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Patterns and prognostic significance of extrapulmonary metastasis at initial diagnosis in primary bone sarcomas: a nationwide registry-based study

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Abstract

Background

Extrapulmonary metastases in primary bone sarcomas remain poorly characterized, particularly across histological subtypes. We aimed to elucidate their incidence, associated clinicopathological factors, and prognostic impact at initial diagnosis using a nationwide registry.

Methods

We retrospectively analyzed 5,399 patients with primary bone sarcomas registered in the Bone and Soft Tissue Tumor Registry in Japan between 2006 and 2019. The incidence and distribution of extrapulmonary metastases were assessed by histological subtype, and associated factors were evaluated using logistic regression. Overall survival by metastatic pattern (lung-only, extrapulmonary-only, or both) was estimated using Kaplan–Meier analysis and compared using log-rank tests with adjustment for multiple comparisons.

Results

At diagnosis, 686 patients (12.7%) had distant metastases and 256 (4.7%) had extrapulmonary metastases, predominantly to bone (87.5%). Extrapulmonary metastases accounted for more than half of metastatic cases in Ewing sarcoma, undifferentiated pleomorphic sarcoma, and leiomyosarcoma of bone. In multivariable analysis, extracompartmental extension, skip metastasis, regional lymph node metastasis, and concomitant lung metastasis were independently associated with extrapulmonary metastasis in the analysis of the entire cohort. Skip metastasis was consistently associated with extrapulmonary metastasis in osteosarcoma, Ewing sarcoma, and undifferentiated pleomorphic sarcoma. Metastatic pattern significantly affected survival in the overall cohort, osteosarcoma, and Ewing sarcoma, but not in conventional chondrosarcoma or undifferentiated pleomorphic sarcoma.

Conclusions

The clinical features of extrapulmonary metastases in primary bone sarcomas differed substantially across histological subtypes. Their risk factors and prognostic impact vary by subtype, which may support histology-specific and risk-adapted systemic staging.

Introduction

Sarcomas are rare mesenchymal tumors arising primarily in bone and soft tissue, accounting for approximately 1% of all malignancies. They comprise more than 80 histologic subtypes, including more than 50 arising in soft tissue, with the remainder arising primarily in bone [1]. Initial staging is essential for determining treatment strategies, including surgery, chemotherapy, and radiotherapy. The lung is well established as the predominant site of distant metastasis in bone and soft tissue sarcomas [2, 3]. Certain soft tissue sarcoma subtypes preferentially metastasize to extrapulmonary sites, and surveillance modalities for these subtypes are described in the National Comprehensive Cancer Network guideline [4]. On the other hand, epidemiological data regarding extrapulmonary metastases in primary bone sarcomas remain limited, probably owing to the lower incidence of primary bone sarcomas compared with soft tissue sarcomas. The impact of extrapulmonary metastasis across primary bone sarcoma subtypes also remains unclear, with evidence derived mainly from osteosarcoma and Ewing sarcoma [5–10].

The aim of this study was to elucidate the incidence, risk factors, and prognostic impact of initial extrapulmonary metastasis at initial diagnosis in primary bone sarcomas using a nationwide database.

Patients and methods

Study Population

We utilized the Bone and Soft Tissue Tumor Registry (BSTT) in Japan: a nationwide organ-specific cancer registry that aimed to describe the nationwide statistics of bone and soft tissue sarcomas in Japan. The registry database contains demographic data, treatment results, and prognostic data on patients with bone and soft tissue tumors. Details of the data collection methods, frequency, and variables collected in the BSTT registry have been described previously [11, 12]. The study protocol was approved by the institutional review boards of the Japanese Orthopaedic Association and Tokyo Metropolitan Komagome Hospital. Patients diagnosed with primary bone sarcomas between 2006 and 2019 were identified in the registry. Cases that were registered at the time of recurrence or metastasis after initial treatment at another institution and unclassifiable sarcomas were excluded. Hemangioendothelioma of bone was also excluded because it can present with multicentric bone involvement, which we considered inappropriate for the objectives of the present study. Applying these inclusion and exclusion criteria, a total of 5,399 patients were included. We extracted the following data: age, sex, primary site (upper extremity, lower extremity, or trunk), size of the primary tumor, tumor subtype, grade, tumor extension (intracompartmental or extracompartmental based on the Enneking classification), the presence of skip metastasis, regional lymph node metastasis, and distant metastasis at initial visit.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges and were compared using the Wilcoxon rank-sum test. For categorical values, Pearson's chi-squared test or Fisher's exact test according to the sample size was applied. Missing values were categorized as "Unknown" and included in the descriptive summaries but excluded from statistical comparisons. Statistical tests used available data for each variable without imputation.

In comparisons of metastatic patterns among histological subtypes, logistic regression model was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for extrapulmonary versus lung-only metastasis. The overall association between histological subtype and metastatic pattern was assessed using a univariate logistic regression, with osteosarcoma as the reference category. Inferential analyses were restricted to histological subtypes with more than 10 metastatic cases, whereas only descriptive results were reported for subtypes with 10 or fewer metastatic cases because of unstable effect estimates.

Factors associated with extrapulmonary metastasis at initial presentation were assessed by binary logistic regression. Univariate logistic regression analyses were initially performed for each candidate variable, and variables identified to be statistically significant were entered into the multivariable logistic regression model. For histological subtype-specific analyses, only subtypes with at least 30 cases of extrapulmonary metastasis were evaluated.

Overall survival was defined as the time from the date of diagnosis to death from any cause. Cumulative OS was estimated using the Kaplan-Meier method and compared by the log-rank test. All tests were two-sided, and a P value of < 0.05 was considered statistically significant. The Benjamini–Hochberg method was applied for multiple comparisons. All the statistical analyses and figure creation were performed using R software version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Incidence and clinical characteristics of extrapulmonary distant metastasis in primary bone sarcomas

In the entire cohort (N = 5,399), the most frequent subtype was osteosarcoma, followed by conventional chondrosarcoma, Ewing sarcoma, chordoma, and undifferentiated pleomorphic sarcoma (Fig. 1). Out of the total 5,399 patients with primary bone sarcoma, 686 (12.7%) presented with initial distant metastasis. Extrapulmonary metastasis at initial diagnosis was found in 256 (4.7%) patients. The incidence of extrapulmonary metastasis at diagnosis varied across histological subtypes (Fig. 2). Bone was the most frequent site of extrapulmonary metastasis; out of the total 256 patients, 224 (87.5%) patients had bone metastasis. The clinical characteristics of patients with distant metastasis at initial diagnosis are shown in Table 1. In the univariate analysis, patients with extrapulmonary metastases were significantly older than those with lung-only metastases (median age, 45 vs. 30 years; $P < 0.001$). Tumor size differed significantly between the two groups; large primary tumors (≥ 8 cm) were less frequent in patients with extrapulmonary metastases than in those with lung-only metastases (60.2% vs. 71.6%; $P = 0.014$). Primary tumor site was also significantly associated with the metastatic pattern ($P = 0.013$), with extrapulmonary metastases occurring more frequently in patients with trunk tumors, compared to those with lower-extremity tumors. Extrapulmonary metastases were also more frequent in patients with skip metastases ($P < 0.001$) and regional lymph node metastases ($P = 0.025$). No significant differences were observed with respect to sex, histological grade, or tumor compartment. The metastatic pattern at initial presentation varied substantially among histological subtypes (Table 2). Osteosarcoma and conventional chondrosarcoma predominantly exhibited lung-only metastases, accounting for 72.1% and 69.0% of metastatic cases, respectively. In contrast, more than half of metastatic patients with Ewing sarcoma (53.6%), undifferentiated pleomorphic sarcoma (58.9%), and leiomyosarcoma of bone (65.2%) presented with extrapulmonary metastases. Consistent with these findings, comparisons within the metastatic cohort demonstrated that Ewing sarcoma (OR, 2.98 [95% CI, 1.93–4.59]), undifferentiated pleomorphic sarcoma (OR, 3.70 [95% CI, 2.08–6.59]), and leiomyosarcoma of bone (OR, 4.84 [95% CI, 1.99–11.74]) were significantly associated with a higher likelihood of extrapulmonary metastasis compared with osteosarcoma. Although the number of patients was limited, fibrosarcoma had the highest proportion of extrapulmonary metastases, with six of seven metastatic patients (85.7%) exhibiting extrapulmonary involvement. All the extrapulmonary metastatic lesions in patients with fibrosarcoma involved the bone (Fig. 2). Consequently, we analyzed factors associated with initial extrapulmonary metastasis (Table 3). In the univariate logistic regression analysis, larger tumor size (≥ 8 cm), extracompartmental tumor extension, skip metastasis, regional lymph node metastasis, and the presence of lung metastasis were significantly associated with extrapulmonary metastasis at initial presentation (all $P < 0.001$). In the multivariate analysis, extracompartmental tumor extension (OR, 1.60; 95% CI, 1.11–2.29; $P = 0.011$), skip metastasis (OR, 9.43; 95% CI, 6.40–13.90; $P < 0.001$), regional lymph node metastasis (OR, 2.61; 95% CI, 1.39–4.87; $P = 0.003$), and concomitant lung metastasis (OR, 3.91; 95% CI, 2.76–5.52; $P < 0.001$) remained independent risk factors for extrapulmonary metastasis. We subsequently performed histology-specific analyses of risk factors for extrapulmonary metastasis in osteosarcoma, Ewing sarcoma, and undifferentiated pleomorphic sarcoma, each of which included at least 30 patients with extrapulmonary metastases. The multivariable models included five variables: the four factors that were independently associated with extrapulmonary metastasis in the overall cohort—extracompartmental extension, skip metastasis, regional lymph node metastasis, and lung metastasis—and tumor size, which has previously been reported as a risk factor for bone metastasis in patients with primary bone sarcomas [13]. The results of the multivariable logistic regression analyses are shown in Fig. 3. In osteosarcoma, skip metastasis (OR, 7.79; 95% CI, 4.37–13.88; $P < 0.001$) and lung metastasis (OR, 5.56; 95% CI, 3.44–9.01; $P < 0.001$) were independently associated with extrapulmonary metastasis. In Ewing sarcoma, skip metastasis (OR, 9.94; 95% CI,

4.34–22.78; P < 0.001) and regional lymph node metastasis (OR, 3.92; 95% CI, 1.32–11.61; P = 0.014) were significant risk factors, whereas in undifferentiated pleomorphic sarcoma, only skip metastasis was significant (OR, 7.07; 95% CI, 1.81–27.63; P = 0.005). Thus, skip metastasis was the only factor consistently associated with extrapulmonary metastasis across all three histological subtypes.

Table 1
Clinical characteristics according to metastatic pattern

Characteristic	Metastatic pattern			
	Overall	Only lung metastases	Extrapulmonary metastases ± lung metastases	P
		N = 430	N = 256	
Age, years	38 (16–66)	30 (15–65)	45 (20–68)	< 0.001
Sex				0.879
Male	386 (56.3%)	241 (56.0%)	145 (56.6%)	
Female	300 (43.7%)	189 (44.0%)	111 (43.4%)	
Tumor size				0.014
< 8 cm	181 (26.4%)	102 (23.7%)	79 (30.9%)	
≥ 8 cm	462 (67.3%)	308 (71.6%)	154 (60.2%)	
Unknown	43 (6.3%)	20 (4.7%)	23 (9.0%)	
Primary site				0.013
Upper extremity	58 (8.5%)	42 (9.8%)	16 (6.3%)	
Lower extremity	274 (39.9%)	201 (46.7%)	73 (28.5%)	
Trunk	279 (40.7%)	173 (40.2%)	106 (41.4%)	
Unknown	75 (10.9%)	14 (3.3%)	61 (23.8%)	
Grade				0.720
High	630 (91.8%)	392 (91.2%)	238 (93.0%)	
Low	29 (4.2%)	19 (4.4%)	10 (3.9%)	
Unknown	27 (3.9%)	19 (4.4%)	8 (3.1%)	
Compartment				0.751
Intra	139 (20.3%)	86 (20.0%)	53 (20.7%)	
Extra	510 (74.3%)	323 (75.1%)	187 (73.0%)	
Unknown	37 (5.4%)	21 (4.9%)	16 (6.3%)	
Skip metastasis				< 0.001

Characteristic	Metastatic pattern			
	Overall	Only lung metastases	Extrapulmonary metastases ± lung metastases	P
		N = 430	N = 256	
No	531 (77.4%)	369 (85.8%)	162 (63.3%)	
Yes	120 (17.5%)	45 (10.5%)	75 (29.3%)	
Unknown	35 (5.1%)	16 (3.7%)	19 (7.4%)	
Regional lymph node metastasis				0.025
No	591 (86.2%)	384 (89.3%)	207 (80.9%)	
Yes	53 (7.7%)	26 (6.0%)	27 (10.5%)	
Unknown	42 (6.1%)	20 (4.7%)	22 (8.6%)	
Age is presented as median (interquartile range [IQR]); categorical variables are presented as n (%).				

Table 2
Metastatic pattern according to histological subtype

Histological subtype	Case distribution		Metastatic pattern among metastatic cases		Logistic regression for extrapulmonary metastasis		
	All cases, n	All metastatic cases, n (% of all cases)	Only lung metastases, n (% of metastatic cases)	Extrapulmonary metastases ± lung metastases, n (% of metastatic cases)	OR for extrapulmonary metastasis	95% CI	P
Osteosarcoma	2,333	383 (16.4%)	276 (72.1%)	107 (27.9%)	Reference	—	—
Ewing sarcoma	438	112 (25.6%)	52 (46.4%)	60 (53.6%)	2.98	1.93–4.59	< 0.001
Conventional chondrosarcoma	1,495	58 (3.9%)	40 (69.0%)	18 (31.0%)	1.16	0.64–2.11	0.626
Undifferentiated pleomorphic sarcoma	256	56 (21.9%)	23 (41.1%)	33 (58.9%)	3.70	2.08–6.59	< 0.001
Leiomyosarcoma	96	23 (24.0%)	8 (34.8%)	15 (65.2%)	4.84	1.99–11.74	< 0.001
Dedifferentiated chondrosarcoma	97	17 (17.5%)	10 (58.8%)	7 (41.2%)	1.81	0.67–4.87	0.243
Chordoma	407	14 (3.4%)	9 (64.3%)	5 (35.7%)	1.43	0.47–4.37	0.527
Fibrosarcoma	42	7 (16.7%)	1 (14.3%)	6 (85.7%)	—	—	—
Malignant giant cell tumor	40	7 (17.5%)	5 (71.4%)	2 (28.6%)	—	—	—
Mesenchymal chondrosarcoma	37	7 (18.9%)	4 (57.1%)	3 (42.9%)	—	—	—

OR, odds ratio; CI, confidence interval.

Table 3
Risk factors for extrapulmonary metastasis at initial presentation

Variable		Univariate analysis		Multivariate analysis	
	Category	OR (95% CI)	P	OR (95% CI)	P
Age	< 40	Reference			
	40–59	0.97 (0.69–1.36)	0.857		
	≥ 60	1.20 (0.91–1.59)	0.198		
Sex	Male	Reference			
	Female	1.00 (0.78–1.29)	1.000		
Tumor size	< 8 cm	Reference		Reference	
	≥ 8 cm	1.82 (1.38–2.39)	< 0.001	1.04 (0.74–1.46)	0.815
Compartment	Intracompartmental	Reference		Reference	
	Extracompartmental	2.95 (2.16–4.02)	< 0.001	1.60 (1.11–2.29)	0.011
Skip metastasis	No	Reference		Reference	
	Yes	16.00 (11.60–22.05)	< 0.001	9.43 (6.40–13.90)	< 0.001
Regional lymph node metastasis	No	Reference		Reference	
	Yes	11.81 (7.29–19.13)	< 0.001	2.61 (1.39–4.87)	0.003
Lung metastasis	No	Reference		Reference	
	Yes	6.69 (5.10–8.77)	< 0.001	3.91 (2.76–5.52)	< 0.001

OR, odds ratio; CI, confidence interval.

Prognostic impact of extrapulmonary metastasis in primary bone sarcomas

Overall survival differed significantly by metastatic pattern in the overall metastatic cohort (log-rank P < 0.001), as well as in patients with osteosarcoma (P < 0.001) and Ewing sarcoma (P < 0.001) (Fig. 4a–c). In the overall cohort, the 1-, 3-, and 5-year overall survival rates were 72.3%, 38.9%, and 30.7%, respectively, in patients with lung-only metastases; 70.2%, 32.1%, and 19.0% in those with extrapulmonary-only metastases; and 52.8%, 11.8%, and 5.9% in those with both lung and extrapulmonary metastases. Pairwise log-rank analyses with Benjamini–Hochberg adjustment showed significantly poorer survival in patients with both lung and extrapulmonary metastases than in those with lung-only or extrapulmonary-only metastases (both adjusted P < 0.001), whereas the difference between the lung-only and extrapulmonary-only groups did not reach statistical significance (adjusted P = 0.051). In osteosarcoma, the 1-, 3-, and 5-year overall survival rates were 70.9%, 36.2%, and 26.6%, respectively, for lung-only metastases; 70.4%, 41.9%, and 24.8% for extrapulmonary-only metastases; and 53.4%, 13.1%, and 8.7% for both lung and extrapulmonary metastases, respectively. Patients with both lung and extrapulmonary metastases had significantly poorer survival

than those with lung-only (adjusted P < 0.001) or extrapulmonary-only metastases (adjusted P = 0.006), whereas survival did not differ between the lung-only and extrapulmonary-only groups (adjusted P = 0.775). In Ewing sarcoma, the corresponding 1-, 3-, and 5-year overall survival rates were 83.7%, 52.6%, and 49.9% for lung-only metastases; 83.5%, 27.8%, and 11.7% for extrapulmonary-only metastases; and 56.7%, 6.3%, and 6.3% for both lung and extrapulmonary metastases. All pairwise comparisons were statistically significant (adjusted P = 0.007 for extrapulmonary-only vs lung-only metastases, P < 0.001 for both lung and extrapulmonary vs lung-only metastases, and P = 0.007 for both lung and extrapulmonary vs extrapulmonary-only metastases). In contrast, overall survival did not differ significantly according to metastatic pattern in conventional chondrosarcoma (log-rank P = 0.411) or undifferentiated pleomorphic sarcoma (P = 0.950), and none of the pairwise comparisons were significant (Fig. 4d-e).

Discussion

To our knowledge, this is the first large-scale study to comprehensively characterize extrapulmonary metastases at initial presentation across histological subtypes of primary bone sarcoma. Using a nationwide multicenter database, we demonstrated that extrapulmonary metastases were present in 4.7% of patients at initial diagnosis and that their frequency and metastatic patterns varied substantially by histological subtype. Bone accounted for the vast majority of extrapulmonary metastatic sites. Clinicopathological factors associated with extrapulmonary metastasis were also identified, along with histology-specific differences in its prognostic impact.

Most previous population-based studies have focused specifically on bone metastasis rather than extrapulmonary metastasis overall. Bone metastases at initial diagnosis have been reported to be 4.8% in patients with primary malignant bone neoplasms [13], while an earlier population-based study reported lung and bone metastases in 11.2% and 4.6% of patients, respectively [14]. In the present study, extrapulmonary metastases were identified in 4.7% of patients at initial presentation, a frequency consistent with the previously reported incidence of bone metastasis. This concordance is likely explained by our finding that bone was by far the predominant extrapulmonary metastatic site, accounting for 87.5% of patients with extrapulmonary metastases. This observation is also consistent with previous osteosarcoma studies showing that bone metastases occur considerably more frequently than other extrapulmonary metastases, such as liver or brain metastases [6, 15].

Another notable finding of this study was the high frequency of extrapulmonary metastases in rare histological subtypes, particularly primary leiomyosarcoma and fibrosarcoma of bone. To our knowledge, the incidence and distribution of extrapulmonary metastases in these rare primary bone sarcomas have not been systematically characterized. Although skeletal metastasis is a recognized manifestation of leiomyosarcoma arising from soft tissue or visceral organs [16], previous studies specifically excluded primary leiomyosarcoma of bone. Thus, our findings suggest that these rare primary bone sarcoma subtypes may have a previously underrecognized propensity for extrapulmonary, particularly skeletal, metastasis.

We investigated risk factors associated with extrapulmonary metastasis in primary bone sarcomas. Previous population-based studies have primarily focused on skeletal metastasis and have identified larger tumor size, extension beyond the periosteum, axial tumor location, regional lymph node involvement, and histological subtype as factors associated with bone metastasis at diagnosis [13]. Because the majority of extrapulmonary metastases in the present cohort involved the bone, we added these previously reported factors as candidate variables in the multivariable analysis of extrapulmonary metastasis. A noteworthy finding of the present study was the strong and consistent association between skip metastasis and extrapulmonary metastasis. Skip metastasis was independently associated with extrapulmonary metastasis in osteosarcoma, Ewing sarcoma, and undifferentiated pleomorphic sarcoma, and was the only risk factor shared across all three subtypes. Although skip metastasis is anatomically

distinct from distant metastasis, both skip lesions and distant extrapulmonary metastases may reflect a propensity for tumor dissemination through vascular routes [17]; their association is biologically plausible. Notably, skip metastasis remained strongly associated with extrapulmonary metastasis even in subtypes in which concomitant lung metastasis was not independently associated. Thus, skip metastasis may represent a marker of propensity for extrapulmonary dissemination. Further biological and prospective clinical studies are needed to clarify this relationship.

The present findings may also have implications for systemic staging at initial diagnosis. The optimal strategy for detecting extrapulmonary metastases in bone sarcomas varies by histology; thorough whole-body surveillance using FDG PET-CT or bone scan for osteosarcoma, Ewing sarcoma, and undifferentiated pleomorphic sarcoma is recommended, whereas there is no clearly established guideline of initial workup for other rare subtypes [18]. Our findings suggest that dedicated surveillance for extrapulmonary, particularly bone, metastasis should be considered for histological subtypes with a higher incidence of extrapulmonary metastasis than osteosarcoma.

Previous studies of osteosarcoma and Ewing sarcoma have reported substantially poorer survival in patients with extrapulmonary involvement than in those with lung-only metastases, with extrapulmonary metastasis associated with an increased risk of mortality [5, 10]. The present findings were broadly consistent with these previous observations. In contrast, this study detected no statistically significant survival differences by metastatic pattern in undifferentiated pleomorphic sarcoma or conventional chondrosarcoma. Evidence directly comparing lung-only and extrapulmonary metastases in these histological subtypes remains scarce [19]. These findings suggest that extrapulmonary involvement should not necessarily be regarded as a uniform prognostic entity across primary bone sarcomas; rather, its prognostic significance may depend on both histological subtype and the extent of metastatic dissemination. The present database lacked sufficient details on treatment of metastatic lesions, including the number and resectability of metastases and the use of metastasectomy, radiotherapy, or other local therapies. Therefore, we could not determine whether the observed survival differences were attributable solely to metastatic biology or were also influenced by differences in treatment opportunities.

This study has several limitations. First, this was a retrospective registry-based study and was therefore subject to the inherent limitations of retrospective data collection, including missing information and potential selection and information biases. Second, because the database comprised patients treated at numerous institutions throughout Japan, imaging modalities and staging protocols used to detect extrapulmonary metastases at initial diagnosis were not standardized and their details were unavailable. Third, despite the use of a large nationwide cohort, extrapulmonary metastases were uncommon; histology-specific multivariable analyses could be performed for only some subtypes, and even within these analyses the limited number of events may have resulted in insufficient statistical power. Fourth, detailed information on metastatic disease burden, including the number and precise anatomical distribution of metastatic lesions, was unavailable. Information on treatment of metastatic lesions was also insufficient to distinguish treatment strategies by metastatic site or timing, precluding assessment of the effects of metastatic burden and metastasis-directed treatment on survival. Fifth, the anatomical definition of skip metastasis could not be fully verified. Historically, skip metastasis has referred to two situations: discontinuous lesions within the same bone and transarticular lesions involving an adjacent bone [20]. In the more recent AJCC staging system, skip metastasis was narrowed down to the first definition [21]. Although the present data were intended to align with the AJCC definition, we could not validate that because our database did not provide the detailed location of skip metastasis. Finally, histopathological diagnoses were made at participating institutions without central pathological review.

In conclusion, this nationwide registry-based study provides a comprehensive characterization of extrapulmonary metastases at initial diagnosis across histological subtypes of primary bone sarcoma. The frequency and distribution of extrapulmonary metastases varied substantially by histological subtype, with particularly high proportions observed in Ewing sarcoma, undifferentiated pleomorphic sarcoma, leiomyosarcoma of bone, and fibrosarcoma of bone. Among clinical factors associated with extrapulmonary dissemination, skip metastasis was consistently associated across major histological subtypes. The prognostic significance of metastatic distribution was also histology-dependent: concomitant pulmonary and extrapulmonary metastases were associated with particularly poor outcomes, whereas the impact of isolated extrapulmonary metastasis varied by subtype. Collectively, these findings underscore the heterogeneity of clinical behavior in primary bone sarcoma and support a histology-specific and risk-adapted approach to initial systemic staging, with particular attention to skeletal metastases in selected high-risk patients.

Declarations

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Data availability

The data analyzed in this study are not publicly available because they are subject to restrictions imposed by the data provider. The data may be available from the corresponding author upon reasonable request and with permission from the Japanese Orthopaedic Association.

Author contributions

T. H. wrote the manuscript and reviewed the literature. L.Z., K.O.,

Y.T., T.A., K.N., S.Y., Y.I., K.O., A.K., and H.K. contributed to the research design and planning and substantially revised the manuscript.

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Figures

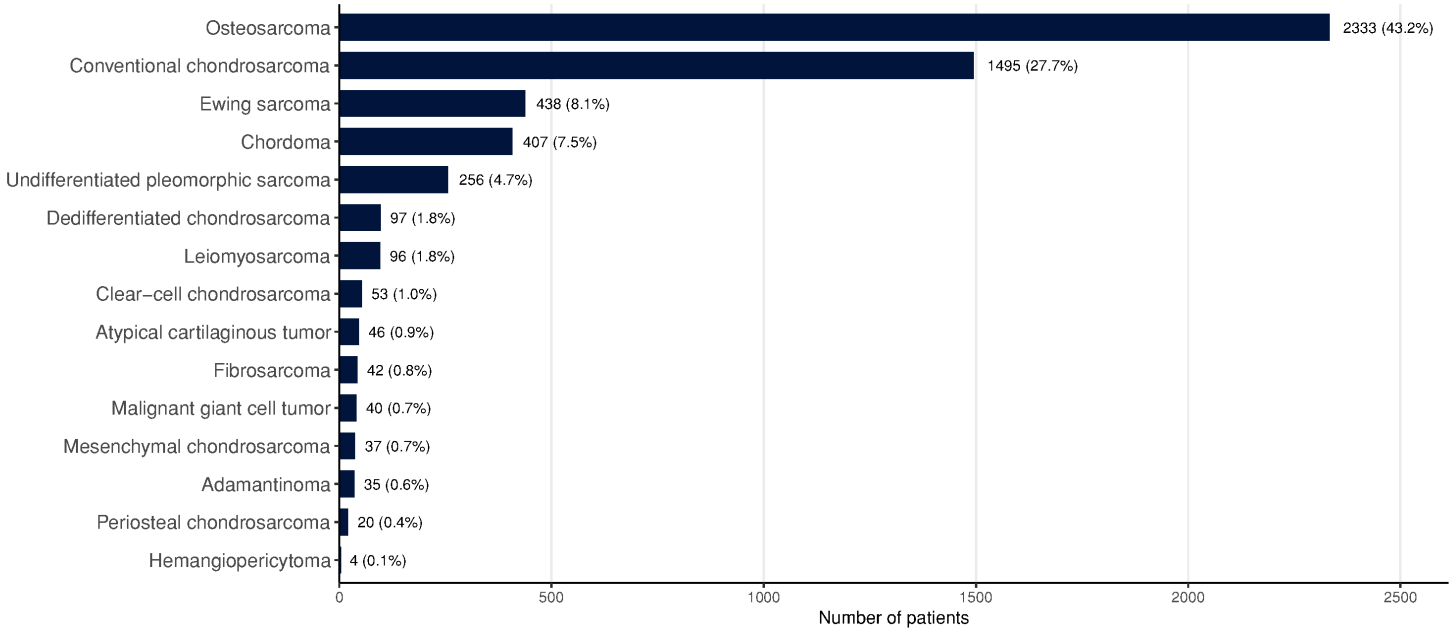


Figure 1

Distribution of histological subtypes among 5,399 patients with primary bone sarcomas included in the study

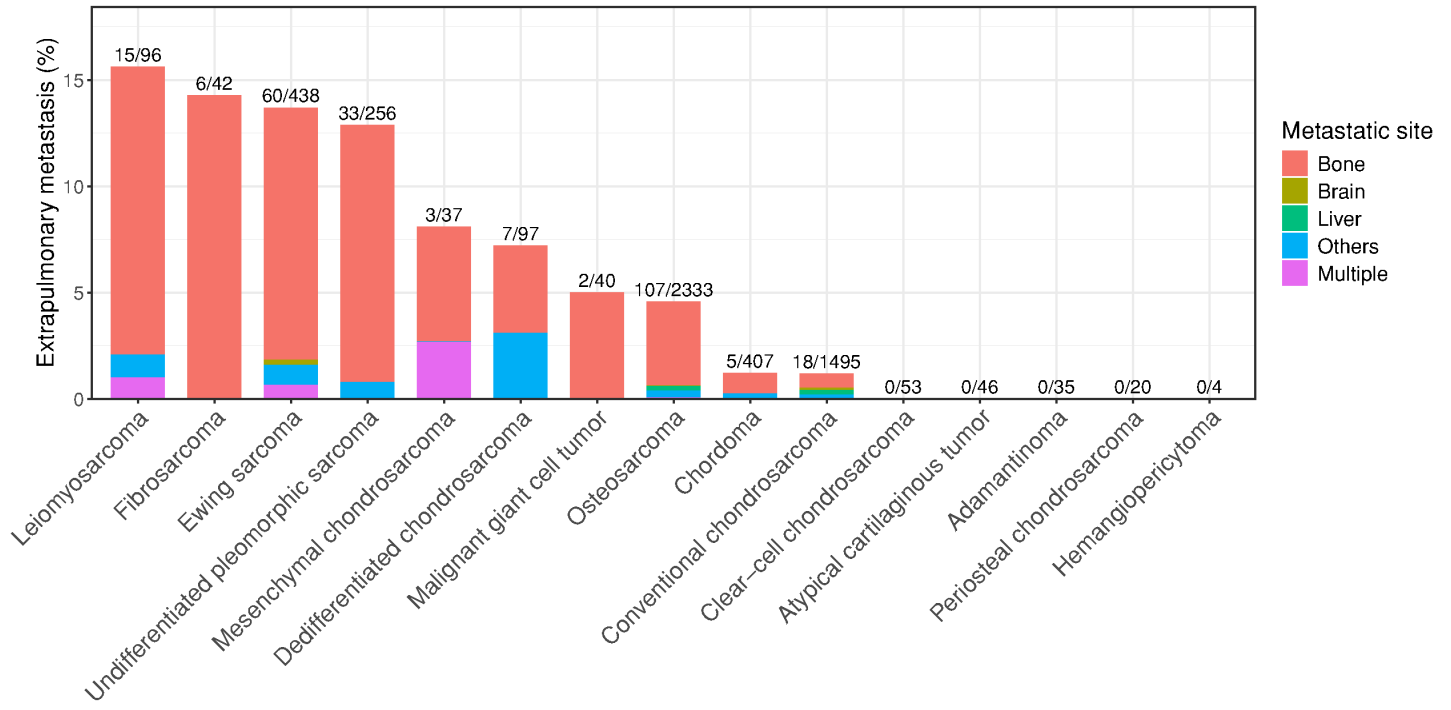


Figure 2

Incidence and distribution of extrapulmonary metastases at initial diagnosis by histological subtype. ‘Multiple’ indicates involvement of ≥2 extrapulmonary metastatic sites. Numbers above the bars indicate the number of patients with extrapulmonary metastasis relative to the total number of patients

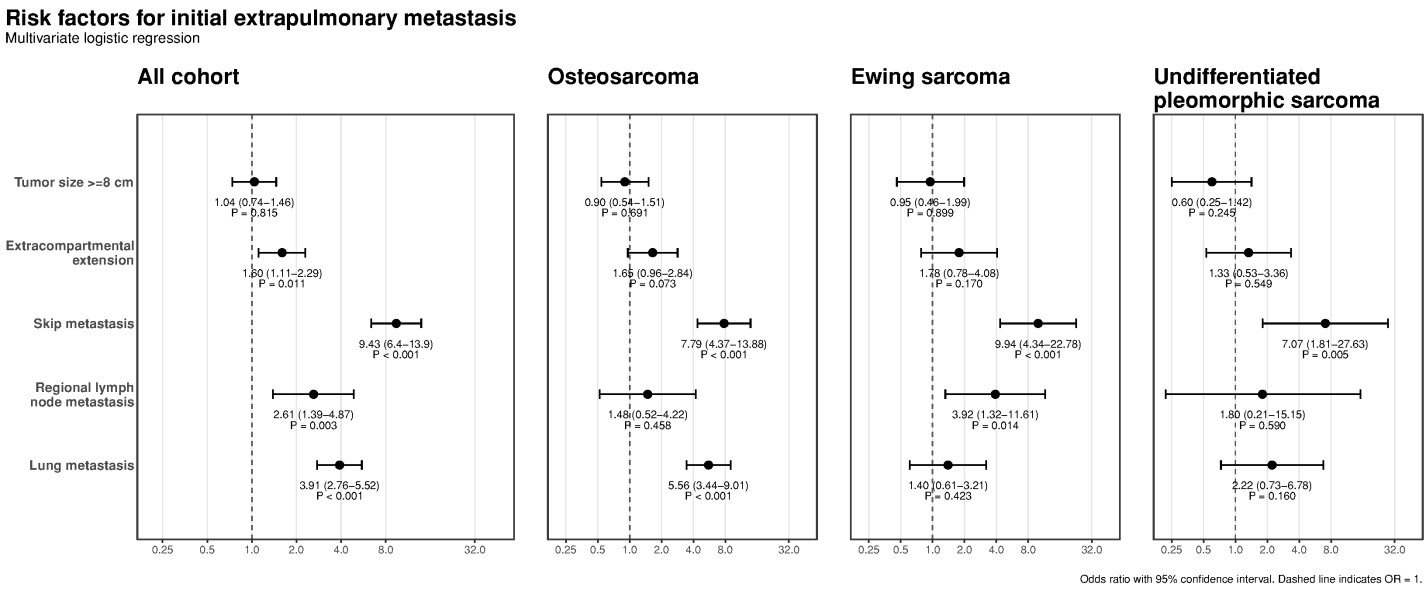


Figure 3

Risk factors for extrapulmonary metastasis in the entire cohort and by histologic subtype. Odds ratios (ORs) with 95% confidence intervals are described. The dashed line indicates OR = 1

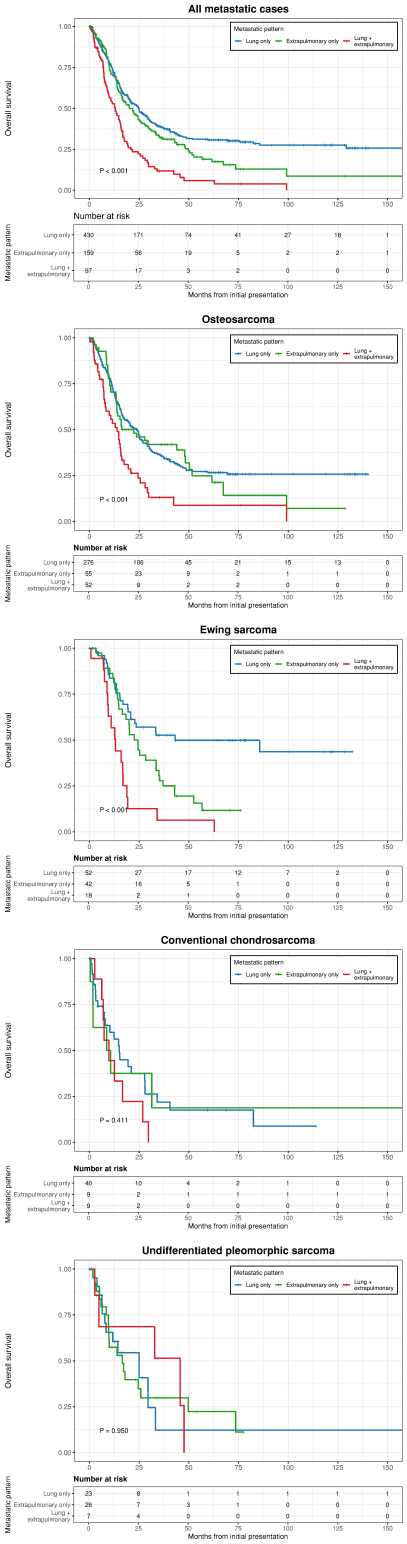


Figure 4

Overall survival by metastatic pattern at initial presentation. Kaplan–Meier curves for patients with lung-only metastases, extrapulmonary-only metastases, and both lung and extrapulmonary metastases are shown for (a) the overall metastatic cohort, (b) osteosarcoma, (c) Ewing sarcoma, (d) conventional chondrosarcoma, and (e) undifferentiated pleomorphic sarcoma. P values were calculated using the log-rank test