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ORIGINAL PAPER

Stereotactic radiosurgery alone for patients with 1–4 radioresistant brain metastases

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Abstract Brain metastases from radioresistant histologies are perceived to be less responsive to WBRT compared to other histologies, and stereotactic radiosurgery (SRS) may provide better local control. The aim of this study was to examine the outcomes of patients with 1–4 brain metastasis from radioresistant histologies (renal cell carcinoma and melanoma) treated with SRS alone. Thirty-eight patients with 1–4 radioresistant brain metastases (66 lesions) were treated with SRS alone. The median age was 55 years. Fourteen and 24 patients had renal cell carcinoma (RCC) and melanoma brain metastases, respectively. Distribution of number of lesions was as follows: one lesion, 22 patients; 2 lesions, 8 patients; 3 lesions, 5 patients; and 4 lesions, 3 patients. Distribution of RTOG recursive partitioning analysis (RPA) classes was as follows: II, 37 patients and III, 1 patient. The median marginal dose was 20 Gy. The median follow-up was 6.1 months. The 3-, 6-, 9-, 12-, and 18-month local control (LC) rates were 87.9, 81.4, 67.9, 67.9, and 60.3%, respectively. The corresponding free-from-distant-brain failure (FFDBF) rates were 71.3, 58.1, 49.8, 40.2, and 27.6%. The corresponding progression-free survival (PFS) rates were 55.3, 41.9, 33, 23.3, and 13.3%. RCC histology was associated with better LC ($P = 0.0055$). Although SRS alone could yield reasonable LC in patients with 1–4 radioresistant brain metastases, the risk of distant brain failure was substantial. The approach of routine omission of WBRT outside of a trial setting should be used judiciously.

Keywords Stereotactic radiosurgery · Radioresistant · Brain metastases

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Introduction

Brain metastasis is the most common intracranial malignancy. Patients with histologies such as renal cell carcinoma (RCC) and melanoma are at risk of developing brain metastasis [1]. Whole brain radiotherapy (WBRT) is an integral part of the treatment for brain metastasis. For patients with a single brain metastasis, addition of surgical resection or stereotactic radiosurgery (SRS) has been demonstrated to confer benefits in terms of local control and overall survival [2, 3]. For patients with 2–4 metastases, addition of SRS has been demonstrated to confer benefits in terms of local control [3, 4].

Brain metastases from radioresistant histologies, such as RCC and melanoma, are perceived to be less responsive to

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WBRT compared to other histologies [5, 6]. Furthermore, long-term survivors of brain metastases are at risk of developing neurocognitive deficits after WBRT [7]. The role of WBRT in the treatment of radioresistant brain metastasis has been questioned. Data from retrospective SRS series of radioresistant brain metastases did not appear to show negative impact on survival with the omission of WBRT [5, 8–15].

The aim of this study was to examine the outcomes of patients with 1–4 brain metastasis from radioresistant histologies (renal cell carcinoma and melanoma) treated with SRS alone.

Methods and materials

Exempt review was granted by our cancer hospital institutional review board for the collection of data for patients with radioresistant brain metastases treated with gamma-knife-based SRS in our department. At our cancer hospital, patients with brain metastasis are evaluated by medical oncology, neuro-oncology, radiation oncology, and neurosurgery, and the treatment recommendations are made by the team. In the period from 2000 to 2007, a total of 97 patients with radioresistant brain metastases were treated with SRS. Patient clinical data, tumor volumetric data, and treatment details were retrospectively entered into a database. All the patient identifiers were removed, and each patient was assigned a number. Out of the 97 patients, 38 patients (20 men and 18 women) with newly diagnosed 1–4 radioresistant brain metastases (66 lesions) were treated with SRS alone. The median age was 55 years (range, 27–81 years). Fourteen and 24 patients had RCC and melanoma brain metastases, respectively. Ten of the 14 patients with renal cell carcinoma also received sunitinib (Sutent) before or after SRS for their extracranial systemic disease. Distribution of number of lesions was as follows: one lesion, 22 patients; 2 lesions, 8 patients; 3 lesions, 5 patients; and 4 lesions, 3 patients. Distribution of Radiation Therapy and Oncology Group (RTOG) recursive partitioning analysis (RPA) classes (RPA class I, KPS $\geq$ 70, $<$ 65 years of age with controlled primary, and no extracranial metastases; RPA class III, KPS $<$ 70; and RPA class II, remaining populace) was as follows: II, 37 patients and III, 1 patient. Out of 38 patients, 4 had stable extracranial disease. Table 1 summarizes the characteristics of the 38 patients.

SRS was carried out on the Leksell ^{60}Co Gamma Knife for all patients (Elekta AB, Stockholm, Sweden). Before June 2006, a B-model was used; starting from June 2006, a 4C-model equipped with automatic positioning system was used. To be eligible for gamma-knife-based SRS, the size of any individual lesion could not exceed 4 cm in maximum diameter based on the most recent diagnostic brain MRI. On the day of the procedure, a Leksell Model-G stereotactic head frame was fixed to the patient with local anesthesia of the pin sites. A thin-cut (1.2- to 1.5-mm slices) multi-planar, gadolinium (double-contrast)-enhanced MRI was performed for target delineation. A spoiled gradient recalled acquisition (SPGR) sequence was typically used for treatment planning. Every stereotactic double contrast MRI study was reviewed by a neurosurgeon, a radiation oncologist, and a neuro-radiologist to confirm the number of metastasis prior to treatment planning. The target was delineated in three dimensions in the treatment planning software provided by Leksell ^{60}Co Gamma Knife (Elekta AB, Stockholm, Sweden).

Table 1 Patient characteristics ($n = 38$)

Mean age (range)	55 (27–81)
Gender (%)	
Male	20 (53)
Female	18 (47)
Primary cancer, no. (%)	
Melanoma	24 (63)
Renal cell carcinoma	14 (37)
Median KPS (range)	90 (60–100)
RPA class no. (%)	
II	37 (97)
III	1 (3)
Extracranial disease status (%)	
Stable	4 (11)
Progressing	34 (89)
Mean target volume, ml (range)	4.4 (0.054–17.3)
Mean prescription dose, Gy (range)	19 (15–22)

The combined target volume ranged from 0.054 to 15.9 cm^3. The prescribed SRS dose was determined by the tumor size, shape, and location. The dose ranged from 15 to 22 Gy (median 20 Gy) delivered to the 50% isodose line in a single session.

Follow-up

After SRS, a brain MRI was performed at 3- to 4-month intervals for follow-up, and a SPGR sequence was routinely included. Patients were typically evaluated clinically by radiation oncology, neuro-oncology, or medical oncology at follow-up intervals of 2–3 months or less. For patients who received chemotherapy or systemic therapy after SRS, they were followed by medical oncology at much shorter intervals. Any significant increase in the size of a treated lesion was coded as a local recurrence.

Endpoints and statistical analysis

The endpoints included overall survival (OS), progression-free survival (PFS), local control (LC), and free-from-distant-brain recurrence (FFDBR). OS was defined as survival regardless of the intracranial disease status; PFS was defined as survival without evidence of intracranial failure; LC was defined as absence of evidence of local tumor progression; FFDBR was defined as absence of evidence of distant recurrence of brain metastasis.

StatView software (SAS Institute, Inc, Cary, NC) was used for statistical analysis. Kaplan–Meier analysis was used to calculate OS, PFS, LC, and FFDBR rates. Crude rates were used to calculate the response and distant brain failure rates.

Results

Survival

At follow-up intervals ranging from 6.1 to 30.9 months (median 6.1 months), 9 patients were alive (4 without intracranial progression) and 29 patients had died. The median OS was 6.5 months. The 3-, 6-, 9-, 12-, and 18-month OS rates after SRS were 78.9, 54.5, 45.5, 36.2, and 24.1%, respectively (Fig. 1). The 3-, 6-, 9-, 12-, and 18-month PFS rates were 55.3, 41.9, 33, 23.3, and 13.3%, respectively. Table 2 shows the univariate analysis of various prognostic factors.

Local control

The 3-, 6-, 9-, 12-, and 18-month LC rates were 87.9, 81.4, 67.9, 67.9, and 60.3%, respectively (Fig. 2). The median local control was not reached. Twenty-one (95.5%) of 22 RCC brain metastases and 29 (65.9%) of 44 melanoma brain metastases achieved local control. Patients with RCC had superior local control on Kaplan–Meier analysis ($P = 0.006$) (Fig. 3).

Free-from-distant-brain failure

Twenty (58%) of the 38 patients developed distant brain failure; 7 (50%) of the 14 patients with RCC brain metastasis and 15 (62.5%) of the 24 patients with melanoma developed distant brain recurrence. The 3-, 6-, 9-, 12-, and 18-month free-from-distant-brain recurrence (FFDBR) rates were 71.3, 58.1, 49.8, 40.2, and 27.6%, respectively (Fig. 4). The median FFDBF was 10.4 months. Neither number of metastasis (1 vs. 2–4), histology (RCC vs. melanoma), nor extracranial disease status predicted FFDBR (P values were 0.30, 0.54, and 0.36, respectively, by log-rank test).

Salvage treatment

Twenty-six patients developed intracranial failure (local and/or distant brain), and all of them also had concurrent

Table 2 Univariate analysis of prognostic factors for overall survival (OS) and progression-free survival (PFS)

	OS[a]	PFS[a]
Number of lesions: 1 vs. 2–4	$P = 0.85$	$P = 0.87$
Histology: Renal cell carcinoma vs. melanoma	$P = 0.70$	$P = 0.49$
Extracranial disease: Controlled vs. progressive	$P = 0.27$	$P = 0.29$
Age: <65 years vs. ≥65 years	$P = 0.57$	$P = 0.4$

[a] Logrank test

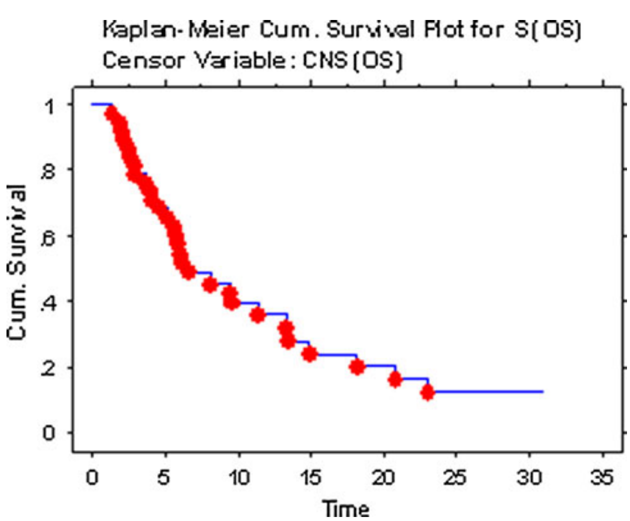

Fig. 1 Kaplan–Meier curve for overall survival (time in months)

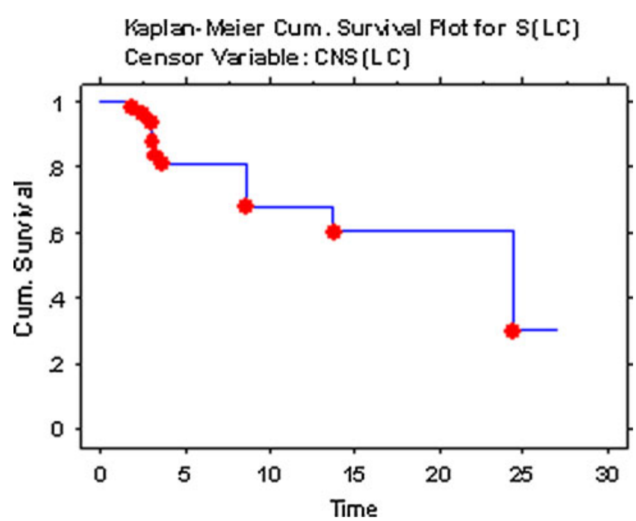

Fig. 2 Kaplan–Meier curve for local control (time in months)

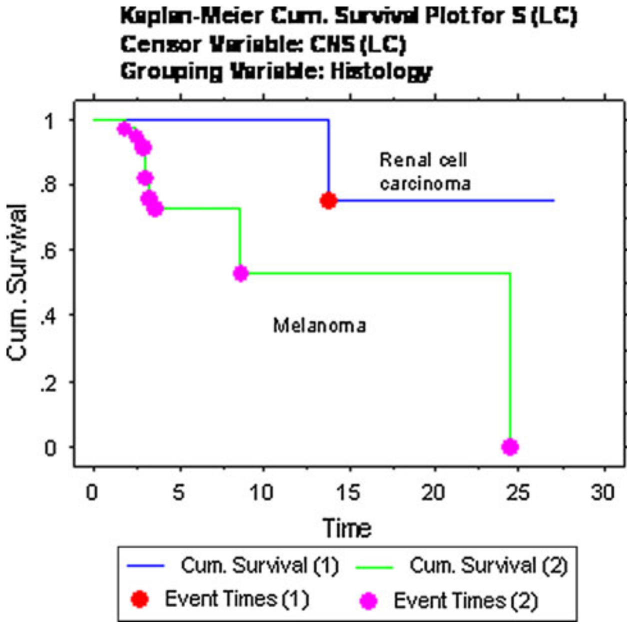

Fig. 3 Kaplan–Meier curve for local control renal cell carcinoma vs. melanoma (time in months)

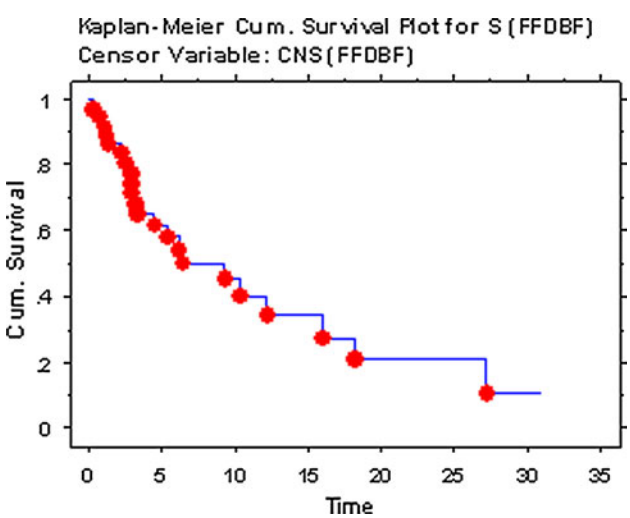

Fig. 4 Kaplan–Meier curve for free-from-distant-brain failure (time in months)

systemic disease progression. Seven (18.4%) of them received further SRS. Most other patients received WBRT with or without chemotherapy (temozolomide for patients with melanoma) as salvage therapy.

Toxicities

Four patients had worsening of neurologic symptoms within 6 months after SRS, but none of them were related to SRS. Those symptoms were determined to be caused by disease progression or other cancer treatments. None of the 38 patients developed any late complications, and this may be related to the fact that the follow-up intervals of this cohort of patients were relatively short.

Discussion

SRS involves the delivery of a single high dose of radiation to a target volume with a very steep radiation dose radian beyond the target. SRS has the advantage of being able to treat surgically inaccessible lesions and multiple lesions with greater ease. Data from retrospective studies and randomized trials had demonstrated that local tumor control was improved with the addition of SRS to WBRT [3–5]. In a large randomized trial coordinated by RTOG where 333 patients with 1–3 brain metastases were randomized into receiving WBRT alone or WBRT + SRS, a survival benefit was demonstrated for patients with single brain metastasis, and improved Karnofsky functional score was observed across all patients in the WBRT + SRS group [3]. The response rates and local control of the treated lesions were also improved with the addition of SRS to WBRT.

Controversies arise as to whether upfront WBRT is necessary in patients with one to three/four brain metastases, especially in the patients with radioresistant histologies. WBRT is theoretically beneficial because it addresses potential microscopic disease in distant sites in the brain. However, WBRT also has long-term impact on neurocognitive function [7]. The best supporting evidence should come from a prospective phase III randomized trial. Attempts have been made to address this research question. However, the progress has been slow. Aoyama et al. [16] from Japan reported the results of the first randomized trial addressing this issue. Patients with 1–4 brain metastases were randomized into SRS alone and a combination of WBRT + SRS. The addition of WBRT decreased the risk of local and distant brain failure [16]. However, the rate of neurologic death did not increase in patients who did not receive WBRT. There was also no difference in the systemic and neurologic function of preservation or treatment toxicity regardless of whether WBRT was given or not [16]. This may be related to the fact that 92% of patients enrolled in the trial had at least one post-SRS MRI, which would be able to detect any asymptomatic intracranial recurrence early such that salvage treatment to prevent neurologic deterioration can be offered. In a separate analysis, the neurocognitive function of 110 out of 132 patients enrolled in the trial was evaluated using mini-mental state examination (MMSE). Their findings suggested that intracranial tumor control was the most important factor for a stable neurocognitive function, but the long-term negative effect on neurocognitive function from WBRT was not negligible [17]. In a phase III randomized trial of SRS alone versus

SRS combined with WBRT conducted at MD Anderson Cancer Center, patients randomized to receive WBRT had improved local control and distant brain control at the expense of a higher probability of neurocognitive decline (52 vs. 24% in patients who only received SRS based on Hopkins verbal learning tests) [18]. The finding of this data suggested that the post-treatment decline in learning and memory was more likely due to the effects of WBRT rather than intracranial tumor progression. In a European Organisation for Research and Treatment of Cancer (EORTC) phase III randomized trial comparing adjuvant whole brain radiotherapy (WBRT) and observation after local treatment (surgery or radiosurgery) for brain metastases, 359 patients were enrolled. WBRT reduced the rates of intracranial relapses (31.4 vs. 54% at 24 months) and neurologic deaths (25 vs. 42%) but did not prolong the time period of functional independence (9.8 months for both arms) and overall survival time (10.9 months for both arms) [19]. Results from these 3 trials have consistently demonstrated that WBRT improved intracranial tumor control but had no impact on overall survival. Brain metastasis and extracranial disease represent competing risks, and overall survival can be affected by either one or both of them.

In all those studies mentioned above, various different histologies, including radioresistant histologies, were included [16, 19]. It is unclear whether the conclusion drawn from those studies would apply to radioresistant brain metastasis. Based on the data from retrospective series from the literature, the addition of WBRT did not consistently confer benefit in terms of LC, FFDBR, and OS for radioresistant histologies [5, 8–15]. In a phase II trial of SRS for 1–3 newly diagnosed brain metastases from radioresistant histologies, 36 patients were enrolled and 31 were eligible for analysis. The median follow-up was 32.7 months. The 3- and 6-month intracranial failure rate with SRS alone was 25.8 and 48.3%, respectively [20]. Corresponding in-field and distant intracranial failure rates were 19.3 and 32.2%, and 16.2 and 32.2%, respectively. Neurologic deaths occurred in 38% of the patients [20]. The median mental state examination scores did not vary significantly after SRS.

In our series, the 3- and 6-month in-field failure rates were 12.1 and 18.6%, respectively; the corresponding distant intracranial failure rates were 28.7 and 41.9%, respectively. At 12 and 18 months, only 40.2 and 27.6% of patients remained free from distant brain failure. The higher rate of distant intracranial failure rates may be related to the high percentage of patients (34 out of 38 patients) in this series with uncontrolled extracranial disease, which provided a source of reseeding of the tumor cells in the brain. The patients in this series were being followed very closely with serial clinical examination and diagnostic MRI with a SPGR sequence, and nearly all cases of intracranial progression were detected on the diagnostic MRI without associated neurologic symptoms. All 26 patients with intracranial failure also had concurrent systemic progression, and as a result, it is difficult to determine the exact cause of death (neurologic vs. nonneurologic vs. combined) in those patients. In this study, patients with RCC had much better local control compared to those with melanoma. Of note, ten of 14 patients with RCC also received sunitinib before or after SRS. Intracranial tumor response to sunitinib has been observed [21], and it is unclear whether this has contributed to the better local control for patients with RCC in this study.

In the determination of best treatment option for patients with one to three/four radioresistant brain metastases, the risks are to be balanced against the benefits, and it is crucial to involve the patient in treatment decision. SRS alone provides the benefit of normal brain parenchyma sparing, and it also renders future salvage of intracranial failure with WBRT possible. However, omission of WBRT may result in a significantly increased risk of intracranial progression, which, if detected early, may not impact negatively on neurocognitive function or overall survival. Until there is a randomized trial comparing SRS and SRS + WBRT for patients with 1–3 or 1–4 radioresistant brain metastases, the approach of routine omission of WBRT should be used judiciously.

Conclusion

In summary, based on the data from the medical literature and our study, SRS alone for patients with 1–4 radioresistant brain metastases results in reasonable local tumor control, but the risk of distant brain failure is substantial. The approach of routine omission of WBRT outside of a trial setting should be used judiciously.

Conflict of interest Actual or potential conflicts of interest do not exist for the authors.

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