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ORIGINAL RESEARCH

Cystic brain metastases had slower speed of tumor shrinkage but similar prognosis compared with solid tumors that underwent radiosurgery treatment

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Purpose: Traditionally, radiosurgery was considered less effective for patients with cystic brain metastases. However, comparisons of prognosis between cystic and solid brain metastases in cancer patients have been seldom reported. We aimed to compare the survival between cystic and solid brain metastases and assess risk factors for overall survival after brain metastases (BMOS) in patients who underwent radiosurgery treatment.

Patients and methods: The Kaplan–Meier method and multivariate Cox regression analysis were used to compare survival time and evaluate risk factors for BMOS.

Results: A total of 356 patients (including 498 brain metastases) were analyzed in our study, including 67 patients (67/356, 18.8%) with 75 cystic brain metastases. There is no statistical significance in BMOS between patients with cystic (17 months, range: 3–64 months) and solid (17.5 months, range: 1–65 months) brain metastases (P=0.148). However, the volume of cystic brain metastases decreased more slowly than solid brain metastases (P<0.05). The results indicated that high recursive partitioning analysis classification (P=0.006), large volume of brain metastases (P=0.006), and different primary lesion (especially gastrointestinal tract tumor) (P=0.001) were associated with poor prognosis in patients with brain metastases.

Conclusion: There is no difference in prognosis and local control between patients with cystic and solid brain metastases who underwent radiosurgery. However, the rate and speed of tumor shrinkage were lower in cystic brain metastases after radiotherapy. Patients with larger brain metastases had shorter survival time, regardless of cystic or solid brain metastases.

Keywords: cystic brain metastases, radiosurgery treatment, tumor shrinkage, overall survival after brain metastases, risk factors

Introduction

Brain metastases are the most common intracranial tumor in adults and an important factor in shortening the lives of patients with malignant tumor.[1–3] In particular, the incidence of brain metastases has increased in recent years due to the developing technologies and prolonged survival time in cancer patients.[4] Brain metastases mainly originate from lung cancer, breast cancer, kidney cancer, melanoma, and gastrointestinal tumors. Approximately 15%–20% of patients with non-small-cell lung cancer (NSCLC) and 60%–80% small cell lung cancer (SCLC) patients who have survived more than 2 years will develop brain metastasis.[5,6] However, the survival of lung cancer patients with brain metastases is very poor, and they can only survive 1–2 months without treatment.

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Developing treatment options, which include surgery, whole brain radiation therapy (WBRT), stereotactic radiotherapy, chemotherapy, and targeted therapy have greatly extended the survival time of patients with brain metastases.[7,8] Stereotactic radiosurgery (SRS) has been a routine and effective treatment option for oligometastasis (less than or equal to five brain metastases).[9–11] CyberKnife, as a relatively new SRS system, has expanded rapidly worldwide because of its precise positioning, noninvasiveness, and high local control rate.[10,12,13] Even so, cystic brain metastases are often deemed not suitable for radiation, which includes CyberKnife, because of cystic lesion insensitivity to radiotherapy and large volume.[14,15]

Traditionally, radiosurgery was considered less effective for patients with cystic brain metastases, and they had shorter survival time than patients with solid brain metastases. However, the comparisons of prognosis between cystic and solid brain metastases in cancer patients have been seldom reported. In this study, we aimed to analyze the survival difference and treatment response to radiosurgery treatment in these two groups and investigate factors related to local control and overall survival after brain metastases (BMOS).

Patients and methods

Patient characteristics

We reviewed 426 patients with brain metastases who had undergone radiosurgery treatment at the Tianjin Cancer Hospital and Institute from January 2012 to December 2016. All patients were assessed by radiation oncologists and physicists. The inclusion criteria were as follows: 1) definite histopathological diagnosis for primary lesion, 2) newly diagnosed brain metastases, 3) without meningeal metastases, 4) patient received radiosurgery treatment, and 5) integrated clinical and follow-up data. At last, a total of 356 eligible patients were included and analyzed in our study. The study was approved by Tianjin Medical University Cancer Institute and Hospital's Ethics Committee and was conducted in strict accordance with the principles of the Declaration of Helsinki. We also obtained the waiver for individual patients' written informed consent for our retrospective study from the committee. To maintain patients' confidentiality, all clinical data and laboratory results were collected anonymously. All data and records for patients were confidential and individuals outside the research team had no access to them.

Radiosurgical technique

All patients received treatment using CyberKnife (Accuray Inc., Sunnyvale, CA, USA). The CyberKnife is equipped with a 6 MV linear accelerator, which is mounted on a computer-controlled robotic arm. All patients were in the supine position, and a thermoplastic mask was molded to the head. The contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT) images of 1.5 mm slice thickness were obtained and fused for treatment planning. We defined gross target volume (GTV) as the enhanced lesion on contrast-enhanced MRI and extended the GTV by 1.25 mm to generate the planning target volume (PTV).

Imaging data

In our study, we defined cystic brain metastasis as the volume of the cystic lesions greater than 50% of the total volume. The typical MRI characteristics were present as shown in Figure 1. Contrast-enhanced MRI is necessary for diagnosing cystic brain metastases. The cystic components revealed hypointense on T1-weighted images, hyperintense on T2-weighted images, and no enhancement.[16] Enhanced MRI was performed every 3 months after the initial treatment.

Treatment

All patients underwent CyberKnife treatment and a total of 88 (24.72%) patients received prior WBRT. The median timing from WBRT to SRS was 1 month (ranging from 0.3 to 40 months). In our center, large brain metastases usually received supplement SRS treatment again 0.5–1 months after WBRT because the dose of WBRT was not enough for the treatment of lesions of large volume. In our study, most patients (63/88, 71.6%) received prior WBRT before SRS because of multiple brain metastases and large volume of isolated lesion. The rest of the patients (25/88, 28.4%) received SRS after WBRT (range: 3–40 months) because of new brain metastases. Detailed CyberKnife treatment parameters are listed in Table 1.

The volume of brain metastases ranged from 0.0565 to 89.975 cm^3. And the volume and site of brain metastases determined the dose and fraction schedule (Table 2). A total of 165 patients received SRS, with median dose 20 Gy (range: 12–23 Gy). Two-fraction and three-fraction SRT were given in 136 and 121 patients, with the same median dose 30 Gy (range: 16–32 and 18–36 Gy, respectively). The prescribed dose covered at least 95% of the PTV.

Statistical analysis

BMOS was defined as the duration of time from the date of brain metastases diagnosis to the date of death or the last follow-up. The follow-up ended on December 30, 2017. The survival estimates were analyzed by the Kaplan–Meier

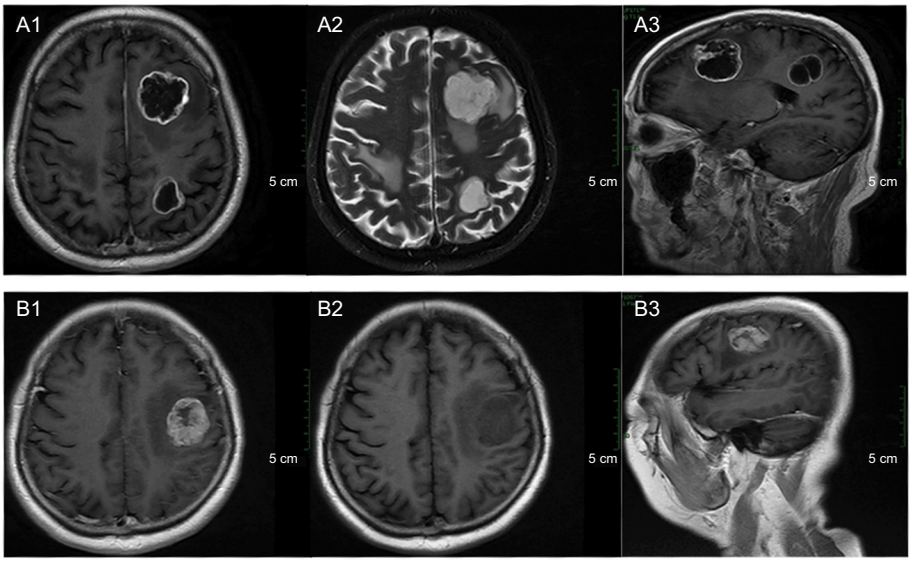

Figure 1 Typical characteristics of cystic (**A1–A3**) and solid (**B1–B3**) brain metastases in magnetic resonance images.
Notes: (**A1**, **B1**) Axial contrast-enhanced T1-weighted magnetic resonance images. (**A2**, **B2**) Axial T2-weighted magnetic resonance images. (**A3**, **B3**) Sagittal contrast-enhanced T1-weighted magnetic resonance images.

Table 1 Characteristics of CyberKnife radiosurgery treatment parameters

Characteristic	Mean	Median	Range
Prescription dose (Gy)	24.52	22	12–42
BED (Gy)	60.13	60	26.4–83.2
Conformity index	1.21	1.18	1.04–1.99
Target volume (cm^3)	6.87	3.073	0.056–89.975
Homogeneity index	1.45	1.47	1.2–1.92
Prescription isodose (%)	68	67	52–83

Abbreviation: BED, biological effective dose.

Table 2 Dose and fraction schedule for patients who underwent CyberKnife treatment

Prior WBRT	Tumor diameter (cm)	Dose/fraction
No	≤1.5	21 Gy/1F
	1.5–2.5	26–28 Gy/2F
	2.5–3.5	27–30 Gy/3F
Yes		12–14 Gy/1F

Abbreviation: WBRT, whole brain radiotherapy.

method, and log-rank test was used for the comparison between patients with solid and cystic brain metastases. Multivariate survival analysis for prognostic factors and cystic brain metastases was performed by using Cox regression and the forward likelihood ratio method. A two-sided test that resulted in $P<0.05$ was considered to be statistically significant.

Results

Patient characteristics

In our study, data from 356 patients (including 498 brain metastases) were analyzed, and their characteristics are listed in Table 3.

A total of 67 patients (67/356, 18.8%) developed 75 cystic brain metastases. The median age for all patients was 59 years (range: 24–86 years). In our study, 63 (17.70%) patients had a recursive partitioning analysis (RPA) classification of I, 280 (78.65%) patients were in class II, and only 13 (3.65%) patients were in class III. Lung cancer was the most frequent primary site (243/356, 68.26%); breast cancer (41/356, 11.52%) were the next. Over half of the patients (206/356, 57.87%) had significant neurologic symptoms, including headaches, dizziness, vomiting, hemiplegia, and so on. Most patients had one to three brain metastases and only ten patients had more than three brain metastases.

Overall survival and local control

Until the last follow-up time, 93 (93/356, 26.12%) patients were still alive (Figure 2), including 25 (25/67, 37.31%) patients with cystic brain metastases. Most patients died of tumor progression and five patients died from heart disease or severe brain edema. The median BMOS is 17 months (range: 1–65 months). There is no significant difference in BMOS between patients with cystic (17 months, range: 3–64 months) and solid (17.5 months, range: 1–65 months) brain

Table 3 Patients characteristics and comparison between cystic and solid brain metastases

Characteristics	No. of all patients (%)	No. of patients with cystic lesions (%)	No. of patients with solid lesions (%)	*P*-value
Age (years)				
<65	244 (68.54)	44 (65.67)	200 (69.2)	0.579
≥65	112 (31.46)	23 (34.33)	89 (30.8)	
Sex				
Male	195 (54.78)	37 (55.22)	158 (54.7)	0.935
Female	161 (45.22)	30 (44.78)	131 (45.3)	
ECOG				
0	7 (1.97)	0 (0)	7 (2.4)	0.407
1	297 (83.43)	58 (86.57)	239 (82.7)	
≥2	52 (14.61)	9 (13.43)	43 (14.9)	
RPA classification				
1	63 (17.70)	11 (16.42)	52 (18)	0.593
2	280 (78.65)	55 (82.09)	226 (78.2)	
3	13 (3.65)	1 (1.49)	11 (3.8)	
Primary tumor				
Lung	243 (68.26)	54 (80.60)	188 (65.1)	0.048
Breast	41 (11.52)	7 (10.45)	34 (11.8)	
Kidney	20 (5.62)	0 (0)	20 (6.9)	
Gastrointestinal tract	23 (6.46)	4 (6.0)	19 (6.6)	
Other	29 (8.15)	2 (3.0)	28 (9.7)	
Prior WBRT				
Yes	88 (24.72)	24 (35.82)	64 (22.1)	0.019
No	268 (75.28)	43 (64.18)	22 (77.9)	
No. of brain metastases				
1	257 (72.19)	45 (67.2)	212 (73.4)	0.758
2	69 (19.38)	16 (23.9)	53 (18.3)	
3	20 (5.62)	4 (6.0)	16 (5.5)	
≥4 lesions	10 (2.53)	2 (3.0)	8 (2.8)	
Neurologic symptoms				
Yes	206	36 (53.7)	170(58.8)	0.447
No	150	31(46.3)	119(41.2)	
The volume of brain metastases (cm^3)				
≤8	211(59.3)	28 (41.8)	183 (63.3)	0.005
8–27	123 (34.6)	34 (50.7)	89 (30.8)	
>27	22 (6.2)	5 (7.5)	17 (5.9)	
≤27	334 (93.8)	62 (92.5)	272 (94.1)	0.628
>27	22 (6.2)	5 (7.5)	17 (5.9)	
Primary tumor status				
Control	134	23	111	0.535
Uncontrol	222	44	178	
Distribution of brain metastases				
Frontal	106	12	94	
Parietal	130	25	105	
Temporal	88	10	78	
Occipital	69	14	55	
Cerebellum	58	10	48	
Other	47	4	43	
Cystic brain metastases				
Yes	67			
No	289			

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RPA, recursive partitioning analysis; WBRT, whole brain radiotherapy.

metastases (P=0.148) (Figure 3A). The BMOS ratios at 1, 2, and 3 years in all patients were 64.89%, 33.15%, and 10.96%, respectively, and were 70.15%, 32.83%, and 10.45% for patients with cystic brain metastases. The local control was 96.2% and 97.0% in patients with solid and cystic metastases, respectively, with no significant difference (P=0.7002) (Figure 3B). Definite local failure occurred in four solid brain metastases and one cystic brain metastasis. In addition, the volume of seven solid brain metastases and one cystic brain metastasis increased significantly with obvious edema. We cannot identify necrosis or relapses because these patients rejected further imaging examinations.

Only 47 patients with cystic brain metastases and 184 patients with solid brain metastases survived for >12 months after brain metastases. Therefore, we measured the volume changes by diameter at 3, 6, 9, and 12 months (Figure 4) after CyberKnife treatment in 39 patients with 41 cystic brain metastases and 153 patients with 174 solid brain metastases. Results showed that the volume of solid brain metastases decreased faster than cystic brain metastases (P<0.05) (Figure 5).

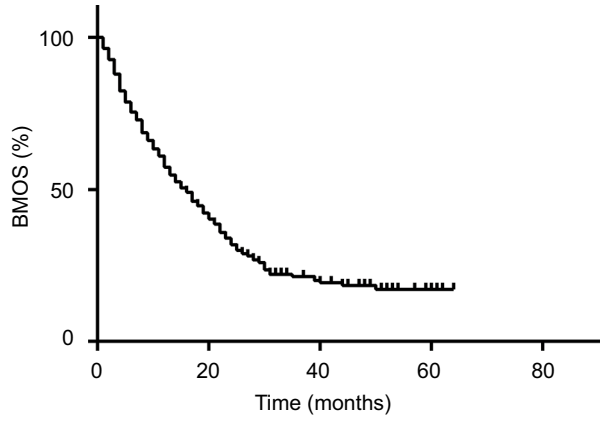

Figure 2 Overall survival after brain metastases curve for 356 patients who underwent CyberKnife treatment.
Abbreviation: BMOS, overall survival after brain metastases.

Risk factors for BMOS

Factors that may be related to BMOS were included in correlational analyses (Table 4). Univariate analysis suggested that age (P=0.032), Eastern Cooperative Oncology Group score (P=0.002), RPA classification (P=0.001), primary tumor (P=0.000), neurologic symptoms (P=0.015), the volume of brain metastases (P=0.011), and extracranial metastases (P=0.006) were the independent influencing factors for BM OS. These factors were included in the multivariate analysis, and the results indicated that high RPA classification (P=0.006) (Figure 6) and large volume of brain metastases (P=0.006) (Figure 7) were associated with poor prognosis in patients with brain metastases. Different primary tumors were also related to prognosis (P=0.001). Compared to lung cancer, gastrointestinal tract cancer had poorer BMOS (HR=2.339, P=0.000).

Because lung cancer accounts for the most of the primary disease, we analyzed risk factors in patients with lung cancer separately (Table 5). RPA classification (P=0.038), extracranial metastases (P=0.049), the volume of brain metastases (P=0.004), and primary tumor condition (P=0.019) were included in the multivariate analysis, and the results indicated that the volume of brain metastases (P=0.001) and primary tumor (P=0.003) condition were independent prognostic factors for the overall survival in patients with brain metastases.

Discussion

Brain metastasis is usually regarded as an important sign of poor prognosis in malignancies, especially in cystic brain metastases, and there still exist controversy about radiotherapy treatment for cystic cerebral metastases.[17] However, in the few studies comparing prognosis between cystic and solid brain metastases, we can only find one retrospective study associated with cystic brain metastases in breast metastases showing that patients with cystic brain metastases

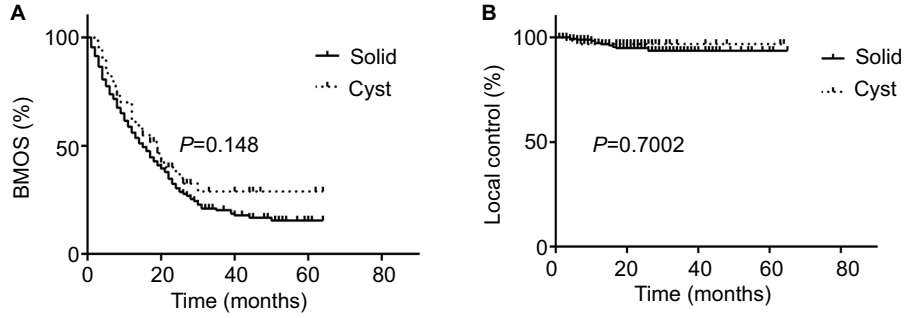

Figure 3 Comparison of survival and local control between patients with cystic (**A**) and solid brain metastases (**B**) after CyberKnife treatment.
Abbreviation: BMOS, overall survival after brain metastases.

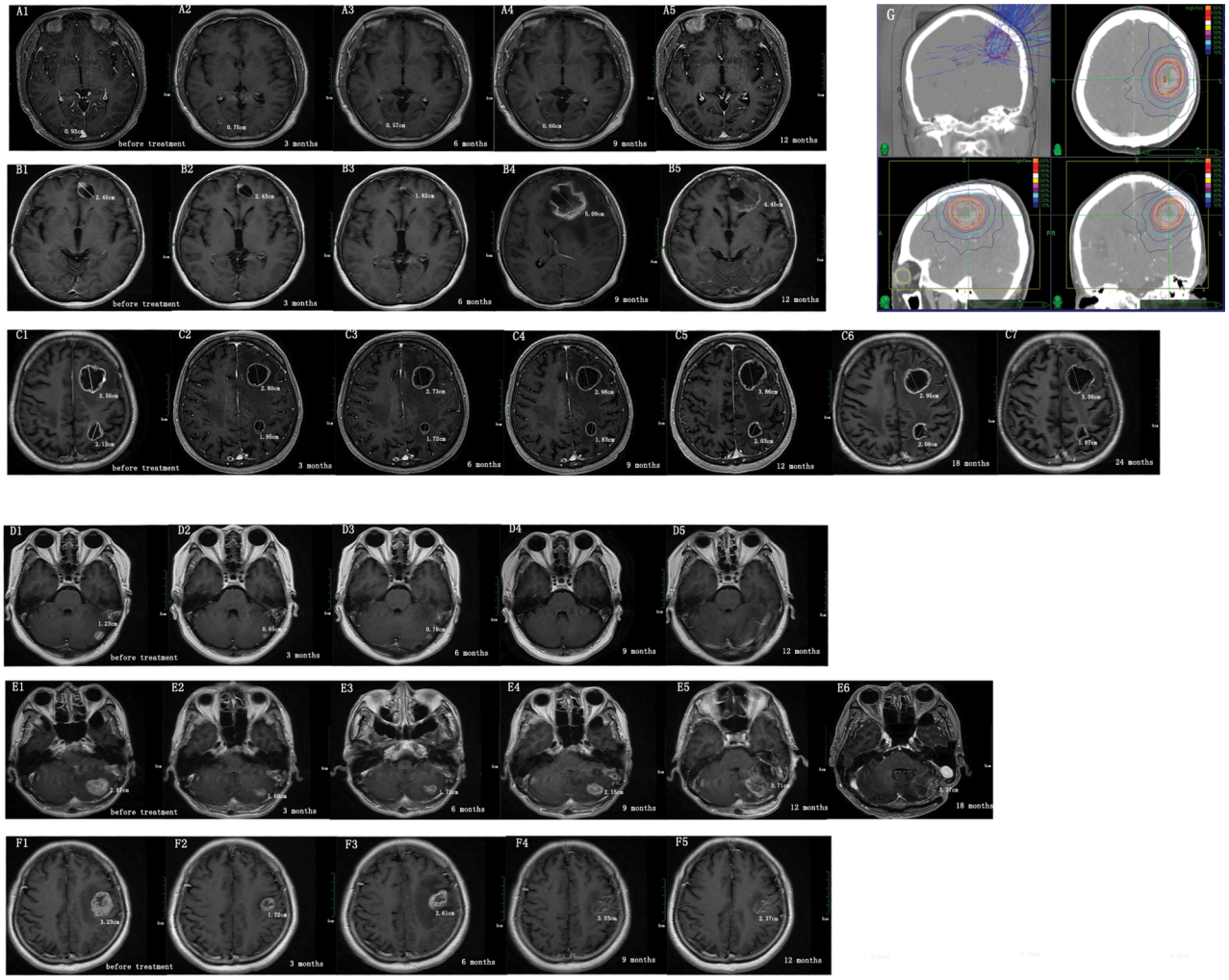

Figure 4 The volume change in patients with cystic and solid brain metastases after CyberKnife treatment.
Notes: We measured the longest diameter of brain metastases at diagnosis (before treatment) and 3, 6, 9, and 12 months after radiosurgery treatment in axial contrast-enhanced T1-weighted magnetic resonance images. **(A–C)** Cystic brain metastases images. (**D–F**) Solid brain metastases images. (**A1, B1, C1, D1, E1, F1)** Brain metastases images before radiosurgery treatment. The change in volume of brain metastases (**A2–A5, B2–B5, C2–C5, D2–D5, E2–E5, F2-F5**) over time. (**A)** A 40-year-old woman with lung cancer received WBRT before radiosurgery treatment. The prescription dose and fraction schedule was 14 Gy/1F. (**B)** A 44-year-old woman with breast cancer, without prior WBRT. The prescription dose and fraction schedule was 30 Gy/3F. (**C)** A 74-year-old man with lung cancer, without prior WBRT. The prescription dose and fraction schedule was 32 Gy/4F. (**D)** A 51-year-old woman with lung cancer, without prior WBRT. The prescription dose and fraction schedule was 20 Gy/1F. (**E)** A 74-year-old man with lung cancer, without prior WBRT. The prescription dose and fraction schedule was 30 Gy/2F. (**F)** A 65-year-old woman with endometrial cancer, without prior WBRT. The prescription dose and fraction schedule was 30 Gy/3F. (**G)** Typical dose distribution images by CyberKnife plans.
Abbreviation: WBRT, whole brain radiotherapy.

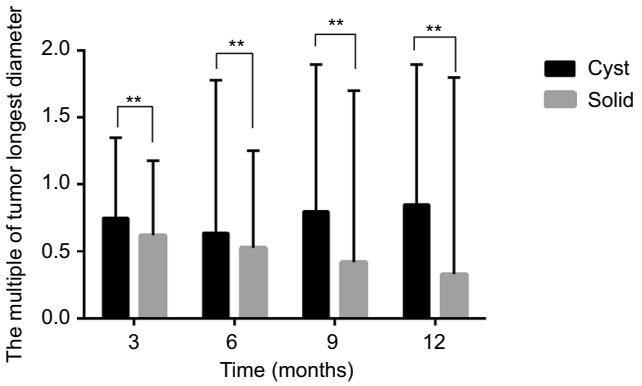

Figure 5 Comparison of volume change between patients with cystic and solid brain metastases after CyberKnife treatment.

have shorter survival time than the patients with solid brain metastases.[18] Apparently, as we have known, our study is the first to compare the prognosis between cystic and solid brain metastases and assess the risk factors for BMOS in patients who had received radiosurgery treatment.

The formation mechanism of cystic brain metastases remains poorly understood; many researchers have come up with hypotheses to explain this phenomenon. A study from the United States proposed that the breakdown of the blood–brain barrier, which could probably cause accumulation of fluids, was the cause of cystic masses.[19] Another study assumed that the primary cancer with abundant mucus

Table 4 Prognostic factors for overall survival after brain metastases in all patients

Characteristics	Univariate analysis		Multivariate analysis		
	X^2	*P*-value	HR	95% CI	*P*-value
Age (years)					
<65	4.602	0.032			
≥65					
Sex					
Male	0.04	0.841			
Female					
ECOG					
0	12.347	0.002			
1					
≥2					
RPA classification					
1	14.645	0.001	1		0.006
2			1.646	1.164–2.329	0.005
3			2.441	1.232–4.835	0.011
Primary tumor					
Lung	28.581	0.000	1		0.001
Breast			1.133	0.771–1.665	0.526
Gastrointestinal tract			2.339	1.476–3.706	0.000
Kidney			1.476	0.894–2.437	0.128
Other			0.731	0.456–1.173	0.194
Prior WBRT					
Yes	0.842	0.359			
No					
No. of brain metastases					
1	3.945	0.267			
2					
3					
≥4 lesions					
Neurologic symptoms					
Yes	5.884	0.015			
No					
Cystic brain metastases					
Yes	2.091	0.148			
No					
Extracranial metastases					
Yes	7.669	0.006			
No					
The volume of total BM (cm^3)					
≤8	9.001	0.011	1		0.006
8–27			1.243	0.958–1.613	0.102
>27			2.146	1.314–3.505	0.002
Primary tumor status					
Control	3.046	0.081			
Uncontrol					

Abbreviations: BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; RPA, recursive partitioning analysis; WBRT, whole brain radiotherapy.

had higher risk of developing cystic metastases.[20] Rapid growth could be another possible cause for generating cystic components. One study also showed that patients with poor histological grade had higher risk of developing cystic brain metastases in breast cancer.[18]

In our study, the local control rate was higher than reported data from several studies related to brain metastases (Table 6),[10,15,21–27] which may be caused by the differences in treatments and primary lesions. In our view, different definitions of local failure were also the main factor that

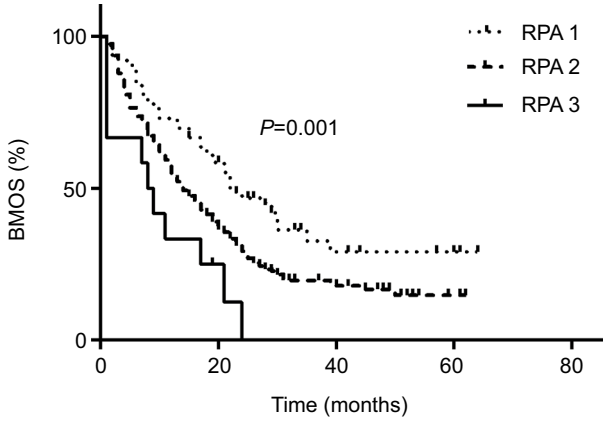

Figure 6 Comparison of survival after brain metastases in patients with different RPA classification.
Abbreviations: BMOS, overall survival after brain metastases; RPA, recursive partitioning analysis.

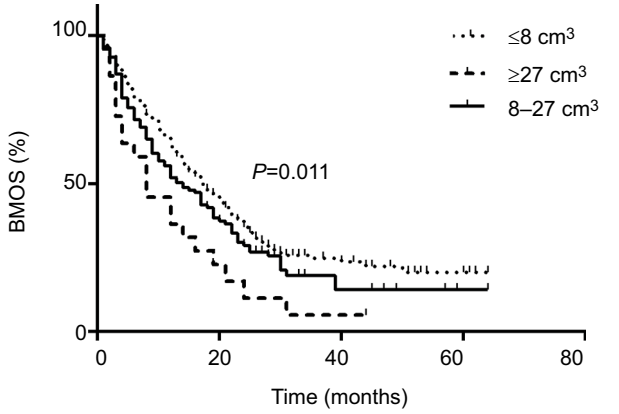

Figure 7 Comparison of survival after brain metastases in patients with different volume of brain metastases.
Abbreviation: BMOS, overall survival after brain metastases.

Table 5 Prognostic factors for overall survival after brain metastases in patients with lung cancer

Characteristics	Univariate analysis		Multivariate analysis		
	X^2	*P*-value	HR	95% CI	*P*-value
Age (years)					
<65	2.397	0.122			
≥65					
Sex					
Male	0.017	0.896			
Female					
ECOG					
0	3.529	0.171			
1					
≥2					
RPA classification					
1	6.557	0.038			
2					
3					
Prior WBRT	0.044	0.834			
Yes					
No					
No. of brain metastases	3.356	0.340			
1					
2					
3					
≥4					
Neurologic symptoms	0.389	0.533			
Yes					
No					
Cystic brain metastases	1.33	0.249			
Yes					
No					
Extracranial metastases					
Yes	3.875	0.049			
No					
The volume of total BM (cm^3)					
≤8	10.937	0.004	1		0.001
8–27			1.108	0.802–1.532	0.533
>27			3.637	1.879–7.038	0.000
Primary tumor status					
Control	5.500	0.019	1		0.003
Uncontrol			1.679	1.186–2.378	

Abbreviations: BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; RPA, recursive partitioning analysis; WBRT, whole brain radiotherapy.

Table 6 Summary of studies of patients with brain metastases who underwent radiotherapy (stereotactic radiosurgery)

Author and publication year	Primary tumor and characteristic of brain metastases	No. of patients	Treatment	Median survival time (months)	Local control
Gerosa et al. (2002)[21]	Multiple primary tumor	804	GK	13.5	1 year: 94%
Pan et al. (2005)[15]	Lung cancer	191	GK	GK alone: 15; WBRT + GK: 14	84.4% (<0.5 cm^3); 94% (0.5–2 cm^3); 89.1% (2–4 cm^3); 93.4% (4–8 cm^3); 85.7% (8–14 cm^3; 87.5% (>14 cm^3)
Franzin et al. (2008)[22]	Multiple primary tumor	30	GK	15	91.3%
Park et al. (2009)[23]	Multiple primary tumor (cystic BM)	24	GK	17.8	79.2%
Fahed et al. (2014)[24]	NSCLC	89	GK	24	1 year: 91.5 2 years: 85.5%
Keisuke et al. (2015)[10]	NSCLC: 64 SCLC: 3	67	CK	13.1	1 year: 83.3% 2 years: 78.5%
Sang et al. (2016)[24]	Multiple primary tumor (cystic BM)	28	GK	17.7	1 year: 82.3%
Wang et al. (2016)[26]	Multiple primary tumor (cystic BM)	48	GK	19.5	91.7%
Antonio et al. (2016)[27]	Multiple primary tumor	223	CK	11	1 year: 85%

Abbreviations: BM, brain metastases; CK, CyberKnife; GK, Gamma Knife; NSCLC, non-small-cell lung cancer; SCLC, small cell lung cancer; WBRT, whole brain radiotherapy.

resulted in different outcomes. Many authors defined local tumor control only according to tumor volume change.[25] But sometimes, it is difficult to identify tumor progression and necrosis after treatment. Especially, tumor progression and necrosis could both cause peritumoral edema. All patients in our study would be advised further magnetic resonance spectroscopy screening and treatment for relieving the cerebral edema once they developed enlarged, inconclusive brain lesions. The results showed that most of them were necrosis caused by radiation treatment and the lesions would gradually shrink with symptomatic treatment. Traditional treatments for necrosis include corticosteroids, mannitol agents, anticoagulants, and so on. In recent years, endothelial cell dysfunction followed by production of vascular endothelial growth factor has been proved to play an important role in necrosis after irradiation. Some relevant researches, which included randomized controlled trials indicated that bevacizumab could offer improved symptomatic relief, especially for patients with poor response to other treatments.[28–30]

There is no difference in survival time and volume between patients with cystic and solid brain tumor; however, we discovered that the volume of cystic brain metastases decreased more slowly than solid brain metastases. We also found that large volume was an independent risk factor for prognosis. Another study, which included 290 breast cancer cases got different results in that patients with cystic brain metastases had poorer survival time ($P<0.001$) and heavier tumor burden ($P=0.005$).[18] The difference indicated that the volume of tumor was real risk factor for prognosis and patients with cystic tumor had poorer BMOS just because of its larger volume. Especially, there was also no significant difference between different proportions of cystic components in prognosis (50%–75% contrast with 75%–100%; $P=0.9358$) in our analysis. Other studies that have got the similar conclusions offer strong support for our hypothesis.[31,32] Besides, in our study, patients received different treatment schedule according to the volume and characteristics of tumor, usually more fractions for larger volume. Multifraction SRS could improve tumor hypoxia effectively, which was an important factor for resistance to radiation in cystic brain tumor. It could also explain the reason why cystic metastases responded well to radio surgery similar to solid tumors. Cystic component was absorbed more slowly compared with solid tumor, and it could explain the difference in volume shrink rate. Further prospective study and longer follow-up are necessary to prove the results.

Conclusion

Our study overturned the previous perception that patients with cystic brain metastases had poorer prognosis, and we advise that radiosurgery could be a suitable treatment option for cystic brain metastases. However, the rate and speed of tumor shrinkage was lower in cystic brain metastases after radiotherapy. Patients with larger brain metastases had shorter survival time, regardless of cystic or solid brain metastases. Of course, further prospective randomized trials are needed to prove the results.

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Author contributions

HW and ZYY designed the study. XGW, YCS, and ZYY recruited patients. XYL, XCJ, HW, JSW, YD, ZQW, and FTL were involved in acquisition of data, follow-up, and statistical analysis. HW wrote the paper with ZYY and YHZ. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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