

# Hypofractionated Stereotactic Radiotherapy and Radiosurgery for the Treatment of Patients with Radioresistant Brain Metastases

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**Abstract.** Aim: To evaluate the efficacy of different radiotherapy treatment modalities in radioresistant brain metastasis. Patients and Methods: A retrospective analysis was conducted on 78 patients with brain metastases from melanoma, sarcoma, or renal cell carcinoma primary tumours who underwent radiosurgery (20 Gy) and/or hypofractionated stereotactic radiotherapy (6×4 Gy or 7×4 Gy) with or without whole-brain radiotherapy at our Center. Results: The actuarial median survival times for melanoma, renal cell carcinoma and sarcoma were 23, 22 and 7 months respectively, with a significant correlation to recursive partitioning analysis class. Discussion: Our results show that these treatments were effective both in symptom palliation and in improving survival, suggesting that although outcomes generally remained poor in this study population, it is possible and important to control intracranial brain metastases.

Brain metastases are a common problem in clinical oncology today since they occur in 15% -30% of cancer patients during the course of their disease (1) and have a negative impact on the quality of life. Indeed a combination of a growing elderly population and better treatment modalities to achieve systemic control has led to

a higher number of elderly patients with a prolonged disease course and subsequently to an increased incidence of brain metastasis.

The median survival of patients with multiple lesions treated with supportive therapies is 1 to 2 months; this can be increased to 3 to 6 months with conventional whole-brain radiation therapy (WBRT). For lesions smaller than 3 cm in diameter, radiosurgery (RS) improves the long-term performance status and can prolong survival (2-4). Indeed, this procedure has had an increasing role in the primary management of patients with brain metastases given its relatively non invasive nature. Hypofractionated stereotactic radiotherapy (HSR) is an effective and safe treatment for brain metastases greater than 3 cm, not amenable to single high-dose RS (5, 6).

Patients with brain metastases from ‘radioresistant’ tumors (*i.e.* sarcoma, metastatic melanoma, renal cell carcinoma) have a poor prognosis. For this selected group of patients, an aggressive management should be considered to achieve both symptom palliation and disease control (prolongation of life). However, it is not clear what the optimal strategies for these typologies of patients are.

Therefore, we conducted a retrospective study on 78 patients with brain metastases from sarcoma, melanoma, or renal cell carcinoma primary tumors who underwent RS and/or HSR with or without WBRT at our Center to evaluate the efficacy of different treatment modalities according to recursive partitioning analysis (RPA) classes (7).

## Patients and Methods

**Patients and treatment characteristics.** Between January 2004 and December 2007, 78 patients with brain metastases from sarcoma, melanoma, or renal cell carcinoma primary tumors underwent brain HSR (6×4 Gy or 7×4 Gy) or RS (20 Gy) with or without WBRT.

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Table I. RPA class definitions. KPS, Karnofsky performance status.

	Recursive partitioning analysis for brain metastases		
	Class 1	Class 2	Class 3
KPS	≥70	≥70	<70
Primary status	controlled	uncontrolled	
Age (years)	<65	≥65	
Extracranial disease status	Brain only	Brain plus other sites	

Patients were assigned to an RPA class based on characteristics at the time of the treatment. These classes, developed by the Radiation Therapy Oncology Group (RTOG), are based on Karnofsky performance status (KPS), primary tumor status, presence of extracranial metastases, and age of the patients (7). Briefly, class I grouped patients with Karnofsky performance status (KPS) ≥70, less than 65 years of age with controlled primary and no extracranial metastases; class III comprised patients with KPS <70; whereas all other patients were classified as RPA class II (Table I).

**Treatment planning and delivery.** All patients were immobilised in a tight thermoplastic stereotactic head mask and underwent contrast-enhanced computed tomographic (CT) imaging using a slide thickness of 3 mm through the entire brain. Targets were defined according to ICRU-50 definitions (8). The gross tumor volume (GTV) consisted of the evident, contrast-enhancing, gross disease, eventually defined also by image fusion with other diagnostic modalities. The clinical target volume (CTV) was considered equivalent to the GTV with no additional margin for potential microscopic extension. The planning target volume (PTV) provided an additional margin of 4 mm in all directions to account for relocatable frame inaccuracies. Treatment planning was performed using ERGO 3D line system (Elekta) with four to six non coplanar arcs technique. The dose was prescribed to the 80% isodose line or higher. Patients were treated with 6 MeV photons using a modified linac-based stereotactic system (Varian, Palo Alto, CA, USA).

**Follow-up.** Follow-up based on magnetic resonance imaging (MRI) was the preferred modality and was used for all patients in the study. Follow up imaging was routinely carried out 1-2 months after radiotherapy. Thereafter, follow-up was performed every 2 to 3 months, or sooner if indicated.

Survival time was calculated from the date of the patient's first radiotherapy until death or until the latest follow-up. The cause of death was classified as due to systemic progression of the disease with local control, or to local progression of the disease, or both. Local tumor progression was radiographically documented as an increase of at least 25% in largest tumor diameter or evidence of new disease within 2 cm of the prescription isodose volume. In the setting of multiple metastases, the patient response was correlated with the last responsive lesion.

Patients were also clinically followed up with a multidisciplinary team (neurologists and radiotherapists) by neurological examinations. Development of neurological deficit was defined by a change in neurological status including decrease in strength, degradation in ambulatory function, development of aphasia or changes in vision or sensation, or alteration in mental status.

Table II. Patient characteristics.

Characteristic	No.	%
Age (years)		
21-30	5	6.4
31-40	7	9
41-50	14	18
51-60	16	20.5
61-70	23	29.5
71-80	13	16.6
Gender		
Male	55	70.5
Female	23	29.5
RPA class		
I	11	14.1
II	53	68
III	14	18
Histology		
Melanoma	51	65.4
Renal cell	24	30.8
Sarcoma	3	3.8
Number of lesions		
1	50	64.1
2	21	26.9
3	7	9
Target volume (cm <sup>3</sup> )		
Range	0.1-28.2	
median	3.3	
Neurological signs and symptoms		
None or minor symptoms	52	66.6%
Motor	10	12.8%
Sensory	8	10.3%
Seizures	8	10.3%

**Statistical analysis.** Kaplan-Meier actuarial survival curves and log-rank *p*-values were generated from the time of brain metastasis radiotherapy to the time of death or last follow-up. Survival curves were also generated for the patients within each of the three RPA classes and histological diagnoses.

## Results

**Patients and treatment characteristics.** Patient characteristics are summarized in Table II. Seventy-eight patients with a total number of 113 brain metastases from sarcoma (3.8%), melanoma (65.4%), or renal cell carcinoma (30.8%) were treated with HSR or RS at our institution. The median age was 57 years (mean 55.7 years). The median volume of the individual metastases was 3.3 cm<sup>3</sup>.

Treatment characteristics of the study population are summarized in Figure 1. Initial RS was used in 65 patients. In 4 patients, WBRT was used as salvage treatment after progression of local disease (evidence of new lesions), whereas 4 patients who were previously treated with WBRT underwent RS for local recurrence.

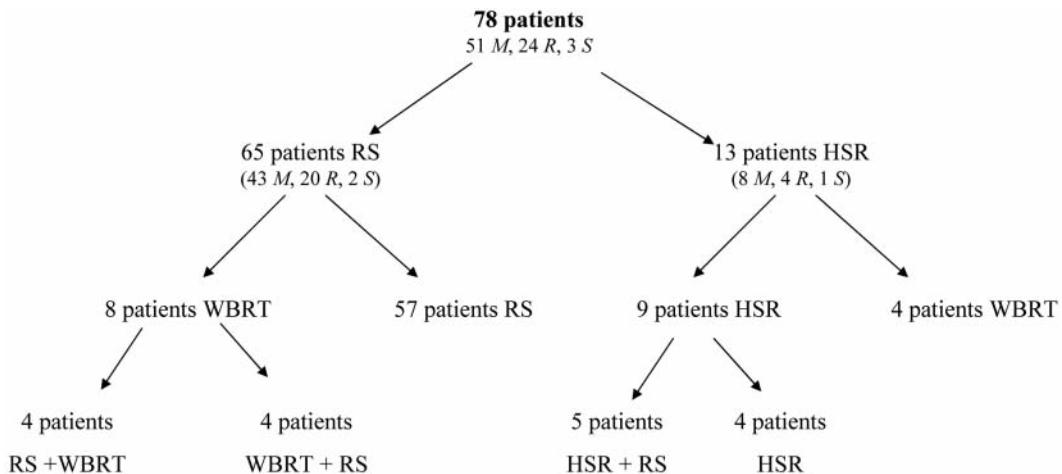


Figure 1. Patient distribution in this study. WBRT, Whole brain radiotherapy; RS, radiosurgery; HSR, hypofractionated stereotactic radiotherapy; M, melanoma; R, renal cell carcinoma; S, sarcoma.

Thirteen patients were treated with HSR and 5 of them were also treated with RS during the course of treatment. Another 4 patients received WBRT as complementary treatment.

The majority of patients (76.9%) had no or only minor neurological symptoms at the time of brain metastasis diagnosis, whereas 12.8% and 10.3% presented motor or sensory signs respectively.

**Survival and local control.** No patient was lost to follow-up. Fifty-six patients had died by the time of analysis. The median follow-up duration in the 22 surviving patients was 13 months, with a range from 6 to 25 months. The actuarial median survival time from radiotherapy was 14 months (Figure 2). The actuarial median survival time for RPA class I, II and III were 35, 14 and 3 months respectively (Figure 3). The actuarial median survival times for melanoma, renal cell carcinoma and sarcoma were 23, 22 and 7 months respectively.

Patient and tumor factors were tested for their significance in survival and local control. The only significant influencing factor on survival was RPA class ( $p<0.001$ ). A trend ( $p=0.11$ ) toward improved median local control was observed in patients with renal cell carcinoma (20 months) compared with patients affected by primary melanoma (14 months) (Figure 5), whereas primary histological diagnosis was not significantly associated with survival time (Figure 4).

The crude rate of local tumor control was 69% (the cause of death was failure only in the brain in 24 out of 78 patients, median follow-up 11 months). None of the patients received chemotherapy due to brain failure.

**Quality of life.** During the 6 months of follow-up, the majority of the patients reported improvement in a number of neurological symptoms including headache (69%), visual

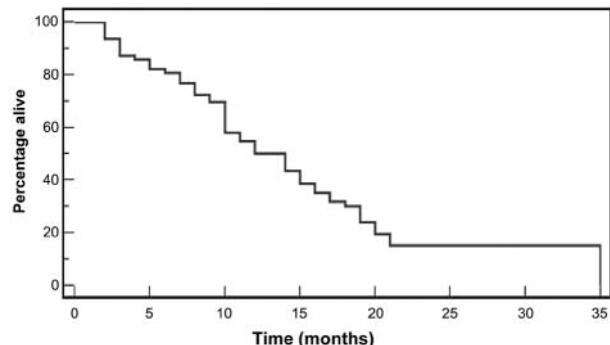


Figure 2. Kaplan-Meier survival curve from the time of the first radiotherapy treatment for brain metastasis.

disturbance (8%), motor loss (12%) and seizure (8%) (Table III). Thus, this analysis highlighted that the treatment was effective both in symptom palliation and in improving survival.

## Discussion

The development of brain metastases represents a critical point along the clinical natural history of melanoma, kidney cancer and sarcoma. In particular, melanoma ranks third in the incidence of brain metastases, after lung and breast cancer; up to 75% of all stage IV melanoma patients develop brain lesions, which are frequently hemorrhagic, with a predilection for the cerebral hemispheres. Moreover, in one-fifth of patients, the brain represents the initial relapse site of metastasis or, alternatively, the most frequent site of recurrence, after a first-line chemo/biochemotherapy for metastatic disease, even in responsive patients.

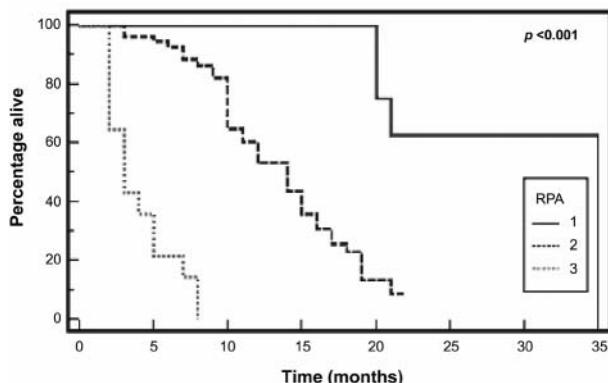


Figure 3. Kaplan-Meier survival curve for each recursive partitioning analysis (RPA) class from the time of the first radiotherapy treatment for brain metastases.

Table III. Measurements of neurological signs and symptoms at 6 months' follow-up ( $n=64$  patients).

	Improved	Worsened	Unchanged	Not present
Headache	44	1	2	17
Visual disturbance	5	0	1	58
Motor loss	8	1	1	54
Seizure	5	0	0	59

There are different options for treating brain metastases: WBRT, stereotactic radiotherapy, RS or surgery. In this paper, we focused our attention on radioresistant brain metastases treated with RS or hypofractionated radiotherapy with or without WBRT.

The only significant influencing factor on survival was RPA class ( $p<0.001$ ); in accordance with other papers (5, 9-11), this supports the use of RPA grouping in an attempt to predict the survival probabilities in patients with brain metastases and would facilitate decision making on individually tailored treatment.

In different studies of HSR (10, 12-14), local control and median survival (5) time are similar to RS data.

In our experience, HSR is used for large volume metastases or those located in critical brain regions, so as to avoid damage to normal brain tissue.

A trend toward improved median local control was observed in patients with renal cell carcinoma (20 months) compared to patients affected by primary melanoma (14 months). This result, as underlined by Chang *et al.* (15) in their large series of radioresistant metastases, confirms that melanoma brain metastases are difficult to treat using RS alone and probably should be treated with combined therapies including chemotherapy or novel agents to improve the effectiveness of radiotherapy.

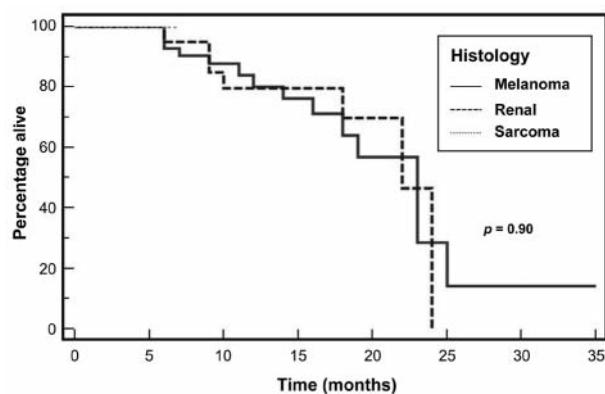


Figure 4. Kaplan-Meier survival curve for each of the three histological diagnoses.

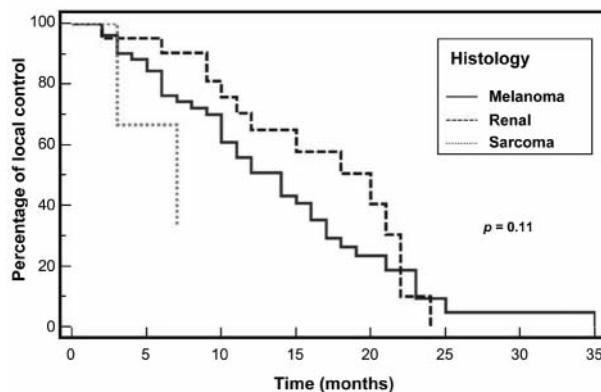


Figure 5. Kaplan-Meier local control curve for each of the three histological diagnoses.

In accordance with other authors, our results have shown that the majority of patients with controlled intracranial disease will die from systemic disease progression rather than from central nervous system progression or recurrence. Therefore, the current availability of chemotherapeutic agents able to cross the blood-brain barrier, especially in the case of melanoma, is particularly important (16). The use of temozolamide or fotemustine in association with brain RT seems to improve the results of the single approaches. While temozolamide showed radiosensitizing properties (17), fotemustine when combined with WBRT in a phase III trial induced a significant advantage over fotemustine alone in terms of time to objective cerebral progression (80 versus 49 days), using the Wilcoxon test ( $p=0.028$ ) (18).

Obviously, these data need to be confirmed in larger clinical trials, but by themselves indicate a clear trend in favour of the RT-chemotherapy approach in treating brain metastases from melanoma. Even testing a combination

with biological therapies, concurrently or sequentially, is going to represent an interesting challenge for future clinical trials.

Sneed and colleagues (19) compared survival probabilities of patients with newly diagnosed brain metastases managed initially with non-fractionated RS alone or combined with WBRT. In this study, with adjustment by RPA class, there was no survival benefit using up-front WBRT. Moreover, Aoyama and co-workers (12) did not find differences in survival for patients with 1 to 4 metastases comparing RS alone with RS plus WBRT.

The absence of survival benefit and the fact that whether WBRT causes neurological deficit is still controversial may support the omission of WBRT at the time of RS in those patients with single or few brain metastases.

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