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ORIGINAL ARTICLE

Survival of patients with primary osteosarcoma and lung metastases

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Summary

Purpose: *To investigate the survival of patients with primary osteosarcoma and lung metastases.*

Methods: *Clinical data of 128 patients with primary osteosarcoma and lung metastases who were admitted to Shenzhen Second People's Hospital from January 2013 to January 2015, were enrolled and retrospectively analyzed. Follow-up lasted for 3 years and after follow-up, patients were divided into survival group (n=54) and death group (n=74) according to their survival status. Univariate and logistic multivariate analyses were conducted on related factors contributing to death in patients with primary osteosarcoma and lung metastases.*

Results: *At the end of follow-up, there were 74 deaths (death group) and 54 survivors (survival group). Among all 128 patients, the 6-month, 1-year, 2-year and 3-year survival rates were 96.87, 92.96, 61.71 and 42.18%, respectively. Univariate analysis showed that tumor diameter, histological subtype, visceral pleural involvement, the number of lung metastatic lesions, the outcome after chemotherapy for the primary tumor, and therapy for lung metastasis were closely associated with death in patients with primary osteosarcoma and lung metastases (p<0.05). Multivariate logistic regression analysis showed that chondrocytes, multiple lung metastatic lesions, poor outcome after chemotherapy for primary tumor, and no surgery-combined treatment for lung metastasis were risk factors contributing to death in patients with primary osteosarcoma and lung metastases (p<0.05).*

Conclusion: *Risk factors contributing to death in patients with primary osteosarcoma and lung metastases include chondrocytes, multiple lung metastatic lesions, poor outcome after chemotherapy for primary tumor, and no surgery-combined treatment for lung metastasis. Surgical resection and preoperative adjuvant chemotherapy can effectively improve the patient survival.*

Key words: *lung metastasis, primary, osteosarcoma, survival*

Introduction

Osteosarcoma is a common malignant bone tumor with an incidence of nearly 3 per million. Due to the large population, the actual number of patients in China is large. Osteosarcoma often occurs in adolescents aged 10 to 25 years, and the incidence ratio in males and females is about 3:2 [1]. For the time being, no cause of osteosarcoma genesis has been confirmed. About 80-90% of osteosarcomas occur in the limb long bones, and about 60% of them are located around the knee [2]. Although surgical amputation was often performed for patients with osteosarcoma before the advent of cancer chemotherapy, about 80% of patients still died of lung metastases. Most patients with lung metastases have no clear symptoms over a long period of time. However, lung metastases can be detected by *in vivo* non-invasive imaging following diagnosis of osteosarcoma. Patients with primary osteosarcoma and lung metastasis have a very poor prognosis and the 5-year overall survival rate is only 25%. Thus, lung metastasis is one of the leading causes of death in patients with osteosarcoma

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[3,4]. In this study, the survival status of patients with primary osteosarcoma and lung metastasis, as well as the related risk factors, were explored, aiming to provide a reference for future clinical treatment of this disease.

Methods

The study was approved by the ethics committee of Shenzhen Second People's Hospital and signed informed consents were obtained from the patients and/or their guardians.

Patients

Clinical data of 128 patients with primary osteosarcoma and lung metastases who were admitted to Shenzhen Second People's Hospital from January 2013 to January 2015 were retrospectively analyzed. There were 88 males and 40 females aged 8-52 years with an average age of 17.53±4.33 years.

The following patients were included: (1) patients confirmed with primary osteosarcoma and lung metastases by classic X-ray imaging and pathological diagnosis [5]; (2) patients without previous history of cancer; (3) patients with complete clinical and follow-up data.

The following patients were excluded: (1) patients during pregnancy or lactation; (2) patients with other acute or chronic diseases; (3) patients with severe immune system disorders; (4) patients who withdrew in the mid of the study or got lost to follow-up.

Data evaluation

All patients were followed up for 3 years after treatment. Patient clinical data were retrospectively analyzed, including postoperative survival time, gender, age, tumor diameter, histological subtype, visceral pleural involvement, number of nodules, time of lung metastasis, number of lung metastatic lesions, metastases at other sites, outcome after chemotherapy for primary tumor, resection margin status, and therapy for lung metastasis. Univariate and multivariate analyses were conducted on related risk factors contributing to death in patients with primary osteosarcoma and lung metastases.

Statistics

The SPSS 20.0 statistical software package was used for statistical analyses. The x^2 test was applied to counting data. Multivariate logistic regression analysis was performed on related factors that were statistically significant on univariate analysis. The difference was statistically significant at $p<0.05$.

Results

Survival

All of the patients (n=128) were followed up for 3 years and had a median survival of 23 months (range 2-26). At the end of follow-up, there were 74 patients that died (death group) and 54 survivors (survival group). Among all 128 patients, the 6-month, 1-year, 2-year and 3-year survival rates were 96.87, 92.96, 61.71 and 42.18%, respectively. The results are shown in Table 1.

Table 1. Patient survival status

Time	*Survival, n (%)*
6 months	124 (96.87)
1 year	119 (92.96)
2 years	79 (61.71)
3 years	54 (42.18)

Univariate analysis of factors contributing to death in patients with primary osteosarcoma and lung metastasis

The following factors were closely associated with death in patients with primary osteosarcoma and lung metastasis: tumor diameter, pathological subtype, visceral pleural involvement, number of lung metastatic lesions, outcome after chemotherapy for primary tumor, and therapy for lung metastasis ($p<0.05$). The detailed results are listed in Table 2.

Multivariate logistic regression analysis of related risk factors contributing to death in patients with primary osteosarcoma and lung metastases

Multivariate logistic regression analysis showed that chondrocytes, multiple lung metastatic lesions, poor outcome after chemotherapy for primary tumor, and no surgery-combined treatment for lung metastasis were significant risk factors contributing to death in patients with primary osteosarcoma and lung metastases ($p<0.05$). The detailed results are shown in Table 3.

Discussion

About 10-20% of patients who are diagnosed with osteosarcoma in the first visit, are diagnosed with cancer metastasis as well. Osteosarcoma is characterized by its strong metastatic potential, mainly to the lung. Patients with osteosarcoma and lung metastases account for about 80%. Clinically, the most effective treatment for patients with lung metastases from osteosarcoma is complete lung resection [6]. Although treatment of patients with osteosarcoma and lung metastases can reduce the primary tumor burden and eliminate tiny metastatic lesions in the lung, about 50% of patients still experience recurrence. In addition, the hazard of developing secondary drug resistance is high in these patients. Therefore, the patients face sig-

Table 2. Univariate analysis of factors contributing to death in patients with primary osteosarcoma and lung metastasis

Factors	*Group*		x^2	*p value*
	Death group, n (%)	*Survival group, n (%)*		
Gender			3.417	0.054
Male	52 (70.27)	36 (66.66)		
Female	22 (29.73)	18 (33.34)		
Age, years				
≤25	59 (79.72)	44 (81.48)	1.746	0.077
>25	15 (20.28)	10 (18.52)		
Tumor diameter, cm			7.586	0.015
<3	31 (41.89)	33 (61.12)		
≥3	43 (58.11)	21 (38.88)		
Pathological subtype			8.036	0.011
Chondrocytes	47 (63.51)	17 (31.48)		
Other	27 (36.49)	37 (68.52)		
Visceral pleural involvement			5.921	0.031
Yes	55 (74.33)	10 (18.52)		
No	19 (25.67)	44 (81.48)		
Number of nodules			2.836	0.060
<3	35 (47.29)	24 (44.45)		
≥3	39 (52.70)	30 (55.55)		
Lung metastasis time			1.519	0.088
First visit	12 (16.21)	9 (16.66)		
During preoperative chemotherapy	15 (20.27)	8 (14.81)		
During postoperative chemotherapy	9 (12.16)	7 (12.96)		
After treatment	38 (51.36)	30 (55.57)		
Number of lung metastatic lesions			6.536	0.025
Single	29 (39.18)	35 (64.81)		
Multiple	45 (60.82)	19 (35.19)		
Metastases at other sites			1.854	0.071
Yes	16 (21.62)	12 (22.22)		
No	58 (78.38)	42 (77.78)		
Outcome after chemotherapy for primary tumor			7.037	0.020
Good	33 (44.59)	35 (64.81)		
Poor	41 (55.41)	19 (35.19)		
Resection margin status			3.399	0.055
R0	56 (75.68)	35 (64.82)		
R1	18 (24.32)	19 (35.18)		
Therapy for lung metastasis			5.837	0.032
Not treated	14 (18.91)	10 (18.51)		
Chemotherapy alone	38 (51.35)	10 (18.51)		
Combined with surgery	15 (20.27)	27 (50.00)		
Combined with γ or photon knife	7 (9.47)	7 (12.98)		

nificant survival challenges [7]. Previous studies suggested that patients with osteosarcoma and lung metastases had very poor prognosis, but treatments' efficacy gradually improved in recent years. For example, the 5-year survival rate has reached 40% [8]. In this study, the related risk factors contributing to patient death were explored, aiming to find a clue to improve the survival of patients with primary osteosarcoma and lung metastasis, and provide a reference for future clinical treatment of this disease.

Multivariate logistic regression analysis showed that chondrocytes, multiple lung metastatic lesions, poor outcome after chemotherapy

Table 3. Multivariate logistic regression analysis of related risk factors contributing to death in patients with primary osteosarcoma and lung metastases

Factors	*Beta*	*SE*	*Wald*	*OR*	*p value*	*95% CI*
Tumor diameter	0.606	0.457	1.756	1.834	0.185	0.593-1.485
Chondrocytes	0.552	0.245	5.047	1.737	0.024	2.397-4.184
Visceral pleural involvement	0.669	0.360	3.453	1.954	0.063	0.499-1.739
Multiple lung metastatic lesions	1.259	0.540	5.417	3.522	0.019	2.025-3.987
Poor outcome after chemotherapy for primary tumor	1.301	0.346	14.111	3.673	0.001	2.017-4.812
No surgery-combined therapy for lung metastasis	0.833	0.379	4.814	2.301	0.028	2.485-4.128

for primary tumor, and no surgery-combined treatment for lung metastasis were significant risk factors contributing to death in patients with primary osteosarcoma and lung metastases ($p<0.05$). Chondrosarcoma is a rare histological subtype, and has certain similarity to chondroblastoma. The most common subtype of chondrosarcoma is central chondrosarcoma of grades I and II. Chondrosarcoma is a low-grade tumor and typically affects adults. The tumor demonstrates certain aggressiveness, resulting in poor prognosis in patients with this disease [9].

It was reported that for every additional lung metastatic lesion in osteosarcoma, the mortality rate increased by 43% [10]. In one respect, patients who had multiple lung metastatic lesions [10] tended to have residual lesions left after surgical treatment due to various reasons. In another respect, the efficacy of postoperative chemotherapy may also be affected due to multiple lesions. Therefore, there was a high incidence of recurrence for these patients, which affected the postoperative survival rate [10]. Neoadjuvant chemotherapy (preop chemotherapy) was administered aiming at reducing the tumor size early in the treatment and eliminating tiny metastatic lesions. Following neoadjuvant chemotherapy, the tumor would show a clear boundary with the surrounding area, allowing for a clear surgical margin. Meanwhile, the effect of neoadjuvant chemotherapy can be used to guide postoperative chemotherapy regimen, allowing for an overall improvement of clinical outcome [11]. Common chemotherapeutic agents that are clinically used for osteosarcoma with lung metastasis include ifosfamide, methotrexate, cyclophosphamide, doxorubicin, actinomycin and bleomycin. Following neoadjuvant chemotherapy, some patients are operated, and some others receive radiotherapy. An improved 5-year survival rate was observed in patients who were administered neoadjuvant chemotherapy, indicating that a positive effect of preoperative chemotherapy was closely associated with survival of patients after treatment [12]. Some authors reported that complete resection of lung metastatic lesions was helpful in predicting survival of patients with osteosarcoma and lung metastases [13]. Some patients whose primary tumor was well-controlled or whose disease-free interval was long after resection of the primary tumor lesion can achieve better clinical prognosis through repeated surgical treatments. A disease-free interval shorter than half year following surgical removal of the primary tumor lesion indicate poor prognosis. To improve the prognosis, multiple operations were necessary [14]. Photon knife or gamma knife, which uses highly-focused beam and causes little trauma to patients, can be employed to treat multiple metastatic lesions at one time or one by one with less patients suffering. In clinic, photon knife or gamma knife are often used in the treatment of tumor lesions with a diameter of less than 3 cm or less than 3 lung metastatic lesions [15]. The treatment plan combining preoperative neoadjuvant chemotherapy and surgery can be applied to a wide range of patients with satisfactory clinical outcomes and the patients would have a good survival after treatment.

In summary, risk factors contributing to death in patients with primary osteosarcoma and lung metastases include chondrocytes, multiple lung metastatic lesions, poor outcome after chemotherapy for primary tumor, and no surgery-combined treatment for lung metastasis. Surgical resection and preoperative adjuvant chemotherapy can effectively improve patient survival.

Author contributions

WL drafted the work and revised it critically for important intellectual content, and he contributed to the conception and design of the work, and was also responsible for the acquisition, analysis and interpretation of data for the work, and approved the final version to be published.

Conflict of interests

The authors declare no conflict of interests.

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