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CLINICAL STUDY

Prognostic stratification of brain metastases from hepatocellular carcinoma

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Abstract The aim of this study is to evaluate prognostic factors of brain metastases from hepatocellular carcinoma. Medical records of 95 patients who have been diagnosed of brain metastases from hepatocellular carcinoma between January 2000 and December 2011 were retrospectively reviewed. The median age at diagnosis of brain metastases is 56.1 years. Eighty-two patients were male. Median interval from diagnosis of hepatocellular carcinoma to brain metastases was 29.5 months. Eighty-eight patents had extracranial metastases, and the lung was the most frequent involved organ. Motor weakness was the most frequent presenting symptom (49.5 %). Intracranial hemorrhage was present in 71 patients (74.7 %). Brain metastases were treated with whole brain radiation therapy (WBRT) alone in 57 patients, radiosurgery alone in 18, surgery and WBRT in 6, surgery and radiosurgery in 3, surgery alone in 3, radiosurgery and WBRT in 2, and conservative management only in 6. Median overall survival was 3.0 months. Multivariate analysis showed ECOG performance status, Child-Pugh class, AFP level, number of brain lesions, and treatment modality were associated with survival ($p < 0.05$). When patients were stratified with four prognostic factors including ECOG performance status, Child-Pugh class, AFP level, and number of brain lesions, median survival time for patients with 0–1, 2, 3–4 risk factors were 5.8 months, 2.5 months and 0.6 months, respectively ($p < 0.001$). In conclusion, we can estimate the survival of patients by prognostic stratification, although overall prognosis of patients with brain metastases from hepatocellular carcinoma is poor.

Keywords Hepatocellular carcinoma · Brain metastases · Prognostic factor

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Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer in men and 7th in women causing about 700,000 deaths worldwide in a year [1]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are known to be the main etiology of the development of HCC, but not the sole etiologic link to HCC. In Korea, HCC is the 4th most common cancer in men and 5th in women, causing 2nd and 4th most common cancer mortality in males and females, respectively in year 2010 [2].

Brain metastases from HCC were very rare [3, 4]. However, the incidence has been increasing because recent developments in the surgical and medical therapy have significantly improved the outcome of patients with HCC, and because advanced neuroimaging studies have detected more lesions than ever [5, 6]. As in other primary tumors, there is no consensus on the optimal treatment for brain metastases from HCC.

For patients with brain metastases, Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification and graded prognostic assessment

(GPA) had been developed for patient grouping with homogeneous prognosis, and its clinical usage has been validated in the clinical settings [7–10]. Decision making based on the expected survival can be a reasonable approach using these prognostic models. Given the prognostic factors for brain metastases varied by primary diagnosis [11], diagnosis-specific GPA (DS-GPA) was recently developed in several primary tumors including non-small cell lung cancer, small cell lung cancer, melanoma, renal cell carcinoma, breast cancer, and gastrointestinal cancer. However, for brain metastases from HCC, DS-GPA has not been developed due to its rarity [12].

In this study, we evaluated prognostic factors of brain metastases from HCC to suggest optimal management for those patients.

Materials and methods

After Institutional Review Board approval, medical records of 95 patients who have been diagnosed with brain metastases from HCC between January 2000 and December 2011 were retrospectively reviewed. All patients were diagnosed radiologically with computerized tomography (CT) or magnetic resonance imaging (MRI).

Clinical data included symptom presentation, performance status, liver function, whether primary lesion controlled or not, presence of extracranial metastases, number of brain lesion, treatment modality and clinical courses. If there was no evidence of viable tumor in the liver through the imaging study after local treatments, it was referred as controlled primary tumor [13].

Overall survival 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 $p < 0.05$ was considered to indicate a statistically significant difference. Analyses were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

A total of 95 patients were enrolled. Of these patients, 82 were male and 13 were female. Median age at the diagnosis of brain metastasis was 56 years. Median time from the diagnosis of HCC to the brain metastasis was 29.5 months. Most common presenting symptom was motor weakness (49.5 %) followed by headache (28.4 %) and visual

Table 1 Clinical characteristics of 95 patients

	No.	%
Median age (range)	56.1 years (33.8–75.0)	
Median time to brain metastasis (range)	29.5 months (2.73–191)	
Sex		
Male	82	86.3
Female	13	13.7
Etiology		
HBV	87	91.6
HCV	5	5.3
NBNC	3	3.2
ECOG PS		
≤2	64	67.4
>2	31	32.6
Child-Pugh class		
A	70	73.7
B	16	16.8
C	9	9.5
AFP (ng/ml)		
≤1,400	47	49.5
>1,400	47	49.5
Unknown	1	
Primary tumor status		
Controlled	35	36.8
Uncontrolled	60	63.2
Presenting symptom*		
Motor weakness	47	49.5
Headache	27	28.4
Visual disturbance	19	20.0
Nausea/Vomiting	10	10.5
Consciousness change	10	10.5
Dysarthria	9	9.5
Seizure	8	8.4
Treatment to liver[a]		
TACE	78	82.1
Resection	29	30.5
PEIT	12	12.6
RFA	7	7.4
Transplantation	3	3.2
Radiation	6	6.3
No treatment	3	3.2
Systemic therapy		
Chemotherapy	55	57.9
Targeted agents	16	16.8
Extracranial metastases[b]		
Lung	84	88.4
Lymph node	32	33.7
Bone	14	14.7
Adrenal	9	9.5
Others	6	6.3

Table 1 continued

	No.	%
None	7	7.4
Number of brain lesion		
1	42	44.2
2	23	24.2
3	8	8.4
≥4	22	23.2
Intracranial tumor location		
Supratentorial	92	96.8
Infratentorial	19	20.0
Both	16	16.8
Intracranial hemorrhage		
Yes	71	74.7
No	24	25.3

ECOG PS Eastern Cooperative Oncology Group performance status, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NBNC* non-B non-C, *TACE* transcatheter arterial chemoembolization, *PEIT* percutaneous ethanol injection therapy, *RFA* radiofrequency ablation

* Each symptom was counted regardless of other symptoms of each patient

[a] Patients could be treated with more than one modalities

[b] Each metastasis was counted regardless of metastasis of other site

disturbance (20 %). Intracranial hemorrhage was present in 71 patients (74.7 %). In 42 patients, brain metastasis presented as a single lesion.

Median value of AFP level was 1,400 ng/ml. Primary tumor was controlled in 35 patients, which means there was no evidence of disease in the liver after local therapy. Local therapy to the liver was diverse including transcatheter arterial chemoembolization (TACE), surgical resection, percutaneous ethanol injection therapy (PEIT), radiofrequency ablation (RFA), transplantation and radiation therapy. Eighty-eight patients had extracranial metastases, and the lung was the most frequent involved organ ($n = 84$). Fifty-five patients received chemotherapy mainly due to the metastatic lesion. ECOG performance status for 31 patients was greater than 2. Child-Pugh classification was evaluated as A for 70 patients, B for 16 patients, and C for 9 patients (Table 1).

Treatment

Seventy-eight patients received single modality therapy. Among them, 57 patients underwent whole brain radiation therapy (WBRT) alone, 18 patients radiosurgery alone, and 3 patients surgery alone. Eleven patients were treated with more than one modalities. Only conservative management was offered to 6 patients because of family choice ($n = 3$), severe brain hemorrhage ($n = 2$), and rapid deterioration ($n = 1$). Details of treatment are summarized in Table 2. Median dose of WBRT was 30 Gy in 10 fractions.

Table 2 Treatment of brain metastasis

Treatment	No.
Observation	6
WBRT only	57
Radiosurgery only	18
Surgery only	3
Radiosurgery + WBRT	2
Surgery + WBRT	6
Surgery + Radiosurgery	3

WBRT whole brain radiation therapy

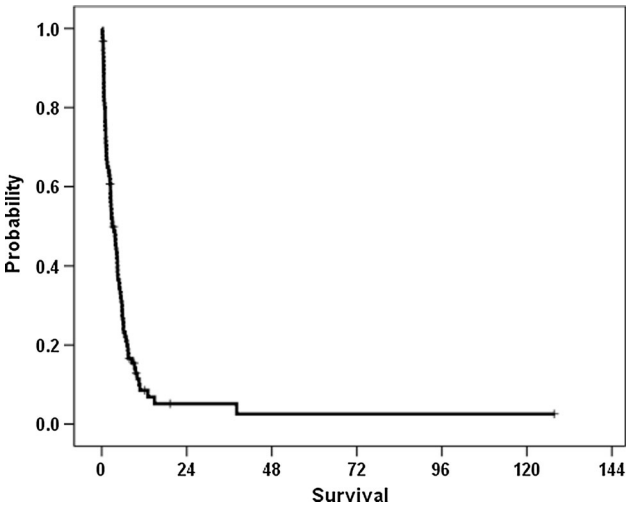

Fig. 1 Overall survival curve

Outcome and prognostic factor analysis

Median overall survival of all patients was 3.0 months (95 % confidence interval 1.7–4.3 months) (Fig. 1). Age, ECOG performance status, Child-Pugh class, AFP level, controlled primary tumor status and number of brain lesion were revealed as significant prognostic factors for overall survival in univariate analysis (Table 3). For whom that received more than one treatment modalities, the median survival was significantly prolonged. Multivariate analysis was performed incorporating the factors which were significant in univariate analysis.

Multivariate analysis revealed that there was survival difference according to ECOG performance status, Child-Pugh Class, AFP level, number of brain lesion, and treatment modality.

Given the results of the multivariate analysis and the fact that number of patients treated with more than one modalities were significantly correlated with Child-Pugh Class and AFP level ($p = 0.035$, 0.045, respectively), patients were categorized into three groups according to the risk factors except treatment modality. The distribution of detailed risk factors of the three groups was shown in Table 4.

Table 3 Univariate and multivariate analyses for overall survival

	No.	Median survival (months)	p* (Univariate)	p^a (Multivariate)
Sex			0.420	–
Male	82	2.75		
Female	13	5.47		
Age			0.018	0.261
≤56 yrs	47	4.90		
>56 yrs	48	2.47		
ECOG PS			0.000	0.000
≤2	64	4.51		
>2	31	1.04		
Child-Pugh class			0.000	0.000
A	70	4.51		
B/C	25	0.66		
AFP[b] (ng/ml)			0.009	0.003
≤1,400	47	4.57		
>1,400	47	2.75		
No. of brain lesion			0.011	0.015
Single	42	4.47		
Multiple	53	2.47		
Primary tumor status			0.001	0.109
Controlled	35	5.20		
Uncontrolled	60	2.11		
Extracranial metastases			0.925	–
Yes	88	3.45		
No	7	1.32		
Intracranial hemorrhage			0.593	–
Yes	71	3.98		
No	24	2.30		
Treatment			0.000	0.039
Single or none	84	2.61		
Multimodality	11	10.56		

ECOG PS Eastern Cooperative Oncology Group performance status

* Log-rank test

[a] Cox regression analysis

[b] Analysis with available data

Median survival time for patients with 0–1, 2, and 3–4 risk factors were 5.8, 2.5 and 0.6 months, respectively ($p < 0.001$). Overall survival curves according to the number of risk factors are presented in Fig. 2.

Cause of death and prognostic factors

At last follow-up, 86 patients were dead, 5 patients were alive, and 4 patients were lost to follow-up. The cause of death was classified as neurologic ($n = 60$) or systemic ($n = 26$), as previously suggested by Patchell et al. [14]. The correlation between the cause of death and the four prognostic factors was shown in Table 5. Neurologic death was more frequently observed in patients with ECOG performance status >2 ($p = 0.025$).

Table 4 The distribution of detailed risk factors according to the number of risk factors

	Number of risk factors			p*
	0–1 ($n = 39$)	2 ($n = 36$)	3–4 ($n = 19$)	
ECOG PS				<0.001
≤2	36	25	3	
>2	3	11	16	
Child-Pugh Class				<0.001
A	38	27	4	
B/C	1	9	15	
AFP[a] (ng/ml)				<0.001
≤1,400	30	10	7	
>1,400	9	26	12	
No. of lesion				<0.001
Single	30	10	2	
Multiple	9	26	17	

* Chi square test or Fisher's exact test

[a] Analysis with available data

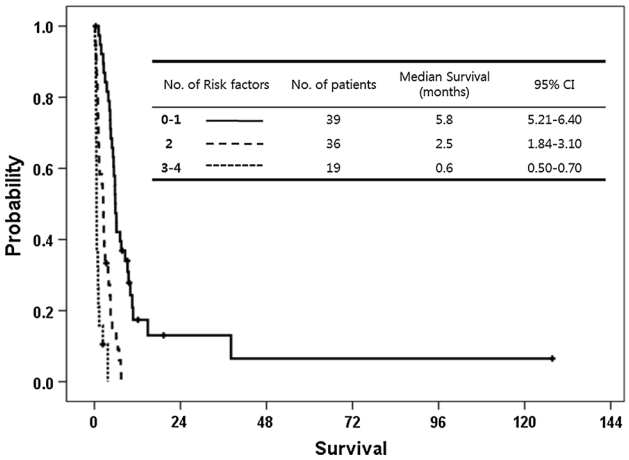

Fig. 2 Overall survival curves according to the number of risk factors

Discussion

Overall prognosis of brain metastases from HCC was known to be very poor [4, 13, 15–17]. Reported median survival ranged from 1 to 3 months. In our study, overall median survival was 3.0 months (95 % CI 1.7–4.3), which was consistent with other studies. There were several studies

Table 5 The correlation between the cause of death and the four prognostic factors

	Cause of death		p*
	Neurologic ($n = 60$)	Systemic ($n = 26$)	
ECOG PS			0.025
≤2	35	22	
>2	25	4	
Child-Pugh Class			0.076
A	39	22	
B/C	21	4	
AFP[a] (ng/ml)			0.482
≤1,400	26	14	
>1,400	33	12	
No. of lesion			0.639
Single	24	12	
Multiple	36	14	

* Chi square test or Fisher's exact test

[a] Analysis with available data

reporting prognostic factors in the advanced HCC. For patients with extrahepatic metastasis, Uchino et al. [18] reported that the controllability of intrahepatic lesions and performance status were important prognostic factors. As for the brain metastases, Choi et al. [13] reported that Child-Pugh's classification, number of brain metastases and AFP level were prognostic factors in multivariate analysis of 62 patients. In the present study, ECOG performance status, Child–Pugh class, AFP level, number of brain metastases, and treatment modality were significant prognostic factors.

Because brain metastases occur in the late stage of the disease course in HCC, liver function was closely related to the survival of the patients. In our study, the patients with Child-Pugh class A had prolonged survival than that of class B or C. Moreover, 35 patients with controlled intrahepatic lesion had better survival than the others in the univariate analysis. However, in the multivariate analysis, this difference did not show statistical significance.

Additionally, AFP is well known to reflect tumor burden. An AFP level >1,400 ng/ml was demonstrated as an adverse prognostic factor in the current study. This association was consistent with previous study [13]. In the present study, 88 patients had extracranial metastases and only 7 patients did not. Median survival of patients with extracranial metastases was longer than the others although the difference was not statistically significant. Jiang et al. [15] also reported that patients with extracranial metastases had prolonged survival and this relationship was statistically significant in multivariate analysis. They implied that the patient with brain metastasis first might have tumor that are more poorly differentiated and result in a more aggressive neurovascular invasion. Further study will be needed to clarify this relationship.

The other important prognostic factors in our analysis were ECOG performance status and the number of brain lesion. These factors were also used as prognostic factors in the RPA classification and GPA, respectively.

Given the 4 prognostic factors except treatment modality in our analysis, patients were divided into three groups. For patients with 0–1 risk factor, we could expect more prolonged survival. Survival differences among the patients with different number of risk factors imply that these prognostic factors might be used for the DS-GPA for HCC. As it could evaluate patient's expected survival, DS-GPA might have clinical importance in the management of the brain metastases from HCC.

Although the treatment modality was excluded from our final prognostic model, it did have a statistically significant correlation with the outcome in multivariate analysis. However, the causal relationship was not clear because patients with low risk group (i.e., good performance status, good liver function, lower AFP and single brain metastasis) might have been treated with multiple treatment modalities. Therefore, the influence of treatment modality on the outcome according to the risk groups was further analyzed (Table 6). While no patient with 3–4 risk factors was treated with multiple modalities and there was no difference of survival in patients with 2 risk factors, there was a survival benefit of multiple treatment modalities in patients with 0–1 risk factor ($p = 0.018$).

Although the decision on the optimal treatment of brain metastases requires several clinical factors such as decline of neurocognitive function or intracranial tumor control as well as expected survival, this study might suggest that multimodality treatment strategy could be beneficial to the patients with low risk group [19–21].

Retrospective nature of this study is a significant limitation. However, considering low incidence of brain

Table 6 The influence of treatment modality on survival according to the number of risk factors

No. of risk factors	Treatment	No.	Median survival (months)	p*
0–1	Single or none	31	5.70	0.018
	Multimodality	8	38.10	
2	Single or none	34	2.30	0.309
	Multimodality	2	4.97	
3–4	Single or none	19	0.60	–
	Multimodality	0	–	

* Log-rank test

metastases from HCC, number of patients in this study were the largest among the studies with respect to the brain metastases from HCC.

In conclusion, although overall prognosis of patients with brain metastases from HCC is poor, we can estimate the survival of patients by prognostic stratification using 4 risk factors including ECOG performance status, Child-Pugh class, AFP level, and number of brain lesion.

Conflict of interest None.

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