Site-specific distant metastases and overall survival in sarcomatoid renal cell carcinoma: A study of 378 patients

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Research Article

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Abstract

Objective: To assess the association between patterns of distant metastases and overall survival(OS), and identify the prognostic factors for site-specific distant metastases.

Methods: Data from the SEER database between 2004 and 2016 were analyzed, OS between different groups were compared by the Kaplan-Meier method and the Log-rank test, prognostic factors associated with OS were identified by univariate and multivariate Cox proportional hazards models.

Results: The median OS of patients with one and multiple metastatic sites was 5 and 3 months, respectively, and the difference was statistically significant ($\chi2=15.544$, $P<0.001$).The median OS of patients with bone metastases only, brain metastases only, liver metastases only, and lung metastases only was 6,5,3, and 5 months, respectively, with no significant difference($\chi2=4.643$, $P = 0.200$).Metastatic sites, surgery, and chemotherapy were prognostic factors for the entire cohort; surgery and chemotherapy were independent prognostic factors for patients with lung metastases only and multiple sites of metastases, and surgery was independent prognostic factors for patients with bone metastases only.

Conclusion: The specific sites of distant metastases were independent prognostic factors affecting the OS. For patients with one site of distant metastases, the specific type of distant metastatic site did not affect the OS. Nephrectomy reduced the risk of mortality in patients with lung metastases only, bone metastases only and multiple sites of distant metastases.Chemotherapy reduced the risk of mortality in patients with lung metastases only and multiple sites of distant metastases, but it was not found to reduce the risk of mortality in patients with bone metastases only.

1. Introduction

Sarcomatoid renal cell carcinoma (sRCC) refers to the sarcomatoid component appearing in renal cell carcinoma and accounts for about 4–5% of all RCC types[1–2]. sRCC has a high degree of malignancy, easy to metastases and recurrence, the overall survival(OS) is significantly lower than that of patients with no sarcomatoid component in renal cell carcinoma[3]. Tumor progression or progression to advanced stages occurs in approximately 60–80% of patients[1, 4], even after surgical treatment of localized sRCC, most patients will still relapse, with a median time to recurrence of 26.2 months[5]. The occurrence of distant metastases in the early stage is a significant features of sRCC, about 70%~80% of patients have developed distant metastases at the time of the first diagnosis, and the common metastatic sites are lung, bone, liver and brain in order[2]. Several studies have shown that the occurrence of distant metastases is significantly associated with poor OS, and the median OS of sRCC patients with metastases is only 6 to 13 months[5–7]. The number and patterns of different metastatic sites may have different effects on the OS of the patients. Understanding the clinical characteristics and prognostic factors with specific sites of metastases ,will plays an important role in improving the treatment and management ,which is crucial to improve the survival rate of the patient.Several published studies mainly analyzed the clinical characteristics and prognostic factors of overall sRCC patients, while few further analyzed the effects of site-specific distant metastases on OS and the prognostic factors for site-specific distant metastases[6–8].The main reason is the low proportion of sRCC patients, and the difficulties of data collection ,in particular, the OS of metastatic sRCC patients is generally only a few months, making it more difficult to obtain complete clinical data.Based on the above reasons, this study retrieved the data of 378 cases of distant metastatic sRCC registered in the National Cancer Institute database (The Surveillance, Epidemiology, and End Results, SEER), aims to investigate the relationship between site-specific patterns of distant metastases and overall survival of metastatic sRCC,and to determine prognostic factors for site-specific distant metastases,in order to provide more accurate reference to improve the diagnosis and treatment of sRCC patients with site-specific distant metastases.

2. Materials And Methods

2.1 General Information

The SEER database from years 2004–2016 was used in this study.We screened out 996 patients with sRCC (ICD-O-3 code: 8318/3)who had developed distant metastases at the time of diagnosis .Then a total of 618 patients were successively excluded by following criteria:whose general data was incomplete (n=13),histological diagnosis was unknown(n=28), first tumor was not sRCC(n=124),information on specific metastatic sites was missed (n=436), survival status at follow-up endpoint was unknown(n=7), and survival time was unknown (n=10) .Finally, 378 metastatic sRCC patients were included in this study.

The variables in the analysis included age, sex, race,tumor side, maximum tumor diameter, T stage, N stage, treatment modality (surgery,regional lymph nodes dissection, chemotherapy, radiotherapy), distant metastases site (bone, brain, liver, lung) . The above variables were completely obtained in the SEER database. The tumor grade was not included in this study due to excessive missing data.The primary endpoint was overall survival in this study.The starting point for follow-up is the date the patient was diagnosed with sRCC and the ending point for follow-up was date of death, loss to follow-up, or last follow-up at the end of 2016.

2.2 Statistical analysis

Continuous variables were reported by the median (range),categorical variables were reported as counts (percentage). Independent prognostic factors for OS were identified using univariate and multivariate Cox proportional hazard models. Variables that were statistically significant in the univariate Cox analysis were fitted in the multivariate Cox proportional hazard model. OS between different groups of patients were compared using Kaplan-Meier analysis and Log-rank tests. A two-tailed *p* value0.05 was considered statistically significant in all analyses. Statistical analyses were performed using SPSS 22.0(IBM Corporation,Armonk,NY, USA),and the figures were drawn using SPSS 22.0.

3. Results

3.1 Demographic and clinical characteristics of study patients

Of the 378 study patients, 271 were male (71.70%) and 107 were female (28.30%).The demographic and clinical characteristics of entire cohort and patients grouped by different patterns of metastatic sites are summarized in Table 1.

3.2 Distribution of the metastatic sites

The number of patients with one, two, three, and four site metastases was 219 (57.94%), 115 (30.42%), 38 (10.05%), and 6 (1.59%), respectively.The most common pattern of metastases at one site was lung metastases (33.86%), followed by bone metastases17.46%, liver metastases4.76%, and brain metastases1.85%.The most common pattern of metastases at multiple sites was "lung + bone" (15.61%)followed by "lung+ liver" (7.14%) and "lung+bone+liver" (7.14%), the proportions of other patterns were less than 5%. Detailed distributions of distant metastatic sites are shown in Table 2.

3.3 Treatment

172 (45.50%) patients received surgery,with radical nephrectomy as the primary surgical type (n=132,76.74%), Partial or subtotal nephrectomy as the secondary surgical type (n=36,20.93%), and 4 (2.33%) had only a biopsy of renal tumor tissue.Among the other treatment methods, 103 (27.25%) patients received regional lymphatic dissection, 209 (55.30%)

patients received chemotherapy ,130 (34.40%) patients received radiotherapy.In addition, 40 patients (10.58%) patients did not receive any of above treatments.

3.4 The impact of site-specific distant metastases on overall survival

By the last one follow-up at the end of December 2016，376 patients were effectively followed up and 2 patients were lost to follow-up.At the follow-up endpoint, 348 (92.06%) patients died, 334 (88.36%) died from sRCC, and another 14 (3.70%) died from other causes.The median OS for the entire cohort was 4 months,and the 6,12,18 ,24 months survival rates were 35.45%, 18.25%,9.52%, 7.41% , respectively.

The median OS of patients with one site and multiple sites of distant metastases was 5 and 3 months, respectively, and the difference of OS was statistically significant (χ^2=15.544, *P* <0.001).Compared to patients with one site of metastases, the death hazard ratio（HR) for patients with multiple sites of distant metastases was 1.494(95%CI: 1.205～1.852).Survival curves are shown in Figure 1.

Among the patients with one site of distant metastases ,the median OS of patients with bone, brain, liver, and lung metastases were 6,5,3, and 5 months, respectively, and the difference of OS was not statistically significant (χ^2=4.643，*P=0.200*）.It indicates that for patients with one site of metastases, the specific type of distant metastatic site did not affect the OS.Survival curves are shown in Figure 2.

3.5 Prognostic factors for site-specific distant metastases

In the entire cohort (n=378), univariate Cox analysis showed that age, N stage, lymph node dissection,metastatic sites, chemotherapy and surgery were significant factors affecting OS (*P* <0.05). The above variables were included in multivariate Cox analysis, which showed that metastatic sites, chemotherapy and surgery were independent prognostic factors affecting OS (*P <0.05*).Detailed data are shown in Tables 3 and 4.

We used the same approach to identify the independent predictors for OS in patients with one site and multiple sites of distant metastases .Given the low sample size of brain and liver metastases only, therefore, patients with lung metastases only (n=128) and bone metastases only (n=128) were chosen for prognostic analysis.The results showed that: for patients with lung metastases only , surgery and chemotherapy were independent prognostic factors (Tables 3，4), the risk of mortality for patients receiving surgery was significantly lower than that in patients not receiving surgery (HR=0.528, 95%CI: 0.360~0.775, *P <0.001*),and the patients receiving chemotherapy had lower risk of mortality compared to those who had not receive chemotherapy(HR=0.499, 95%CI: 0.338~0.737, *P <0.001*).For patients with bone metastases only, surgery was an independent prognostic factor, and the risk of mortality for patients receiving surgery was significantly lower than in those without surgery (HR=0.360, 95%CI: 0.204~0.634, *P <0.001*).For patients with multiple sites of distant metastases, surgery and chemotherapy were independent prognostic factors. Compared with patients who had not received surgery and chemotherapy, the patients receiving surgery (HR=0.490, 95%CI: 0.347~0.693)and chemotherapy (HR=0.377, 95%CI: 0.270~0.527) had a lower risk of mortality (*P <0.001*).The above statistical results show that nephrectomy of the primary tumor side reduced the risk of mortality in patients with lung metastases only, bone metastases only and multiple sites of distant metastases; chemotherapy reduced the risk of mortality in patients with lung metastases only and multiple sites of distant metastases, but it was not found to reduce the risk of mortality in patients with bone metastases only.

4. Discussion

In this study,we described the clinical characteristics of patients with metastatic sRCC, compared the impact of site-specific distant metastases on OS, explored the prognostic factors for patients with different sites of metastases, and

the meaningful results help to improve the treatment and management of patients with distant metastatic sRCC.

In recent years, several studies on OS of sRCC patients [5-7] showed that the median OS for entire patients was 6–13 months ,and for the patients with distant metastases was 5 months,however ,data on survival time of patients with site-specific metastases is lacking. Our study showed that the median OS for entire cohort was 4 months, for the patients with bone metastases only , brain metastases only, liver metastases only and lung metastases only was 6,5,3,5 months, respectively; for the patients with multiple sites of distant metastases was 3 month.These meaningful results further improved the specific survival time data of sRCC patients with different sites of metastases, which is conducive to clinicians to more accurately assess the expected survival time of patients , and provide a basis for more reasonable management and treatment strategies.

There were several researches on the prognosis factors for sRCC patients, and established survival prediction models, to identify risk factors and evaluate patient survival status [6,8] However, the published researches mainly focused on the overall sRCC patients,and generally classified different patterns of distant metastatic sites as one category, the research results were not necessarily applicable to specific metastatic sites of patients. For example, Guangdong Hou[8], in a large study of 428 sRCC patients, concluded that T stage, N stage, different metastatic sites were independent prognostic factors for entire sRCC patients, and chemotherapy was not independent prognostic factor.However, our study showed that for patients with distant metastatic sRCC, nephrectomy and chemotherapy were independent prognostic factors, while T stage and N stage were not independent prognostic factors, and further analysis also showed that although chemotherapy was a prognostic factor for entire distant metastatic sRCC, it was not an independent prognostic factor for patients with bone metastases only.

In this study, the significant conclusion was that receiving nephrectomy and chemotherapy reduced the risk of mortality in patients with distant metastatic sRCC. Heng DY[9] in a study of 189 patients with sRCC reported that the median OS of paitients with and without nephrectomy was 10.2 months versus 5.5 months ,revealed that nephrectomy prolonged the OS of sRCC patients; Michail Alevizakos[4]in a study of 474 patients with metastatic sRCC results showed that the median cancer-specific survival time (DSS) of paitients receiving nephrectomy was 7 months , while the median DSS of patients not receiving nephrectomy was only 4 months, indicating that for sRCC patients, the nephrectomy of primary tumor side could still bring survival benefit.The results of this study further proved that receiving nephrectomy reduced the risk of mortality in patients with lung metastases only, liver metastases only and multiple sites of distant metastases in sRCC, which provided more evidence to support for the rational use of nephrectomy in patients with site-specific metastases.

The application of chemotherapy in the treatment of sRCC patients has been over 20 years, and the results of several studies showed that the application of chemotherapy in sRCC patients could improve survival[10-11], the main drugs were doxorubicin, gemcitabine, etc.However ,our study showed that for sRCC patients with bone metastases only ,chemotherapy did not reduce risk of mortality, suggesting chemotherapy should probably not be recommended as a conventional treatment modality.

Some limitations of this study exist.Firstly,our study was a retrospective study , the potential biases were unavoidable. Secondly,some data included in this study were not enough：there were some missing information on tumor histological grade and distant metastases：the metastatic site information included only the lung, bone, brain and liver). Besides, some important information were not accessible,such as history of smoking and drinking, history of basic diseases, type of radiotherapy, specific drugs of chemotherapy and some blood inflammatory indicators, which might be correlated with the prognosis of patients. Thirdly, some of the emerging therapeutic drugs in recent years have not been included in the database, such as the use of immune checkpoint inhibitors and targeted agents, several studies have shown that the application of these drugs prolonged Progress Free Survival(PFS) and OS in sRCC patients[12-14]. Finally, the sample size

of some specific sites of metastases was too small, mainly the number of patients with liver metastases only and brain metastases only was not enough, leading to the inability to study their survival time and prognostic factors.Moreover, the study subjects included in the database were the US population, and the applicability of the study results is limited.

In conclusion, despite the above limitations, this study demonstrated that the specific sites of distant metastases were independent prognostic factors affecting the OS. Patients with multiple sites of distant metastases had a shorter OS than patients with one site of distant metastases.For patients with one site of distant metastases, the specific type of distant metastatic site did not affect the OS. Nephrectomy reduced the risk of mortality in patients with lung metastases only, bone metastases only and multiple sites of distant metastases.Chemotherapy reduced the risk of mortality in patients with lung metastases only and multiple sites of distant metastases, but it was not found to reduce the risk of mortality in patients with bone metastases only.Of course, more studies with large samples and other national populations are needed to further improve the our research results.

Declarations

Ethical Approval and Consent to participate:our study conformed to the 1964 Helsinki Declaration and its later amendments, and was conducted in accordance with the ethical standards of the research committees of The 73rd Group Army Hospital.

Consent for publication: this manuscript is approved by all authors for publication.

Availability of data and materials:the data sets supporting the results of this article are included within the article and its additional files.

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Tables

Table 1 Clinical Characteristics of patients with distant sites of metastases.

Variable	Entire cohort cohort (n=378)	One site metastases transfer (n=219)	Multiple sites
	N(%)	N(%)	N(%)
Age(year)			
≥65	154(40.70%)	97(44.30%)	57(35.80%)
65	224(59.30%)	122(55.70%)	102(64.20%)
Sex			
Male	271(71.70%)	149(78.00%)	122(76.70%)
Female	107(28.30%)	70(32.70%)	37(23.30%)
Race			
White	304(80.40%)	174(79.50%)	130(81.80%)
Black	44(11.60%)	26(11.90%)	18(11.30%)
Other[a]	30(8.00%)	19(8.60%)	11(69.00%)
Tumor side			
Left	198(51.90%)	115(52.50%)	82(50.90%)
Right	173(45.20%)	100(45.20%)	73(45.30%)
Bilateral	7(1.90%)	4(1.80%)	4(19.00%)
T stage			
T1T2	126(33.40%)	72(32.90%)	54(34.00%)
T3	171(45.20%)	105(47.90%)	66(41.50%)
T4	81(21.40%)	42(19.20%)	39(24.50%)
N stage			
N1	165(43.70%)	85(38.80%)	80(50.30%)
N0	213(56.30%)	134(61.20%)	79(49.70%)
Surgery			
Yes	172(45.50%)	116(53.00%)	56(35.30%)
No	206(54.50%)	103(47.00%)	103(64.80%)
Lymph node dissection performed			
Yes	103(27.20%)	67(30.60%)	36(22.60%)
No	275(72.80%)	152(69.40%)	123(74.40%)
Radiotherapy			
Yes	130(34.40%)	52(23.70%)	78(49.10%)

No	248(65.70%)	167(76.30%)	81(50.90%)
Chemotherapy			
Yes	209(55.30%)	119(54.30%)	90(56.60%)
No	169(44.70%)	100(45.70%S)	69(43.40%)

[a]Other includes American Indian, AK Native and Asian/Pacific Islander.

Table 2 Patterns of distant metastases for the patients.

Sites of distant metastases	N	%
One site	219	57.94%
Bone	66	17.46%
Brain	7	1.85%
Liver	18	4.76%
Lung	128	33.86%
Two sites	115	30.42%
Lung + bone	59	15.61%
Lung + liver	27	7.14%
Lung + brain	10	2.65%
Bone + liver	17	4.50%
Bone + brain	1	0.26%
Brain + liver	1	0.26%
Three sites	38	10.05%
Lung, bone, liver	27	7.14%
Lung, liver, brain	6	1.59%
Lung, brain, bone	5	1.32%
Four sites	6	1.59%
Lung + liver + brain + bone	6	1.59%
Toal	378	100.00%

Table3 Univariate Cox regression analysis of prognostic factors for overall survival in patients with distant sites of metastases

Variable	Entire cohort (n=378)		Lung metastases only(n=128)		Bone metastases only(n=66)		Multiple sites of metastases (n=159)	
	HR(95%CI)	*p* value	HR(95%CI)	*p* value	HR(95%CI)	*p* value	HR(95%CI)	*p* value
Age(year)								
≥65	1		1		1		1	
65	1.398 (1.123, 1.740)	0.003	1.864 (1.267, 2.741)	0.002	1.393 (0.824, 2.357)	0.216	1.266 (0.897, 1.785)	0.18
Sex								
Male	1		1		1		1	
Female	0.881 (0.699, 1.110)	0.283	1.001 (0.668, 1.499)	0.996	0.533 (0.306, 0.929)	0.026	1.064 (0.730, 1.551)	0.748
Race								
White	1		1		1		1	
Black	1.223 (0.889, 1.684)	0.216	1.730 (0.978, 3.063)	0.060	0.915 (0.472, 1.776)	0.793	1.362 (0.829, 2.237)	0.223
Other	0.827 (0.563, 1.213)	0.330	0.926 (0.535, 1.605)	0.785	1.071 (0.331, 3.466)	0.909	0.714 (0.374, 1.363)	0.307
Tumor side								
Left	1		1		1		1	
Right	1.061 (0.849, 1.324)	0.604	1.045 (0.845, 1.293)	0.684	1.052 (0.614, 1.800)	0.854	0.828 (0.598, 1.147)	0.257
Bilateral	0.9 (0.405, 2.002)	0.796						
Tumor size ssssssssisizediameter								
6cm	1		1		1		1	
6 10cm	0.837 (0.629, 1.115)	0.224	0.712 (0.347, 1.462)	0.355	1.215 (0.638, 2.314)	0.554	0.775 (0.502, 1.196)	0.249
10cm	0.931 (0.712, 1.219)	0.604	0.726 (0.359, 1.470)	0.374	0.562 (0.296, 1.064)	0.077	1.106 (0.740, 1.654)	0.622
T stage								

T1、T2	1		1		1		1	
T3	0.779 (0.661, 0.994)	0.045	0.595 (0.374, 0.947)	0.028	0.571 (0.323, 1.009)	0.054	0.941 (0.648, 1.376)	0.75
T4	1.298 (0.972, 1.733)	0.077	1.003 (0.592, 1.698)	0.993	1.461 (0.658, 3.243)	0.352	1.380 (0.900, 2.115)	0.139
N stage								
N1	1		1		1		1	
N0	1.387 (1.121, 1.715)	0.003	1.439 (0.990, 2.094)	0.057	1.159 (0.683, 1.968)	0.584	1.340 (0.972, 1.847)	0.074
Metastatic sites								
Bone only	1							
Brain only	0.639 (0.256, 1.589)	0.338						
Liver only	1.564 (0.909, 2.691)	0.106						
Lungs only	1.063 (0.775, 1.456)	0.076						
Multiple sites	1.580 (1.165, 2.143)	0.003						
Surgery								
Yes	1		1		1		1	
No	0.452 (0.363, 0.564)	< 0.001	0.458 (0.314, 0.667)	< 0.001	0.353 (0.202, 0.618)	< 0.001	0.515 (0.365, 0.727)	< 0.001
Lymph node dissection performed								
Yes	1		1		1		1	
No	1.359 (1.100, 1.769)	0.006	1.353 (0.901, 2.032)	0.145	1.874 (1.017, 3.451)	0.044	1.261 (0.863, 1.843)	0.23
Radiotherapy								
Yes	1		1		1		1	
No	1.008 (0.808, 1.275)	0.943	1.491 (0.777, 2.864)	0.23	0.966 (0.574, 1.627)	0.897	1.313 (0.954, 1.807)	0.094
Chemotherapy								

Yes	1		1		1		1	
No	0.496 (0.400-0.614)	<0.001	0.432 (0.295-0.633)	<0.001	0.630 (0.375-1.509)	0.082	0.393 (0.282-0.558)	<0.001

Table4 Multivariate Cox regression analysis of prognostic factors for overall survival in patients with distant sites of metastases

Variable	Entire cohort (n=378)		Lung metastases only(n=128)		Bone metastases only(n=66)		Multiple sites of metastases (n=159)	
	HR(95%CI)	*p* value	HR(95%CI)	*p* value	HR(95%CI)	*p* value	HR(95%CI)	*p* value
Metastatic sites								
Bone only	1							
Brain only	0.620(0.247-1.554)	0.308						
Liver only	2.136(1.234-3.696)	0.007						
Lungs only	1.250(0.909-1.718)	0.169						
Multiple sites	1.743(1.276-2.380)	<0.001						
Surgery								
Yes	1		1		1		1	
yes	0.478(0.382-0.598)	<0.001	0.528(0.360-0.775)	<0.001	0.360(0.204-0.634)	<0.001	0.490(0.347-0.693)	<0.001
Chemotherapy								
Yes	1		1				1	
No	0.466(0.374-0.580)	<0.001	0.499(0.338-0.737)	<0.001			0.377(0.270-0.527)	<0.001

Figures

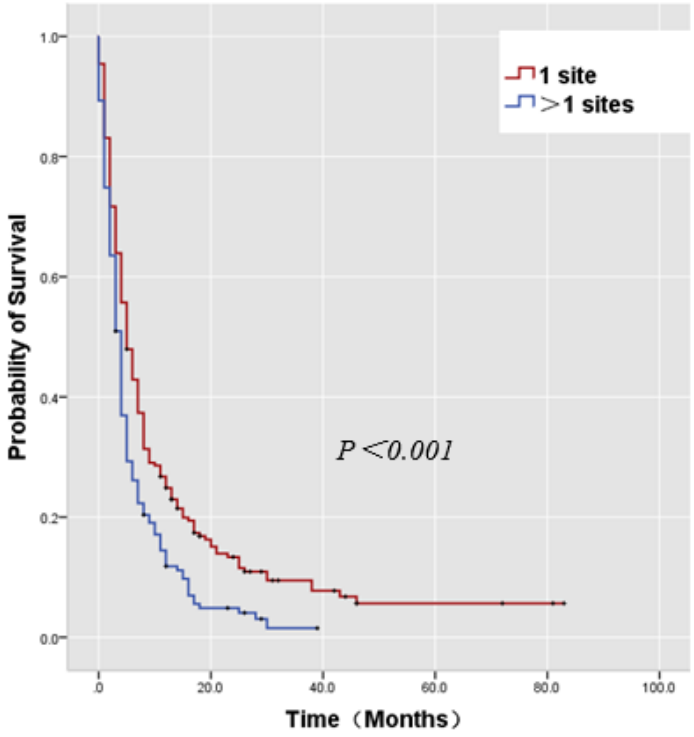

Figure 1

Overall survival for patients with different number of sites of distant metastases.

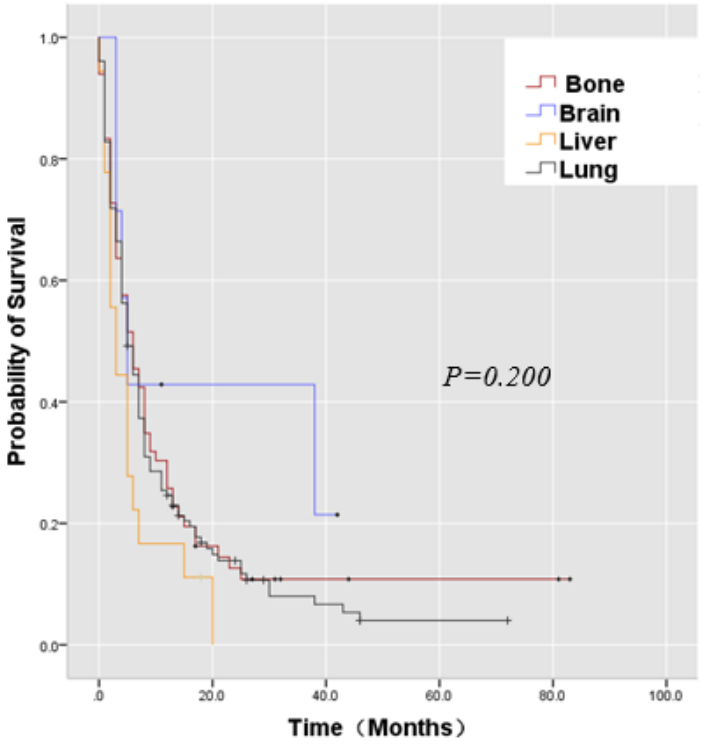

Figure 2

Specific overall survival for patients with different type of single-site of distant metastases.