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Increased Risk of Lung Metastases in Patients with Giant Cell Bone Tumors: A Systematic Review

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Abstract

Giant cell tumors of the bone are rare, usually benign, tumors consisting of large, multinucleated bone cells. Remarkably, these tumors are characterized by aggressive growth. They tend to recur frequently and, in rare cases, metastasize to the lungs. Previous studies tried to identify risk factors for lung metastasis by giant cell bone tumors. Those studies reported different results due to a small number of patients. Therefore, a particularly high risk associated with this type of bone tumor prompted this systematic review and meta-analysis to identify risk factors for the development of lung metastases. The risk factors for lung metastasis by giant cell bone tumors searched for in this study were gender, age, lung metastasis and recurrence period, follow-up time, primary or recurrent tumor, Campanacci grading, tumor localization, disease course, treatment of primary and recurrent tumors, and pulmonary metastases treated by surgery, radiation, and chemotherapy. This meta-analysis identified the features outlined above by comparing the groups of patients with giant cell bone tumors and lung metastases with the control group consisting of patients without lung metastases. The search for suitable studies revealed 63 publications with a total of 4,295 patients with giant cell bone tumors. Of these, 247 (5.8%; 95% confidence interval (95%CI) 5.1–6.5%) patients had lung metastases. Further, the risk factors for lung metastases were the following: recurrence ($p < 0.0001$), lung metastasis time ($p < 0.0001$), Campanacci grade II ($p = 0.028$) and grade III ($p = 0.006$), localization in the lower limbs ($p = 0.0007$), curettage ($p = 0.0005$), and local irradiation of the primary tumor ($p = 0.008$). All studies showed a high-risk bias due to the absence of blinding of the participants, personnel, and outcome assessment. Special attention should be paid to tumor recurrence in the long follow-up time, since more advanced giant cell bone tumors, particularly in lower extremities, tend to reoccur and metastasize to the lung. Surgical treatment and local irradiation should be performed thoughtfully, with extended follow-up periods.

Keywords

Giant cell bone tumor · Lower limbs · Lung metastases · Meta-analysis · Osteosarcoma · Risk factors · Tumor recurrence

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1 Introduction

Giant cell tumors of the bone are rare tumors that are found mostly in the epiphysis of long bones. Although they are classified as benign, they often exhibit locally aggressive growth, have a high risk of recurrence, and, in rare cases, metastasize to the lung (Fletcher et al. 2018; Werner 2006). Histologically, they are characterized by monocytes and mesenchymal stromal cells in addition to osteoclastic giant cells (Elder et al. 2007). Ordinarily, such tumors develop in the second and third decade of life (Kundu et al. 2018), and they are commoner in women than in men (Hu et al. 2016). Affected patients present with subacute to acute pain mainly during exercise (Mavrogenis et al. 2017). In addition, patients often present with newly occurring pathological bone fractures (Cao et al. 2017).

Following the initial findings, discovery of a cystic, juxta-articular, nonresponsive mass via radiography often results in a trial biopsy and curative intervention (He et al. 2017). Surgical management is of great importance, since tumors tend to recede due to its biological properties, but aggressive growth of some local lesions endangers joint preservation. For that reason, surgical en bloc resection, followed by curettage and subsequent filling of defects with bone cement, has become an established treatment for the epiphysis of long bones (Pazionis et al. 2013). Furthermore, after local surgical rehabilitation, radiotherapy is applicable to tumor sites that are not easily accessible, where sufficiently radical surgery with satisfactory results is hardly feasible (Shi et al. 2013). Adjuvant chemotherapy should be proposed for giant cell bone tumors of medium- and high-grade malignancy when the tumors progress and become inoperable (Liang 2018).

In principle, the extent to which lung metastases require pulmonary surgery depends on the number and localization of lung metastasis and tumor-free resection margin. Individual lung lesions can be easily removed by complete resection. Less often, lung wedge resection or lobectomy is required. In case of diffuse metastatic lungs or technical or functional inoperability, radiotherapy may be used in addition to local surgical procedures (Klenke et al. 2011).

The aim of this review was to identify risk factors for the development of lung metastases due to giant cell bone tumors. For that purpose, two groups of patients were compared, based on the literature search, those with and without lung metastases; the latter group was considered the control group. Primary and recurrent tumors were also compared between the two groups, as the recurrent tumor presumably constitutes a risk factor for lung metastasis. Likewise, the recurrence rate was compared between the two groups.

2 Methods

2.1 Patients and Data Collection

The study population consisted of the patients diagnosed with giant cell bone tumors, who were identified in the medical literature during a search conducted in the Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and MEDLINE/PubMed until April 30, 2018. The patients were stratified into those with lung metastases (study group) and without lung metastases (control group). The search for suitable studies was carried out by entering “giant cell tumors of bone” and “lungs” into the search console of the databases. Subsequently, the restrictions “humans” and “abstract available” were applied. The analysis was carried out in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al. 2009).

Inclusion criteria consisted of the information on gender and age; time period for lung metastases; time interval for recurrences; observation period; classification as a primary or recurrent tumor; possible radiological classification according to Campanacci grade I, II, or III

(Campanacci 1976); localization of the tumor; disease process; and surgical or radiological treatment of primary and recurrent tumors or lung metastases due to giant cell bone tumors. The exclusion criterion was defined as the unmet inclusion criteria outlined above. This meta-analysis included all prospective, retrospective, and evaluation studies, as well as case series and case reports of pulmonary metastases due to giant cell bone tumors in humans.

The inclusion criteria outlined above stem from the clinical knowledge about giant cell bone tumors in humans. Such tumors are more likely to appear in middle-aged women, notably in the third decade of life, and the usual location is near the ends of long bones, notably in the knee joint region, followed by the proximal humerus and the distal radius (Fletcher et al. 2018). These regions were considered together in this review as the lower and upper limbs. Other rare localizations, such as the spine, sacrum, and pelvis also were considered.

The survival probability in patients with giant cell bone tumors, with and without lung metastases, was determined in this review, according to the Kaplan-Meier method, after collection of the number of deaths.

2.2 Assessment of Potential Bias for Study Quality

The purpose of this review was to collect studies that met the inclusion criteria using the Cochrane Collaboration tool to assess a potential risk of bias and thus to reduce bias (Savović et al. 2014). There were 23 (36.5%) retrospective studies, 1 (1.6%) evaluation study, 10 (15.9%) case series, and 29 (46.0%) case reports examined for the review. The risk of bias was assessed in the studies. High risk of bias was regarded for blinding patients and medical personnel and blinding the outcome assessment. Low risk of bias was regarded for valued random sequence generation, incomplete outcome data, and selective reporting. Unclear risk of bias considered the allocation concealment and missing data for the duration of treatment and follow-up Fig. 1.

2.3 Statistical Elaboration

Data were presented as means ±SD and proportions of patients (%). 95% confidence intervals (95%CI) were provided for the proportions of patients in the study and control groups. The mean and median values were calculated to compare age differences, time interval for lung metastases, number of recurrences, time interval for recurrences, and follow-up time.

Odds ratios (OR) with 95%CI were used to determine the relationships between the frequency of lung metastases in the total number of bone tumor patients, gender differences, primary or recurrent tumor classification, death, local primary tumor irradiation, spondylectomy, hemipelvectomy, unknown treatment, embolization, treatment of recurrent tumors by joint or prosthesis replacement or arthrodesis, amputation, excision, lung treatment, local irradiation of recurrences, and the lack of surgery for recurrent tumors.

The Mann-Whitney U test was used to determine the significance of two unpaired distributions of age difference, tumor localization, difference in the number of primary tumors in both patient groups, Campanacci grading, time interval to recurrence, follow-up time, number of recurrences, curettage, resection, amputation, arthrodesis or joint or prosthesis replacement, and the treatment of tumor recurrence by curettage, resection, or by unknown therapy. A one-sample *t*-test was used to calculate the mean time of tumor metastasizing to the lungs, to surgical treatment by excision, assuming a hypothetical value of 1, and to manifestations of osteosarcoma, assuming a hypothetical value of 0.

The results of this meta-analysis were considered significant when a suitable significance test for a given type of data provided a p-value <0.05.

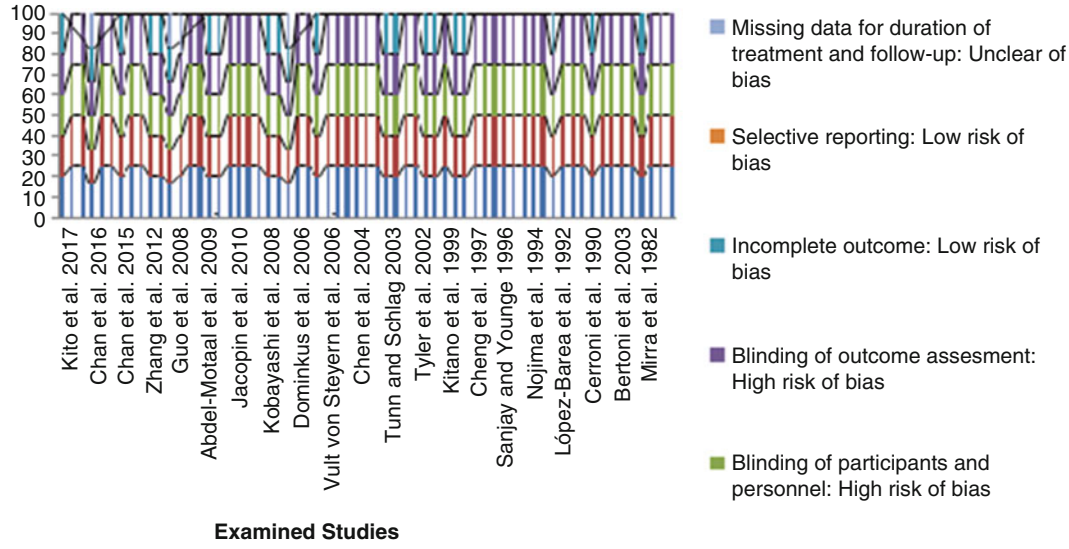

Fig. 1 Valuation of high, low, and unclear biases of risk for the study quality evaluation

3 Aspects of Giant Cell Bone Tumors Addressed in the Literature Searched

3.1 Radiological Classification According to the Campanacci Grading System

Campanacci grading is based on the spread of a tumor over the disease course in all directions within the bone, destruction of the adjacent cortex, and subsequent infiltration of bordering soft tissues. The Campanacci grading system is exclusively based on the evaluation of X-ray images. In grade I, tumor borders are delimited from the environment by a thin rim of mature bone. The cortex is unaffected or slightly diluted, and it is not deformed or broken. In grade II, tumor borders are quite clearly defined without a clear edge defined by mature bone. However, there is a border between the tumor and the surrounding soft tissue. In grade III, the tumor boundaries are blurred, and it extends into the soft tissue (Campanacci 1976).

Typical X-ray of giant cell tumor in a long bone shows eccentric osteolysis, without matrix ossification, and dilution of the bone cortex (Fletcher et al. 2018). In the studies inhere reviewed, X-ray images are used for the diagnosis, followed by computerized tomography (CT) and magnetic resonance imaging (MRI). These examinations also are suitable for tumor staging and surgery planning.

3.2 Time Course of Giant Cell Bone Tumors

The term "primary tumor" was used to describe the first occurrence of a giant cell bone tumor before metastasis. Primary tumors were evaluated in both study and control groups as a potential risk factor for lung metastases. "Tumor recurrence" was referred to as reoccurrence of giant cell bone tumors after complete destruction by surgical removal or radiotherapy, and it also was evaluated as a risk factor for the development of lung metastases. The mean time to tumor recurrence in months was compared between the two groups. "Follow-up" referred to revisiting patients after the last physical examination; it was evaluated in months. Giant cell bone tumors can reoccur after many years, which increases the risk of lung metastases. Therefore, the need for a longer follow-up time was compared between the two groups.

3.3 Pathohistology

The diagnosis was made after taking a biopsy of the primary tumor and performing histological examination of hematoxylin-eosin-stained specimens. Giant cell bone tumor was histologically characterized under light microscopy by mononuclear cells and numerous, diffusely distributed giant cells (Fletcher et al. 2018). In rare cases, giant cell bone tumors could degenerate into highly malignant sarcoma. Such transformation was investigated in this analysis. However, pathohistology served to confirm the diagnosis, suspected on the basis of CT imaging, and it was not the subject of analysis.

3.4 Surgical Treatment

Classical therapy for giant cell bone tumors involves intralesional aggressive curettage, generous opening of the bone cave using a mechanical high-speed milling drill, and physicochemical adjuvants such as bone cement, alcohol, phenol, cryosurgery, or cauterization (Khalil el et al. 2004). These adjuvants were used to reduce a high rate of recurrence of tumors and possible lung metastases. This analysis examined whether surgical technique could reduce the number of lung metastases. For the sake of clarity, individual adjuvants remained undescribed.

En bloc tumor resection is essential for Campanacci grade III aggressive giant cell bone tumors (Pazionis et al. 2013). Radical resection and removal of the actual giant cell bone tumor affect neighboring tissues and lymph nodes. A high probability of recurrence necessitates such radical resection surgery, while a low probability of recurrence may require the curettage only. Due to giant cell bone tumors' ability to invoke hematogenous metastases, difficult cases are treated by extensive amputation (Gupta et al. 2007). This analysis examined whether amputation has been used as a treatment mode in previous studies.

Surgical removal of whole inactive benign giant cell bone tumors is performed in some cases of Campanacci grade I tumors. In advanced cases, accompanied by massive tumor expansion out of the bone and joint involvement, arthrodesis or joint or prosthesis replacement is used as treatment (López-Pousa et al. 2015). In milder cases, marginal excision suffices to remove bone tumor with a margin of surrounding tissue (Guo et al. 2008). Hemipelvectomy is used to remove the whole lower extremities, including one half of the pelvis extending to the sacrum, in cases of severe tumor expansion on one side of the hip and pelvis (Sanjay et al. 1993). Spondylectomy is indicated when the vertebral body is destroyed by a bone tumor, compromising stability and leading to neurological deficits. This procedure involves surgical removal of one or more vertebral bodies with subsequent replacement and stabilization of the spinal column section (Balke et al. 2012; Matsumoto et al. 2007).

Recurrences are sometimes difficult to treat as giant cell bone tumors often reach the articular surface of a bone. Depending on the condition, the intralesional procedure could be repeated. Macroscopically complete removal of a recurring soft tumor mass by curettage is mandatory. The removal should be followed by treatment of the tumor cavity with necrotizing substances and sealing the cavity with bone cement (Xing et al. 2013). For the severe recurrence condition, en bloc resection of a tumor, endoprosthesis, or allografting is recommended (Bergovec et al. 2014). Such procedures are most advantageous for avoiding further growth or infiltration of neighboring tissue (Harris and Lehmann 1983). Incomplete excision of a tumor contributes to increased recurrence rate. If recurrence persists after resection and radiotherapy, amputation of the affected limb is considered (Basu et al. 2012). In the mild condition, recurrence is treated by marginal excision (Xu et al. 2017).

3.5 Radiotherapy

Generally, giant cell bone tumors are irradiated with great success as they are radiosensitive and regress with relatively low irradiation doses. Radiotherapy also is advantageous as it offers substantial possible protection against amputation

and recurrence as after curettage. Indications for radiotherapy include incomplete excision, increased mitotic rate, and pronounced bone involvement.

Irradiation therapy is also considered for giant cell bone tumor recurrences but only as an adjuvant measure when the patient's condition can be hardly controlled by surgery which is the first-line treatment choice for recurrences (Caudell et al. 2003). The possibility of impending limb amputation is another potential indication for radiotherapy. Radiotherapy serves then to reduce tumor mass to keep the area to be amputated as small as possible.

3.6 Embolization

Elective embolization is sometimes useful for controlling difficult giant cell bone tumors. It is performed by radiologically assisted implementation of a liquid plastic substance via a catheter into a patient's artery (Yu et al. 2013).

3.7 Chemotherapy

Adjuvant chemotherapy is proposed for giant cell bone tumors with the intermediate-to-high-grade malignancy after rehabilitative measure. At present, there are no generally accepted and effective chemotherapeutic agents available for treatment of such tumors (Puri and Agarwal 2007). Variable chemotherapeutic regimens have been proposed in the literature, the evaluation of which was beyond the scope of this review.

3.8 Lung Metastases

Giant cell bone tumors could form metastases restricted to the lungs, which should be removed surgically. Solitary lung lesions are usually operable, so that metastasectomy is the method of choice. Surgery enables the histological verification of a diagnosis. Incomplete lung metastasectomy could be performed if metastases are in unreachable locations (Takeuchi et al. 2016; Cheng and Johnston 1997). Pulmonary wedge resection is performed to remove tumorous lung tissue that does not align with the lung anatomical boundaries. Lobectomy is required when there is a widespread metastasis (Muheremu and Niu 2014). Symptomatic, palliative treatment is offered only when no other therapy of lung metastases is possible (Júnior et al. 2016). Lung metastases of giant cell bone tumors sometimes do not show any progressive dynamics of growth and remain of the same size for prolonged periods of time. Some may even spontaneously regress (Kay et al. 1994). In some of the studies, there is no conclusive information on whether surgery was effected or treatment of lung metastases remains unknown. In this review, such cases are referred to as "no lung metastasis surgery" and "unknown", respectively.

In case of problematic or poor resectability of lung metastases, irradiation is an alternative treatment option. However, radiation therapy suffers from the lack of a generally accepted dose or fractionation concept (Roeder et al. 2010).

4 Results

The terms "giant cell tumor of bone" and "lungs" yielded 256 studies in the databases searched. Sixty-three of these studies met the inclusion criteria. Fifty-eight out of the 63 studies were allocated to the study group (giant cell bone tumors with lung metastases), and only were 5 studies allocated to the control group (giant cell bone tumors without lung metastases) (Table 1). In total, 4295 patients were studied, with the study group comprising 247 (5.8%; 95%CI 5.1–6.5%) patients with giant cell bone tumors and lung metastases and the control group comprising 299 (7%; 95%CI 6.2–7.8%) patients without lung metastases. Accordingly, the occurrence of lung metastases increased significantly over the disease course in patients with giant cell bone tumors. Both groups were predominantly male but without appreciable gender or age differences (Table 2).

Table 1 Studies included in this review

Citation	Country	Patients (*n*)	Patients with lung metastases (*n*)	Male (*n*)	Female (*n*)	Mean age (years)
Abdel-Motaal et al. (2009)	Kuwait	1	1	0	1	46.0
Bahri et al. (2003)	Tunisia	1	1	0	1	23.0
Bertoni et al. (2003)	Italy	327	6	5	1	25.3
Bertoni et al. (1988)	USA	97	7	4	3	24.9
Boghani et al. (1994)	India	1	1	0	1	30.0
Cai et al. (2007)	USA	4	4	2	2	27.3
Cerroni et al. (1990)	Austria	1	1	1	0	47.0
Chan et al. (2015)	USA	167	11	5	6	25.3
Chen et al. (2016)	Taiwan	168	7	4	3	39.1
Chen et al. (2004)	Taiwan	1	1	0	1	30.0
Cheng and Johnston (1997)	USA	104	5	2	3	28.6
Dominkus et al. (2006)	Austria	649	14	8	6	27.1
Donthineni et al. (2009)	USA	51	7	4	3	29.9
Erdin and Wegmann (1996)	Switzerland	1	1	1	0	58.0
Faisham et al. (2006)	Malaysia	20	6	5	1	33.7
Feigenberg et al. (2002)	USA	3	3	2	1	27.3
Gresen et al. (1973)	USA	195	2	1	1	57.0
Guo et al. (2012)	China	27	1	0	1	25.0
Guo et al. (2008)	China	16	0	10	6	41.3
Gupta et al. (2008)	India	470	24	15	9	29.1
Hashimoto et al. (2006)	Japan	1	1	0	1	45.0
Hsieh et al. (2012)	Taiwan	1	1	0	1	25.0
Jacopin et al. (2010)	France	1	1	0	1	7.0
Kaiser et al. (1993)	Germany	1	1	0	1	37.0
Kay et al. (1994)	USA	66	6	4	2	28.2
Kitano et al. (1999)	Japan	1	1	0	1	34.0
Kito et al. (2017)	Japan	141	12	9	3	27.0
Kobayashi et al. (2008)	Japan	1	1	1	0	30.0
Kong et al. (2013)	China	79	0	42	37	33.1
Lachat et al. (2004)	Switzerland	1	1	1	0	28.0
López-Barea et al. (1992)	Spain	1	1	1	0	37.0
Maloney et al. (1989)	USA	3	3	1	2	28.0
Mella et al. (1982)	Norway	1	1	0	1	13.0
Miller et al. (2010)	USA	1	1	0	1	29.0
Mirra et al. (1982)	USA	1	1	0	1	45.0
Moon et al. (2012)	South Korea	1	1	1	0	54.0
Muheremu et al. (2015)	China	2	2	1	1	37.5
Nakano et al. (2009)	Japan	1	0	1	0	26.0
Ng et al. (2002)	Malaysia	31	4	2	2	30.2
Nojima et al. (1994)	Japan	1	1	0	1	11.0
Obata et al. (1991)	Japan	1	1	1	0	23.0
Osaka et al. (2004)	Japan	5	5	1	4	21.8
Osaka et al. (1997)	Japan	78	6	3	3	22.3
Powers et al. (1991)	USA	1	1	1	0	45.0
Present et al. (1986)	USA	1	1	1	0	21.0
Qi et al. (2016)	China	12	1	0	1	19.0
Qureshi et al. (2005)	India	1	1	1	0	18.0

(continued)

Table 1 (continued)

Citation	Country	Patients (*n*)	Patients with lung metastases (*n*)	Male (*n*)	Female (*n*)	Mean age (years)
Rock et al. (1984)	USA	31	8	4	4	34.3
Sanjay and Kadhi (1998)	Saudi Arabia	69	3	1	2	22.7
Sanjay and Younge (1996)	Saudi Arabia	1	1	0	1	17.0
Siebenrock et al. (1998)	Switzerland	31	23	11	12	27.0
Tubbs et al. (1992)	USA	475	13	6	7	30.0
Tunn and Schlag (2003)	Germany	87	10	4	6	30.2
Turcotte et al. (2002)	Canada	186	0	90	96	36.0
Tyler et al. (2002)	USA	1	1	1	0	25.0
Viswanathan and Jambhekar (2010)	India	470	23	13	10	26.0
Vult von Steyern et al. (2006)	Sweden	137	1	1	0	21.0
Wan et al. (2012)	China	27	1	0	1	38.0
Yanagisawa et al. (2011)	Japan	11	1	0	1	31.0
Yang et al. (2006)	Taiwan	11	1	0	1	29.0
Yang et al. (2016)	China	17	0	12	5	23.2
Yeo et al. (2015)	Korea	1	1	0	1	22.0
Zhang et al. (2012)	USA	1	1	0	1	43.0

Table 2 Demographic and clinical data of patients with giant cell bone tumors with (study group) and without (control group) lung metastases

Giant cell bone tumor	Study group ($n = 247$)	Control group ($n = 299$)	*p*-value; OR (95%CI)
Male; *n* (%)	129 (52.2)	155 (51.8)	
Female; *n* (%)	118 (47.8)	144 (48.2)	0.928; 1.02 (0.72–1.42)
Patients' age			
Mean age ± SD; years	29.6 ± 9.6	31.9 ± 6.6	0.559
Median (range); years	28.6 (7–58)	33.1 (23.2–41.3)	
Time to lung metastases			
Mean ± SD; months	38.2 ± 52.8	–	**<0.0001;** (24.01–52.30)
Median (range); months	23.8 (0–360)	–	
Time to recurrence			
Mean ± SD; months	19.8 ± 17.2	23.5 ± 10.6	0.351
Median (range); months	12.8 (2–84)	23 (12–36)	
Follow-up time			
Mean ± SD; months	80.4 ± 61.1	123.9 ± 130.2	0.792
Median (range); months	71.7 (1.3–360)	58.8 (51.6–384)	
Tumors, n (%)			
Primary	79 (32.0)	165 (55.2)	0.406
Recurrent	168 (68.0)	134 (44.8)	**<0.0001;** 2.62 (1.84–3.72)
Campanacci grade; *n* (%)			
I	6 (2.4)	8 (2.7)	1.0
II	33 (13.4)	146 (48.8)	**0.028**
III	115 (46.6)	142 (47.5)	**0.006**
Unknown	93 (37.7)	3 (1.0)	**<0.0001**
Localization of tumors; *n* (%)			
Lower limb	139 (56.3)	225 (75.3)	**0.0007**

(continued)

Table 2 (continued)

Giant cell bone tumor	Study group ($n = 247$)	Control group ($n = 299$)	p-value; OR (95%CI)
Upper limb	70 (28.3)	74 (24.7)	0.129
Spine	16 (6.5)	0	0.274
Sacrum	14 (5.7)	0	0.051
Pelvic	8 (3.2)	0	0.356
Disease course; n (%)			
Sarcoma	13 (5.3)	0	0.073
Death	37 (15.0)	0	**0.001;** 106.7 (6.5-174.5)

OR (95%CI), odds ratio with 95% confidence interval; significant p-values are in bold

The time to the occurrence of lung metastases significantly differed among patients with giant cell bone tumors ($p < 0.0001$). Sometimes, lung metastases were found at the time of diagnosis of the primary tumor, but occasionally they occurred during the disease course some years later. The time to tumor recurrence did not differ between the patients with and without lung metastases. Nor was the follow-up period different between the two groups of patients (Table 2).

There was no difference in the number of primary giant cell bone tumors diagnosed in the two groups of patients. However, patients with lung metastases had a significantly greater proportion of recurrent tumors ($p < 0.0001$). In both groups of patients, there was a significantly greater rate of Campanacci grade II ($p = 0.028$) and III ($p = 0.006$) tumors according to the radiological classification of tumors. Giant cell bone tumors were significantly more often localized in the lower extremities ($p = 0.0007$). Osteosarcoma was occasionally detected histologically in patients with bone tumors and lung metastases, but not in those without lung metastases. Death rate was significantly greater in patients with bone tumors and lung metastases ($p = 0.001$) (Table 2).

In patients with primary giant cell bone tumors and lung metastases, curettage was performed significantly less often than in those without lung metastases ($p = 0.0005$). In contradistinction, local radiation was performed more often in patients with lung metastases ($p = 0.008$). Surgery apparently tended to be shunned or not undertaken in these patients. Interestingly, radiographic endovascular embolization did not play an appreciable role in treatment of patients with primary tumors and lung metastases (Table 3).

En bloc resection was the most frequent surgical procedure in patients in the control group who had recurrent giant cell bone tumors without lung metastases ($p = 0.004$), which was followed by curettage. In patients with lung metastases, joint or prosthesis replacement, arthrodesis, limb amputation, and local radiotherapy predominated (Table 3).

Treatment of lung metastases in patients with giant cell bone tumors depended on the extent of metastases. Surgical treatment included complete resection, wedge resection, incomplete resection, and, less often, lobectomy. Symptomatic treatment also was considered an important component of a comprehensive treatment plan, particularly in case of progressive lung metastases of giant cell bone tumors (Table 4).

For unknown reasons, in a few studies reviewed, it was decided not to surgically treat lung metastases by giant cell bone tumors. In hopeless cases, lung irradiation was promising and used in some cases of lung metastases tumors. Due to tumor progression, chemotherapy was used in nearly one-third of the cases of lung metastases; all these interventions were with statistical significance (Table 4).

There were 37 (15%) deaths in the study group of giant cell bone tumors with lung metastases. The mortality risk was increased due to giant cell bone tumors with an OR of 106.7 (95%CI 6.5–174.5%) ($p = 0.001$) (Table 2). Survival probability in the study group was 85.0% (95% CI 80.2–89.8%) according to the Kaplan-Meier method.

Table 3 Treatment of primary and recurrent giant cell bone tumors in patients with (study group) and without (control group) lung metastases

	Study group	Control group	
	$n = 247$	$n = 299$	p-value
Primary giant cell bone tumors			
Surgical treatment; *n* (%)			
Curettage	101 (40.9)	253 (84.6)	**0.0005**
En bloc resection	48 (19.4)	41 (13.7)	0.061
Arthrodesis, joint or prosthesis replacement	19 (7.7)	1 (0.3)	0.582
Amputation	31 (12.6)	4 (1.3)	0.206
Hemipelvectomy	5 (2.0)	0	0.078
Marginal excision	4 (1.6)	0	0.500
Spondylectomy	2 (0.8)	0	0.244
No surgery; *n* (%)	5 (2.0)	0	0.078
Unknown; *n* (%)	5 (2.0)	0	0.078
Local irradiation; *n* (%)	17 (6.9)	0	**0.008**
Embolization; *n* (%)	2 (0.8)	0	0.244
Recurrent giant cell bone tumors			
Surgical treatment of recurrent tumors; *n* (%)			
Curettage	31 (18.5)	37 (27.6)	0.089
En bloc resection	17 (10.1)	69 (51.5)	**0.004**
Arthrodesis, joint or prosthesis replacement	26 (15.5)	0	**0.006**
Amputation	17 (10.1)	0	**0.017**
Marginal excision	3 (1.8)	0	0.252
Spondylectomy	1 (0.6)	0	0.591
No surgery; *n* (%)	1 (0.6)	0	0.591
Unknown; *n* (%)	58 (34.5)	28 (20.9)	0.180
Local irradiation of recurrent tumors; *n* (%)	15 (8.9)	0	**0.022**

Significant p-values are in bold

Table 4 Treatment of lung metastases in patients with giant cell bone tumors (study group)

Treatment	Study group ($n = 247$)	p-value
Surgical; *n* (%)		
Complete metastasectomy	88 (35.6)	**0.0001**
Wedge resection	36 (14.6)	**0.001**
Incomplete metastasectomy	15 (6.1)	**0.010**
Lobectomy	7 (2.8)	**0.045**
Symptomatic; *n* (%)	24 (9.7)	**0.004**
Observation; *n* (%)	14 (5.7)	**0.012**
Lack of surgery; *n* (%)	29 (11.7)	**0.002**
Unknown; *n* (%)	5 (2.0)	0.078
Refusal of treatment; *n* (%)	6 (2.4)	0.059
Lung radiation; *n* (%)	23 (9.3)	**0.004**
Chemotherapy; *n* (%)	80 (32.4)	**0.0001**

Significant p-values are in bold

5 Discussion

The present review of the literature demonstrates that giant cell bone tumors increase the risk of lung metastases. The probability of being inflicted with lung metastases amounts to 39.5%. The percentage of patients with pulmonary metastases is 5.8%, and the frequency of lung metastases varies from 1% to 6% (Tubbs et al. 1992). Large fluctuations in the time to the development of lung metastasis were noted in the publications. Lung metastases were present in only four (1.6%) patients at diagnosis (Moon et al. 2012; Jacopin et al. 2010; Bahri et al. 2003; Nojima et al. 1994). One patient exhibited lung metastasis 30 years after the first presentation (Erdin and Wegmann 1996). Such extremely divergent time intervals show how giant cell bone tumors can be unpredictable.

The probability of lung metastases increases when there is a local tumor recurrence. The recurrence rate in this meta-analysis was 68.0%, the highest reported amounted to 82.6% (Siebenrock et al. 1998), among patients with lung metastases and 44.8% among those without lung metastases. Yang et al. (2017) have come to the same conclusion, finding a local recurrence rate of 73.9% and a correlation between local recurrence and lung metastasis. Therefore, performing careful therapy and ongoing controls at regular intervals to prevent local recurrence is of great importance.

The Campanacci radiological classification of giant cell bone tumors describes a tumors' tendency to expand beyond the cortical bone and to destroy it (Campanacci 1976). This classification is based on the projected radiographic appearance of the bony lesion. In conventional X-rays, giant cell bone tumors are predominantly observed as expansive, transparent, and osteolytic bone lesions in the epiphysis. The classification stratifies the tumors into three grades, with the predominance of grade II and III lesions (Panzica et al. 2014). These higher Campanacci grades have been reported to be risk factors for progression of lung metastasis (Kito et al. 2017; Yang et al. 2016; Muheremu et al. 2015; Faisham et al. 2006). A majority of giant cell tumors are classified as grade II or III at the first diagnosis. Therefore, the use of the Campanacci classification is essential to foretell the likelihood of lung metastases due to giant cell bone tumors.

Giant cell bone tumors are most commonly located in the lower extremities, such as in the distal femur and proximal tibia. The upper extremities, such as the distal radius, come in second place of localization frequency (Muheremu and Niu 2014). In the present meta-analysis, giant cell bone tumors were mostly identified in the lower extremities. The presumption might be that the location of a primary tumor at the axial skeleton could lead to more lung metastases due to the immediate proximity of the lungs to the skeleton. However, these locations are less frequently invaded by tumors than the limbs are. Therefore, primary tumor localizations do not appear a worthwhile prognostic of the development of lung metastases.

Giant cell bone tumors may transform into malignant sarcoma. The frequency of osteosarcoma amounted to 5.8% in the studies inhere reviewed, which was rather high. In contrast, Bertoni et al. (2003) have reported a 1.8% frequency of osteosarcoma. The incidence of osteosarcoma also has been smaller in some other previous studies (Miller et al. 2010; Donthineni et al. 2009; Hashimoto et al. 2006; Lachat et al. 2004; Mella et al. 1982).

Giant cell bone tumors are usually benign (Gresen et al. 1973). They may, rarely, become malignant, leading to death. As with any other tumor-based disease, giant cell bone tumors may lead to reduced life expectancy when they spread to other parts of the body (Amanatullah et al. 2014; Tunn and Schlag 2003). In this meta-analysis, death was more common in patients with giant cell bone tumors that metastasized to the lungs. Seven (18.9%) of such cases were caused by osteosarcoma. The remaining 30 (81.1%) deaths were during the disease course that was uncomplicated by lung metastases.

Since giant cell bone tumors constantly grow larger and constrict the surrounding tissue, such as tendons and joints, they ought to be removed by surgery. Currently, surgical removal of a primary giant cell bone tumor offers the only chance

of recovery, although there is a high rate of recurrence, which, in turn, is associated with increased risk of metastatizing to the lungs (Rigollino et al. 2017). The method of choice for locally aggressive giant cell bone tumors is curettage and implantation of bone cement (Stan et al. 2016). However, single curettage with spongy filling is bound to a high rate of recurrence, so that a careful treatment of the tumor cavity with necrotizing substances, such as phenol, and blinding the cavity is preferred (Fraquet et al. 2009). Extensive, radical surgical treatments, such as en bloc resection or, in the most severe cases, amputation, were used less frequently to treat primary tumors. Recurrent giant cell bone tumors may be retreated by curettage, using a high-speed bur in combination with adjuvant treatment. Again, curettage was the most common surgery performed to treat recurrent tumors in patients with lung metastases, belonging to the study group in this review, although the choice of this treatment option failed to achieve statistical significance. The next most common treatments were en bloc resection, arthrodesis, joint or prosthesis replacement, and amputation.

Small lung lesions can be removed by complete lung metastasectomy. This was the most commonly performed lung metastasis surgery found in the literature review (see, e.g., Kito et al. 2017; Chen et al. 2016; Muheremu et al. 2015; Chan et al. 2015; Guo et al. 2012). Larger lung metastases had to be removed by wedge resection, which was the second most common surgical technique found (see, e.g., Yeo et al. 2015; Cai et al. 2007; Dominkus et al. 2006; Feigenberg et al. 2002; Erdin and Wegmann 1996). Incomplete resection of lung metastases took place rather rarely in cases of unfavorable localization or multiple metastases (see, e.g., Kito et al. 2017; Dominkus et al. 2006; Siebenrock et al. 1998; Kay et al. 1994; Rock et al. 1984). Lobectomy was unavoidable in only a few cases (see, e.g., Hsieh et al. 2012; Dominkus et al. 2006; Hashimoto et al. 2006; Kitano et al. 1999; Tubbs et al. 1992). Symptomatic treatment was more often performed when lung metastases were inoperable or when surgical treatment was refused (see, e.g., Muheremu et al. 2015; Viswanathan and Jambhekar 2010; Gupta et al. 2008; Faisham et al. 2006; Ng et al. 2002). There was a spontaneous regression of lung metastases noticed in a minority of patients, which was subject of observation rather than surgery (see, e.g., Kito et al. 2017; Chen et al. 2016; Chan et al. 2015; Yanagisawa et al. 2011; Abdel-Motaal et al. 2009). Surgical removal of lung metastases was not equally suitable for all patients. Extensive pulmonary metastases were often associated with alleviation of symptoms and, for various reasons, tumor-specific surgical therapy had to be abandoned.

Radiation therapy to compensate for incomplete curettage or excision for therapeutic or functional motives was commonly recommended for very aggressive tumors, especially in those localized to the spinal column (Sobti et al. 2016). Pulmonary irradiation was used to compensate for incomplete lung metastasectomy or to treat uncontrollably progressing metastases (Bennett Jr et al. 1993). Local irradiation of the primary tumor had to be performed in some cases (see, e.g., Chan et al. 2015; Donthineni et al. 2009; Gupta et al. 2008; Tyler et al. 2002; Siebenrock et al. 1998). Somewhat more frequently, recurrent tumors had to be irradiated (see, e.g., Donthineni et al. 2009; Hashimoto et al. 2006; Osaka et al. 2004; Lachat et al. 2004; Ng et al. 2002). The relationship of secondary sarcomatous transformation to the area of radiation-treated giant cell bone tumors has been discussed in the past (Mondal et al. 2002).

Chemotherapy is administered mainly to treat progression and malignant transformation of lung metastases. It was used in almost one-third of cases with lung metastases due to giant cell bone tumors in the reviewed literature (see, e.g., Kito et al. 2017; Chen et al. 2016; Chan et al. 2015; Moon et al. 2012; Viswanathan and Jambhekar 2010). It is worthwhile to note that different chemotherapy regimens were employed. However, evaluation of the effectiveness of individual regimens was beyond the scope of this review. Currently, there are no generally accepted chemotherapy regimens for treatment of giant cell bone tumors (Sobti et al. 2016).

There are studies indicating that women are more likely than men to suffer from giant cell bone tumors (Tunn and Schlag 2003). Likewise,

women are more likely to form lung metastases (Estrada-Villaseor et al. 2015). In the present review, however, the findings were opposite in that more men than women were found to have lung metastases. In addition, the gender difference was small and without statistical significance.

Giant cell bone tumors occur most commonly in the third and fourth decades of life (Tunn and Schlag 2003). That was confirmed in the present review as the mean age at diagnosis ranged from 29.6 to 31.9 years, for the patients with and without lung metastases, respectively, which made no significant difference ($p > 0.05$). A previous study by Estrada-Villaseor et al. (2015) has examined the patients' age, among other clinical and pathological aspects, in relation to the development of lung metastases due to giant cell bone tumors, compared to other tumors. The mean patients' age reported in that study has been 36 ± 16 years, with no significant difference to metastases, which is grossly in line with the present findings. It appears, therefore, that age at diagnosis of giant cell tumors is not a potential risk factor for the capacity to develop lung metastases.

In conclusion, there is increased likelihood of lung metastases in patients with giant cell bone tumors, even a long time after the initial occurrence of tumor. The probability of lung metastases increases in recurrent tumors and in severe cases of the Campanacci grade II and III tumors. However, randomized controlled studies of the risk factors for lung metastases due to giant cell bone tumors are missing, which might be due to the rarity of this type of bone tumor as well as for ethical reasons. Giant cell bone tumors favor the lower extremities. The tumors are most often described as being benign, but they may occasionally become fatal. Care should be paid to the disease progress and to the follow-up after curettage treatment. Generally, the long-term follow-up of many years is recommended for the giant cell bone tumors.

Conflicts of Interest The author declares no conflicts of interest in relation to this article.

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