

## A Retrospective Analysis of Osteosarcoma among inpatients with Metachronous Metastatic Relapse

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### Abstract

**Aim:** Despite standardized treatments for osteosarcoma patients, metachronous metastatic recurrence still reduces overall survival (OS). The goal of this study was to examine the clinicopathological characteristics and predictive variables of individuals with metachronous metastatic recurrence of osteosarcoma.

**Methods:** 50 patients were retrospectively examined used the Chi-square test to identify the variations in clinicopathological traits between individuals with early and late metastatic disease, as well as those with longer and shorter survival times used the Cox step proportional hazard test to examine the prognostic factors related with OS and the Kaplan-Meier method to assess the variables.

**Result:** Tumour size  $\geq$  8 cm, histological grade G2, Enneking stages II, anatomic location of the distal femur, pathology of conventional kinds, and elevated alkaline phosphatase (ALP) level at diagnosis were strongly associated with early metastatic patients ( $p=0.04$ ). Parallel to this, the factors that were most

strongly associated with shorter survival times in patients included tumour size 8 cm, histological grade G2, Enneking stages II, early metastasis, multiple pulmonary metastases, lack of curative treatment after metastasis, elevated levels of ALP at diagnosis, and elevated levels of LDH after metastasis ( $p=0.04$ ). The Univariate evaluations of the predictive factors revealed that patients with these clinicopathological traits such as male, tumour size 8 cm, Enneking stage IIB, multiple pulmonary metastases, lack of curative treatment after metastasis, elevated ALP at diagnosis, elevated ALP and LDH after metastasis—had a worse OS in osteosarcoma patients with metachronous metastatic relapse, ( $p=0.04$ ). The multivariate analyses revealed that, in osteosarcoma patients with metachronous metastatic relapse, tumour size, type of metastasis, and ALP level at assessment were independent predictors for overall survival ( $p=0.04$ ).

**Conclusion:** These findings suggested that specific characteristics of osteosarcoma patients with

metachronous metastatic relapse may be used to accurately predict the risk of an early metastatic relapse and the prognosis.

**Keywords:** Clinicopathological Characteristics, Metastatic Relapse, Osteosarcoma, Prognosis.

### **Introduction**

The much more prevalent primary malignant bone tumour that adversely affects adolescents and children in particular is osteosarcoma [1]. Currently, neoadjuvant and adjuvant poly-chemotherapy as well as extensive tumour excision somewhere between chemotherapy cycles are used as the main treatments for osteosarcoma. The overall survival (OS) rate is increased by this multi-modal therapeutic approach from 10 to 70%, but metastasis still poses the greatest challenge to clinical prognosis [2]. Mesenchymal cells, such as immature bone and bone-like tissue, are the source of osteosarcoma, which contributes to its high intrusiveness and early metastasis [3]. The survival of osteosarcoma patients with or without distant metastases showed striking differences [4]. Patients with synchronous distant metastases frequently miss the chance to get normal treatment, which makes their prognosis worse. Some patients get metastases while undergoing therapy, and their prognosis is dismal, similar to that of synchronous distant metastases. The main cause of clinical treatment failure, however, is that patients with metachronous metastatic relapse usually experience metastases following standard treatment, particularly during the follow-up [5-7]. To identify more pieces of information and clinicopathological factors for predicting the outcome of patients after receiving conventional treatment, it is crucial to synthesise the characteristics of patients with metachronous metastatic relapse. Additionally, a future examination or treatment

may be used to prevent metastasis from occurring and to identify a metastatic relapse at an early stage by efficient follow-up. Few studies have examined the clinicopathological features of osteosarcoma patients who have experienced metachronous metastatic recurrence. Therefore, it is crucial to carry out an extensive investigation that takes into account all potential prognostic markers for these patients. In this research, clinicopathological features and prognostic variables among around 50 patients with metachronous metastatic relapse were significantly and thoroughly analysed and compared. We identified the theoretical foundation for looking for potential mechanisms to lower the rate of metachronous metastatic relapse and further improve the prognosis of patients with osteosarcoma by verifying the characteristics of patients who are more likely to progress to early metastatic recurrence following standard treatment.

### **Materials and Methods**

The study was used as a retrospective examination of patients with metachronous metastatic relapse of paediatric and adolescent osteosarcoma. Every patient signed the informed consent form. The study included these patients who met various inclusion and exclusion criteria.

**Treatment regimens:** Patients who fulfilled the aforementioned requirements underwent a typical course of care that included preoperative neoadjuvant chemotherapy for two cycles lasting two weeks each, radical surgery, and postoperative chemotherapy for an additional seven cycles (G1 patients only underwent surgery). Cisplatin and doxorubicin made up the neoadjuvant chemotherapy treatment. Doxorubicin was used as part of the postoperative chemotherapy protocol, either with or without ifosfamide. Treatments used after

metastasis included first-line and second-line chemotherapy, surgery, radiotherapy, and clinical testing, albeit the therapeutic approaches varied.

**Data Collection:** Trained examiners gathered data from the patient history including the fundamental patient characteristics, clinicopathological characteristics, laboratory values, imaging exams, and therapy details.

**Statistical Analysis:** The Chi-square test was employed to examine associations between categorical variables, such as the various patient groups and clinicopathological information. The survival data was assessed using the Kaplan-Meier method. The prognostic variables connected to overall survival were examined using the cox step proportional hazard test. It was determined that the two-sided P 0.04 was statistically significant.

**Results: Characteristics of the group as a whole:** Based on the established criteria, this retrospective cohort included 50 patients with metachronous metastatic recurrence of osteosarcoma, of which 62.6% fell into the EM group, 37.2% into the LM group, 59.2% into the SS group, and 40.6% into the LS group. The primary metastatic organ was the lung. In comparison to 37 cases of multiple pulmonary metastases, there were 13 cases of a single pulmonary metastasis. Bone and the liver were among the other metastatic organs. The patients' 15-month median time to metastatic disease. The ratio of men to women was 2.18:2, and the median age was 14.

**Clinical signs and a test result:** At the time of diagnosis, 84.6% of patients had arthralgia, 76.2% had tumour mass, 37.3% had claudication, and 11.8% had a pathological fracture. Overall fatigue (40.5%), fever (20.2%), weight loss (15.2%), and anaemia (13.5%) were additional frequent symptoms. Patients with increased levels of lactic dehydrogenase (LDH) and alkaline phosphatase (ALP) at diagnosis made up, respectively, 66.0% and 16.8% of the patient population.

**Overall rate of survival:** 41 patient fatalities have occurred by the conclusion of the follow-up period. Overall, the rates of event-free survival after one, two, and three years were 79.6%, 28.7%, and 23.6%, respectively. The survival rates after one, two, and three years were 69.4%, 40.6%, and 30.4%, respectively. The median overall survival (OS) was 30 months, while the EM and LM groups' median OS was 23 months and 82 months, respectively.

**Characteristic of Tumors:** The majority of malignancies (81.3%) were found close to the knee joint. The tumor median diameter ranged from 2.2 to 17.4 cm. The majority of the tumours (93.1%) and the majority of them (93.1%) were Enneking stage II.

**Predictive variables:** We assessed the survival data using the Kaplan-Meier method, and we looked at the prognostic variables linked to OS in patients with metachronous metastatic relapse using the Cox step proportional hazard test (**Table 1**).

Table 1: Univariate and multivariate analyses of the prognostic factors for osteosarcoma patients with metachronous metastatic relapse

Variables	Multivariate 95% CI	HR	P	Univariate 95% CI	HR	P
Gender						
Male vs Female	0.74-6.45	2.19	0.15	1.20-4.44	2.31	0.01
Age(years)						
≥15vs <15				0.38-1.35	0.71	0.30
Duration of symptoms(months)						
≥3vs <3				0.27-1.30	0.59	0.19
Size(cm)						
≥8vs<8	1.28-9.51	3.49	0.01	2.10-8.82	4.31	0.00
Histological grade						
G1vsG2				24.59	0.29-207	0.15
Site of primary tumor						
T1vsT2				0.75-2.71	1.42	0.27
Enneking stage						
II B vs I-II A	0.58-3.23	1.37	0.46	1.20-4.41	2.30	0.01
Pathologic fracture						
Yes vs No				0.64-4.22	1.64	0.29
Pathological types						
Conventional vs Nonconventional				0.87-15.23	365	0.07
Surgical methods						
Amputation vs Limb salvage				0.30-1.07	0.56	0.08
Type of metastasis						
Solitary pulmonary vs Multiple pulmonary or other organs	0.09-0.79	0.26	0.01	0.07-0.57	0.20	0.03
Treatment after metastasis						
Curative vs Palliative or no treatment	0.22-1.19	0.51	0.12	0.19-0.69	0.36	0.02
ALP level at diagnosis						
Elevation vs Normal	3.08-24.67	8.71	0.00	2.56-15.04	6.20	0.00
LDH level at diagnosis						
Elevation vs normal				0.96-4.10	1.99	0.06
ALP level after metastasis						

Elevation vs Normal	0.32-4.58	1.22	0.76	1.08-5.15	2.36	0.03
LDH level after metastasis						
Elevation vs Normal	0.28-3.30	0.97	0.96	1.74-6.53	3.37	0.00

Tumour size greater than 8 cm, Enneking stage IIB, type of metastasis, lack of curative treatment after metastasis, high level of ALP at diagnosis, and elevated level of ALP and LDH after metastasis were found to be factors negatively affecting overall survival (p=0.03). ALP level at diagnosis, tumour size, and type of metastasis (solitary pulmonary vs. numerous pulmonary or other organs), were all independently associated with OS.

**Discussion**

A significant contributing factor to the poor prognosis of osteosarcoma patients who underwent aggressive surgery and conventional chemotherapy is Metachronous metastatic recurrence [8]. Studies revealed that the circulation is where osteosarcoma metastasizes most frequently [1, 4, 9]. The lung serves as the organ for blood exchange and is frequently where malignancies spread after initial growth. The lung was the primary implicated metastatic organ in our sample, and pulmonary metastasis occurred in 86.3% of patients. Compared to patients with a single pulmonary metastasis or another organ metastasis, patients with multiple pulmonary metastases had a shorter survival time and a worse prognosis. The majority of them lack overt symptoms. e. The key mediators of OS lung tropism, IL-6 and CXCL8, and proposed pleiotropic, redundant methods by which they may influence metastases [10]. According to Zhang Y and his coworkers' research, osteosarcoma invasion and lung metastasis are inhibited when Skp2 expression is down regulated [11]. Human osteosarcoma patients' overexpression of ONZIN was strongly correlated with pulmonary metastasis, a poor prognosis, and survival [12]. Future research may allow

for the early detection of lung metastasis in osteosarcoma patients using cytokines or specific markers, and it may also allow for the adoption of new molecular targeted therapies in individuals who have metastatic relapse. The male to female ratio in this study was 2.18:2.

This may be due to the higher risk of metastatic relapse in male individuals. Additionally, early Metachronous metastatic relapse of osteosarcoma will spread more quickly in men. The outcome was in line with a prior study that demonstrated that, overall, male patients with osteosarcoma typically have a worse prognosis than female patients [13]. A study that examined 333 individuals with high-grade osteosarcoma indicated that female patients who received multidisciplinary combination therapy had better outcomes than male patients (14). Prostate cancer and lung cancer, two diseases with a high frequency in men, were found to be associated with increased free testosterone, according to research by Hyde Z and colleagues [15]. The Metachronous metastatic relapse of osteosarcoma may be significantly influenced by an up-regulated production of the male hormone. The size of the tumour was a key prognostic predictor for cancer patients, according to recent research. The size of the tumour was discovered to be a critical prognostic factor for broadly invasive follicular thyroid cancer in a research published concurrently [16].

Additionally, tumour size was an accurate predictor of prognosis for individuals with gastric cancer, and its evaluation might be useful for staging and managing the disease [17]. The occurrence of metastasis, primary

tumour size, and site were discovered to be significant prognostic variables in a comprehensive review of osteosarcoma prognostic factors [18]. Patients with high-grade osteosarcomas have a poor prognosis and are more likely to develop distant metastases [19]. We had reached the same conclusion in our investigation. According to Anja Luetke's summary, patients with high-grade osteosarcoma also exhibited low sensitivity to chemotherapy and radiation [20]. According to Topkas E's research, TXNRD2 may be a novel druggable target that might be used to lessen the occurrence of lethal lung metastases in OS patients [21]. Immune checkpoint inhibitors may be a novel treatment for lung metastases of advanced paediatric solid tumours, according to research by Shimizu T. and colleagues [22]. Patients in this study who consented to curative treatment fared better in terms of survival. Although the treatment plan was not very consistent, and we were unable to tell whether treatment was more successful, it is still important to provide patients with metastatic osteosarcoma with the proper care. The Enneking stage was a prognostic predictor for osteosarcoma patients with metachronous metastatic relapse, according to our survival analysis. The Enneking stage has a significant role in determining surgical treatment and how long patients with osteosarcoma will live [23]. The Enneking phases and distant metastases were proven to be related to the prognosis of osteosarcoma patients by some researchers [24]. ALP is a well-known enzyme connected to osteosarcoma. Alkaline phosphatase that is only found in bones (BALP) was examined to investigate the function of ALP in bone cancer [25]. Scientists discovered that the serum BALP level was associated with osteosarcoma metastasis. Patients with a consistently or escalating

higher. Serum BALP concentration would be regarded as aggressive probe during the aftercare. The greater intensity of ALP was also connected to distant metastases following. This study solely examined the clinicopathological characteristics and prognostic factors of 50 cases of osteosarcoma patients with Metachronous metastatic relapse, taking into account the morbidity of the disease, the standard of care, and the restrictions of the patients who were enrolled. In order to increase the overall survival of patients with osteosarcoma, it is important to identify potential mechanisms of metachronous metastatic relapse, particularly the early metachronous metastatic relapse, and to implement practical measures to stop or delay metastasis. In order to develop a more solid theoretical foundation for the risk of metastasis and prognostic variables in osteosarcoma patients, future studies should be carried out with multicenter cooperation for a larger range of retrospective or prospective investigations.

### **Conclusion**

Some characteristics of osteosarcoma patients who have experienced metachronous metastatic recurrence can be used to predict the probability of early metastasis and the patient's prognosis. The findings of this study may encourage further research for patients with metachronous metastatic relapse of osteosarcoma, despite the fact that the precise mechanisms behind this condition are still poorly known. Surgery on a patient with osteosarcoma [26].

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