

## Disease Presentation and Outcome in Young Patients (<40 Years) with Brain Metastases from Malignant Melanoma

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**Abstract.** While elderly patients with brain metastases from malignant melanoma apparently have an unfavourable prognosis, little information is available on disease presentation and treatment outcome in youngest patients. Considering this, our experience with radiation therapy in this particular subset was evaluated. Our database with 48 melanoma patients contained three patients aged <40 years. All received whole-brain radiation therapy plus steroids and individual systemic measures according to the institutional policy. In one case, brain metastases were present already at first diagnosis of melanoma. The maximum interval to diagnosis of brain metastases was 21 months. All the patients were male and had multiple lesions (at least 6) plus extracranial metastases. None of them died from extracranial disease. The maximum survival was 5 months. Thus, our young patients with brain metastases did not achieve a better outcome than intermediate age groups. Whole-brain radiation therapy was not able to provide durable CNS control. Prospective studies on treatment intensification appear warranted.

Malignant melanoma is, next to lung cancer, the most frequent cause of brain metastases. These metastases usually develop late in the course of the disease (1). In a large study, only 7% of patients had brain metastases disclosed at the time of initial diagnosis (2). The course of the disease is typically characterised by rapid progression and short overall survival time despite various local and systemic treatment approaches (3, 4). Advanced age ( $\geq 65$  years) has been shown to represent an adverse prognostic factor in the large

analysis that led to the development of the recursive partitioning analysis (RPA) classes in irradiated patients with brain metastases (5). This finding has been confirmed by evaluations restricted to malignant melanoma patients (2). However, little information is available on disease presentation and treatment outcome in young patients. Therefore, an evaluation of our experience with radiation therapy in this particular subset was undertaken.

### Patients and Methods

All patients <40 years of age treated with radiation therapy for brain metastases from malignant melanoma were retrospectively analysed. They were identified from the Munich hospitals database. All had histological confirmation of their primary tumor. Whole-brain radiation therapy (WBRT) was administered *via* standard lateral opposed 6 MV beams from a linear accelerator with 5 fractions of 3 Gy per week and the use of a thermoplastic mask fixation of the head. The dose was prescribed to the midline. Dexamethasone was given in individual doses depending on the clinical symptoms. A baseline clinical examination was performed within 1 week before the start of WBRT. Follow-up took place every 3 months and included contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI).

### Results

Out of 48 patients with brain metastases from malignant melanoma in the database, three (6%) were <40 years old when treatment for brain metastases was started. Table I contains the individual patient data. The institutional treatment policy consisted of WBRT for patients with more than 3 lesions, whereas patients with 3 or fewer lesions were considered for either surgery or radiosurgery followed by WBRT by a multidisciplinary neuro-oncology board. No simultaneous chemotherapy was given, but temozolomide, dacarbazine or fotemustine were administered for extracranial metastases as indicated. The patients with brain metastases did not receive biological agents such as interferon.

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Table I. Patient characteristics.

Patient	Age, gender	Presentation of brain metastases	Primary tumor*	Extracranial distant metastases	Karnofsky performance status	Treatment of brain metastases	Previous other treatments	Additional treatment after RTx	Outcome and OS after RTx
1	23, male	21 months after primary diagnosis, more than 5 lesions up to 40 mm	T4 N3	bone	70	WBRT, 3 Gy x 10	2 lines of CTx	further CTx	developed visceral metastases, but died from brain disease, OS 5 mo.
2	39, male	9 months after primary diagnosis, more than 5 lesions, up to 13 mm	T3 N1b	multiple sites	70	WBRT 3 Gy x 10	1st line CTx	2nd line CTx	died from brain disease, OS 4 mo.
3	36, male	synchronous, more than 5 lesions, up to 45 mm	T3 N2b	liver	40	WBRT 3 Gy x 10	none	1st line CTx	died from brain disease, OS 2 mo.

\* American Joint Committee on Cancer staging system for cutaneous melanoma 2002; OS: overall survival from start of radiotherapy (RTx), WBRT: whole-brain radiotherapy, CTx: chemotherapy.

All three of the patients were male. In one case, brain metastases were present already at first cancer diagnosis, while two patients had metachronous presentations after 9 and 21 months, respectively. All the patients had multiple brain lesions and were not suitable for surgery or radiosurgery in addition to WBRT. The Karnofsky performance status (KPS) was 70% or lower. According to post WBRT imaging, none of the patients achieved a partial or complete remission. All the patients died from their central nervous system (CNS) disease. The maximum survival was 5 months from the start of WBRT.

## Discussion

The present retrospective analysis is to our knowledge the first one that focused on young patients with malignant melanoma metastatic to the brain. As published by other groups, the median age at diagnosis of brain metastases is in the order of 50-60 years (2, 6) and the median interval from primary diagnosis to the development of brain metastases is approximately 2-3 years (2). It appears that young patients tended to harbour multiple cerebral lesions, which were found either at initial cancer diagnosis or early during the course of the disease. These features might suggest the presence of an aggressive malignancy. The fact that all the patients had lymph node and extracranial organ metastases supports this statement.

The effects of WBRT on local control were disappointing and eventually all three patients died within 5 months. Comparable results have been reported from larger series with median survival times of 3-6 months (2, 7, 8). Taking the limitations of retrospective analyses and the group size into account, young patients did not appear to have a better prognosis than other groups. Based on this experience, it might be worthwhile investigating radiosurgery also in

patients with more than 3 brain metastases from melanoma in order to improve local control and thereby survival. The median survival in radiosurgery series was 8-11 months (9-11) and less than 50% of the patients died from the brain metastases (6, 10). Efforts to improve the outcome might also include the simultaneous administration of temozolomide to WBRT (12) and the integration of biological agents into the whole treatment concept (13, 14). Majer *et al.* reported on 20 patients with brain metastases treated with radiosurgery and biochemotherapy (dacarbazine or temozolomide with interleukin-2 and interferon-alpha-2B) (15). The median survival from the time of diagnosis of metastatic disease was 15.8 months in this group, compared to 11.1 months in 50 patients without CNS involvement that received the same treatment.

## Conclusion

Young patients with brain metastases do not achieve a better outcome than intermediate age groups and whole brain radiation therapy is not able to provide durable CNS control. Therefore, prospective studies on treatment intensification are warranted.

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