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Surveillance for lung metastasis from giant cell tumor of bone

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Background and Objectives: Literature on surveillance for lung metastasis from giant cell tumor of bone (GCTB) is scarce. We aimed to develop one by determining: (1) the optimal surveillance schedule by analyzing time-to-event data, taking into account the predictive factors, and (2) the effective diagnostic modality.

Methods: A total of 333 patients who underwent surgery for GCTB were followed for at least 2 years. All had chest radiography, and 169 had additional CT for surveillance. Time to lung metastasis and cumulative incidence were calculated, and diagnostic performance between chest radiography and CT was compared.

Results: Twenty-five (7.5%) of 333 patients developed lung metastasis, and local recurrence (LR) was the only predictive factor (RR = 6.54). Median interval from LR to metastasis was 15 months, and 17 (85%) of the 20 metastases with LR occurred within 3 years of LR. Cumulative post-LR incidences at 1, 3, and 5 years were 15.4%, 21.5%, and 21.5%, respectively. CT was more sensitive (100% vs 32%), and had higher positive predictive value (81% vs 57%) and accuracy (96% vs 93%).

Conclusions: Intensified lung surveillance is warranted for GCTB patients with LR, especially for 3 years from diagnosis of LR. CT is effective for detecting lung metastasis from GCTB.

KEYWORDS
chest CT, chest radiography, giant cell tumor, local recurrence, lung metastasis, surveillance guideline

1 | INTRODUCTION

Lung metastasis from giant cell tumor of bone (GCTB) occurs with an incidence ranging from 1% to 9%.[1–6] The natural history of lung metastases is unpredictable and can range from spontaneous remission to consistent growth resulting in patient's death.[1,2,7] Because of the unpredictable behavior, no standard treatment for GCTB lung metastasis exists, and treatment options can vary from metastasectomy, chemotherapy, radiation, or simple observation.[6,8,9] Denosumab, an antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), has recently been introduced for treating GCTB lung metastases.[10] Thus, early detection of lung metastasis would be beneficial in establishing treatment and follow-up strategy. However, to the best of our knowledge, no study on effective surveillance strategy for lung metastasis from GCTB has been published.

To develop an effective surveillance strategy for an event of interest, stratification of patients by the degree of risk of developing the event is needed. Several risk factors for lung metastasis from GCTB have been reported, such as local recurrence (LR), tumor location, and radiographic stage.[3,4,7,9,11–14] Tailoring of surveillance strategy based on the presence or absence of the risk factors is needed for GCTB lung metastases.

Chest radiography is cheap and easily performed, and thus is the commonly used diagnostic modality in the surveillance for lung

metastases from GCTB.[2] Computerized tomography (CT), which is generally accepted as having a higher sensitivity than chest radiography in the detection of tumors of the thorax, is advocated in some institutions in the surveillance for lung metastases.[2,9] However, the diagnostic performance of chest radiography versus chest CT has not been compared in the surveillance for lung metastases from GCTB. Thus, the appropriate diagnostic modality for lung surveillance from GCTB is not clear.

In this regard, this study aimed to propose an effective surveillance strategy for lung metastasis after surgery for GCTB by analyzing a large cohort of patients from a single institution. The purposes of this study were to determine: (1) the optimal surveillance schedule by analyzing time-to-event data for lung metastasis, taking into account the risk factors for lung metastasis and (2) the effective diagnostic modality for lung metastasis by comparing the diagnostic performance of chest radiography and chest CT.

2 | MATERIALS AND METHODS

A retrospective review of our institutional database identified 368 patients who underwent surgery for histologically confirmed GCTB from 1996 to 2014. Institutional review board approval was obtained. Among the 368 patients, 24 patients with fewer than 2 years of follow-up after surgery and 11 with insufficient medical records were excluded, which left 333 patients for analysis. Of the 333 patients, 64 (19%) had surgery for their primary tumors at outside institutions, 36 of whom presented at our institution with locally recurrent disease. There were 163 (49%) men and 170 (51%) women, with a mean age of 35 years (range 5-78). Fourteen patients (4%) were <15 years (Table 1). Two hundred thirty-nine (72%) patients underwent intralesional curettage, while 94 (28%) had wide resection. None of the patients received adjuvant bisphosphonates or Denosumab. Mean follow-up after surgery was 8 years (range, 2-43).

Upon the diagnosis of GCTB, chest imaging was performed to evaluate concurrent lung metastasis. For post-operative surveillance for lung metastasis, chest imaging was performed every 3-4 months for 2 years, then every 6 months for the next 2 years, and then annually. All patients underwent routine chest radiography, while 169 (51%) had additional chest CT. The decision to proceed with additional chest CT was based on the surgeon's preference and was not based on a prospectively selected criteria. LR was monitored with radiographs and additional magnetic resonance imaging (MRI) when findings of the radiographs were suggestive of LR.

Medical records were reviewed for the reported risk factors for lung metastases from GCTB: age at presentation, location of the primary tumor, Enneking radiographic stage,[15] and presence of LR (Table 1).[3,4,7,9,11–14] Mean age of patients at presentation was 35 years, and 143 (43%) were younger than 30 years. There were 21 different locations of the primary tumor, with axial sites accounting for 15%, while a distal radial location accounted for 8%. Twelve (3%) tumors were Enneking stage 1, 102 (31%) were stage 2, and 219 (66%) were stage 3. Of the 333 patients, 118 (35%) had LR. Thirty-six (31%) of the 118 cases with LR presented to our institution with LR. Mean interval from surgery to LR was 35.4 months (range, 7–424).

Lung metastasis was diagnosed when histological documentation of the metastatic lesion was confirmed or when radiologic findings met the following criteria: (1) development of abnormal lesions as single or multiple pulmonary nodules on chest radiography[2,6,7,9] or nodular,

TABLE 1 Patient characteristics*

Age	
<30 years	143 (43)
≥30 years	190 (57)
Sex	
Male	163 (49)
Female	170 (51)
Surgery of the primary tumor	
Extended curettage	239 (72)
Wide resection	94 (28)
Location	
Skull	2 (0.6)
Scapula	3 (0.9)
Proximal humerus	16 (4.8)
Proximal radius	2 (0.6)
Ulnar shaft	1 (0.3)
Distal radius	25 (7.5)
Distal ulna	5 (1.5)
Hand	10 (3)
Proximal femur	16 (4.8)
Femoral shaft	1 (0.3)
Distal femur	110 (33)
Patella	2 (0.6)
Proximal tibia	64 (19.2)
Proximal fibula	16 (4.8)
Tibial shaft	1 (0.3)
Distal tibia	5 (1.5)
Distal fibula	1 (0.3)
Rib	1 (0.3)
Spine	17 (5.1)
Pelvis	27 (8.1)
Foot	8 (2.4)
Radiographic stage	
1	12 (3)
2	102 (31)
3	219 (66)
Local recurrence	
Absent	215 (65)
Present	118 (35)

[a]Presented as the number with the percentage in parentheses.

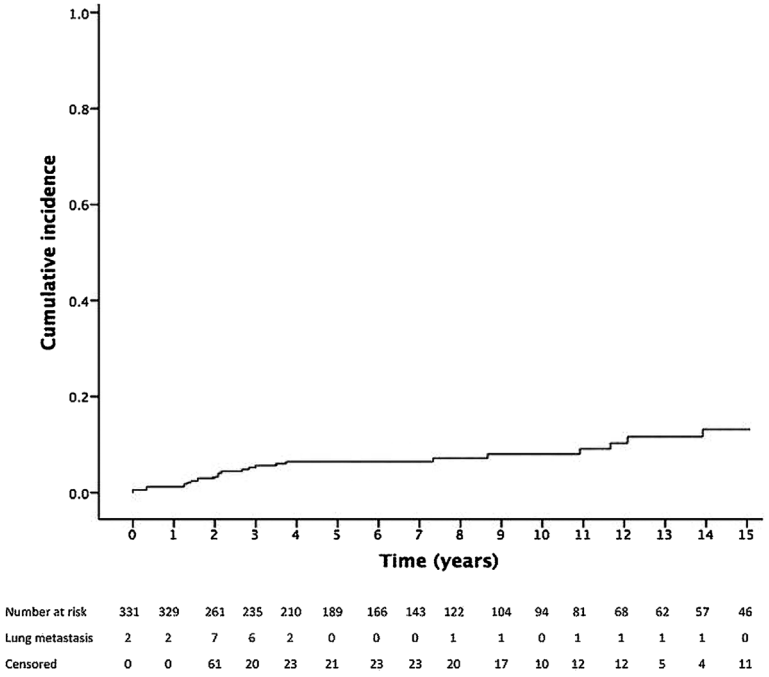

FIGURE 1 Cumulative incidence of lung metastases from the time of surgery

rounded, well-defined opacities on chest CT,[6] and (2) growth either in number or size of the lesions during follow-up. Lesions that showed no growth for 3 years were not regarded as metastasis. Patients with less than 3 years of follow-up for lung metastasis were excluded from analyses. Time to lung metastasis was calculated from the time of operation of the primary tumor or the time of LR. Time to last follow-up was documented in all cases.

To compare the diagnostic performance of chest radiography and chest CT, the formal reports of each examination by the radiologists were reviewed. For each readout, the documentation of lung metastasis was noted.

To identify risk factors for lung metastases, metastasis-free survival was estimated using Kaplan-Meier survival curves. For univariate analysis, the log-rank test was performed. To eliminate bias due to confounders, multivariate analysis was performed using the Cox proportional hazards model on the variables with *P* values of <0.15 from the univariate analysis. Time to lung metastasis was calculated from the time of operation for the

TABLE 2 Univariate analysis of factors associated with lung metastasis

	Total (*n*)	Metastasis (*n*)	Metastasis-free survival (years)[a]	95%CI	*P*-value (log rank)
Age					0.201
<30 years	143	14	36.2	32.5-39.9	
≥30 years	190	11	33.7	32.0-35.4	
Location					0.159
Axial	50	6	17.7	15.7-19.7	
Appendicular	283	19	38.4	36.2-40.5	
					0.570
Distal radius	25	1	16.2	15.0-17.3	
Other extremity	308	24	37.9	35.8-40.0	
Radiographic stage					0.141
3	219	20	33.2	30.2-36.3	
1 or 2	114	5	37.6	35.3-39.9	
Local recurrence					<0.001
Present	118	20	28.7	25.5-31.9	
Absent	215	5	41.7	40.7-42.7	

[a]Survival estimate by Kaplan-Meier analyses, CI; confidence interval.

TABLE 3 Multivariate analysis of factors associated with lung metastasis

	Relative risk	95% confidence interval	*P*-value
Radiographic stage			0.150
3	2.05	0.8-5.5	
1 or 2	1		
Local recurrence			<0.001
Present	6.54	2.4-17.5	
Absent	1		

primary tumor or the time of first LR. Patients without lung metastasis were censored at the time of last follow-up. Cumulative incidence functions were used to estimate the cumulative incidence and 95% confidence interval. To compare the diagnostic performance of chest radiography and chest CT, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated.[16] All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY). A *P*-value of less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Incidence and timing of lung metastasis after surgery of the primary tumor

Twenty-five (7.5%) of the 333 patients developed lung metastasis. Of the 25 patients, 14 metastases were histologically confirmed and 11 metastases were diagnosed radiologically. The median interval from surgery for the primary tumor to the detection of lung metastasis was 25 months (range, 0-167). Two (8%) of the 25 metastases were detected concurrently at the time of the primary tumor diagnosis. Nineteen (76%) metastases were detected within 4 years of surgery. Cumulative incidence of lung metastasis at 1, 3, 5, and 10 years were 1.2% (0.6 to 1.8%), 5.6% (4.3 to 6.9%), 6.5% (5 to 8%), and 8% (6.2 to 9.8%), respectively (Fig. 1).

3.2 | Incidence and timing of lung metastasis taking into account the risk factors

On univariate analyses of possible factors related to lung metastasis, patients with LR had significantly shorter metastasis-free survival than patients without LR (28.7 ± 1.6 years vs 41.7 ± 0.5 years, $P < 0.001$) (Table 2). Seventeen percent of the patients with LR (20/118) developed lung metastasis, whereas only 2% of the patients without LR (5/215) developed lung metastases ($P < 0.001$). Patient age, radiographic stage, and primary tumor location were not associated with development of metastasis. On multivariate analysis, LR was the only independent factor associated with development of metastasis (relative risk [RR] = 6.54, $P < 0.001$) (Table 3).

As LR was found to be an independent risk factor for lung metastasis, further analysis was performed to determine the incidence and timing of lung metastasis in patients who developed LR ($n = 20$). Median interval from LR to metastasis was 15 months (range 4-116). Of the 20 metastases, 17 (85%) occurred within 3 years of LR. Cumulative post-LR incidence of lung metastasis at 1, 3, 5, and 10 years were 15.4% (13.2–17.6%), 21.5% (16.6–26.4%), 21.5% (16.6–26.4%), and 44.5% (32.5–56.5%), respectively (Fig. 2).

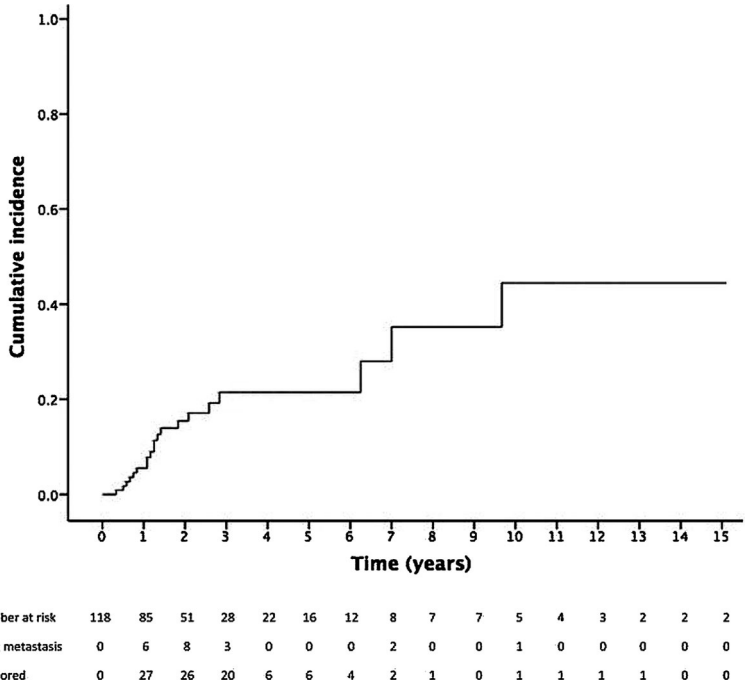

FIGURE 2 Cumulative incidence of lung metastases from the time of local recurrence

TABLE 4 Diagnostic performance of chest radiography

	Metastasis-positive	Metastasis-negative	
CR-positive	8	6	PPV: 57%
CR-negative	17	294	NPV: 95%
	Sensitivity: 32%	Specificity: 98%	

CR, chest radiography; PPV, positive predictive value; NPV, negative predictive value.

3.3 | Comparison between chest radiography and chest CT in detecting lung metastasis

For lung metastasis surveillance, all patients underwent routine chest radiography, while 169 (51%) underwent additional chest CT. In all, 14 cases developed abnormal lesions on chest radiography (Table 4). Of the 14 chest radiography-positive cases, 8 cases (57%) were found to have lung metastases. Six cases were rediagnosed as lung metastasis from malignant transformation of GCTB ($n = 3$), with absence of growth of the abnormal lesions on follow-up ($n = 2$), and concurrent lung carcinoma ($n = 1$). In 17 of the 25 metastatic cases (68%), radiographs were reported as normal. Of these 17 patients, 14 cases were eventually diagnosed as metastases by histological documentation and 3 by the radiologic criteria. Chest radiography was thus very specific (98%) but not sensitive (32%), and it had a low PPV (57%), with an overall diagnostic accuracy of 93% (302/325).

In all, 39 cases developed abnormal lesions on chest CT. Of the 39 CT-positive cases, 8 cases, which were histologically unconfirmed, showed no growth either in number or size of the lesions, and with less than 3 years of follow-up, were excluded as the metastases could not be determined. Of the remaining 31 CT-positive cases, 25 cases (81%) were found to have lung metastases (Table 5). Six cases were rediagnosed as lung metastasis from malignant transformation of GCTB ($n = 3$), with absence of growth of the abnormal lesions on follow-up ($n = 2$), and concurrent lung carcinoma ($n = 1$). Chest CT had a PPV of 81%, NPV of 100%, sensitivity of 100%, specificity of 96%, and an overall diagnostic accuracy of 96%.

TABLE 5 Diagnostic performance of chest CT

	Metastasis-positive	Metastasis-negative	
CT-positive	25	6	PPV: 81%
CT-negative	0	130	NPV: 100%
	Sensitivity: 100%	Specificity: 96%	

CT, computed tomography; PPV, positive predictive value; NPV, negative predictive value.

4 | DISCUSSION

GCTB is a locally aggressive tumor with the potential to metastasize to the lung.[17,18] Although some of these metastases may spontaneously regress, treatment such as metastasectomy is needed in some cases.[1,2,7] Thus, early detection of lung metastasis from GCTB may lead to better outcomes. Despite the consensus on the necessity for lung surveillance in GCTB, literature on effective surveillance strategy for lung metastasis from GCTB is scarce. This study sought to propose an effective surveillance strategy by analyzing: (1) the incidence and timing of lung metastasis with regard to the risk factors, and (2) diagnostic performance of chest radiography and chest CT.

The study has several limitations. First, the use of radiologic criteria for diagnosis of lung metastasis ($n = 11$) might have resulted in overestimation of lung metastasis. However, the strict radiologic criteria employed in this study would have minimized overestimation of lung metastasis. Second, lung metastasis rate of 7.5% in this study is relatively high compared to the rates of previous studies.[1–6] Relatively large proportion of patients with LR (35%) might have contributed to this finding. Of note, 31% of patients with LR had surgery at outside hospitals and presented to our institution with LR. The risk for lung metastases was not different between the patients who presented to our institution with LR and the patients who developed LR after initial treatment in our institution (5/36 [14%] vs 15/82 [18%], $P = 0.557$). Third, relatively small number of patients might have prevented from identifying additional independent risk factors for lung metastasis other than LR. Identification of multiple risk factors would provide more detailed and effective surveillance strategy for lung metastasis from GCTB. Given the rarity of lung metastases from GCTB, multi-institutional study encompassing large number of patients might be necessary. Fourth, the surveillance schedule was not standardized. Prospective comparative study is necessary to verify the performance of chest radiography and CT in diagnosing lung metastasis from GCTB.

The mean interval between surgery of the primary tumor and lung metastases was 3.9 years in the present study, which is similar to those of larger series with a mean interval of 2.0-4.1 years.[7,9,14] Seventy-six percent of the metastatic cohort developed lung metastases within 4 years of surgery. This finding is in line with two previous studies which reported on the timing of lung metastases after surgery. In a series of 24 patients with lung metastasis, 22 metastases (92%) occurred within 3 years of surgery. In another study, 11 of 14 patients (79%) developed lung metastases within 3 years of surgery. Taken together, surveillance for lung metastases after surgery of the primary tumor is most likely to be effective in the initial 3-4 years. However, the possibility of prolonged time course to metastasis is possible, as one patient developed metastasis 14 years after surgery. In addition, two cases presented with concurrent metastasis at the time of diagnosis. We agree with suggestions that lung surveillance at the time of presentation is needed in GCTB.[7,9,14]

Stratification of patients according to the risk factors for lung metastasis is necessary to provide effective surveillance strategy. In agreement with the results of this study, LR has been consistently

TABLE 6 Studies associating local recurrence with development of lung metastasis in giant cell tumor of bone

Study	Year	Metastases (*n*)	Metastases with LR (*n*)	Metastases without LR (*n*)	Interval from LR to metastasis (years)		Timing of metastases
					Median	Range	
Siebenrock et al[7]	1998	23	19 (83%)	4 (17%)	1.3	0 to 9.2	80% within 4 years of LR
Dominkus et al[9]	2006	14	10 (71%)	4 (29%)	0.6	0 to 8.2	85% within 4 years of LR
Viswanathan et al[6]	2010	24	13 (54%)	11 (46%)	1.1	0 to 5.6	92% within 3 years of LR
Present study	2017	25	20 (80%)	5 (20%)	1.3	0 to 9.7	85% within 3 years of LR

LR: Local recurrence.

reported as the most significant risk factor for lung metastasis from GCTB.[4,8] The proportion of lung metastasis in patients who develop LR was 80%, which falls in the reported range of 54-83% (Table 6).[6,7,9] However, few studies have been published with regard to the timing of lung metastasis from the time of LR. In a study of 24 patients with lung metastasis from GCTB, 13 patients had LR before or at the time of metastasis.[6] Of these 13 patients, 12 patients (92%) developed metastasis within the 3 years of LR. In other studies, 80% (8/10)[9] and 85% (16/19)[7] developed lung metastases within 4 years of LR. These findings are in agreement with the results of this study, supporting the need for intensified surveillance for the initial 3 years from the diagnosis of LR.

Among the patients with LR, patients who developed metastases had shorter interval to LR than patients who did not develop metastases (26.8 months vs 37.3 months, $P = 0.456$). Intensifying lung surveillance for the tumors developing LR with a shorter interval, therefore, seems prudent. Although whether LR acts as a precursor of metastatic nidus or is just a sign of aggressive tumor biology remains unclear, these findings highlight the importance of local control of the primary lesion in GCTB.

As only 2% (5/215) of patients without LR developed lung metastases, risk factors to stratify are needed in this subgroup of patients. Interestingly, patients without LR had a shorter mean interval to lung metastasis from surgery than patients with LR (19.4 months vs 53.8 months, $P = 0.025$). Moreover, all five cases had Enneking stage 3 tumor. These findings suggest that patients with aggressive tumor biology, even without LR, are at risk for developing lung metastases. Better biomarkers that reflect the tumor biology are needed in GCTB.

The advantage of chest CT rests on the greater sensitivity than chest radiography in detecting lesions.[19–21] Although some studies have suggested that the greater sensitivity of chest CT is questionable in terms of clinical advantage,[19,20,22] the inferior performance of chest radiography, as shown by the low sensitivity (32%) and PPV (57%), shows that the overall incidence of pulmonary lesions would be greatly underestimated if chest CT is not used. Chest radiography has been mostly used for lung surveillance in GCTB,[2] possibly due to the increased cost of and radiation risk from chest CT, along with the lack of published studies comparing the two modalities.[21] A prospective comparative cost-effectiveness analysis is warranted to validate chest CT as the standard for lung surveillance in GCTB.

Few published guidelines exist on the surveillance interval for lung metastases from GCTB. The authors suggest a surveillance interval by extrapolating from the surveillance guidelines for low grade sarcomas. In line with the recommended surveillance interval of 6 months for low grade sarcomas[23,24] which carry a 2-10% risk for developing lung metastases,[25,26] surveillance interval of 6 months may be adequate for GCTB, which carries a 1-9% risk for developing lung metastases after surgery.[1–6] However, shorter surveillance intervals are warranted in patients who are diagnosed with LR, as the risk for lung metastasis increases significantly (17% in this study).

The increased radiation exposure from surveillance CT is a source of concern, even more so as GCTB mostly affects young adults. Patients with GCTB can receive radiation dose as high as 21 mSv per year based on the suggested surveillance interval by this study,[27] although the increase in cancer risk with 1 <100 mSv of exposure is controversial.[28] However, the clinical benefit related to the use of surveillance CT needs to be validated and weighed against the risks of radiation in GCTB.

Whether early detection and management of GCTB lung metastases directly translate to better outcomes remains to be proven, as tumor biology itself rather than the timing of detection may determine the outcome. Patients with fewer metastatic lesions who are treated aggressively are reported to have better prognoses than patients with widespread and unresectable metastases.[7,9,11] Denosumab has been used successfully for control of metastatic lung disease and may make resection of previously unresectable metastases possible.[29,30] However, there is major concern that Denosumab withdrawal is associated with a high rate of subsequent progression.[29,31] Lack of biomarkers that can predict the behavior of lung metastases from GCTB necessitates early detection and close monitoring of these lesions. Taken together, the authors believe that an effective surveillance strategy for lung metastases proposed by the present study may lead to improved outcomes in GCTB.

5 | CONCLUSIONS

In conclusion, intensified surveillance for lung metastasis is warranted in GCTB patients with LR, especially for 3 years from the diagnosis of LR. Chest CT is an effective diagnostic modality for detecting lung metastasis from GCTB.

DISCLOSURES

All authors have nothing to disclose.

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SYNOPSIS

We sought to propose an effective surveillance strategy for lung metastasis from benign giant cell tumor of bone (GCTB) by analyzing: 1) the incidence and timing of lung metastasis with regard to risk factors, and 2) the diagnostic performance of chest radiography versus chest computed tomography (CT). Our study found that intensified surveillance for lung metastasis is merited in GCTB patients with local recurrence (LR) especially for 3 years from the diagnosis of LR, and that chest CT is an effective diagnostic modality for detecting lung metastasis from GCTB.