgery alone compared to 15 patients (50%) with denosumab administration who experienced local recurrences. The occurrence of lung metastases was similar between the two groups ($p = 0.589$); however, the occurrence of local recurrences was significantly higher in the patients with denosumab administration ($p < 0.0001$). Of the 60 matched patients after propensity score matching, only 3 patients experienced lung metastases; therefore, because of the small number of patients, a Kaplan–Meier survival analysis is not possible in this cohort, because a minimum of ten events (10 patients with lung metastases) is needed in order to perform a Kaplan–Meier survival analysis.

At the last follow-up, 313 patients were continuously disease-free, 73 had no evidence of disease after treatment for a local recurrence, 10 patients had no evidence of disease after treatment for a lung metastasis, nine patients were alive with lung metastases, and six patients were dead of other diseases. Eleven patients with lung metastases were treated with open metastasectomy alone; six of these patients had a part of their multiple lung metastases resected, and since then, their remaining lung metastases were stable in follow-up CT scans. One patient with lung metastases was treated with additional denosumab administration and open metastasectomy of a part of his multiple lung metastases, and since then, his remaining lung metastases were stable in follow-up CT scans. Seven patients with lung metastases were treated with observation alone as their lung metastases were stable. All patients with open metastasectomy had histological confirmation of their GCT lung metastases.

Denosumab administration was not an important predictor for lung metastases. Univariate analysis showed that Campanacci stage III vs. stage I/II tumors ($p < 0.0001$) and type of surgery (resection/amputation vs. curettage, $p < 0.0001$) were the only important predictors for lung metastases (Table 2). A stepwise multivariable analysis was conducted using all the clinical variables in Table 2. Multivariable analysis showed that type of surgery (resection/amputation vs. curettage, $p = 0.001$) and occurrence of local recurrence ($p = 0.018$) were the only important predictors for lung metastases (Table 3). Response results for the patients with denosumab administration showed partial response in 22 patients (73.3%) and stable disease in eight patients (26.7%). Adverse events of denosumab administration included a periapical abscess and a grade III periodontal disease (one patient each).

Histological sections of tumor tissue from the diagnostic biopsies, primary tumors, and resected lung metastases showed findings typical of GCT in all patients with surgery alone (Fig. 2). These included an admixture of neoplastic mononuclear cells and numerous evenly distributed osteoclast-type giant cells associated with haemosiderin deposits and focal reactive bone formation. The mononuclear cells showed a strong nuclear immunoexpression of H3F3A. Sections of resected lung metastases did not show any histological features that would indicate a malignancy (Fig. 3). Histological sections of primary tumors and lung metastases showed changes related to a denosumab effect in all patients with denosumab administration (Fig. 4). These included disappearance of osteoclast-like giant cells, formation of cellular areas characterized by sheets of round/ovoid tumour cells or spindle cells in a storiform pattern with little or no extracellular matrix, and areas with an abundant fibrillary extracellular matrix organized in trabecular structures or with increased honeycomb pattern within bones. These histological patterns were not haphazardly distributed in resected specimens but followed a zonal distribution, with more cellular areas at the tumours' central portion and matrix-rich areas in the periphery. At the tumours' periphery, the osteoid-like matrix appeared to merge with the host bone. Interestingly, viable tumor was present in all tumour specimens of the 30 patients with denosumab administration.

Table 2 Univariate predictors for lung metastasis-free survival of the patients included in this series

Variables	All patients ($n = 411$)	Five-year lung metastasis-free survival (95% CI)	p value
Age			
< 30 years	207	96.6% (92.6–98.5)	0.861
≥ 30 years	204	98.3% (94.9–99.5)	
Sex			
Male	196	98.3% (94.7–99.4)	0.881
Female	215	96.7% (92.8–98.5)	
Site			
Distal radius	45	93.6% (77.9–98.4)	0.053
Other sites	366	97.8% (95.4–98.9)	
Campanacci stage			
Stage I/II	239	99.6% (96.9–99.9)	<0.0001*
Stage III	172	94.4% (89.1–97.2)	
Previous surgery			
None	342	97.2% (94.5–98.6)	0.544
1	69	98.5% (90.3–99.8)	
Type of surgery			
Curettage	247	99.6% (97.0–99.9)	<0.0001*
Resection/amputation	164	94.4% (89.2–97.2)	
Denosumab administration			
Yes	30	87.5% (46.3–98.3)	0.332
No	381	97.6% (95.3–98.8)	
Local recurrence			
None	338	98.3% (96.0–99.3)	0.070
≥ 1	73	92.7% (81.9–97.2)	

*Statistically significant

Table 3 Multivariable predictors for lung metastasis-free survival of the patients included in this series (Cox regression analysis)

Variable	Hazard ratio (95% CI)	p value
Type of surgery		
Curettage vs. resection/amputation	8.66 (2.50–30.03)	0.001*
Local recurrence		
≥ 1 vs. none	3.29 (1.23–8.83)	0.018*

*Statistically significant

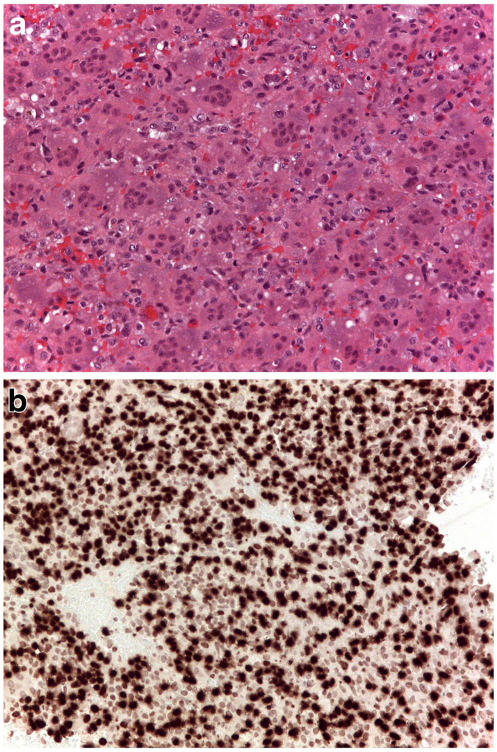

Fig. 2 **a** Histological section of GCT shows the presence of numerous large osteoclast-like giant cells associated with round or spindle-shaped mononuclear cells (stain: haematoxylin and eosin; original magnification, × 200). **b** The mononuclear cells show a strong nuclear immunoexpression of H3F3A (H3F3A; original magnification, × 200)

Discussion

Denosumab administration has been associated with a favorable outcome with respect to tumour response and surgical morbidity in patients with GCT [12, 14, 15]. However, there are conflicting reports regarding the outcome of GCT patients [13, 16–20], and to the best of our knowledge, there are no published studies on the effect of denosumab on lung metastases in these patients. In contrast to previous reports, results

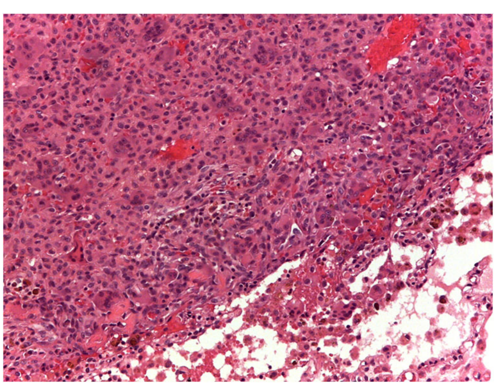

Fig. 3 Histological section of GCT lung metastasis shows the presence of numerous large osteoclast-like giant cells associated with round or spindle-shaped mononuclear cell (stain: haematoxylin and eosin; original magnification, × 200)

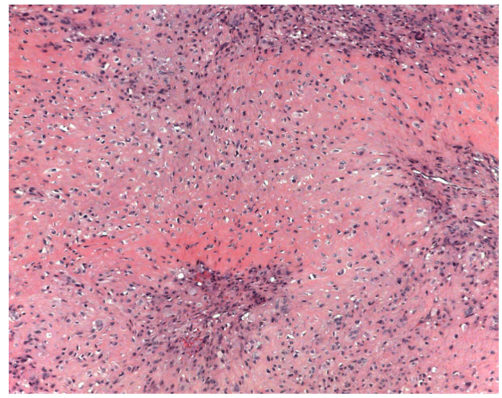

Fig. 4 Histological section of GCT after denosumab administration: osteoclast-like giant cells disappear, and an abundant fibrillary extracellular osteoid-like matrix is evident. The round or spindle-shaped mononuclear cells do not show significant cytological atypical features (stain: haematoxylin and eosin; original magnification, × 200)

of the present study showed that denosumab administration in patients with GCT at the extremities significantly increased the risk for local recurrences after curettage, without any effect on lung metastases. Denosumab was not found an important predictor of lung metastases in either univariate or multivariate analysis of variables; the only important predictors for lung metastases were type of surgery and local recurrences.

We see four limitations in this study. First, the study was retrospective with its inherent limitations. The patients with denosumab administration were compared to a control of patients treated by different surgeons over a 24-year period. We acknowledge this limitation; however, we believe that well-designed retrospective studies are very informative for treatment approaches. The patients included in this series were treated as part of a protocol at a single institution that is considered a tertiary tumour centre, using the same technique refined through the years, and were followed to the last follow-up for the purpose of this study by the same physicians. We believe that in this setting, our methods and results are useful. Second, the number of patients with surgery alone and those with denosumab administration was not similar at baseline, and a power analysis was not done; these may increase the risk for confounding variables and bias, and in this respect, our results should be considered with caution. Specifically, although the occurrence of local recurrences was significantly higher in the patients with denosumab administration, because this group had more tumors located in the distal radius (an area associated with a higher rate of local recurrence) and more frequently underwent curettage, causation could not be proved. Third, the number of patients with denosumab administration and those with lung metastasis in this study was relatively small for a multivariate analysis. Therefore, we performed stepwise multivariate analysis that included all univariate variables (even if not significant). This analysis excluded denosumab administration as an important multivariate predictor for lung metastases. Interestingly, Campanacci stage that may be considered a possible index for GCT aggressiveness was also not found an important multivariate predictor for lung metastases in this study. Four, we did not account for size of the lung nodules of the patients with GCT included in this series, and we have a histological documentation for the lung nodules only for the patients who underwent resection of their lung metastases. Previous studies on osteosarcoma patients reported that lung nodules may be benign in up to 24.2% of the patients [25], and the cutoff size to distinguish between metastatic and benign lung nodules may be as low as 6 mm [26]. Additionally, one may consider that normal, healthy patients may present with small lung nodules, potentially multiple. However, most patients with bone GCT are young patients and, therefore, it is not so frequent to have lung nodules, especially new; therefore, when we see in staging new nodules, there is a high probability that these represent lung metastases.

Recent studies showed that local recurrence is a significant risk factor for lung metastases in patients with GCT [3–5]. Rosario et al. reported a 7.5% rate of lung metastasis in their patients with GCT and reported that local recurrence was the only multivariate predictor for the development of lung metastasis [4]. Wang et al. reported a 6.5% rate of lung metastasis in their patients with GCT; the number of local recurrences was also an important multivariate predictor for lung metastases in their study, in addition to malignancy, tumor-bearing time, and tumor size [5]. Other authors reported an increased rate of lung metastases for patients with Campanacci stage III GCT [9]. Kito et al. suggested that patients with GCT without a predisposition for metastasis would not trigger lung metastasis even after local recurrence due to inadequate curettage. In contrast, patients with a predisposition for metastasis may possibly experience local recurrence and lung metastasis even if they undergo wide resection of their tumour [27]. This predisposition may lead to aneuploidy that is more common in recurrent and metastatic GCT patients [28]. A specific anatomic location has also been associated with an increased risk for lung metastases, with conflicting reports, however [2, 8]. In a smaller series, Tubbs et al. [8] reported that GCT at the distal radius was more commonly associated with lung metastases, whereas Dominkus et al. [2] observed that GCT around the knee was the primary site associated with lung metastases. In the present study, 4.6% of patients experienced lung metastases and 17.8% of patients experienced local recurrences. Type of surgery and local recurrences were the only important predictors for lung metastases. Lung metastases were more common in patients with resection/amputation; this may be explained by the higher number of larger, Campanacci stage III, and recurrent tumors treated by resection/amputation. In contrast to previous reports [2, 8], GCT location at the distal radius was not found to be significantly associated with lung metastases.

There are conflicting reports regarding the effect of denosumab on the outcome of the patients with GCT [12–20]. Although some studies reported a favourable outcome with respect to tumor response and surgical morbidity in patients with GCT after denosumab administration [12, 14, 15], other studies reported a less optimal outcome [13, 16–20]. Mak et al. studied GCT cell cultures and found that although giant cells were not present in denosumab-treated specimens, there existed neoplastic stromal cells that continued to proliferate at a slower rate than the untreated tumour [16]. This may be explained by the finding that denosumab caused only minimal inhibitory effects in GCT stromal cell lines and did not trigger apoptosis [17]. Observation of an H3F3A mutation in pre- and post-treatment surgical specimens of GCT [18] and rapid local recurrence after discontinuation of long-term denosumab therapy [20] further supports the hypothesis that denosumab does not eliminate the tumour cells. In a previous study [19], we reported that denosumab administration increased the incidence of local recurrence after curettage of GCT in the extremities; tumour cells may hide within the thickened cortex and subchondral bone that develop after denosumab administration, where the neoplastic cells may initiate proliferation once the microenvironment is free of denosumab [19]. The new osseous tumor matrix and the thickened cortical bone that develop with denosumab administration raise a new surgical challenge through not allowing the surgeon to delineate the true extent of the tumour, thereby increasing the risk of local recurrence.

The present study evaluated the effect of denosumab for lung metastases. Although denosumab administration was not found an important predictor for lung metastases, local recurrences were significantly more in the patients with denosumab administration and were found an important predictor for lung metastases. Therefore, one may assume that denosumab administration in GCT patients indirectly increases the risk for lung metastases by increasing the risk for local recurrences. This remains to be proved in a larger study with increased sample size and/or follow-up.

Conclusion

Denosumab does not decrease the risk of lung metastases in patients with bone GCT; the only important predictors for lung metastases in these patients are type of surgery and local recurrence. However, because the number of patients with lung metastases was small for a multivariate analysis, the possibility of denosumab's effect could not be completely eliminated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the independent ethics committee of senior author's institution and is registered with ClinicalTrials.gov (identifier NCT02996734).

Informed consent Informed consent was obtained from all individual participants included in the study.

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