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Stereotactic Radiosurgery Alone for One to Two Brain Metastases from Cancer of Unknown Primary

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Abstract. *Background/Aim: The use of stereotactic radiosurgery (SRS) alone has become popular for treating patients with a limited number of brain metastases. In very few patients, the primary tumor leading to cerebral spread is unknown. This study investigated the role of SRS for this rare situation. Patients and Methods: Eight patients with 1-2 brain metastases from cancer of unknown primary (CUP) received SRS alone (median dose 20 Gy). Five clinical factors were evaluated for association with local control of the irradiated lesions, freedom from new cerebral lesions and survival. Results: Six-month and 12-month survival rates were 63% and 63%, respectively. Improved survival was associated with male gender and only one cerebral lesion. Local control rates at 6 and 12 months were 100%. Six-month rate of freedom from new cerebral lesions was 86%. Conclusion: SRS appeared effective and resulted in promising local control and survival rates in patients with 1-2 brain metastases from CUP.*

Treatment with stereotactic radiosurgery (STS) alone instead of SRS plus whole-brain irradiation for patients with very few brain metastases has become more popular in order to reduce the risk of radiation-related side-effects (1). Randomized studies have shown that the addition of whole-brain irradiation to SRS can reduce the rate of new brain metastases outside the areas treated with SRS. Unfortunately, the addition of whole-brain irradiation also results in significantly higher rates of neuro-cognitive dysfunction (2, 3). However, since new cerebral metastases can also impair the patient's neuro-cognitive function, the most appropriate treatment regimen for those with a very limited number of cerebral lesions is controversial. The most appropriate treatment also depends on the type of primary tumor, its radiosensitivity, the probability of development of multiple cerebral lesions following SRS alone, and the patient's expected survival time (1).

If the primary tumor that metastasized to the brain is unknown, the decision to use SRS alone or a combination of SRS and whole-brain irradiation is even more difficult. Patients with very few brain metastases from a cancer of unknown primary (CUP) are quite rare (4). Many of them have a poor survival prognosis and may not live long enough to experience new brain metastases following SRS alone, or progression of the lesions treated with SRS. Neuro-cognitive deficits caused by whole-brain irradiation can occur within a few months of treatment and may have a negative impact on the patient's quality of life (2, 3). Thus, it appears reasonable to use SRS alone in these patients. However, only very few data are available for this particular situation. Therefore, the present study was performed to investigate the effect of SRS alone for patients with one to two cerebral metastases from cancer of unknown primary.

Patients and Methods

The data of eight patients (Table I) who were treated with SRS alone for one to two brain metastases from CUP were retrospectively analyzed for local control of the irradiated lesions, freedom from new cerebral lesions, and survival. In addition, the potential impact of five clinical factors was investigated. These factors were age (≤61 *vs.* >61 years), gender, number of cerebral lesions (one *vs.* two), presence of extracranial metastasis (no *vs.* yes) and recursive partitioning analysis (RPA) class (1 *vs.* 2) (5). Patients belonging to RPA class 1 had a Karnofsky performance score of ≥70 or more, a controlled primary tumor, no extracranial metastases and were aged 64 years or younger. RPA class 2 patients also had a Karnofsky score of ≥70 but did not have all three other favorable characteristics. Local control of the irradiated lesions, freedom from new cerebral

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Key Words: Cancer of unknown primary, brain metastases, stereotactic radiosurgery, local control, freedom from new cerebral lesions, survival.

Table I. *Clinical factors evaluated for treatment outcomes*.

Factor	Number of patients
Age	
≤61 Years	4
>61 Years	4
Gender	
Female	4
Male	4
Number of cerebral lesions	
1	5
2	3
Extracranial metastasis	
No	4
Yes	4
Recursive partitioning analysis class	
Class 1	3
Class 2	5

Table II. *Analysis of survival*.

Factor	At 6 months	*p*-Value
Age		
≤61 Years	75	0.62
>61 Years	50	
Gender		
Female	25	**0.040**
Male	100	
Number of cerebral lesions		
1	100	**0.040**
2	25	
Extracranial metastasis		
No	60	0.99
Yes	67	
Recursive partitioning analysis class		
Class 1	100	0.13
Class 2	40	
Entire cohort	63	

Bold: Significant values.

lesions and survival were references from the day of SRS and calculated with the Kaplan–Meier method (6). Those clinical factors achieving significance ($p<0.05$) on univariate analysis (log-rank) were subsequently analyzed in a multivariate manner using a Cox regression model.

Results

For the entire cohort, the 6- and 12-month actuarial survival rates were 63% and 63%, respectively (Table II). Median survival time was not reached during the period of follow-up. On univariate analysis, improved survival was associated with male gender ($p=0.040$) and presence of only one cerebral lesion ($p=0.040$). On subsequent Cox regression analysis, a trend was found for both gender ($p=0.096$) and number of cerebral lesions ($p=0.096$).

Recurrence within the irradiated areas of the brain was not observed in any of the patients. Thus, the local control rates were 100% at both 6 and 12 months. New cerebral lesions outside the irradiated areas were observed in two patients after 2, and 7 months, respectively. The rate of freedom from new cerebral lesions at 6 months was 86% (Table III). The corresponding rate at 12 months was not available. However, the rate of freedom from new cerebral lesions at 10 months was 64%. None of the investigated clinical factors reached significance with respect to any association with freedom from new cerebral lesions.

Table III. *Analysis of freedom from new cerebral lesions*.

Factor	At 6 months	*p*-Value
Age		
≤61 Years	100	0.92
>61 Years	75	
Gender		
Female	67	0.25
Male	100	
Number of cerebral lesions		
1	80	0.75
2	100	
Extracranial metastasis		
No	100	0.63
Yes	67	
Recursive partitioning analysis class		
Class 1	100	0.92
Class 2	86	
Entire cohort	86	

Discussion

Brain metastases develop in about one-third of patients with cancer (4). The most common primary tumor types resulting in brain metastases are lung and breast cancer. In a small proportion of patients (fewer than 1%) with cerebral metastases, the primary tumor is unknown (CUP). Although many studies are available regarding the diagnosis, treatment and prognosis of CUP, in general, there is a lack of data regarding CUP associated with brain metastases (7-11). If a patient presents with multiple cerebral lesions, whole-brain irradiation is the standard treatment (1). In the case of very few brain metastases, local therapies are often used. Neurosurgery is usually limited to a single lesion that is accessible and likely to be removed completely. SRS can be used for a single lesion, particularly if it is not suitable for

neurosurgical resection, and also for more than one lesion (1). The diameter of each such lesion should not be more than 3-4 cm (1). Currently, there is controversy regarding whether SRS should be administered alone or in combination with whole-brain irradiation.

Two randomized trials have shown that the addition of whole-brain irradiation to SRS resulted in more pronounced neuro-cognitive deficits (2, 3). The trial of Chang *et al*. was stopped by the Data Monitoring Committee after 58 patients, because there was a probability of 96% that patients receiving SRS plus whole-brain irradiation were significantly more likely to experience a decline in neuro-cognitive function than those receiving SRS alone (52% *versus* 24% at 4 months) (2). In the trial of Brown *et al*., at the 3-month follow-up, there was less decline in neuro-cognitive function following SRS alone than following SRS plus whole-brain irradiation (63.5% *versus* 91.7%, $p<0.001$) (3). Furthermore, the patients' quality of life was better following SRS alone ($p=0.001$).

In another randomized trial, omitting whole-brain irradiation resulted in worse intracerebral control (2, 3, 11). In the trial of Chang *et al*., the 12-month intracerebral control rates were 27% after SRS alone and 73% after SRS plus whole-brain irradiation, respectively ($p<0.001$) (2). In the trial of Brown *et al*., the time to intracranial failure was significantly shorter after SRS alone than after the combined approach ($p<0.001$) (3). In a third randomized trial from Japan, the 12-month intracerebral control rates were 24% and 53%, respectively ($p<0.001$) (11). However, in none of the three trials did the improvement in intracerebral control with whole-brain irradiation lead to better survival (2, 3, 11). Thus, many radiation oncologists do not add whole-brain irradiation to SRS in patients with very few cerebral metastases and adminster SRS alone.

In the present study, the patients received SRS alone for one to two brain metastases from CUP. SRS resulted in excellent local control of the treated lesions; the local control rates at 6 and 12 months were 100% and 100%, respectively. In addition, the results regarding freedom from new cerebral lesions outside the irradiated areas and regarding survival were promising. The 12-month survival rate of 63% was similar to the 57% reported in a previous study of Gamma Knife radiosurgery for brain metastases from CUP (12). In that study, the local control rate was 88.5%, which was slightly lower than in the present series but still promising (12).

In summary, SRS alone showed efficacy with favorable local control and survival rates, and freedom from new brain metastases in patients treated for one to two brain metastases from CUP.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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