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## Original Paper

# Radiosurgery without Whole Brain Radiotherapy in Melanoma Brain Metastases

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**To evaluate the effectiveness of radiosurgery without whole brain radiotherapy in the palliative treatment of melanoma brain metastases, we retrospectively assessed the results in 35 patients: 4 with a solitary brain metastasis, 13 with a single brain metastasis and metastases elsewhere and 18 with multiple brain metastases. The local control rate was 98.2% (55/56 metastases) at 3 months. Median survival was 22 months in patients with a solitary brain metastasis, 7.5 months in patients with a single brain metastasis and metastases elsewhere, and 4 months in patients with multiple brain metastases. Complications were unusual and surgery was required in 2 of 35 patients. These results show for the first time that melanoma patients with a unique brain metastasis with or without metastases elsewhere clearly benefit from tumour control easily obtained by radiosurgery. Although the comparison of radiosurgery with surgery and/or whole brain radiotherapy cannot be adequately addressed, radiosurgery alone seems to provide similar results with lower morbidity and impact on quality of life.**


**Key words: melanoma, metastases, brain, radiosurgery, stereotactic surgery, gamma knife, palliative therapy, fotemustine, surgery, radiotherapy, quality of life**
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## INTRODUCTION

RADIOSURGERY OR gamma knife is a neurosurgical procedure where narrow ionising beams given in a single high dose fraction are used to destroy a predetermined target volume without opening the skull and with minimum risk of damage to the surrounding non-target neural tissue [1]. Recently, radiosurgery with or without whole brain radiotherapy (WBR) has been shown to achieve a high rate of local control of brain metastasis of cancers [2–6], with minimum risk and maximum comfort.

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The brain is the initial site of distant metastasis in 12–20% of melanomas, and 36–54% of patients have brain metastasis at autopsy [7]. In patients with multiple cerebral metastases, the standard treatment is radiotherapy with fractionated WBR, although it has only a palliative effect and median survival does not exceed 3 months [8]. Fotemustine, which is the only chemotherapy to have shown impact on brain metastases [9], has been proposed as an alternative to WBR. In patients with a solitary surgically accessible brain metastasis, surgery with or without WBR [8] is usually considered as the treatment of choice. Although long-term survival has been achieved in some cases [10], most patients die rapidly, raising the question of whether all patients with a solitary brain metastasis should be subjected to surgery plus radiotherapy.

Radiosurgery represents an interesting alternative to conventional surgical resection or to conventional radiotherapy in patients with brain metastases. The only study focusing on brain metastasis of melanoma is a series of 23 patients presenting mainly solitary metastases treated by a combination of radiosurgery and WBR [11]. However, radiosurgery without WBR has never been evaluated in cerebral metastatic melanoma, although very high rates of control are reported in other metastatic brain tumours with radiosurgery alone [5]. Neither has radiosurgery been evaluated as a palliative therapy in melanoma patients with multiple metastases. In this regard, it seems reasonable to speculate that this method could lengthen survival or at least improve quality of life simply by controlling one of the major causes of death. The purpose of this report is to describe our experience in a series of 35 patients with one to three brain metastases treated by radiosurgery without WBR.

## PATIENTS AND METHODS

*Patients*

We report the data of 35 consecutive patients, suffering from cerebral metastatic melanoma with or without other metastatic sites, who were referred between 1993 and 1996 by several dermatology centres to the Neurosurgery–Radiosurgery Department in Marseille, France for radiosurgery therapy. Radiosurgery was performed when the maximum number of brain metastases was three, their maximum diameter was under 30 mm, as assessed by magnetic resonance imaging (MRI), the patient had no other immediately life-threatening metastases elsewhere and their Karnofsky index was > 60. There were no other selection criteria. The mean age of the patients was 56.6 years (range 29–82 years). 4 patients had previously undergone surgery to remove a brain metastasis. 20 patients had received various regimens of chemotherapy before radiosurgery (cisplatin, dacarbazine, vindesine, cystemustine).

At the time of radiosurgery, 4 patients had a solitary brain metastasis, 13 had one brain metastasis and one or more extracerebral metastases, 18 patients had two or three brain metastases without ($n = 2$) or with at least one metastasis elsewhere ($n = 16$). 29 patients were treated once: 15 patients for one brain metastasis, 9 patients for two tumours simultaneously, and 5 patients for three tumours simultaneously. 6 patients were treated by a second radiosurgery on new brain metastases, 3–12 months after a first successful radiosurgery. No patient was treated twice at the same site. A total of 70 tumours were thus treated by radiosurgery. The lesions were located in the cerebral hemispheres ($n = 62$), the brain stem ($n = 3$) and the cerebellum ($n = 5$). The maximum lesion diameter ranged from 2 to 32 mm (mean diameter 18 mm).

*Radiosurgery protocol*

All radiosurgery procedures were carried out in the same centre (Hôpital Timone, Marseille, France), using the Leksell 201-source Cobalt 60 Gamma Knife (Elekta Instrument, Stockholm) [1, 12]. After application of a stereotaxic co-ordinate headframe, either contrasted computed tomography (CT) or a multiplanar gadolinium enhanced MRI scan was performed to derive the spatial co-ordinates of the target. These data were used in a Microvax II computer to calculate the radiosurgical dose planning, including the three-dimensional isodose configuration, number of radiation isocentres, dose to the tumour margins and surgical time. Selection of dosimetric parameters (dose, marginal isodose, number of isocentres) was made according to the size, shape, location, and relationship of the lesion to critical structures based on prior experience in our and other centres and the prediction of complications as determined by 'integrated logistic formula' [13]. The total dose was delivered in a single session. The 50% isodose line was used to match the tumour margin in most patients. The marginal dose ranged from 14 to 40 Gy (Figure 1) and the maximum tumour dose ranged from 28 to 80 Gy (mean maximum dose 59.2 Gy).

All patients entered the department at 5 pm and left before 12 am the next day. The evening before treatment was dedicated to extensive explanation of the treatment procedure. On the morning of the treatment, an imaging-compatible Leksell stereotactic frame (Electra instrument) was applied to the patient's head using local anaesthesia. A high resolution contrast enhanced CT scan was performed to localise the target and the surrounding radiosensitive structures. For irradiation, the patient's head with the attached sterotaxic

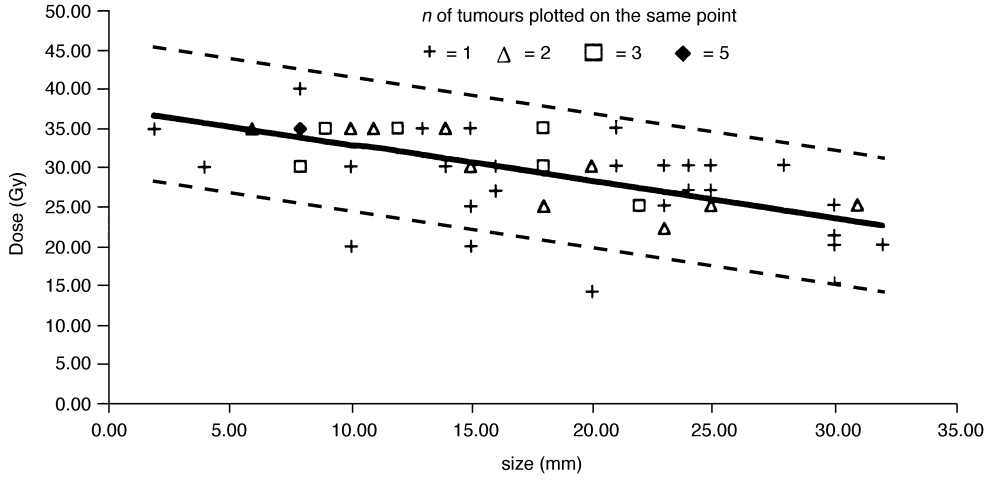


**Figure 1. Correlation between marginal dose and maximum tumour size. Doses were selected according to size, shape, location and relationship of the lesion to critical structures. The regression line and the 95% confidence interval (CI) lines (broken lines), show that dosimetric parameters are almost a linear function of the tumour size. The four points below or on the 95% CI line correspond to specific situations in which lower doses were used: primary motor cortex once, brain stem twice, and 1 patient who underwent whole brain radiotherapy 2 years before.**

frame, was placed within the appropriate collimator helmet. The radiosurgery is completely painless and in our experience, drug sedation was never required. Frame delivery occurred within 3 h of frame application (range 1–6 h); 30% of the patients experienced a headache after frame removal; this symptom was successfully treated by first-line analgesics.

*Associated treatment*

No patients underwent WBR after radiosurgery. At the time or after radiosurgery, 23 patients from some centres received fotemustine, a chemotherapy with a possible impact on brain metastases [9]. After radiosurgery, patients with extracerebral metastases were administered various regimens, including interferon alpha 2B, dacarbazine and eldisine.

*Evaluation*

In all patients, CT scan imaging was performed at the end of the first month to detect complications, at the end of the third month to assess response and every 3 months thereafter.

As radiosurgery induces a focal necrosis, an immediate disappearance of the image of the tumour on CT scan is not expected after successful radiosurgery. A therapeutic success can be associated with a stability or a small increase in the CT scan imaging. The tumour response is thus not correlated to the change in the CT scan imaging. We therefore used specific criteria to assess the response. Changes in CT scan imaging were classified into four categories: $CT_C$ defined as complete disappearance of the image; $CT_D$ defined as a decrease of more than 30% in the maximum diameter of the tumour image; $CT_N$ defined as no change in the tumour image, i.e. between less than a 30% decrease and less than a 25% increase in the maximum diameter of the tumour image; and $CT_I$ defined as an increase of 25% or more in the maximum diameter of the tumour. In the analysis of results, local control was defined as an absence of any sustained increase in tumour volume (> 25%) and by disappearance of the peritumoral oedema. Progression was defined as an increase of 25% or more in the maximum diameter of the tumour, not measuring peritumoral oedema. Survival from the time of radiosurgery (or from the first radiosurgery when radiosurgery was repeated on new metastases) was estimated according to the Kaplan–Meier method and the log rank test was used to compare survival data in different groups.

## RESULTS

*Response rate*

Seventy metastases were treated in 35 patients. The maximum diameter ranged from 2 to 32 mm (mean 18 mm; Figure 1). Because of early death in many patients, 56 treated metastases were available for evaluation at the third month, 36 at the sixth month, 22 at the ninth month, and 8 at the 12th month. Out of evaluable metastases, 55 of 56 (98.2%) were controlled at 3 months after radiosurgery, 36 of 36 (100%) at 6 months, 21 of 22 at 9 months (95.4%), and seven of eight at 12 months (87.5%) (Table 1). The rate of progression was thus very low. However, in 2 patients whose cause of death was unknown, and in 7 patients who died with neurological symptoms, we were unable to rule out a progression of eight radiosurgery-treated metastases at 3 months, seven at 6 months, one at 9 months, and four at 12 months. If we admit the unlikely hypothesis that all tumours progressed in these undocumented cases, the maximal rate of progression of radiosurgery-treated lesions would be nine of 70 (12.8%) at 3 months, eight of 57 (14%) at 6 months, one of 37 (2.7%) at 9 months, and five of 22 (22.7%) at 12 months.

*Clinical response*

Of the 21 patients who had neurological symptomatology (epilepsy, motor or sensory deficit) at inclusion, 2 (9.6%) recovered completely, 7 (33%) improved, 6 (28.6%) did not change, 3 (14.3%) deteriorated (2 cerebral haemorrhages, 1 epilepsy), and in 3 cases information was missing. 1 of the asymptomatic patients deteriorated (epilepsy).

*Survival (Figure 2)*

Median survival was 7 months. As expected, there was a significant ($P = 0.001$, log rank) difference in survival between patients with solitary brain metastasis (median survival 22 months, and 2 patients still alive), patients with one brain metastasis and one or more metastases elsewhere (median survival $7.5 \pm 1.3$ months), and patients with multiple brain metastases and one or more metastases elsewhere (median survival $4 \pm 1$ months) (Figure 2). Survival was significantly longer in those with a single brain metastasis with or without metastases than in those with several brain metastases ($P < 0.005$, log rank). 3 of 4 patients with a solitary brain metastasis, 3 of 13 patients with a single brain metastasis and 1 of 18 patients with more than one brain metastasis were still alive 1 year after radiosurgery.

The cause of death was unknown in 4 cases, was attributed to non-neurological disease in 7 cases, was documented as growth of new neurological metastases in the central nervous system in 13 cases, was attributed to melanoma meningitis in 2 cases, and to neurological disease without any precision in 6 cases. Surgery, which was performed in 1 patient because of a 30% increase in CT scan image ($CT_I$), found a haemorrhage

*Table* 1. *Impact of radiosurgery (RS) on* 70 *melanoma brain metastases*

| | At RS | 3 months after RS | 6 months after RS | 9 months after RS | 12 months after RS |
|---|---|---|---|---|---|
| No. of evaluable metastases (No. of RS-treated metastases in patients alive at evaluation) | 70 | 57 | 36 | 22 | 8 |
| No. of metastases evaluated (% of evaluable metastases) | 70 (100%) | 56 (98%) | 36 (100%) | 22 (100%) | 8 (100%) |
| $CT_C$ (% of evaluable metastases) | / | 12 (21%) | 11 (31%) | 10 (45%) | 5 (62.5%) |
| $CT_D$ (% of evaluable metastases) | / | 19 (34%) | 12 (33%) | 5 (23%) | 2 (25%) |
| $CT_N$ (% of evaluable metastases) | / | 24 (43%) | 13 (36%) | 6 (27%) | 0 (0%) |
| $CT_I$ (% of evaluable metastases) | | 1 (1.8%) | 0 (0%) | 1 (4.6%) | 1 (13%) |
| Total rate of control (% of evaluable metastases) | / | 98.2% | 100% | 95.4% | 87.5% |

$CT_C$, complete disappearance of image on computed tomography scan; $CT_D$, decrease of more than 30% in the maximum diameter of the tumour image; $CT_N$, no change in the tumour image; $CT_I$, increase of 25% or more in the maximum diameter of the tumour image.

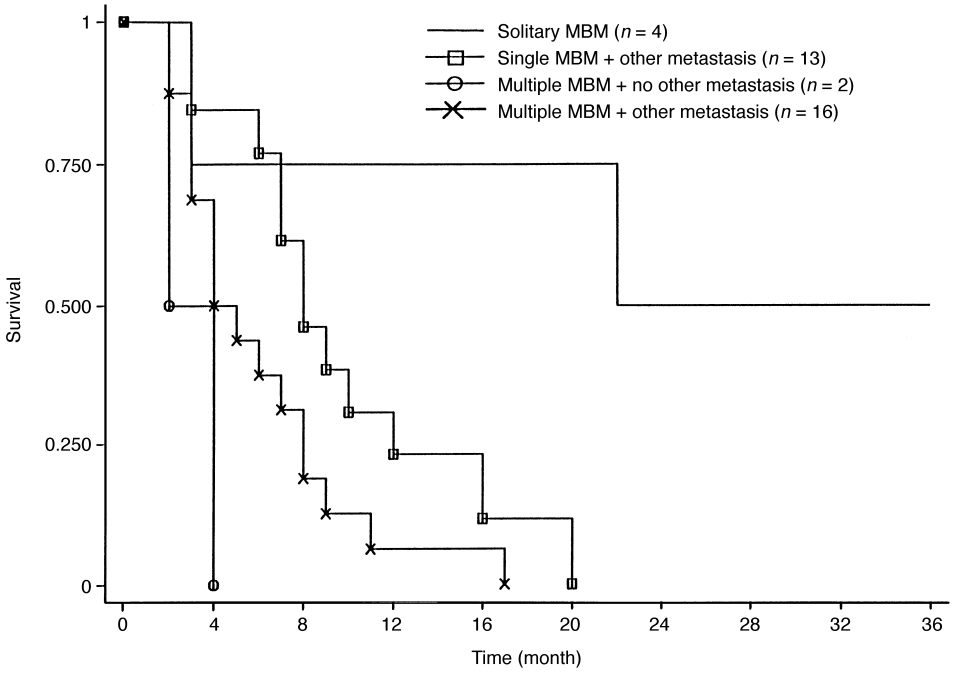


**Figure 2. Survival from time of radiosurgery in 35 patients with melanoma brain metastasis (MBM).**

without metastatic tissue. A local recurrence was suspected in 1 case and documented histologically 15 months after radiosurgery, when the patient's clinical state deteriorated. None of the deaths occurring during follow-up was attributed to a radiosurgery-treated lesion.

Median survival was not significantly different ($P = 0.29$) in patients treated by radiosurgery alone (median survival 8 months) and in those who had fotemustine (median survival 6.5 months).

*Tolerance*

Intratumoral bleeding was documented in four of 56 evaluated tumours (7.1%). Epilepsy was observed in 2 of 35 patients (6%). Surgery was required in only 2 of 35 patients (5.7%). All patients returned to their pre-operative level of function or employment within 5–7 days after treatment. Haemorrhagic necrosis was observed on CT scan and MRI in four tumours. 2 patients also experienced bleeding in an untreated (no radiosurgery) new cerebral metastasis. 2 patients suffered from epilepsy, several months after radiosurgery, which was attributed to radionecrosis.

## DISCUSSION

Radiosurgery has been shown to be useful in the treatment of intracranial metastases [2–6, 14, 15]. However, the histological type of the primary cancer is crucial since prognosis depends on the sensitivity to standard radiotherapy often combined with radiosurgery and on the possibility of treatment of the systemic disease to which many patients succumb. Patients with melanoma brain metastases have a consistently poorer prognosis than do patients with other histological types, and sensitivity to radiotherapy and chemotherapy is lower than in most other cancers [16]. Therefore, the data from the treatment of brain metastases from lung, renal or breast cancers using radiosurgery combined with WBR [2–4, 6] are not necessarily true for melanoma brain metastases.

In our experience, radiosurgery achieved a 80–100% rate of local control in brain metastases and these results have been reported consistently [2–6, 11, 15]. It must be noted that a residual lesion on CT scan does not mean a residual tumour. Radiosurgery is responsible for a scar which accounts for the $CT_D$ and $CT_N$ aspects. However, a histologically documented recurrence 15 months after radiosurgery in 1 patient, indicates the possibility of late recurrence. This problem of occasional late recurrence after radiosurgery is clinically relevant only in the few patients who survive a long time.

Complications of radiosurgery are very limited. Intratumoral bleeding was documented in four out of 56 evaluated tumours (7.1%). Epilepsy was observed in 2 of 35 patients (6%). Surgery was required in only 2 of 35 patients (5.7%). Whether or not radiosurgery is responsible for intratumour bleeding can be debated since spontaneous haemorrhaging is usual in brain metastases from melanoma [8]. In this regard, bleeding was also observed in this series in two new metastases which had not been treated by radiosurgery.

Our data show that local control of brain metastases by radiosurgery without WBR can offer a long survival ($\geq 12$ months) at least in some melanoma patients (7 of 35). These results are in agreement with those of Somaza and colleagues [11] in patients with brain metastases of melanoma and with those of other authors in patients with brain metastases from various cancers [2–6].

In patients with a solitary brain metastasis, surgery with or without WBR is usually considered as the treatment of choice [8], with a median survival between 8 and 15 months and occasional long-term survival [17–19]. Radiosurgery with WBR has been shown to produce results similar to conventional surgery [11]. Our patients clearly benefited from radiosurgery (median survival 22 months, and 2 of 4 patients still alive after 2 years). In clinical practice, the attending physician who wants to avoid a useless craniotomy in patients who will rapidly develop new metastases, but does not want

to miss the opportunity of a prolonged survival after resection, is faced with the dilemma of deciding whether to undertake surgery or not. Radiosurgery eliminates this dilemma, since it is not limited by factors such as surgical morbidity, accessibility of the tumour, and risk of surgical sequelae. Radiosurgery can be performed with comfort and safety in a single half-day treatment without general anaesthesia. Therefore, radiosurgery extends the scope of 'resectability' of brain metastases. Radiosurgery has also been shown to have a better cost-effectiveness [18] in the treatment of solitary brain metastases from various tumours. Furthermore, radiosurgery can be used in patients whose tumours are not accessible to conventional surgery and is repeatable on a new lesion. Until a prospective randomised study compares surgery with radiosurgery in solitary melanoma brain metastases, the many advantages of radiosurgery indicate that it should be preferred to surgery unless the metastasis is larger than 30 mm or the histological type of the tumour has to be ascertained.

Benefit from radiosurgery is certainly not limited to solitary brain metastases: 3 of 13 patients (23%) with a single brain metastasis and other visceral metastases were still alive 12 months after radiosurgery, 10 of 13 patients (77%) after 6 months. Motor and/or sensory deficit regressed or improved in 4 of 6 cases (67%), and 5 of 13 patients (38%) did not die from neurological complications. Although the median survival (7.5 months) seems to be higher than that reported in the literature using conventional therapy [2, 16, 19–21], this comparison cannot be addressed retrospectively. However, there is evidence that radiosurgery without WBR can improve comfort and provide long survival with minimal morbidity in these patients.

In melanoma patients with several brain metastases, we expected that radiosurgery could prolong survival and improve quality of life by safely controlling a major cause of death. Median survival was only 4 months and only 7 of 18 patients (38.8%) had a survival exceeding 6 months, compared with 1–2 months' survival without treatment reported in the literature [10]. Motor and/or sensory deficit improved in 4 of 9 cases (44%), and only 3 of 18 patients (16.6%) did not die from neurological disease. The survival benefit due to the control of brain metastases is probably weak, but this is also true for a combination of focal and whole brain radiotherapy [8, 16, 20, 21], which is probably less comfortable for the patient.

The preventive effects of WBR for development of new melanoma brain metastases are controversial. Although some groups use radiosurgery alone [5], it has usually been combined with WBR [2–4, 6, 11]. The present study is the first to include only melanoma patients with brain metastases treated by radiosurgery without WBR. When radiosurgery is performed before or after WBR, lower radiosurgery doses must be used. This explains why the doses were much higher in our series than in the previous study [6, 11]. Although no WBR was performed, 14 of 35 patients (40%) did not develop new intracranial metastases. In a palliative setting for melanoma patients, simplicity and rapidity of treatment are major issues. Combination with WBR certainly complicates treatment and impacts on the quality of life, since it requires several weeks of treatment, and is responsible for hair loss and asthenia. In long-term survivors, long-term neurotoxicity has also to be taken into account. Until a prospective controlled study shows whether or not WBR improves prognosis of patients with melanoma brain metastases treated by radiosurgery or by surgical resection, we consider that there is no reason to combine radiosurgery with WBR [9]. This attitude is often accepted in Europe and debated in the U.S.A.

23 of 35 patients (65.7%) received fotemustine at the time or after radiosurgery. Although this drug has shown a 25% response rate in melanoma brain metastases, survival in patients treated with fotemustine was not significantly different ($P = 0.29$) than in those treated by radiosurgery alone. Fotemustine is thus unlikely to account for a significant part of the results presented here. We consider that there is no reason to combine radiosurgery with chemotherapy unless this treatment is required for extracerebral metastases.

Radiosurgery without WBR offers the possibility of relatively long-term survival in patients with solitary or single brain metastasis with no counterpart in terms of morbidity and impact on quality of life. Therefore, we consider it as the treatment of choice in patients with a single brain metastasis with or without extracerebral metastases. Controlled randomised trials assessing palliative effect, quality of life and cost are needed to confirm these data.


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