Prognostic Analysis for Children with Hepatoblastoma with Lung Metastasis: A Single-Center Analysis of 98 Cases

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Abstract

Background To analyze the factors affecting prognosis of hepatoblastoma (HB) with lung metastasis in children.

Patients and Methods: 98 HB patients with lung metastases admitted to Beijing Tongren Hospital, Capital Medical University were collected and analysed.

Results 64 patients had lung metastases at diagnosis (median age, 22.3 months). 34 patients developed lung metastases whilst on treatment (median time, 6.5 months). The time of diagnosis of lung metastasis in patients with HB did not significantly affect survival time or 3-year survival rate (P = 0.37). The survival time and 5-year survival rate of patients with standard treatment was significantly longer than that of without standard treatment (P < 0.001). The survival time and 3-year survival rate of patients with lung metastasis alone or underwent lung metastasectomy was significantly longer than that of patients with extrapulmonary involvement or without lung metastasectomy (P = 0.007, P = 0.099). Lung metastasis accompanied with extrapulmonary involvement was risk factors affecting prognosis (HR = 0.460, 95% CI 0.239–0.888).

Conclusions The overall prognosis of HB with lung metastasis in children was poor, and the prognosis of patients with lung metastasis alone was better than those with extrapulmonary involvement. Standardized treatment and resection of lung tumor may prolong the survival of HB patients with lung metastasis.

Introduction

Hepatoblastoma (HB) is a rare malignant tumor and justly accounts for about 1% of all pediatric tumors, although it is the most common pediatric liver tumor among children [1]. It usually occur in the first 2 years of life [2]. Over the past 30 years, the neoadjuvant chemotherapy has been made significant advances in tumors, and nowly becomes the standard treatment for most cases [3]. For treatment of HB, Neoadjuvant chemotherapy combined with surgical resection increased the cure rate of about 70%, greatly increasing the cure rate of 30% than in the 1970s.

Lung is a common site for HB recurrence, about 10–20% of HB is associated with lung metastasis, and the overall survival rate of these cases is 25–50% [4, 5]. Therefore, lung metastasis is still the main factor for poor prognosis of HB [6–8]. Currently, the widely accepted treatment scheme for HB with lung metastasis is firstly received chemotherapy, and lung tumor resection if patients still has tumor with lung metastasis after chemotherapy [5, 9, 10]. For example, Japan Children's Cancer Group (JCCG) liver tumor committee (JPLT) found that lung metastasectomy is clearly effective for cases of HB with lung metastasis at the time of diagnosis and complete resection of the primary liver lesion after chemotherapy [11].

The prognosis of HB depends on a number of factors, including serum α-fetoprotein (AFP) levels, age at diagnosis, integrity of tumor resection, and clinical stage of the disease [12]. In this study, the treatment outcome and prognosis characteristics of 98 HB patients with lung metastatic in our department was retrospectively analyzed. This study was to explore the effects of prognostic factors, such as the time of diagnosis of lung metastasis, extrapulmonary viscera involvement, standardized treatment, and lung metastasectomy on the prognosis of children with lung metastatic HB, which may provide guidance for clinical treatment of HB with lung metastasis.

Material And Methods

Clinical data

The HB patients with lung metastasis who were hospitalized between January 2010 and December 2017 in pediatrics department of Beijing Tongren Hospital, Capital Medical University were consecutive collected and recorded their detailed clinical data. All patients were examined by general examination, including abdominal CT, lung CT, bone marrow cytology and bone scan, if necessary, head CT or head MRI, to exclude patients with metastasis to other sites. The inclusion criteria of patients were as following: (1) age ≤ 14 years; (2) diagnosed as HB by pathologically or liver biopsy; (3) HB with lung metastasis (Lung metastasis was diagnosed by radiologists through enhanced lung CT or positron emission tomography/computed tomography (PET/CT), which indicated pulmonary nodules, circular or quasi-circular nodular shadow, enhanced scan significantly enhanced); (4) patients with extrapulmonary metastasis had corresponding imaging evidence (Based on the retrospectively reviewed imaging findings, extrapulmonary metastasis was mainly vascular involvement, extrahepatic abdominal viscera involvement and mediastinal and bone, bone marrow and brain metastasis). The patients with lung metastasis who underwent surgery were finally confirmed as lung metastasis of HB by pathology. According to the histological characteristics, the pathology of HB was divided into two types: epithelial type (fetal type, embryonic type, combined fetal and embryonal type, small cells undifferentiated type, macrotrabecular type and cholangioblastoma type) and mixed epithelial-mesenchymal type [13, 14]. Extrapulmonary viscera involvement was defined to extrapulmonary organ involvement and vascular involvement.

Treatment procedure

The comprehensive treatments mainly were chemotherapy and surgery. Chemotherapy regimens were as following: C5VD (cisplatin, fluorouracil, vincristine and doxorubicin); PLANDO (cisplatin and doxorubicin); ICE (Ifosfamide, carboplatin, etoposide); doxorubicin + cyclophosphamide + cisplatin regime; doxorubicin + etoposide + cisplatin regime; ITEC (ifosfamide + pirarubicin + etoposide + carboplatin); vincristine + irinotecan + cyclophosphamide + cisplatin regime or vincristine + irinotecan + fluorouracil + cisplatin regime [15]. One cycle of chemotherapy were 21–28 days, with detection of AFP serum, routine blood, routine biochemical and in each cycle. Primary and metastatic lesions were evaluated every 2 cycles of chemotherapy. The surgeries included hepatectomy, thrombectomy, and lung mass resection. Liver

transplantation was performed in children without distant metastasis and without vascular involvement, but with unresectable liver tumor. Other treatment measures (interventional therapy, radiofrequency ablation, ultrasound focused scalpel, etc.) should be selected according to the tumor situation. Ethical approval was given by the Medical Ethics Committee of the Beijing Tongren Hospital, Capital Medical University (No.20180212). Written informed consent was obtained from all participants' guardians before treatment.

Evaluation of efficacy and prognosis

Curative effect according to the following criteria [16]: Complete remission (CR) refers to that physical examination and CT or MRI showed complete disappearance of the tumor, and AFP is normal for more than 4 weeks. Partial remission (PR) refers to tumor volume shrinkage ≥ 50%, and no evidence of any new or disease progression. Stable disease (SD) refers to tumor volume shrinkage < 50%, and no evidence of any tumor enlargement or new lesions. Progressive disease (PD) means tumor volume magnify ≥ 25%, or have new tumor or AFP elevation. Recurrence is defined as biopsy confirmation, with clear imaging evidence and serum AFP was increased 3 times continuously within 4 weeks. Overall survival (OS) was defined as the time interval between the date of diagnosis and the date of death (as a result of any cause) or the date of the last follow-up. In this study, the endpoint of follow-up was December 31 2018. Deleted cases were defined as patients who died of non-tumor causes.

Statistical analysis

Statistical analysis was determined by SPSS 21.0 software (SPSS Inc, Chicago, IL, USA). Data are presented as median and interquartile range. The Kaplan-Meier method was used to derive the survival curves. The log-rank test was used for comparison of the survival probability between groups. Variables with a P-value < 0.05 in univariate analysis were entered into the multivariate Cox proportional hazards regression model. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

A total of 321 HB patients were enrolled in this study, finally 98 HB patients (64 boys and 34 girls) with lung metastasis met the inclusion criteria. All patients were with mean age 22.3 months (range 0-11.8 years), among them 62 (63.27%) patients age were lower than 2 years. 64 (65.31%) patients were confirmed HB with lung metastases at the first diagnosis. While the 34 patients (34.69%) developed lung metastases whilst on treatment after HB diagnosis of 6.5 months (range, 2–20 months). Among the 98 patients, 53 (54.08%) patients were epithelial HB (pure fetal (n = 2), pure embryonal (n = 4), combined fetal and embryonal (n = 40), small cell undifferentiated HB (n = 1), macrotrabecular (n = 4), fetal and macrotrabecular (n = 2)), 43 (43.87%) patients were mixed epithelial-mesenchymal HB, 2 (2.04%) patients were untyped. Patients were staged according to PRETEXT system before treatment [17]. 21 patients were PRETEXT III, 77 patients were PRETEXT IV. At the time of initial diagnosis, only 2 patients (1 case

small cell undifferentiated HB, 1 case embryonal subtype of HB epithelia) AFP were lower than 100 ng/mL, others AFP were more than 1000 ng/mL.

62 (63.27%) patients had lung metastasis alone. 36 (36.73%) patients had extrapulmonary viscera involvement, of which 16 (16.33%) patients had vascular involvement (hepatic vein, portal vein and vena cava, 3 (3.06%) patients had right atrial aneurysm thrombus, 3 (3.06%) patients had mediastinal metastasis; 10 (10.20%) patients had abdominal metastasis (4 (4.08%) patients had direct invasion of diaphragmatic metastasis, 3 (3.06%) patients had abdominal lymph node metastasis, 2 (2.04%) patients had renal and supradrenal gland metastasis, 1 (1.02%) case had transverse colon metastasis caused by intraperitoneal implantation), 13 (13.27%) patients had brain metastasis, 1 (1.02%) case had spinal cord metastasis, 4 (4.08%) cases had bone metastases, 1 cases had bone marrow metastases. 23 patients give up standardized treatment, and 75 patients were given standardized chemotherapy (≥ 6 months) and /or lung surgery. For the 75 patients, median preoperative and postoperation chemotherapy cycle were 3 times (range, 0–8 times) and 13 times (range, 4–39 times), respectively; 49 patients underwent lung metastasectomy, of which 36 patients underwent 1 time lung metastasectomy, 5 patients underwent 2 times lung metastasectomy, 6 patients underwent 3 times lung metastasectomy, and 2 patients underwent 4 times lung metastasectomy; 26 patients did not undergo lung metastasectomy.

Prognosis

Effect of standardized treatment on prognosis

By the end of December 31 2018, the median followed up time was 48.0 months (range, 12–150 months). The median survival time of lung metastases was 41 months (range, 8-114 months). The survival time of lung metastases without standardized treatment was 19.57 ± 2.04 months, the 5-year survival rate was 0%. The survival time of lung metastases with standard chemotherapy for more than 6 cycles was 76.90 ± 5.70 months, the 5-year survival rate was 56.3%. There were statistically significant differences between the two groups ($P < 0.001$). The survival curve of HB patients with/without standard chemotherapy was shown in Fig. 1. Treatment outcome of 98 cases of HB with lung metastasis was shown in Fig. 2.

Effect of different time to diagnose lung metastasis on prognosis

Among 75 patients treated with standard chemotherapy more than 6 cycles, 31 patients developed lung metastases whilst on treatment, the survival time of these patients was 71.06 ± 6.36 months, the 3-year survival rate was 75.5%. While, 44 patients had lung metastases at diagnosis, the survival time was 73.28 ± 7.83 months, and the 3-year survival rate was 63.3%. There was no statistical difference between the two groups ($\chi^2 = 0.805$, $P = 0.37$). The survival curve of patients with/without lung metastases of HB at diagnosis was shown in Fig. 3, which might indicate the time of diagnosis of lung metastasis had no significant effect on prognosis.

Effect of extrapulmonary involvement on prognosis

46 patients with lung metastases alone, of which 9 patients died, the median survival time was 90.85 ± 6.87 months, and the 3-year survival rate was 82.3%. 29 patients with extrapulmonary viscera involvement, of which 9 patients died, the median survival time was 57.99 ± 7.72 months, and the 3-year survival rate was 55.2%. There had statistical difference between the two groups (χ^2 = 7.33, P = 0.007). The survival curves of HB patients with lung metastasis alone or with extrapulmonary involvement was shown in Fig. 4.

Effect of lung metastasectomy on prognosis

26 patients without lung metastasectomy, of which 12 (46.15%) achieved CR, and 11 (42.31%) died. The median survival time were 43.81 ± 5.21 months, the 3-year survival rate was 56.1%. 49 patients underwent lung metastasectomy, of which 29 (59.18%) achieved CR, and 12 (24.49%) died. The median survival time were 83.47 ± 6.45 months, the 3-year survival rate was 73.3%. Survival time and survival rate of patients with lung metastasectomy were higher than those without lung metastasectomy, but there was no statistical difference between the two groups (χ^2 = 2.728, P = 0.099). The survival curve was shown in Fig. 5.

Univariate and multivariate cox proportional hazards model for patient prognosis

The univariate analysis showed that age (P = 0.021, 95% CI 1.115–3.770), recurrence and progression with lung metastasis (P = 0.001, 95% CI 1.520-25.951), lung metastasectomy (P = 0.000, 95% CI 1.692–6.472), and extrapulmonary involvement (P = 0.010, 95% CI 1.286–6.472) had better prognosis as shown in Table 2. All above factors were drawn into multivariate Cox proportional-hazards regression model, which revealed that extrapulmonary involvement (HR = 0.460, 95% CI 0.239–0.888) could be considered as a risk factor contributing to poorer prognosis (Table 3).

Table 1
Clinical characteristics of HB patients with lung metastases

Characteristic	Case (n, %)
Gender	
Male	64 (65.31%)
Female	34 (34.69%)
Age (Year)	
< 2	62 (63.27%)
≥ 2	36 (36.73%)
Histopathology type	
Epithelial	53 (54.08%)
Pure fetal	2 (2.04%)
Embryonal	4 (4.08%)
Combined fetal and embryonal	40 (40.81)
Small cell undifferentiated	1 (1.02%)
Macrotrabecular	4 (4.08%)
Fetal and macrotrabecular	2 (2.04%)
Mixed epithelial-mesenchymal	43 (43.88%)
Untyped of HB	2 (2.04%)
Metastasis type	
Lung metastasis alone	62 (63.27%)
Extrapulmonary involvement	36 (36.73%)
Vein metastasis	16 (16.33%)
Right atrial aneurysm thrombus	3 (3.06%)
Mediastinal metastasis	3 (3.06%)
Abdominal metastasis	10 (10.20%)
Brain metastases	13 (13.27%)
Spinal cord involvement	1 (1.02%)

HB, hepatoblastoma.

Characteristic	Case (n, %)
Bone metastasis	4 (4.08%)
Bone marrow metastasis	1 (1.02%)
HB, hepatoblastoma.	

Table 2
Univariate cox regression analysis in prognosis

Affect factors	*P*	HR	95% CI	
			Lower limit	Upper limit
Age	0.021	2.050	1.115	3.770
Recurrence and progression after pulmonary metastasis	0.001	6.281	1.520	25.951
Lung metastasectomy	0.000	3.149	1.692	6.472
Extrapulmonary involvement	0.010	2.885	1.286	6.472
Pathological type	0.198	0.260	0033	2.025
AFP level	0.517	21.407	1.520	225551.88
AFP, α-fetoprotein.				

Table 3
Multivariate cox regression analysis of multiple factor in prognosis

Affect factors	*P*	HR	95% CI	
			Lower limit	Upper limit
Age	0.222	1.183	0.903	1.551
Recurrence and progression after pulmonary metastasis	0.641	0.888	0.423	1.698
Lung metastasectomy	0.280	0.839	0.609	1.154
Extrapulmonary involvement				
Yes		1.00		
No	0.021	0.460	0.239	0.888

Discussion

HB is a malignant embryonal tumor that is the most frequent liver tumor among children, and most tumors develop in children younger than 2 years old. Arora et al. [18] found that the age ranged of 157 patients was from 12 to 24 months. In this study, median age at diagnosis was 22.3 months, the number of patients age were lower than 2 years old was 62 (63.27%), which are similar to previous literature [1, 19]. The lung is the most common site of metastasis, 20% of children with HB present with lung metastases at the time of diagnosis [20, 21]. Moreover, lung is also the most common recurrence site in children with HB [6–8, 10]. In this study, all patients with lung metastases, 65.31% patients initially diagnosed with lung metastasis, which is far beyond the previous reports [20, 21]. In present study, 34 patients diagnosed with lung metastasis in during treatment (range, 2–20 months; median time 6.5 months). Therefore, in the first diagnosis of HB without distant metastasis, it is still necessary to closely monitor the nail fetus and imaging changes during the treatment process, so as to detect early whether there is lung metastasis, especially within half a year after diagnosis.

Neoadjuvant chemotherapy and postoperative chemotherapy have significantly improved the overall survival rate of HB. When neoadjuvant chemotherapy was first used in HB treatment, the 3-year overall survival rate had risen from 20–25% to 30–40% [22]. Complete resection rate was over 90% after neoadjuvant chemotherapy [23]. Compared with patients without standard treatment, patients with standard treatment had a better survival time and 5-year rate (76.90 ± 5.70 vs 19.57 ± 2.04, 56.3% vs 0%, $P < 0.001$). The 5 years rate slightly lower than the 3-year rate (56.3% vs 79%) reported in the JPLT-2 study [24]. The reason was that the follow-up time in this study was long and 36.73% of the cases were combined with multiple other viscera invasion, which affected the overall survival rate.

Lung surgery is frequently used for the treatment of metastasis in children. However, there is no consensus on the need for lung metastasectomy in patients with HB. Currently, the recommended treatment scheme is: chemotherapy should be given first for patients with lung metastasis, and lung metastasectomy is feasible for patients with lung metastasis that still have tumor after chemotherapy [5, 9, 10]. Several studies have documented an increased survival rate of children with HB by combined treatment of surgery and chemotherapy [25–27]. Literature reports that 49% (19/39) of patients with lung metastasis can achieve complete remission after chemotherapy [5], which is similar to the 46.15% rate of complete remission after chemotherapy in the group without surgery in this paper (12/26). In this study, compared with patients without lung metastasectomy, patients with lung metastasectomy had a slightly better survival time and 3 years rate (83.47 ± 6.45 vs 43.81 ± 5.21, 73.3% vs 56.1%, $P = 0.099$). The sample size should be expanded to further confirm the value of pulmonary surgery in the treatment of HB lung metastasis.

In this study, the effects of the time of diagnosis of lung metastasis, involvement of extrapulmonary abdominal organs, standardized treatment, and lung metastasectomy on the prognosis of HB were studied. The time of diagnosis of lung metastasis in patients with HB did not significantly affect survival time or 3-years survival rate (73.28 ± 7.83 vs 71.06 ± 6.36, 63.3% vs 75.5%, $P = 0.37$). Extrapulmonary involvement can be seen in many patients with HB, 36.73% patients in present study were diagnosed with extrapulmonary involvement after diagnosis of lung metastasis. Chen et al. found that 29.1% had distant

metastasis at diagnosis in Taiwanese [28]. Yu et al. found the rate of patient with distant metastasis is 37.5% [29]. The prognosis of patients with lung metastasis and extrapulmonary involvement is worse than those with lung metastasis alone. The survival time and 3 years rate of patients with lung metastasis alone were higher significantly than that with lung metastasis and extrapulmonary involvement (90.85 ± 6.87 vs 57.99 ± 7.72, 82.3% vs 55.2%, $P < 0.001$). Studies showed that age (above 5 years old), PRETEXT stage (III or IV), pathology subtypes, serum AFP level (AFP < 100 ng/mL), and metastasis were prognostic factors of HB in children [30–32]. We have also study the risk factors affecting the prognosis, such as age, recurrence and progression after pulmonary metastasis, lung metastasectomy, and extrapulmonary involvement. The results demonstrated that extrapulmonary involvement was the risk factors affecting the prognosis.

However this study has some limitations. As this study is a retrospective study, selective bias cannot be excluded, and patient AFP was lower than100ng/mL are few, which all have certain influence on the results. Prospective cohort studies are possible in the future to verify the high risk factors affecting the prognosis of children with HB with lung metastasis.

Conclusion

In generally, children with lung metastatic HB with standardized treatment, the 3-year survival rate for those with lung metastatic HB alone was significantly longer than that with extrapulmonary involvement. Extrapulmonary involvement might be a high-risk factor affecting the prognosis. In children with lung metastases that do not completely disappear after adjuvant chemotherapy, lung metastasectomy may prolong survival and improve prognosis.

List Of Abbreviations

HB, hepatoblastoma; AFP, alpha-fetoprotein; JCCG, Japan Children's Cancer Group; PET, positron emission tomography; CT, computed tomography; CR, Complete remission; PR, Partial remission; SD, Stable disease; PD, Progressive disease.

Declarations

Ethical review committee statement

This study was approved by the ethic committee of Beijing Tongren Hospital, Capital Medical University and followed the Declaration of Helsinki. Informed consent were received from all patients.

Consent for publication: The patient was given his consent for information about himself to be published in World Journal of Surgical Oncology.

Availability of data and material: All data generated or analysed during this case report are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: HH, WZ, and DH conceived and designed this study; DH provided administrative support; WZ, YW, and YZ provided materials and samples; HH, YG, and YY collected and collated data; HH and LC analyzes and interpreted data.

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Figures

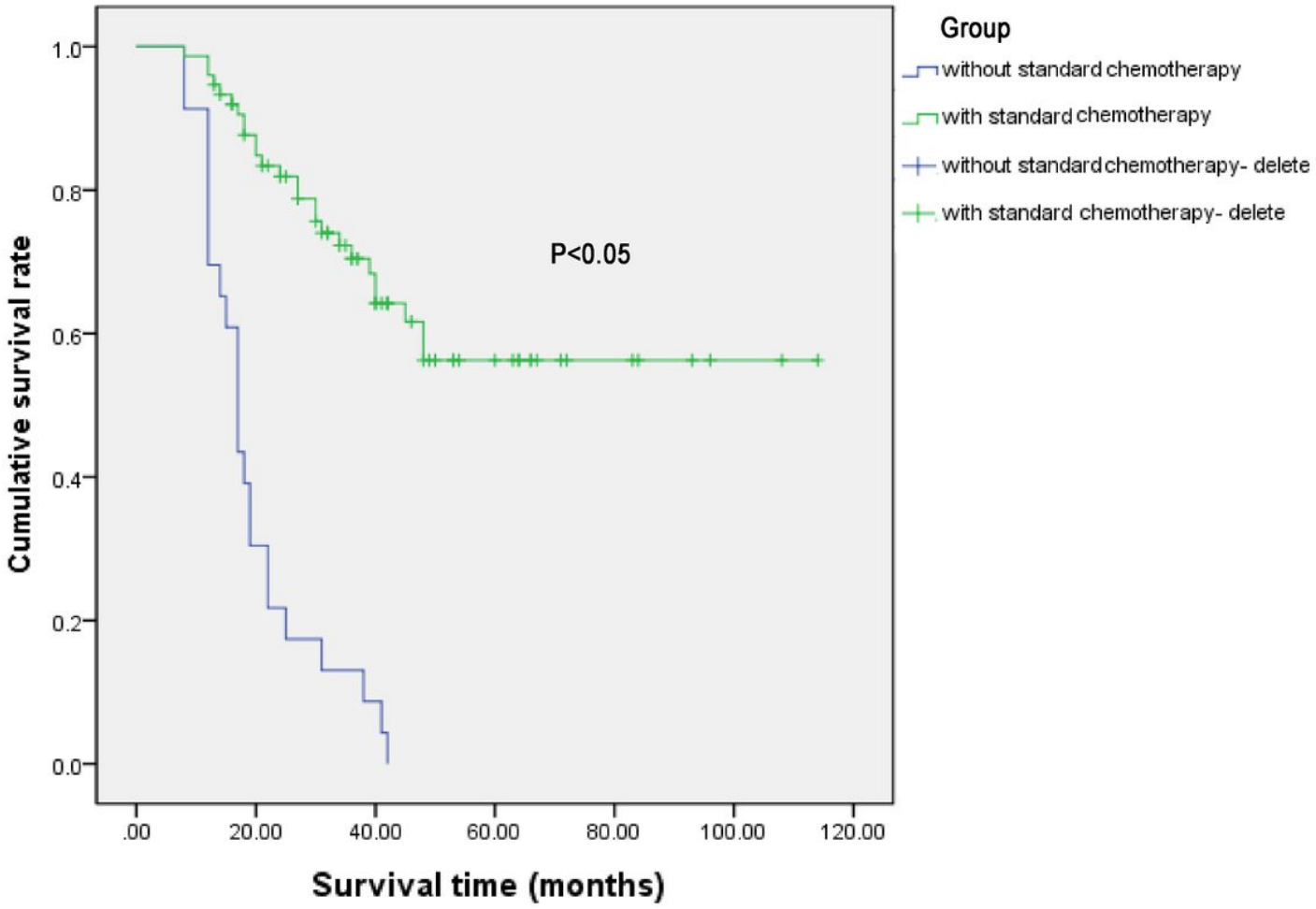

Figure 1

Survival curves of HB patients treated with standardized and patients given up standardized treatment.

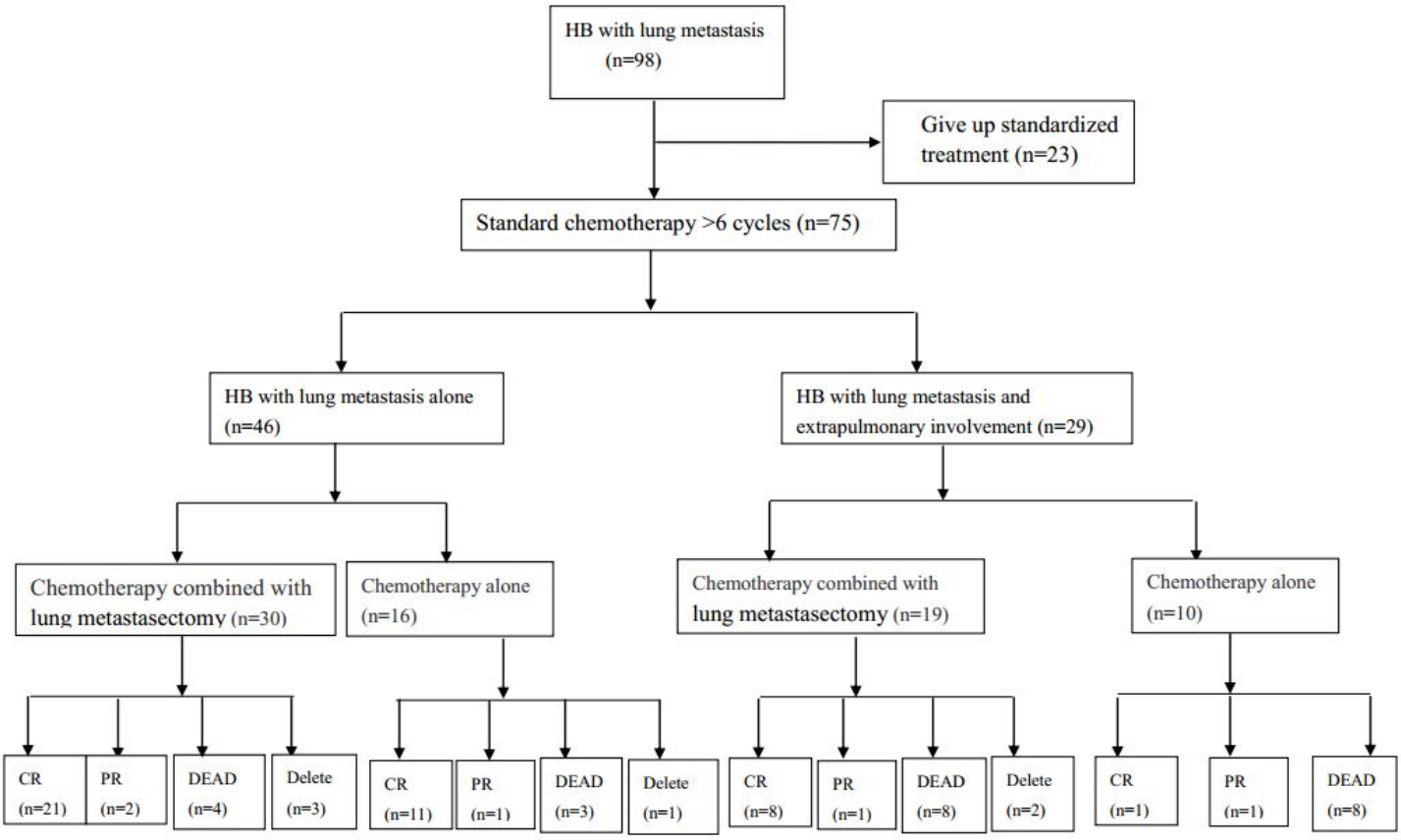

Figure 2

Treatment and outcomes of 98 HB patients with lung metastasis. CR, Complete response; PR, Partial response.

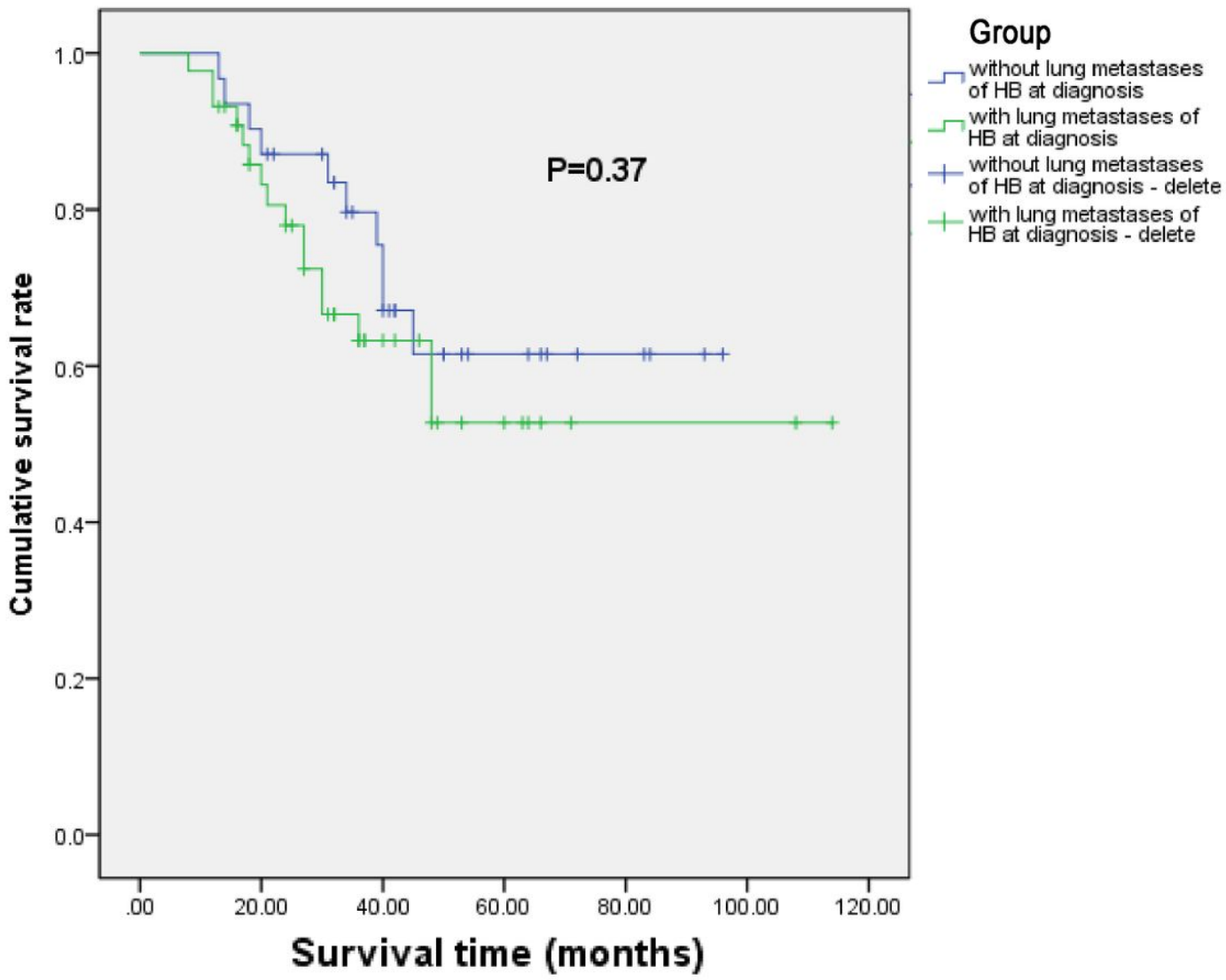

Figure 3

Survival curves of HB patients had lung metastases at diagnosis and patients did not lung metastases at diagnosis.

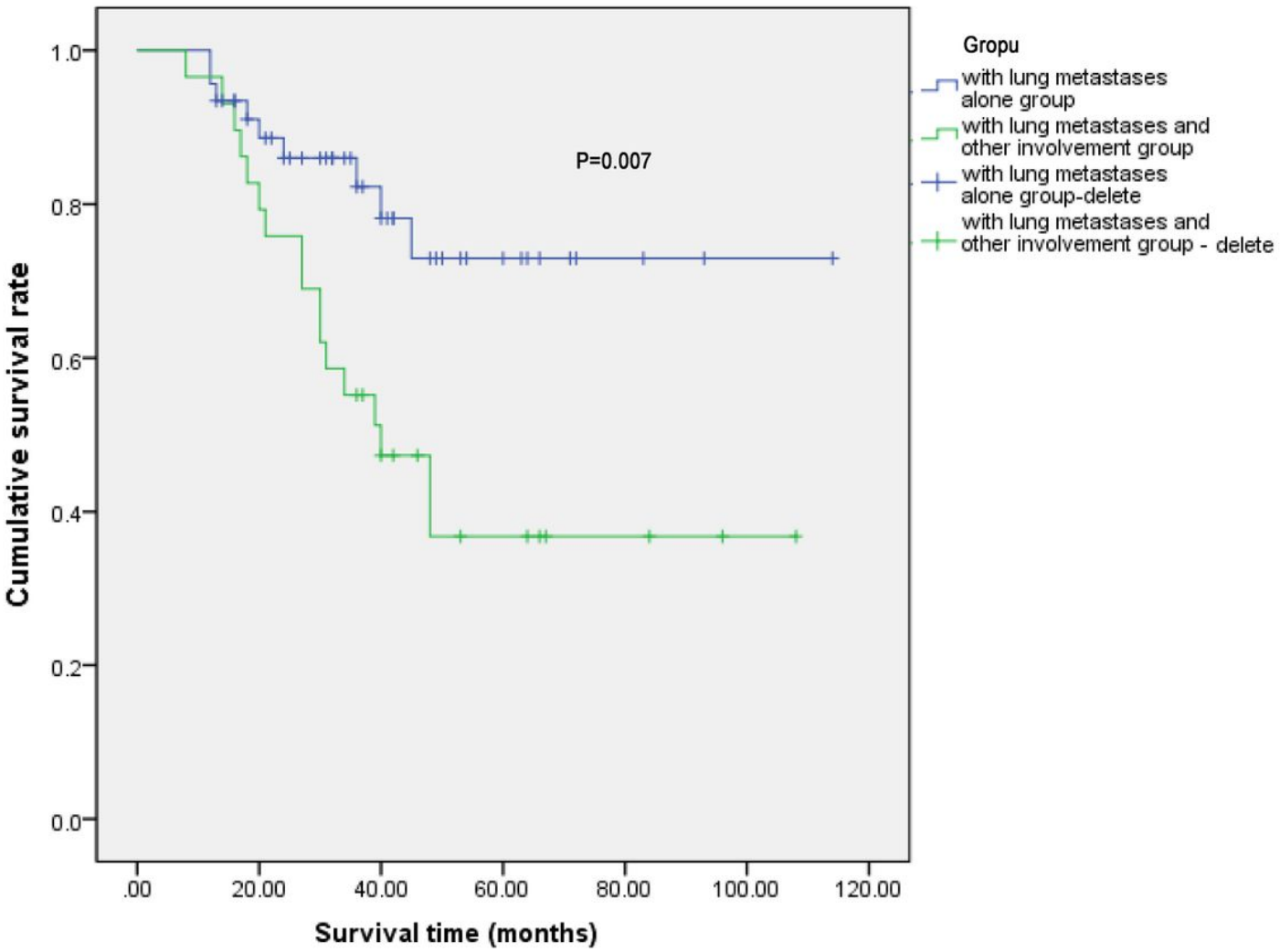

Figure 4

Survival curves of HB patients with lung metastasis alone and with extrapulmonary involvement

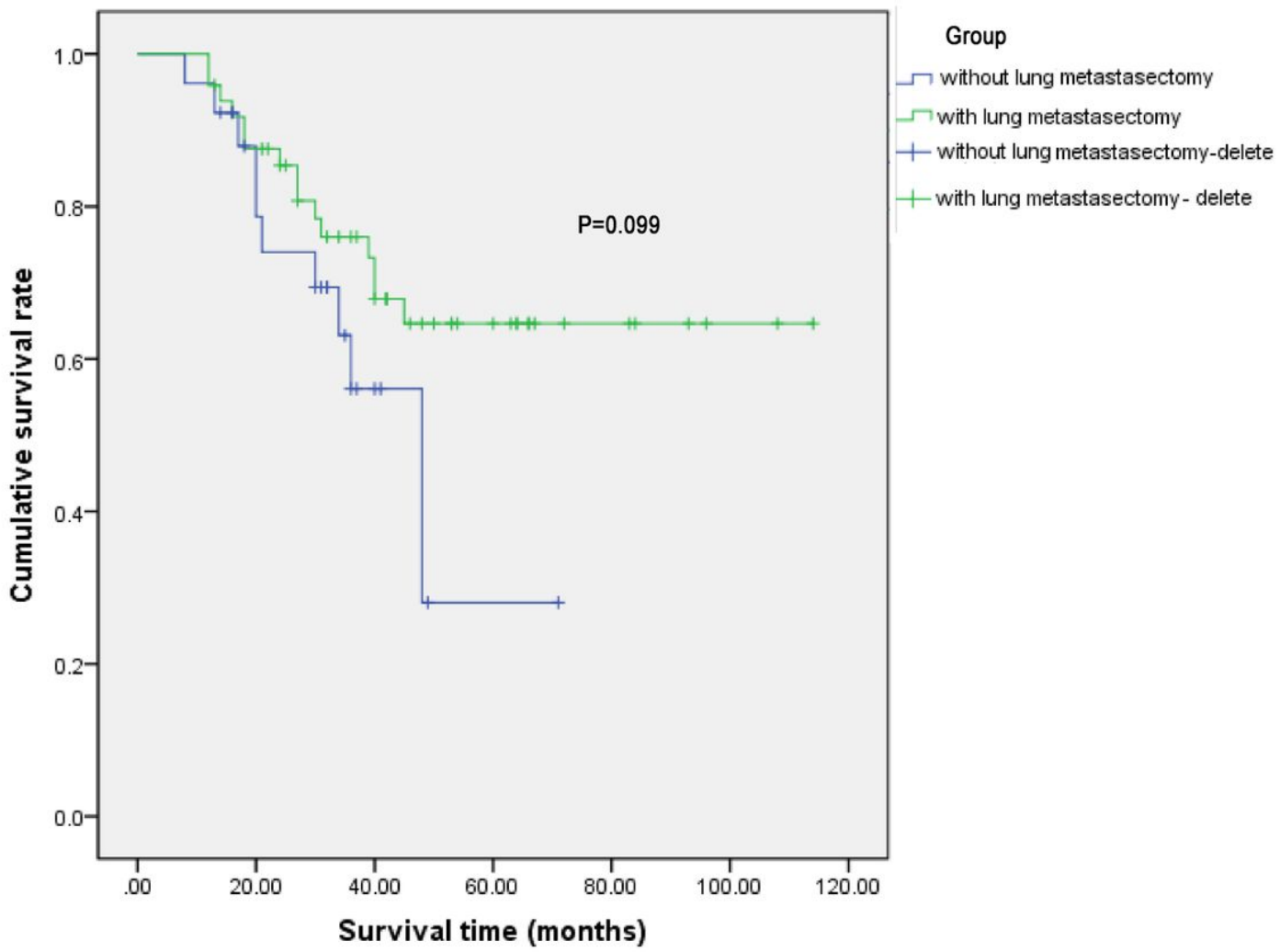

Figure 5

Survival curves of HB patients with lung metastasectomy and patients without lung metastasectomy