

■ Original Article

The relationship between recurrence and lung metastasis in giant cell tumor of bone

Kemiğın dev hücreli tümörlerinde rekürrens ve akciğer metastazı arasındaki ilişki

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ABSTRACT

Aim: The aim of this study is to evaluate the relationship between recurrence and lung metastasis in patients diagnosed with giant cell tumor of bone treated in our clinic and to present the other factors affecting the recurrence.

Material and Methods: The patients who were treated and followed up for a giant cell tumor of the bone between 2002 and 2018 were retrospectively reviewed. A total of 114 patients with a mean age of 31.6 ± 13.3 were included in the study.

Results: The mean follow-up period was 63.1 ± 33.4 months. Recurrence occurred in 26.3% (30 patients) of the patients in a mean of 17.1 months, while metastasis in the lung was found in 4.4% (5 patients). When the patients were evaluated according to their recurrence status, lung metastasis was observed in 13.3% of the patients with recurrence, while lung metastasis was observed in 1.2% of the patients without recurrence. Lung metastasis was found to be significantly higher in patients with recurrence than in the group without recurrence ($p = 0.017$). For lung metastasis, Hazard Ratio (HR) was calculated as 12.8 (95% CI: 1.4-119.5; $p = 0.026$).

Conclusion: Giant cell tumors of the bone are locally aggressive tumors with unpredictable behavior. In our study, when the patients were evaluated according to their recurrence status, lung metastasis was observed in 13.3% of the patients with recurrence, and 1.2% of the patients without recurrence. Lung metastasis was found to be significantly higher in patients with recurrence than in the group without recurrence.

Keywords: Giant cell tumor of bones; recurrence; lung metastasis

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ÖZ

Amaç: Bu çalışmanın amacı, kliniğimizde kemiğin dev hücreli tümörü tanısı ile takip ve tedavi edilen hastalarda rekürrens ve akciğer metastazı arasındaki ilişkiyi değerlendirmek ve rekürrensi etkileyen diğer faktörleri sunmaktır.

Gereç ve Yöntemler: Bu çalışma kesitsel tanımlayıcı tipte bir çalışmadır. Ankara Onkoloji Eğitim ve Araştırma Hastanesi Ortopedi ve Travmatoloji kliniğinde Ocak 2002- Aralık 2018 tarihleri arasında kemiğin dev hücreli tümörü nedeniyle tedavisi ve takibi yapılan hastalar retrospektif olarak taranmıştır. Tanı yaş ortalaması $31,6 \pm 13,3$ (8-69) olan 52'si erkek 62'si kadın toplam 114 hasta çalışmaya dahil edilmiştir.

Bulgular: Bu çalışmaya katılan hastaların ortalama takip süresi $63,1 \pm 33,4$ (14-192) aydır. Hastaların %26,3'ünde ortalama 17,1 ayda (6-36 ay arası) rekürrens gelişirken, %4,4'ünde (5 hasta) akciğerde metastaz saptanmıştır. Rekürrens gelişen hastaların %13,3'ünde akciğer metastazı gözlenirken rekürrens gelişmeyenlerin %1,2'sinde akciğer metastazı gözlenmiştir. Rekürrens gelişen hastalarda rekürrens gelişmeyen gruba göre akciğer metastazı istatistiksel olarak anlamlı düzeyde daha fazla gözlenmiştir ($p=0,017$). Akciğer metastazının rekürrense kadar geçen süreler dikkate alınarak rekürrens gelişmesi üzerine olan etkisi Cox Regresyon analizi ile incelenmiştir. Akciğer metastazı için hesaplanan Hazard Ratio (HR): 12,8 (%95 GA:1,4-119,5; $p=0,026$) bulunmuştur.

Sonuç: Kemiğin dev hücreli tümörleri, öngörülemez davranışları olan lokal agresif nadir metastaz yapan tümörlerdir ve en sık metastaz akciğerleredir. Çalışmamızda hastalar rekürrens durumlarına göre değerlendirildiğinde rekürrensi olan hastaların % 13,3' ünde, rekürrensi olmayan hastaların % 1,2' sinde akciğer metastazı gözlemlendi. Akciğer metastazı, rekürrens olan hasta grubunda rekürrens olmayan gruba göre anlamlı derecede yüksek bulunmuştur.

Anahtar Kelimeler: Kemiğin dev hücreli tümörü; rekürrens; akciğer metastazı

Introduction

Giant cell tumor of bone is a benign but locally aggressive neoplasm involving epiphysometaphyseal junction of long bones. It consists of undifferentiated cells and a large number of multinucleated giant cells are seen. [1, 2] Although histogenesis remains unclear, it is one of the most researched tumors.

It is most commonly seen in young adults aged 20-40 years. It is rare before epiphysis closes. It is slightly more common in women than in men. [3, 4] In general, it constitutes 5% of all bone tumors. [5] It is most commonly located in distal femur, proximal tibia, and distal radius. [2]

The most common complaint is pain. Swelling, increased temperature, and limited range of motion in the affected joint may be associated with pain. Surrounding soft tissue involvement is also present in Campanacci grade 3 lesions. Pathological fracture is also among the most common complaints. [6]

Direct radiography is important in diagnosis. That indicates pathological fracture. The most common direct X-ray findings in the epiphysometaphyseal region are expansive mass appearance, fluid-fluid levels, geographic pattern and cortex destruction. Magnetic Resonance Imaging (MRI) is valuable in differential diagnosis and especially in Campanacci grade 3 lesions with soft tissue involvement. [7]

Treatment varies according to grade and location of the tumor. The most important goal in the treatment is to provide local control. The most commonly used treatment method is curettage [8, 9]. Despite an effective curettage, recurrence has been reported in the literature by 5% for grade 1 lesions, 30% for grade 2 lesions, and 80% for grade 3 lesions. [10]

Giant cell bone tumor is a borderline neoplasm and metastasizes 1-9%. Publications have associated metastasis with local recurrence. [11] This reveals the importance of providing local control in primary treatment.

Giant cell tumors of the bone are metastasize to the lungs in rare cases. 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. [12] The aim of this study is to evaluate the relationship between recurrence and lung metastasis in patients diagnosed with giant cell tumor of bone treated in our clinic and to present the other factors affecting the recurrence.

Material and Methods

The patients who were treated and followed up for a giant cell tumor of the bone between January 2002 and December 2018 in the orthopedics and traumatology clinic of our hospital were retrospectively reviewed. Patients who were diagnosed as giant cell tumor after pathology after tru-

cut or open biopsy were included in the study. Of the 146 patients with giant cell tumor diagnosis, a total of 32 patients with a follow-up period of less than 1 year and lack of file or hospital patient information system were excluded from the study. The mean age of diagnosis was 31.6 ± 13.3 (8-69). Demographic and clinical data of 114 patients, 52 male and 62 female, were obtained from patient information system and patient archive files of our hospital. 7% of the patients were younger than 18 years. When the follow-up periods were calculated, the period between the date of diagnosis and the last date of the patients' visit was calculated in months. In addition, the time to recurrence was calculated as the time between the final surgical treatment and the date of surgery for recurrence. The relationship between lung metastasis and recurrence was evaluated statistically. Study was approved by hospital ethical committee. Written informed consents were obtained from each participants before enrollment.

Statistical Analyses

SPSS 22.0 (Chicago) was used for statistical analysis of the research data. In the descriptive statistics section, categorical variables are presented as numbers, percentages, and continuous variables are presented as mean \pm standard deviation and median (minimum- maximum value). The suitability of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). As a result of the normality analyzes, it was found that the data of continuous variables did not show normal distribution among the groups. Mann-Whitney U test was used for comparison analysis between two groups. Chi-square tests were used in comparison analysis for categorical variables between independent groups. Univariate analyzes showed that the presence of lung metastasis was significantly different between the recurrence and non-recurrent groups. The effect of recurrence on lung metastasis was examined by Univariate Cox Regression analysis. Cox regression analysis results are presented with Hazard Ratio (HR) and 95% Confidence Interval (CI). According to Kaplan Meier method and Log-Rank test, the rates of lung metastasis development were evaluated association of the recurrence. In this study, statistical significance level was accepted as $p < 0.05$.

Results

The mean follow-up period was 63.1 ± 33.4 (14-192) months. When tumor locations of the patients diagnosed were examined; 35 femoral (30.8%) patients (28 distal, 7 proximal), 25 tibial (21.9%) patients (22 proximal, 3 distal), 20

(distal radius) 17.5) patients, 12 (10.5%) patients with short and middle bones of the hand and foot, 9 (7.9%) patients with proximal fibula, 6 (5.3%) patients with pelvis, 4 (% proximal) with humerus 3,5) patients and 3 (2.6%) patients with ulna. The most commonly used surgical method was curettage + adjuvant therapy (cauterization / cryotherapy) + grafting (81.6%) and was applied to 93 patients. In the surgical procedure, after a large cortical window was opened to the bone, curettage was performed so that no tumor tissue remained. After the lavage was performed using saline, the curetted surface was cauterized. After repeated lavage with saline, the cavity was filled with autograft. Curettage + adjuvant therapy (cauterization / cryotherapy) + cementation in 6 patients (5.2%), endoprotesthetic reconstruction after en block tumor resection in 10 patients (8.8%), and biological reconstruction (autograft fibula) in 5 patients (4.4%) or iliac wing) (Table 1).

In this study, 53.5% of tumors were on the right side. Distribution according to Campanacci grading; 28 patients (24.6%) were grade 1, 46 patients (40.4%) were grade 2 and 40 patients (35%) were grade 3. Recurrence occurred in 26.3% of the patients in a mean of 17.1 months (6-36 months), while metastasis in the lung was found in 4.4% (5 patients). The relapse development status according to the settlements is given in Table 2. The most common surgical procedure after recurrence was endoprotesthetic reconstruction after en block tumor resection with 13 patients (43.3%). Other surgeries after recurrence; curettage + cryotherapy / cauterization + grafting / cementation, arthrodesis, biological reconstruction and amputation (Table 1). Three of the lung metastases were proximal to the tibia and 2 were distal to the femur.

The overall complication rate was 9.6% (11 patients). Complications were postoperative infection and pathological fracture. The most common postoperative complication was infection and was seen in 7% (8 patients).

Table 3a shows the comparison results according to gender and recurrence. There was no statistically significant difference in the distribution of characteristics of side, lung metastasis and recurrence ($p > 0.05$). When the patients were evaluated according to their recurrence status, lung metastasis was observed in 13.3% of the patients with recurrence, while lung metastasis was observed in 1.2% of the patients without recurrence. Lung metastasis was found to be significantly higher in patients with recurrence than in the group without recurrence ($p = 0.017$) (Table 3b). Age, gender and side of both groups were similar ($p > 0.05$).

Table 1. Demographic Characteristics

Characteristics (n=114)	
Age, year	
Mean±sd	31.3±13.5
Median (min-max)	30 (8-69)
Sex, n(%)	
Male	52 (45.6)
Female	62 (54.4)
Side, n(%)	
Right	61 (53.5)
Left	53 (46.5)
Localization, n(%)	
Femur	35 (30.8)
Pelvic	6 (5.3)
Tibia	25 (21.9)
Fibula	9 (7.9)
Humerus	4 (3.5)
Radius	20 (17.5)
Ulna	3 (2.6)
Others*	12 (10.5)
Surgical Treatment, n(%)	
Curettage +Bone grafting	79 (69.3)
Curettage +Bone grafting + Fixation	14 (12.3)
Curettage + Cementing	3 (2.6)
Curettage + Cementing + Fixation	3 (2.6)
Wide resection + Reconstruction with tumor prosthesis	10 (8.8)
Wide resection + Reconstruction with fibular grafting	5 (4.4)
Lung Metastases	
Yes	5 (4.4)
No	109 (95.6)
Recurrence, n(%)	
Yes	30 (26.3)
No	84 (73.7)
Recurrence Surgical Treatment (n=30), n(%)	
Curettage +Bone grafting	8 (26.7)
Curettage +Bone grafting + Fixation	2 (6.7)
Curettage + Cementing + Fixation	1 (3.3)
Wide resection + Reconstruction with tumor prosthesis	13 (43.3)
Wide resection + Reconstruction with fibular grafting	1 (3.3)
Arthrodesis	4 (13.3)
Amputation	1 (3.3)

ss: standard deviation
*:short and middle bones of hand and foot

Table 2. Recurrence Distribution by Location

Localization, n(%)	Recurrence Yes	Recurrence No	Total n
Femur Distal	9 (32.1)	19 (67.9)	28
Femur Proximal	1 (14.3)	6 (85.7)	7
Tibia Distal	1 (33.3)	2 (66.7)	3
Tibia Proximal	7 (31.8)	15 (68.2)	22
Fibula Proximal	1 (11.1)	8 (88.9)	9
Pelvic Ring	3 (50)	3 (50)	6
Humerus Proximal	1 (25)	3 (75)	4
Radius Distal	4 (20)	16 (80)	20
Ulna	0	3 (100)	3
Others*	3 (25)	9 (75)	12

*:short and middle bones of hand and foot

Table 3a. Evaluation of Patients Groups According to Sex

	Sex		P
	Male (n=52)	Female (n=62)	
Age, year			0.827*
Mean±sd	31.6±13.3	31.2±13.8	
Median (min-max)	30.5(8-69)	30(9-66)	
Side, n(%)			0.492**
Right	26(50)	35 (56.5)	
Left	26(50)	27 (43.5)	
Lung Metastases			0.176**
Yes	4(7.7)	1 (1.6)	
No	48(92.3)	61 (98.4)	
Recurrence, n(%)			0.351**
Yes	11(21.2)	19 (30.6)	
No	41(78.8)	43 (69.4)	

*Mann-Whitney U test
**Chi-Square Test

Table 3b. Evaluation of Patients Groups According to Recurrence Status

N=114	Recurrence		P
	Yes (n=30)	No (n=84)	
Age, year			0.648*
Mean±sd	31.4±13.4	31.3±14.3	
Median (min-max)	30.5 (9-54)	29.5 (8-69)	
Sex, n(%)			0.252**
Male	11 (36.7)	41 (48.8)	
Female	19 (63.3)	43 (51.2)	
Side, n(%)			0.508**
Right	14 (46.7)	47 (56)	
Left	16 (53.3)	37 (44)	
Lung Metastases			0.017**
Yes	4 (13.3)	1 (1.2)	
No	26 (86.7)	83 (98.8)	

*Mann-Whitney U test
**Chi-Square Test

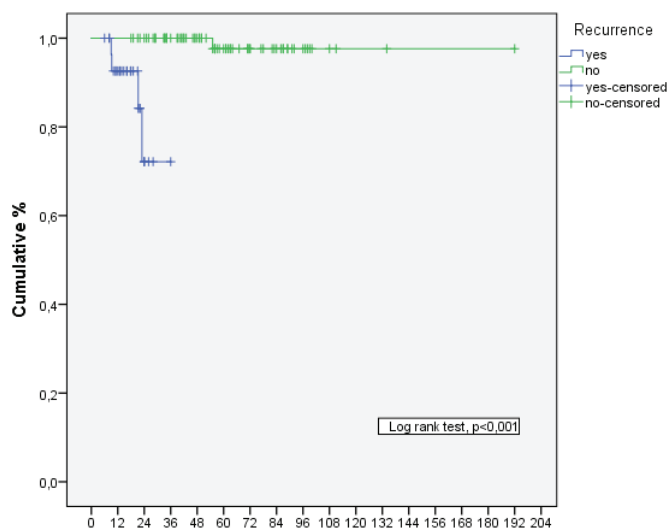


Figure 1. Kaplan–Meier curves of lung metastases rates according to recurrence

Discussion

In this study, in our orthopedic clinic specialized in cancer, we reviewed the 16-year data of patients treated with the diagnosis and treatment of giant cell tumors and analyzed the relationship between recurrence and lung metastasis. Lung metastasis was found to be significantly higher in patients with recurrence than in the group without recurrence. Accordingly, patients with recurrence have an increased 12.8 times risk of lung metastasis. Therefore, the risk factors that increase the recurrence should be well known and the local control in primary treatment should be provided.

Six different surgical procedures were performed according to the location and grade of the tumor. The most common surgical procedure was intralesional curettage. In our study, the recurrence rate was 26.3% and the complication rate was 9.6%.

In the literature, recurrence rates are reported in a wide spectrum ranging from 0% to 65% depending on the location of the tumor, size of the tumor, the stages of the patients and the types of treatment applied. While the highest recurrence rates are seen in patients undergoing only curettage, better results can be achieved by adding adjuvant therapies such as cauterization, high speed burr, phenol, liquid nitrogen, polymethylmethacrylate in addition to curettage. The best results can be obtained by en-block resection. Which patient should be treated aggressively, and which patient will be treated with curettage, this decision should be made specifically for each patient according to the location and localization of the tumor, and the surgical experience of the clinician. [13, 14]

Teixeira et al. investigated non-surgical factors associated with local recurrences Campanacci classification and tumor

diameter increased postoperative recurrence rates. [15] In this study, the relationship between recurrence and lung metastasis was evaluated while evaluating the factors affecting recurrence. Lung metastasis was found to be high in patients with recurrence. Most studies showed that recurrence rate of giant cell tumor of bones is risk factor for lung metastasis. [16]

Complication risk rates vary depending on the type of procedure being performed. Cases with pathological fractures have higher recurrence rates and lower functional outcomes. [17] The most common complication is infection and it occurs between 2% and 25% and the rate of infection after aggressive surgeries is higher. [18] In our study, the most common complication was also infection.

Giant cell tumor of bone is a disease of individuals whose epiphysis is closed; it is seen in 3% of children. An epiphyseal lesion detected in a patient with incomplete skeletal maturation is most likely chondroblastoma, while the diagnosis in the completed patient is probably a giant cell tumor. This tumor has been reported to be equal in men and women in some studies, although it is known to be a little more common in women. More than 75% of the lesions were seen in the long bones and more than 50% of all lesions were located around the knee. [14, 18] In our study, the demographic data of the patients were consistent with the literature, the majority of cases were in adults (93%), the most common site was knee circumference (35%) and more frequent in women (54%).

Giant cell tumors of the bone are locally aggressive tumors with unpredictable behavior. They are local recurrence-prone tumors, rarely metastasize, and the most common metastasis is in the lungs.

Although various classifications have been described in the light of histological clinical or radiological findings related to giant cell tumors, none of them provide a prognostic idea. Jaffe et al. described a histological classification in 1940, while Campanacci et al. described a clinical and radiological classification in 1987. [19, 20] We analyzed the patients according to gender, tumor direction and tumor location, and there were no significant findings.

Giant cell tumors of the bone may rarely malign, their prevalence is reported to be below 1%. [21] We did not find any patients with malignant transformation during the follow-up period.

Giant cell tumors can sometimes accompany Paget disease, especially in terms of orthopedic locations of giant cell

tumors, pelvic and vertebral locations are associated with Paget disease. [22] In our data, only 5.3% of the patients were located in the pelvic / vertebral region and we did not find any Paget association.

Conclusion

Giant cell tumors of the bone are locally aggressive tumors with unpredictable behavior. In our study, when the patients were evaluated according to their recurrence status, lung metastasis was observed in 13.3% of the patients with recurrence, and 1.2% of the patients without recurrence. Lung metastasis was found to be significantly higher in patients with recurrence than in the group without recurrence. Therefore, the risk factors that increase the recurrence should be well known and careful follow-up of patients with recurrence is recommended in terms of lung metastasis.

Declaration of conflict of interest

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