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Predictive Factors for Lung Metastasis in High-Grade Osteosarcoma: A 5 Years Experience from Tertiary Referral Hospital

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Metastasis stands as one of the most prominent prognostic factors in osteosarcoma. Over 70% of metastatic osteosarcoma occurrences affect the lung. Nonetheless, to date, there has been a scarcity of research addressing predictive factors for lung metastasis risk in osteosarcoma. The objective of this study is to identify the predictive factors that have a role in the risk of lung metastasis in osteosarcoma. This is a retrospective study conducted between January 2018 until January 2023. From the obtained research subjects, an assessment selection was carried out using inclusion and exclusion criteria. Subsequently, preoperative data related to predictive factors will be collected from the research subjects, followed by a clinicopathological conference, chemotherapy, and surgery. Afterward, an evaluation of pulmonary metastasis will be conducted six months after the diagnosis. A total of 47 osteosarcoma patients who met the inclusion and exclusion criteria were analyzed. Bivariate and multivariate logistic regression analyses revealed statistically significant predictive factors for the risk of pulmonary metastasis in osteosarcoma: ALP levels (p=0.014), LDH levels (p=0.038), presence of pathological fractures (p=0.025), and tumor size (p=0.027).

Keywords: Osteosarcoma, Pulmonary metastasis, Predictive factor, Survival rate, lung metastasis.

INTRODUCTION

Osteosarcoma is the most common type of bone cancer in children and young adults, with an annual reported incidence of approximately 3-4 cases per million1. Since the implementation of multi-agent chemotherapy in the 1980s, the survival rates for patients with nonmetastatic osteosarcoma have significantly improved. Based on findings from 2260 patients collected from April 2005 to June 2011 in the European and American Osteosarcoma study, the overall 5-year survival (OS) and disease-free survival (DFS) rates from respective biopsies were 71% (68%–73%) and 54% (52%–56%)[1]. However, the prognosis for patients with distant metastasis remains unfavorable[2]. In comparison to patients with localized osteosarcoma, the 5-year survival rate for patients with metastasis is less than 30%[3]. Distant metastasis has been acknowledged as a major concern in the management of osteosarcoma.

Due to the absence of significant symptoms in organs with early-stage metastasis that can be observed, distant metastasis is challenging to identify at the right time accurately. Therefore, many cancer patients experience distant metastasis at the time of initial diagnosis[4,5]. The incidence of early distant metastasis in osteosarcoma patients is approximately 15%[6], and the precise prevalence of metastasis is estimated to be less accounted for. Cancer may be the most significant medical issue worldwide, and substantial medical and financial resources have been allocated to cancer prevention and treatment. Therefore, increased attention should be given to patients at high risk of metastasis to detect potential metastasis promptly and provide appropriate treatment.

As reported, over 70% of metastatic sites involve the lungs[7], And pulmonary metastasis significantly reduces the survival of patients. The 5-year overall survival rate and disease-free survival rate after pulmonary metastasis are 30% and 21%, respectively[8]. The survival of patients with osteosarcoma after pulmonary metastasis is 16.0 months[9]. Regular lung CT scans are recommended in cases of osteosarcoma, and associated risk factors serve as indicators for patients potentially at risk for pulmonary metastasis[10]. Therefore, identifying prognostic and predictive factors is crucial for predicting patients at a high risk of

pulmonary metastasis, aiming to improve the survival rates of osteosarcoma patients[11].

Interestingly, there has been limited research or specialized tools to date regarding which factors should be thoroughly considered in determining the risk of pulmonary metastasis in osteosarcoma patients[4].

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

The inclusion criteria for this study encompassed a primary high-grade osteosarcoma diagnosis, a maximum age of 25 years, no prior history of cancer, and an evaluation period extending up to six months post-operation. All patients underwent a Clinicopathological conference, chemotherapy, and surgery. Meanwhile, the exclusion criteria for this research included patients with abnormal liver and kidney function, a history of metastasis at the time of diagnosis, and patients with pre-existing diseases. However, we excluded patients aged 4-5 decades, representing the second peak of osteosarcoma. This decision was influenced by the limited number of patients in this age group at our center, with the majority having comorbidities that could impact their outcomes.

Data Source and Study Design

We followed the methods of Guijun Xu et al. 2022[35]. This study is a retrospective study conducted from January 2018 to January 2023 at a single center, tertiary referral hospital. The data collection was done using medical records from our hospital to obtain the research sample. The research subjects comprised 47 male and female patients diagnosed with osteosarcoma who met the inclusion criteria and underwent a Clinicopathological conference, chemotherapy, and surgery.

Outcome Measures

According to the status of lung metastasis, patients were subgrouped into patients without lung metastasis and patients with lung metastasis. The diagnosis of lung metastasis using Chest CT-Scan. Predictive factors for the risk of pulmonary metastasis in high-grade osteosarcoma at six months post-diagnosis were evaluated, including gender, age, tumor location, levels of Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH), Erythrocyte Sedimentation Rate (ESR), C- Reactive Protein (CRP), histological subtype, type of surgical procedure, pathological fractures, and tumor size.

Statistical Analysis

We conducted data analysis using SPSS 2.7 software. For bivariate analysis, the data was categorized, and the Chi-Square test was employed for analysis. The analysis further extended to logistic regression.

RESULTS

Demographic and clinical characteristics

In this study, there were 47 subjects diagnosed with osteosarcoma who met the inclusion criteria as research subjects. Among them, 23 (48.9%) were female, and 24 (51.1%) were male. Additionally, 41 (87.2%) subjects were aged 14 years or older, and 6 (12.8%) were under 14 years of age. Out of the total 47 subjects, 28 (59.6%) experienced pulmonary metastasis at 6 months post-diagnosis, while 19 (40.4%) subjects did not develop pulmonary metastasis (Table I).

Predictive factors for developing lung metastasis

In this study, 11 variables were considered as predictive factors for the risk of pulmonary metastasis in high-grade osteosarcoma patients. The detailed data is shown in Table I.

Out of the 11 predictive factors for the risk of pulmonary metastasis in osteosarcoma, four significant predictive factors were identified based on bivariate analysis: ALP levels, LDH levels, a history of pathological fractures, and tumour size. To further assess the probability of these predictive factors on the risk of pulmonary metastasis in osteosarcoma, a multivariate logistic regression analysis was conducted.

Based on the multivariate logistic regression analysis of the 4 predictive factors for the risk of pulmonary metastasis in osteosarcoma, four statistically significant predictive factors were identified: ALP levels $\geq$ 200 U/L, LDH levels $\geq$ 240 U/L, a history of pathological fractures, and tumor size $\geq$ 200 cm3 (Table II).

DISCUSSION

Osteosarcoma is the most prevalent primary bone sarcoma. The emergence of metastatic conditions in the lungs among osteosarcoma patients has been identified as a negative prognostic factor. However, the lack of specific symptoms until the initiation of lung metastasis has contributed to a low survival rate. The absence of prominent symptoms in early-stage metastases poses a challenge in accurately identifying

Table I. — Bivariate analysis of predictive factor variables.

n		No Lung Metastasis		Lung Metastasis		Total	P	OR	95% CI	
		%	n	%				Min	Max	
Gender	Male	10	41,7	14	58,3	24	0,859	1,111	0,346	3,566
	Female	9	39,1	14	60,9	23				
Age	< 14 y,o	2	33,3	4	66,7	6	0,705	0,706	0,116	4,303
	> 14 y.o	17	41,5	24	58,5	41				
Tumor Site	Lower Extremity	16	42,1	22	57,9	38	0,720	1,455	0,316	6,705
	Upper Extremity	3	33,3	6	66,7	9				
ALP	< 200 U/L	15	55,5	12	44,5	27	0,018	5	1,319	18,960
	≥ 200 U/L	4	20	16	80	20				
LDH	< 240U/L	15	53,6	13	46,4	28	0,036	4,327	1,145	16,355
	≥ 240 U/L	4	21,1	15	78,9	19				
ESR	< 20 mm/hour	4	40	6	60	10	0,975	0,978	0,235	4,066
	≥ 20 mm/ hour	15	40,5	22	59,5	37				
CRP	< 5mg/L	2	28,6	5	71,4	7	0,685	0,541	0,94	3,132
	≥ 5mg/ L	17	42,5	23	57,5	40				
Histological subtype	Osteoblastic	6	37,5	10	62,5	16	0,769	1,124	0,349	4,152
	Others	13	41,9	18	58,1	31				
Surgery Type	Salvage	8	42,1	11	57,9	19	0,847	1,124	0,344	3,677
	Amputation	11	39,3	17	60,7	28				
Pathologic Fracture	Yes	5	22,7	17	77,3	22	0,036	4,327	1,213	15,439
	No	14	56	11	44	25				
Tumor Size	< 200 cm^3	15	55,5	12	44,5	27	0,018	0,2	0,053	0,758
	≥ 200 cm^3	4	20	16	80	20				

Table II. — Multivariate logistic regression analysis of the predictive factor variables.

		Beta coefficient	Standard error	Wald	Statistical Signifiance
Step 1[a]	ALP	-2.206	.894	6.096	.014
	LDH	-1.898	.914	4.315	.038
	Fracture	-1.981	.883	5.038	.025
	Tumor Voume	-2.051	.927	4.895	.027
	Constant	4.779	1.366	12.244	.000

distant metastasis at a presenting time. According to this study, four factors emerge as significantly meaningful predictive indicators for pulmonary metastasis in high-grade osteosarcoma: ALP, LDH, pathological fracture, and tumor size.

Despite the availability of various treatments such as surgery and chemotherapy, the five-year survival rate for osteosarcoma patients remains below 70%[12] and statistically, metastasis occurs in 30-40% of osteosarcoma patients13, where pulmonary metastasis is the most commonly affected site[14,15]. Osteosarcoma exhibits a crucial characteristic, which is the occurrence of isolated pulmonary metastasis, representing the most common systemic relapse pattern that occurs in 65-80% of relapse cases in Osteosarcoma[16]. From an epidemiological perspective, the five-year survival rate for patients with Osteosarcoma experiencing pulmonary metastasis is less than 30%[17]. Hence, the screening of high-risk Osteosarcoma patients for pulmonary metastasis holds significant implications in guiding medical decisions, both for physicians and patients.

In this study, four factors significantly serve as predictive factors for the risk of pulmonary metastasis in high-grade osteosarcoma patients: ALP levels, LDH levels, a history of pathological fractures, and tumor size. Experimental studies have shown that serum ALP is a valuable tumor marker with high specificity in osteosarcoma, and the diagnostic performance

of ALP for osteosarcoma diagnosis and metastasis is superior to well-known tumor markers in other cancers[18]. Elevated serum ALP levels are significantly associated with decreased overall survival and disease-free survival in Osteosarcoma[19,20-22]. Hence, we believe that osteosarcoma is in an active stage and carries a higher risk of metastasis when ALP levels are elevated.

A significantly elevated serum LDH level was found to be higher in Osteosarcoma patients with metastasis compared to Osteosarcoma patients without metastasis. In these patients, the 5-year disease-free survival was 39.5% for those with high LDH levels and 60% for those with normal values[23]. In the study we conducted, we found that a significant increase in LDH levels can serve as a predictive factor for the occurrence of pulmonary metastasis in osteosarcoma patients.

The prognostic significance of pathological fractures in osteosarcoma patients remains a subject of extensive debate. Some studies have found that the presence of pathological fractures is not associated with differences in overall survival and disease-free survival[24,25]. On the contrary, a retrospective multicenter cohort study has shown a significant correlation between the presence of pathological fractures in osteosarcoma cases and a higher rate of local recurrence and lower overall survival[25]. Several other groups have also reported that the presence of pathological fractures is correlated with poor outcomes in osteosarcoma patients[26-28]. The incidence of metastasis in patients with pathological fractures is higher when compared to patients without pathological fractures, with the hypothesis that if osteosarcoma is more aggressive with greater cortical bone infiltration and marrow involvement, the likelihood of pathological fractures and vascular invasion will increase. Hence, invasion may disrupt the bone architecture and increase the chances of pathological fractures as well as the rate of vascular invasion. Furthermore, the proportion of patients with pathological fractures who have pulmonary metastasis is much higher compared to those without bone fractures (50% vs. 32%)[29].

Changes in tumor volume may be closely related to its biological behavior[30-32]. Tumor size reflects the tumor burden and/or extent of the disease. Larger primary tumors are more likely to be associated with distant metastasis. In osteosarcoma patients, important prognostic factors for pulmonary metastasis include tumor size and the proportion of tumors showing necrosis after preoperative chemotherapy[33]. In one study, it was found that an increase in tumor volume is associated with an increased risk of pulmonary metastasis, with a positive predictive value of 69%. The rate of pulmonary metastasis is 34% and 69% in patients with tumor volumes <371 cm^3 and ≥371 cm^3, respectively[34]. This aligns with other studies that reported a lower rate of pulmonary metastasis risk at 12% in patients with tumor volumes ≤150 cm^3 and a higher rate at 44% in the group with tumor volumes >150 cm^3 [30]. In our study, the presence of a tumor size ≥ 200 cm^3 significantly correlates with the risk of pulmonary metastasis in high-grade osteosarcoma patients when compared to a tumor size < 200 cm^3. This implies that a tumor size ≥ 200 cm^3 can serve as a predictive factor for the risk of pulmonary metastasis in high-grade osteosarcoma patients.

Based on our studies, the identification of ALP, LDH, pathological fractures, and tumor size holds considerable clinical significance as predictive factors for lung metastasis in patients with high-grade osteosarcoma. The findings of this study are expected to enhance the overall management of osteosarcoma patients. The potential for early detection of lung metastasis is broader, promising to improve the effectiveness of the management given to patients.

CONCLUSIONS

Lung metastasis is the factor that significantly affects the survival rate of osteosarcoma patients. Based on our research, significantly meaningful predictive factors for the risk of pulmonary metastasis in high-grade osteosarcoma patients include ALP levels, LDH levels, the presence of pathological fractures, and tumor size.

Data availability: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval and consent: This publication was approved by the Ethical Committee Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada (MHREC) with the ID Number KE/FK/1641/EC/2023.

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