



# Control of intracranial disease is associated with improved survival in patients with brain metastasis from hepatocellular carcinoma

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## Abstract

**Background** Brain metastasis is a rare event in patients with hepatocellular carcinoma (HCC). This retrospective study aimed to identify the prognostic factors and determine the outcomes of patients with brain metastases from HCC.

**Methods** About 86 patients with brain metastases (0.6%) from HCC were identified from two institutions; of them, 32 underwent tumor-removing surgery or stereotactic radiosurgery (SRS) with or without adjuvant whole brain radiotherapy (WBRT) (group 1), 30 had WBRT alone (group 2), and 24 received conservative treatment (group 3). Estimates for overall survival (OS) after brain metastases were determined, and clinical prognostic factors were identified.

**Results** The median OS after development of brain metastases was 50 days. About 75 (87.2%) patients had lung metastases at the time of brain metastasis diagnosis. Group 1 showed better OS, followed by group 2 and group 3, sequentially ( $p < 0.001$ ). Univariate analyses showed that treatment with curative intent (surgery or SRS), Child–Pugh class A, alpha-fetoprotein level  $< 400$  ng/ml, and recursive partitioning analysis classification I or II were associated with improved survival ( $p < 0.001$ , 0.002, 0.029, and 0.012, respectively). Multivariate analysis showed that treatment with curative intent and Child–Pugh class A was associated with improved OS ( $p < 0.001$  and 0.009, respectively).

**Conclusion** Although the overall prognosis of patients with brain metastases from HCC is extremely poor, patients actively treated with surgery or radiosurgery have prolonged survival, suggesting that interventions to control intracranial disease are important in these patients.

**Keywords** Hepatocellular carcinoma · Brain metastasis · Overall survival

Hee Chul Nam and Pil Soo Sung contributed equally in this study.

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## Introduction

Hepatocellular carcinoma (HCC) is the major cause of cancer-related mortality worldwide, especially in Asia [1]. Unlike other malignancies, the incidence and mortality rates of HCC will continue to increase over the next 20 years in some countries [2]. Furthermore, a recent improvement in the treatment options for HCC has prolonged the survival of HCC patients [3]. The incidence and clinical significance of extrahepatic metastasis is expected to increase steadily due to the longer survival of HCC patients. The most common sites of extrahepatic metastasis of HCC are the lungs, abdominal lymph nodes, and bones [4].

The incidence of brain metastasis is very rare and has been reported to occur in about 0.2–2.2% of HCC patients [5–10]. Kawaguchi et al. reported that HCC cells do not tend to settle in the brain; therefore, brain metastasis is not likely to occur [11]. In several previous studies, HCC with brain metastasis showed dismal prognosis with a median overall survival (OS) of 3 months [12–20]. In addition, according to Chan et al., the prognosis of HCC patients with isolated extrahepatic metastasis to the brain is poorer than that of patients with metastasis to the lung or bone [7]. However, recent studies have shown that controlling intracranial disease through curative measures is associated with improved prognosis in advanced HCC [21–24], although there is no established guideline for proper treatment yet.

In this study, we aimed to investigate the survival outcomes and prognostic factors of patients with intracranial metastasis from HCC. In particular, we focused on whether treatment for intracranial diseases with curative intent is associated with improved patient survival.

## Materials and methods

### Patient population

After approval from the Institutional Review Board (XC18REDI0006), we identified 13,581 patients with HCC treated at Seoul St. Mary's Hospital and Incheon St. Mary's Hospital between 1995 and 2017 (10,162 and 3419 for each hospital, respectively) by retrospective review. Of them, 86 patients (72 and 14 for each hospital, respectively) were diagnosed with brain metastasis from HCC with an incidence of 0.6%.

The diagnosis of HCC was made based either on the histological report of the primary tumors or on the results of dynamic imaging modalities in accordance with the

latest international guidelines including those from the American Association for the Study of Liver Diseases [1]. Diagnosis of brain metastasis was confirmed through contrast-enhanced cranial computed tomography (CT) and/or magnetic resonance imaging (MRI).

### Clinical information

All clinical data at the time of diagnosis of brain metastasis, including patient characteristics, Eastern Cooperative Oncology Group (ECOG) performance status, alpha-fetoprotein (AFP) level, presenting symptoms, number and size of brain lesion, presence of intracranial hemorrhage, treatment modality, Radiation Therapy Oncology Group recursive partitioning analysis (RPA) classification [25], and survival times, were assessed. Additionally, we evaluated the location of the metastatic brain lesion, presence of portal vein tumor thrombus (PVTT) and extracranial metastasis, treatment modalities prior to the event of brain metastasis, and whether primary lesion was controlled or not. The term “controlled primary tumor” refers to primary tumors in complete remission or partial response based on the modified response evaluation criteria in solid tumors after proper treatment. Survival was confirmed through the National Health Insurance Service.

### Treatment strategies for the metastatic brain lesion

There are no established treatment guidelines for patients with brain metastasis from HCC. During the study period, treatment decisions were made by a multidisciplinary team from our institutes, considering the patient's neurologic status, number and location of the metastatic brain lesion, performance status, and the estimated benefits from the treatment. Treatment modality included surgical resection, SRS, WBRT, and conservative care. Active treatment with curative intent included surgical resection and SRS. Patients underwent total removal of metastatic brain lesions, confirmed with early (within 24 h) post-operative contrast-enhanced CT and/or MRI.

For surgically accessible symptomatic lesions, surgical removal was considered as a treatment option. Gross total tumor removal was achieved intraoperatively and was confirmed with a post-operative MRI, which was performed within 48 h. When two or more lesions were detected, surgery was usually performed in patients with the most symptomatic lesion, and the remaining lesions were treated with SRS. When the symptomatic lesion was surgically inaccessible, SRS was performed using the CyberKnife system (Accuray Inc., Sunnyvale, CA, USA). Patients who refused to undergo open surgery and those at risk for surgery also followed this course. The mean marginal dose of SRS prescribed to the 80% isodose line was 19.3 Gy (range

16.7–21.4 Gy) and was mostly given in a single fraction (78%). When the lesions were close to an eloquent area of the brain or were too large with higher maximal dose risking radiation necrosis, hypofractionated SRS was performed. Patients who underwent surgery or SRS with or without WBRT comprised group 1.

When patients refused to undergo definitive treatments (surgery or SRS), they received radiation therapy alone as primary treatment. Moreover, patients enrolled from Incheon St. Mary's Hospital usually received WBRT because the hospital does not offer CyberKnife or Gamma Knife treatment. Additionally, when the metastatic lesions were identified without any distinguishable neurologic symptoms, WBRT was often selected as the primary treatment option. The mean radiation dose was 27.8 Gy (range 12–45). These patients were categorized as group 2.

For patients with poor performance status, only conservative care was provided. This included corticosteroids and hyperosmotic agents to control intracranial pressure. Patients who refused further active treatment also followed this course and were categorized as group 3.

## Statistical analysis

Chi-square test and Fisher's exact test were used to compare the categorical variables between the two groups. OS was calculated from the diagnosis of brain metastases to death or last day of follow-up according to Kaplan–Meier method. Prognostic factors were analyzed using log-rank test for univariate analysis, and Cox regression analysis was used for multivariate analysis. A *p* value of <0.05 indicates a significant difference. Analyses were performed using PASW Statistics for Windows, Version 24.0 (SPSS Inc., Chicago, IL), and data were considered significant when the *p* value was <0.05.

## Results

### Patient characteristics

A total of 86 patients diagnosed with brain metastases from HCC were included in the present study. The baseline characteristics of the patients are shown in Table 1. Median age at diagnosis of brain metastasis was 54 (range 32–79) years. The median interval between diagnosis of HCC and diagnosis of metastasis was 20.1 (range 0–144.1) months. There were 57 (66.3%) male and 29 (33.7%) female patients. Hepatitis B virus infection was detected in most patients (83.7%), and 7.1% of patients were infected with hepatitis C virus. Five patients had brain metastasis at the time of initial HCC diagnosis.

**Table 1** Baseline characteristics of the patients with brain metastasis from HCC

Variables	Number	Percent
Age at diagnosis of BrM (years)		
< 60	60	69.8
≥ 60	26	30.2
Sex		
Male	57	66.3
Female	29	33.7
Etiology		
Hepatitis B	72	83.7
Hepatitis C	6	7.0
Hepatitis non-B, non-C	8	9.3
Initial presentation of brain lesion		
Yes	5	5.8
No	81	94.2
ECOG performance status		
1 or 2	33	38.4
2 or 3	53	64.6
Child–Pugh classification		
A	59	68.6
B	18	20.9
C	9	10.5
AFP (ng/ml)		
< 400	38	44.2
≥ 400	48	55.8
Number of intrahepatic HCC		
Single	23	26.7
Multiple	63	73.3
Maximum size of intrahepatic HCC (cm)		
≤ 5	33	38.4
> 5	53	61.6
PVTT		
Absent	65	75.6
Present	21	24.4
Number of BrM		
Single	51	59.3
Multiple	35	40.7
Mean value (standard deviation)	1.9 (1.3)	
Location of BrM		
Frontal	29	33.7
Parietal	28	32.6
Occipital	27	31.4
Temporal	10	11.6
Cerebellar	6	7.0
Multiple locations	35	40.7
Size of metastasis (cm)		
≤ 3	45	52.3
> 3	41	47.7
Intracranial hemorrhage		
Yes	34	39.5
No	52	60.5

**Table 1** (continued)

Variables	Number	Percent
<b>Types of symptoms</b>		
Motor weakness	34	39.5
Mental deterioration	15	17.4
Headache	13	15.1
Vomiting	13	15.1
Seizure	7	8.1
Visual disturbance	5	5.8
Dizziness	2	2.3
No symptoms	2	2.3
<b>Site of extracranial metastases</b>		
Lungs	75	87.2
Bone	35	40.7
Lymph nodes	27	31.4
Peritoneal seeding	9	10.5
Adrenal gland	7	8.1
None	1	1.2
<b>Previous treatment before diagnosis of BrM</b>		
Hepatic resection	24	27.9
Liver transplantation	5	5.8
Radiofrequency ablation	16	18.6
Transarterial chemoembolization	70	81.4
Hepatic arterial infusion chemotherapy	8	9.3
Sorafenib	25	29.1
Supportive care	5	5.8
<b>RPA classification</b>		
I or II	33	38.4
III	53	61.6
<b>Intrahepatic response at diagnosis of BrM</b>		
CR	16	18.6
PR	11	12.8
SD	15	17.4
PD	39	45.3
<b>Extrahepatic response at diagnosis of BrM</b>		
CR	1	1.2
PR	4	4.7
SD	4	4.7
PD	64	74.4
Untreated	13	15.1

*HCC* hepatocellular carcinoma, *BrM* brain metastasis, *ECOG* Eastern Cooperative Oncology Group, *AFP* alpha-fetoprotein, *PVTT* portal vein tumor thrombus, *RPA* recursive partitioning analysis, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Approximately 68.6% of patients had Child–Pugh class A at the time of diagnosis of brain metastases, while 31.4% had Child–Pugh class B or C. Elevated AFP levels greater than or equal to 400 ng/ml were identified in 48 patients, and 21 patients had PVTT at the time of brain metastasis diagnosis. Single intrahepatic HCC was found in 26.7% of patients and

**Table 2** Treatment of brain metastasis from HCC ( $n=86$ )

	No. of patients	%
Resection only	16	18.6
Resection + SRS	2	2.3
Resection + WBRT	7	8.1
SRS only	7	8.1
WBRT only	30	34.9
Conservative treatment	24	27.9

*HCC* hepatocellular carcinoma, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiotherapy

61.6% had an intrahepatic tumor of > 5 cm. Single brain metastasis was found in 59.3% of patients, and the mean number of brain metastasis was 1.9 (standard deviation 1.3). Among the enrolled patients, 39.5% were associated with intracranial hemorrhage. According to RPA classification for the estimation of prognosis, 33 patients were classified as I or II, and 53 patients into III. The most common presenting symptom was motor weakness (39.5%), followed by mental deterioration and headache. 75 (87.2%) patients had already developed lung metastases at the time of brain metastasis diagnosis. Only one patient had no other extracranial metastasis.

Treatment modalities before the onset of brain metastases were as follows: transarterial chemoembolization (TACE) was performed in 81.4% of patients, followed by hepatic resection or liver transplantation (33.7%), and sorafenib (29.1%). Additional demographic data are shown in Table 1.

### Treatment modalities in patients with intracranial metastasis from HCC

Table 2 shows the summary of the types of treatment modalities performed for metastatic brain lesion. About 25 patients underwent surgical resection for metastatic brain lesions. Among them, seven patients underwent additional WBRT, while two underwent additional radiosurgery. When divided into three groups, 32 patients underwent tumor-removing surgery or SRS with or without WBRT (group 1), 30 had WBRT alone (group 2), and 24 received conservative treatment (group 3). The mean maximal and marginal doses of SRS prescribed to the 80% isodose line were 26.26 (range 22.5–35.7) Gy and 19.3 (range 16.7–21.4) Gy. The usual fractionation schedule for WBRT was 30 Gy in ten fractions (mean dose: 27.8 Gy; range 12–45 Gy).

Table 3 shows the clinical parameters between the two groups with surgical resection or SRS (group 1,  $n=31$ ) and WBRT only or conservative care (groups 2 and 3,  $n=55$ ) as the treatment modalities for brain metastasis. No significant differences were observed between patient groups by initial treatment modality in terms of age, sex,

**Table 3** Comparison between the two groups with different treatment modalities for brain metastasis

Variables	Resection or SRS (n=31)	WBRT or conservative (n=55)	p value
Age			
< 60	20	40	0.469
≥ 60	11	15	
Sex			
Female	12	17	0.485
Male	19	38	
ECOG			
≤ 2	16	17	0.068
> 2	15	38	
Child–Pugh classification			
A	24	35	0.231
B or C	7	20	
Platelet count			
> 100,000	17	34	0.648
≤ 100,000	14	21	
AFP (ng/ml)			
< 400	15	23	0.653
≥ 400	16	32	
PVTT at diagnosis of BrM			
Absent	26	39	0.203
Present	5	16	
Number of metastases			
Single	22	29	0.114
Multiple	9	26	
Size of metastasis (cm)			
≤ 3	13	32	0.180
> 3	18	23	
Coexisting lung metastasis			
Absent	4	7	1.000
Present	27	48	
RPA classification			
I or II	16	17	0.068
III	15	38	
Intrahepatic objective response			
CR, PR	14	13	0.053
SD, PD, untreated	17	42	

SRS stereotactic radiosurgery, WBRT whole brain radiotherapy, ECOG Eastern Cooperative Oncology Group, AFP alpha-fetoprotein, PVTT portal vein tumor thrombus, BrM brain metastasis, RPA recursive partitioning analysis, CR complete response, PR partial response, SD stable disease, PD progressive disease

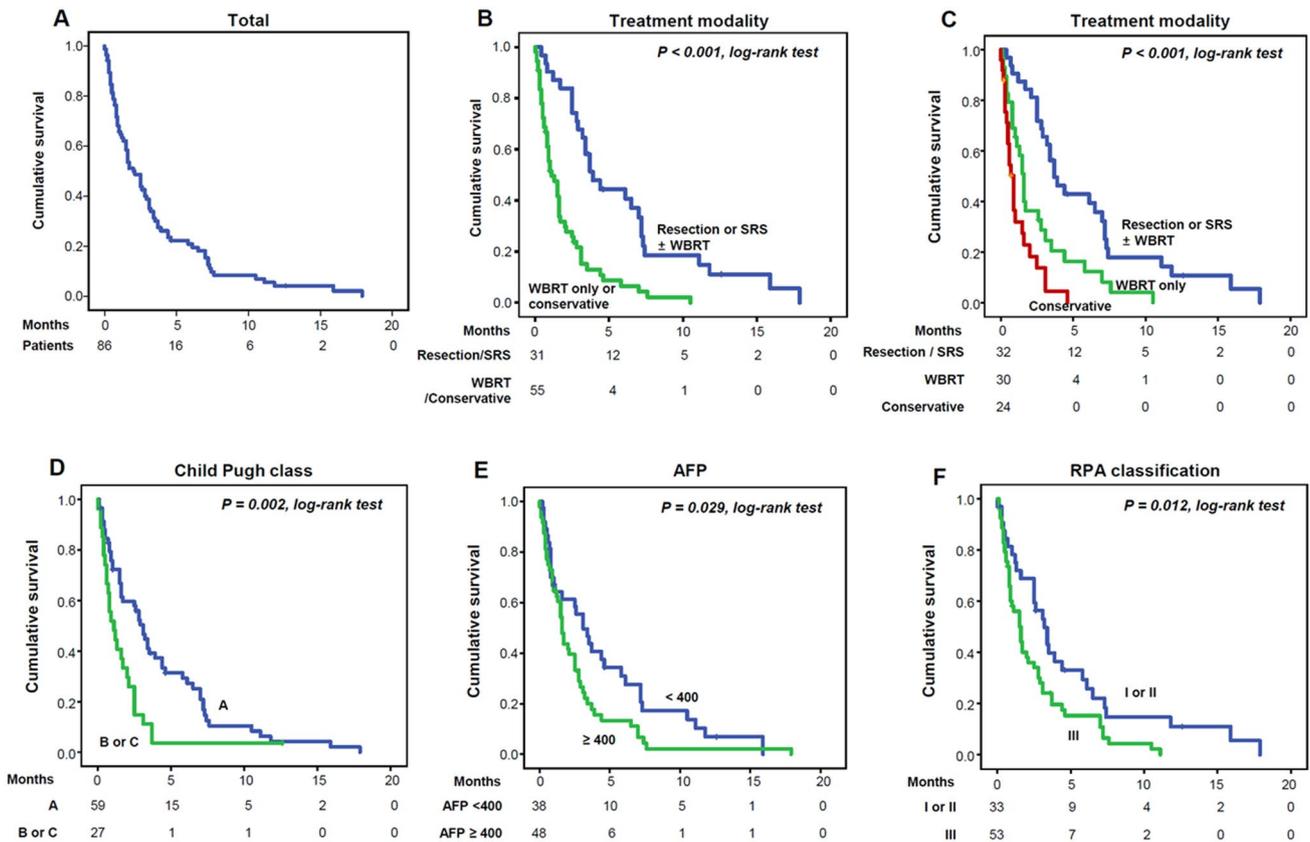
ECOG status, Child–Pugh class, AFP level, number and size of metastatic lesion, RPA classification, and intrahepatic objective response rate.

### Survival outcomes and prognostic factors in patients with intracranial metastasis from HCC

The median OS after diagnosis of brain metastasis was 8.4 weeks (Fig. 1a; 95% confidence interval [CI] 4.9–11.9 weeks). Only one patient who underwent surgical resection survived at the last follow-up visit. A total of 79 patients died, and 5 were lost to follow-up. The causes of death were classified into consequence of systemic diseases (tumor progression, hepatic decompensation, acute respiratory failure, etc.) and metastatic brain diseases. About 47 patients died from systemic disease, 29 died from brain lesion, and 3 had an unidentified cause of death. In group 1, 20 patients died due to systemic disease and 5 died due to brain disease. In groups 2 and 3, 27 died due to systemic disease and 24 died due to brain disease. The number of deaths due to brain disease in groups 2 and 3 was significantly higher than that in group 1, and the odds ratio was 3.556 ( $p=0.026$ , 95% CI 1.156–10.938).

A univariate analysis was performed using the log-rank test for factors influencing survival after diagnosis of brain metastasis. As a result, a longer survival time was observed in patients with Child–Pugh class A, AFP level < 400 ng/ml, and RPA classification I or II, and those who underwent surgical resection or SRS treatment (Table 4). With regard to treatment modality, the median survival was 16.0 weeks for patients who underwent surgical resection or SRS regardless of the additional WBRT and 4.2 weeks for patients who received WBRT or conservative care only ( $p<0.001$ , Fig. 1b). When the three groups (surgery and SRS, WBRT only, and conservative care) were compared, patients with surgical resection or SRS also showed significant survival improvement ( $p<0.001$ , Fig. 1c). Child–Pugh class A group had significantly longer median survival time than the Child–Pugh classes B or C group (13.1 weeks vs. 4.9 weeks,  $p=0.002$ , Fig. 1d). Patients with AFP level < 400 ng/ml had significantly longer median survival time than those with higher AFP level (13.3 weeks vs. 6.9 weeks,  $p=0.029$ , Fig. 1e). Patients with RPA classification I or II had significantly longer median survival time than those with RPA classification III (13.6 weeks vs. 6.9 weeks,  $p=0.012$ , Fig. 1f). Patients with single brain metastasis showed survival improvement with marginal statistical significance (12.3 weeks vs. 6.3 weeks,  $p=0.059$ ).

Child–Pugh class and treatment modality remained significant on multivariate analysis (Table 4). Child–Pugh class A (hazard ratio [HR] 0.485, 95% CI 0.282–0.835,  $p=0.009$ ) and active treatment with curative intent (surgical resection or SRS) (HR 0.228, 95% CI 0.119–0.437,  $p<0.001$ ) were independent prognostic factors for survival. In particular, when resection or SRS was performed, a large decrease in HR was observed and hence was judged to be the strongest prognostic factor.



**Fig. 1** Kaplan–Meier survival curves for overall survival (OS) in patients with brain metastasis from HCC. **a** All patients, **b–f** overall survival according to the treatment modality (**b, c**), Child–Pugh class

(**d**), AFP level (**e**), and RPA classification (**f**). OS overall survival, SRS stereotactic radiosurgery, WBRT whole brain radiotherapy, AFP alpha-fetoprotein, RPA recursive partitioning analysis

### Subgroup analysis in patients with single brain metastasis from HCC

A subgroup analysis was performed in patients with single brain metastatic lesion ( $n = 51$ ). The results of univariate analysis in this patient group were similar to those of the entire study patients (Table 5). The median OS of single brain metastasis was 12.3 weeks (Fig. 2a; 95% CI 8.7–15.9 weeks). Patients who received treatment with curative intent had significantly longer survival time than those with WBRT or conservative care (19.0 weeks vs. 5.4 weeks, respectively,  $p < 0.001$ , Fig. 2b). The improved prognosis of treatment with curative intent persisted when the patients who received WBRT and conservative care were divided into different groups ( $p = 0.012$ , Fig. 2c). The Child–Pugh class A group had significantly longer survival time than the Child–Pugh classes B or C group (14.7 weeks vs. 7.1 weeks,  $p = 0.049$ , Fig. 2d). Patients with RPA class I or II had significantly longer median survival time than those with RPA classification III (15.1 weeks vs. 7.0 weeks,  $p = 0.008$ ). In the multivariate analysis, active treatment with curative intent was revealed as

the only independent prognostic factor (HR 0.305, 95% CI 0.130–0.718,  $p = 0.007$ ).

### Discussion

Extrahepatic metastases occur in 13.5–41.7% of HCC patients [6, 10]. Recent advances in systemic treatment of HCC will prolong patient survival. Moreover, patients with metastatic disease might benefit from these new systemic agents such as lenvatinib or regorafenib, or immune checkpoint inhibitors such as nivolumab or pembrolizumab. For patients with advanced HCC, intracranial metastasis used to be underdiagnosed as it was difficult to differentiate it clinically from hepatic encephalopathy. However, recent technical progress and improved availability in imaging modalities have made it easier to diagnose brain metastasis from HCC [7]. At least 0.28% of HCC patients were known to have nervous system involvement, which is the initial presentation in 0.04% of cases [26]. In our study, the incidence of intracranial metastasis was 0.6%, and five patients were diagnosed with intracranial metastasis at initial presentation of HCC.

**Table 4** Factors for overall survival after diagnosis of brain metastasis

Variables	Univariate analysis for OS			Multivariate analysis for OS		
	No. of patients	Median survival (weeks)	95% CI	<i>p</i> value (log-rank)	<i>p</i> value	HR (95% CI)
<b>Age</b>						
< 60	60	7.3	3.3–11.3	0.140		
≥ 60	26	12.0	1.9–22.1			
<b>Sex</b>						
Female	29	10.7	4.1–17.3	0.808		
Male	57	7.3	2.9–11.7			
<b>Child–Pugh classification</b>						
A	59	13.1	10.0–16.2	0.002	0.009	0.485 (0.282–0.835)
B or C	27	4.9	2.4–7.4			
<b>AFP (ng/ml)</b>						
< 400	38	13.3	7.5–19.1	0.029	0.285	0.768 (0.474–1.245)
≥ 400	48	6.9	5.8–8.0			
<b>PVTT at diagnosis of BrM</b>						
Absent	65	10.7	5.2–16.2	0.142		
Present	21	4.0	0.0–8.0			
<b>Intracranial hemorrhage</b>						
Absent	52	9.1	4.4–13.7	0.863		
Present	34	7.1	1.0–13.1			
<b>Number of metastases</b>						
Single	51	12.3	8.7–15.9	0.059	0.170	0.704 (0.426–1.162)
Multiple	35	6.3	3.5–9.1			
<b>Size of metastasis (cm)</b>						
≤ 3	45	6.9	4.8–9.0	0.253		
> 3	41	10.7	8.3–13.1			
<b>Coexisting lung metastasis</b>						
Absent	11	18.7	10.3–27.1	0.131		
Present	75	7.1	3.2–11.0			
<b>RPA classification</b>						
I or II	33	13.6	8.7–18.5	0.012	0.454	0.819 (0.486–1.381)
III	53	6.9	4.5–9.3			
<b>Intrahepatic objective response</b>						
CR, PR	27	13.1	4.4–21.8	0.438		
SD, PD, untreated	59	7.1	4.4–9.8			
<b>Treatment of brain metastasis</b>						
Resection or SRS	32	16.0	10.3–21.7	< 0.001	< 0.001	0.228 (0.119–0.437)
WBRT only	29	6.9	5.3–8.5		0.061	0.549 (0.293–1.028)
Conservative care	25	3.9	2.2–5.6			

OS overall survival, CI confidence interval, HR hazard ratio, AFP alpha-fetoprotein, PVTT portal vein tumor thrombus, BrM brain metastasis, RPA recursive partitioning analysis, CR complete response, PR partial response, SD stable disease, PD progressive disease, SRS stereotactic radiosurgery, WBRT whole brain radiotherapy

Patients with intracranial metastasis usually have poor prognosis and quality of life. Previous reports demonstrated that many factors, including biologic characteristics of the primary tumor or various clinical parameters, help predict prognosis after brain metastasis. Such variables include performance status, systemic disease status, AFP level,

Child–Pugh class, number of metastatic lesions, and treatment modality [27]. AFP reflects the tumor burden, while Child–Pugh class reflects liver function; these two factors are HCC specific and their prognostic values have been confirmed in several previous studies. In our data, Child–Pugh class score and AFP level were also significant factors for

**Table 5** Factors for overall survival after diagnosis of single brain metastasis

Variables	Univariate analysis for OS			Multivariate analysis for OS		
	No. of patients	Median survival (weeks)	95% CI	<i>p</i> value (log-rank)	<i>p</i> value	HR (95% CI)
Age						
< 60	35	10.9	5.2–16.6	0.212		
≥ 60	16	14.4	5.3–23.5			
Sex				0.545		
Female	16	13.1	7.0–19.2			
Male	35	11.0	7.0–15.0			
Child–Pugh classification				0.049	0.166	0.603 (0.294–1.235)
A	36	14.7	7.8–21.6			
B or C	15	7.1	3.3–10.9			
AFP (ng/ml)				0.096	0.507	1.245 (0.652–2.376)
< 400	28	15.1	9.1–21.1			
≥ 400	23	10.6	7.0–14.2			
PVTT at diagnosis of BrM				0.144		
Absent	38	14.7	11.8–17.6			
Present	13	7.1	1.0–13.2			
Intracranial hemorrhage				0.314		
Absent	28	13.4	8.0–18.8			
Present	23	12.3	8.4–16.2			
Size of metastasis (cm)				0.405		
≤ 3	30	13.4	5.3–21.5			
> 3	21	11.0	8.6–13.4			
Coexisting lung metastasis				0.152		
Absent	6	18.7	9.5–27.9			
Present	75	10.9	6.7–15.1			
RPA classification				0.008	0.111	0.589 (0.308–1.129)
I or II	24	15.1	8.7–21.5			
III	27	7.0	3.2–10.8			
Intrahepatic objective response				0.365		
CR, PR	15	14.7	12.0–17.4			
SD, PD, untreated	36	10.6	6.2–15.0			
Treatment of brain metastasis				0.012	0.007	0.305 (0.130–0.718)
Resection or SRS	23	19.0	2.9–35.1			
WBRT only	14	7.0	4.1–9.9			
Conservative care	14	4.0	1.3–6.7		0.448	0.713 (0.298–1.706)

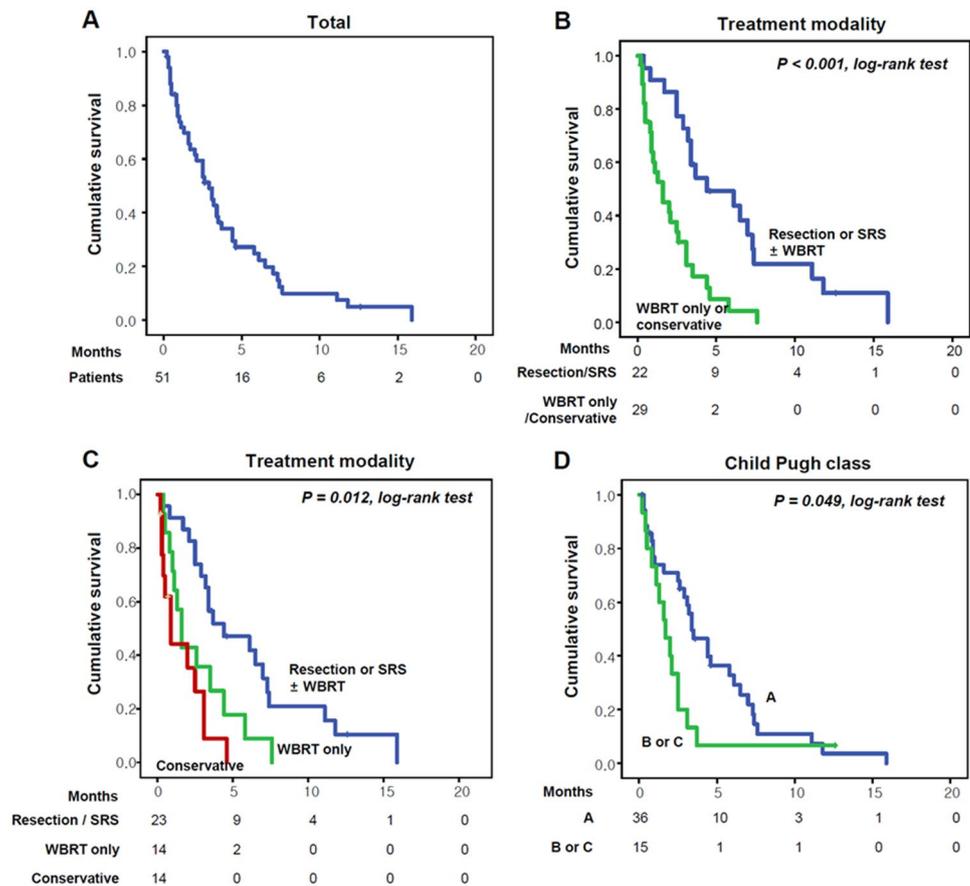
OS overall survival, CI confidence interval, HR hazard ratio, AFP alpha-fetoprotein, PVTT portal vein tumor thrombus, BrM brain metastasis, RPA recursive partitioning analysis, CR complete response, PR partial response, SD stable disease, PD progressive disease, SRS stereotactic radiosurgery, WBRT whole brain radiotherapy

survival in univariate analyses, suggesting that liver function and tumor burden are still important factors for survival in patients with intracranial metastasis.

In advanced HCC, the mortality due to extrahepatic metastasis was reported to be 7.6% only, and the leading cause of death was progression of intrahepatic diseases [28]. Previous studies demonstrated that intrahepatic disease control is more efficacious than metastatic disease control in prolonging patient's survival, because

patient survival critically depends on the progression of liver function determined by intrahepatic tumor burden [28–31]. Therefore, several groups have reported that the targeted intrahepatic tumor control by TACE in multinodular HCC without PVTT significantly prolongs survival, even in the patients with extrahepatic metastasis [28–31]. However, our analyses highlighted the role of intracranial tumor control in patients with brain metastasis from HCC. Previous studies also demonstrated that patient survival is

**Fig. 2** Kaplan–Meier survival curves for overall survival (OS) in patients with single brain metastasis from HCC. **a** Overall survival in patients with single brain metastasis. **b–d** Overall survival according to the treatment modality (**b, c**), and Child–Pugh class (**d**). OS overall survival, SRS stereotactic radiosurgery, WBRT whole brain radiotherapy



more favorable when they undergo surgery and/or WBRT (14.7–33.6 weeks) [7, 13, 14, 18, 21, 32] than WBRT alone (2.8–4.3 weeks) [18, 32] or conservative care with corticosteroids (1.0–6.0 weeks) [8, 12–14, 21, 32]. Our results are in line with these findings in that intracranial disease control is associated with prolonged patient survival in patients with brain metastasis from HCC.

HCC is a hypervascular tumor, and brain metastasis from HCC is occasionally accompanied by intratumoral hemorrhage which frequently leads to sudden neurological deterioration and poor performance. The association of intratumoral hemorrhage with survival outcome of brain metastasis from HCC is controversial [12, 19, 33]. In our cohort, 39.5% of patients had radiological intratumoral hemorrhage of metastatic tumors, and tumor size was significantly associated with intratumoral hemorrhage ( $p = 0.037$ ). However, cerebral hemorrhage by metastatic HCC was not associated with OS of patients by univariate analyses. ( $p = 0.863$ ). Pathological intratumoral hemorrhage, which was confirmed in surgical specimens, was present in 72% (18/25) of the patients who underwent surgery, and two patients without radiological hemorrhage had pathological intratumoral hemorrhage. Again, pathological intratumoral hemorrhage was not associated with the OS of the patients, either ( $P = 0.568$ ).

These results should be further validated in a future larger cohort.

In our cohort, some patients refused to undergo surgery or SRS for brain metastasis due to the poor performance and old age, and others refused aggressive treatment because their intrahepatic tumor had been on progression. These reasons for not choosing surgery or SRS are associated with worse overall survival of the patients and may cause the selection bias of the survival analyses. However, to minimize the selection bias, we enrolled patients in two different hospitals and pooled patient data. Then, we divided the total patients into two groups with or without curative treatment, whose baseline characteristics were not significantly different (Table 3). This could be obtained because patients tended to receive curative treatment in one hospital and receive conservative treatment in the other hospital. Furthermore, some patients refused to receive surgery or SRS because they did not experience neurologic symptoms or were unable to manage the treatment cost. These factors alleviated the selection bias of our study. Overall, surgery or SRS of intracranial metastasis from HCC was an independent factor predicting prolonged survival in patients with advanced HCC, unlikely with metastasis to other organs. Particularly, in our study, a subgroup analysis of patients with single intracranial

metastasis showed that performing resection or SRS was the only prognostic factor for prolonged survival. This finding suggests that patients with single intracranial metastasis should be treated with curative intent.

This study had important limitations. First, this study could not completely exclude the patient selection bias due to the nature of a retrospective analysis. Although the total HCC patient population is large, data were collected over a 23-year interval during which considerable changes were made in the management of HCC. Therefore, prospective validation is critical to confirm the findings of our study.

In conclusion, our data suggest that patients actively treated with surgery or radiosurgery have prolonged survival, suggesting that interventions to control intracranial disease are critical, although the overall prognosis of patients with brain metastases from HCC is extremely poor. To detect intracranial metastasis earlier, brain imaging is required to confirm intracranial metastases when patients with lung metastases from HCC present neurologic symptoms.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interests.

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