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RADIATION THERAPY FOR BRAIN METASTASES FROM MALIGNANT MELANOMA

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Abstract

Thirty-nine patients who completed whole-brain irradition treatment for brain metastases from malignant melanoma were analyzed. Median survival was 2 months, mean survival 4 months. Only 3 patients survived for 1 year, the longest survival being 19 months after irradiation. Twenty-one (53.8%) showed marked clinical improvement and 6 (40%) of the 15 evaluable patients had some objective regression of the brain metastases. A treatment of 7 fractions of 4.8 Gy in 9 to 14 days and concomitant chemotherapy with dacarbazine and lomustine in 16 patients was well tolerated. This seems to be a beneficial treatment for patients with a comparatively small intracranial tumour burden.

The incidence of malignant melanoma is rapidly increasing in Norway. About 450 new cases are reported annually to The Norwegian Cancer Registry. Malignant melanoma is now the most frequent form of cancer in the 20 to 39 year age groups, if both sexes are viewed together (3).

The prognosis for localized tumours is comparatively good, but about 40 per cent of the patients sooner or later develop distant metastases (4). Brain metastases are found at autopsy in about 50 to 75 per cent of patients dying of malignant melanoma (1, 6). This tumour type is the third commonest cause of brain metastases (2, 7).

The median survival of patients with untreated brain metastases from malignant melanoma is only about one month. Corticosteroids may relieve the symptoms by reducing the edema of brain tissue surrounding the metastases. This effect is usually of short duration, however, the mean survival being about two months if only corticosteroids are given (2).

Chemotherapy has virtually no effect on brain metastases from malignant melanoma (2). In selected cases, with single brain metastases, surgery is the treatment of choice. Unfortunately, brain metastases from malignant melanoma are multiple in most patients. Although malignant melanoma is comparatively resistant to radiation, whole-brain irradiation has been advocated as a palliative treatment for these patients (9).

Irradiation with a high dose per fraction may be more efficient than 'conventionally' fractionated irradiation in malignant melanoma (11). On the other hand, a high dose per fraction increases the risk of acute edema and late radiation damage. Concomitant administration of corticosteroids may reduce the risk of short term toxicity for brain irradiation.

A retrospective analysis of the experiences with radiation therapy for brain metastases from malignant melanoma has been carried out in two Norwegian cancer clinics. It was considered of particular interest to ascertain whether any effects of different fractionations or concomitant use of chemotherapy could be demonstrated.

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Material and Methods

Between December 1973 and July 1980, 45 patients began radiation treatment for brain metastases from malignant melanoma, 10 at Ullevål Hospital and 35 at The Norwegian Radium Hospital. Patient selection differed at the two hospitals. At the Radium Hospital patients came mostly from long distances away and were hospitalized for treatment. At Ullevål Hospital all patients came from the immediate vicinity and were treated usually as outpatients. Of the 45 patients, 39 (26 males, mean age 47 years, range 22–68 years; 13 females, mean age 47 years, range 28–73 years) completed the therapy, 30 at the Radium Hospital and 9 at Ullevål Hospital. The interval, in years, from primary diagnosis to start of treatment was 0 to 1.5 for 6 patients, 1.5 to 3 for 6, 3 to 5 for 11, 5 to 10 for 1, and 10 to 15 for 5 patients. At the former hospital, one patient refused treatment after two fractions. In 5 patients, one of them at Ullevål Hospital, the treatment was discontinued because of marked progression of the disease. These 5 patients were all dead within one month from the start of the treatment. The main characteristics of the 39 evaluable patients are summarized in Tables 1 and 2.

The treatment was given with two opposed lateral fields with high energy photons from a linear accelerator at the Radium Hospital or a betatron at Ullevål. This gives a comparatively uniform dose distribution within the whole brain including the cerebellum and medulla oblongata.

The fractionation and the total dose of radiation varied (Table 3). When fractions of 4.8 Gy were given, the patients always received dexamethasone 4 mg×4 daily, in order to reduce the risk of acute intracranial edema.

The corticosteroid medication was continued for at least 1 to 2 months after irradiation. After 2 to 3 months the medication was tapered and discontinued if no clinical signs of increased intracranial pressure were observed.

Twelve of the 14 patients who received fractions of less than 4.8 Gy also received corticosteroids during radiation therapy.

Twenty-one patients received cytotoxic chemotherapy during radiation therapy or shortly afterwards as part of a combined treatment. Most of these patients had extracerebral metastases, or had just had extracerebral metastases surgically removed. These 21 patients all received dacarbazine (DTIC), 18 of them also received lomustine (CCNU) and 8 received a 3-drug combination of DTIC, CCNU and vincristine (VCR). The dosage was: DTIC 250 mg/m^2 days 1 to 5, CCNU 120 mg/m^2 day 1, VCR 2 mg day 1. The chemotherapy was repeated at 6 week intervals until clear progression of the disease was noted.

Sixteen of the 25 patients who received 7 fractions of 4.8 Gy (total dose 33.6 Gy) also received concomitant chemotherapy with DTIC and CCNU with or without VCR.

The characteristics of this subgroup of patients

Table 1

Documentation of brain metastases (figures denote number of patients)

Scintigraphy	CT	Cerebral angiography	EEG	Cells in cerebrospinal fluid	Histology	Clinically only*
34	14	2	2	1	4	2

* Supported by the relief of symptoms following corticosteroid medication.

Table 2

Number of brain metastases and number of patients with concomitant extracerebral metastases

	Number of patients with	
	Extracerebral metastases	No extracerebral metastases
Uncertain	2	0
Single	9	9
More than one	8	11
Total	19	20

Table 3

Total dose and fractionation schedule for 39 patients who completed planned radiation therapy

Dose per fraction (Gy)	Total dose (Gy)	Equivalent dose*	No. of fractions	Duration (weeks)	No. of patients
2–2.9	50	1 095–1 375	17–31	4–6	6
3	30–36	1 080–1 190	9–12	2–3	5
3.65–4.5	40–45	1 390–1 620	10–11	2–4	3
4.8	33.6	1 385–1 520	7	1.3–2	25

* According to formula of WARA et coll. (2): $ED = D_{tot} \cdot N^{-377} \cdot T^{0.058}$.

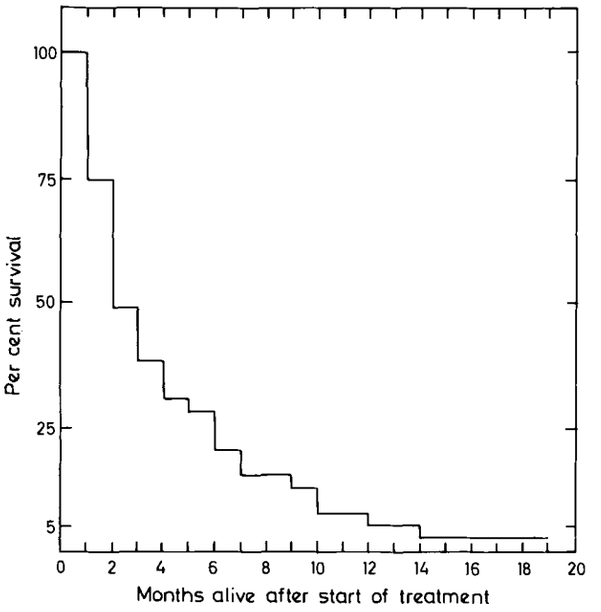

Fig. 1. Survey of survival for 39 patients who completed a course of irradiation for brain metastases from malignant melanoma. Survival: Median 2 months, mean 4 months, 1 week.

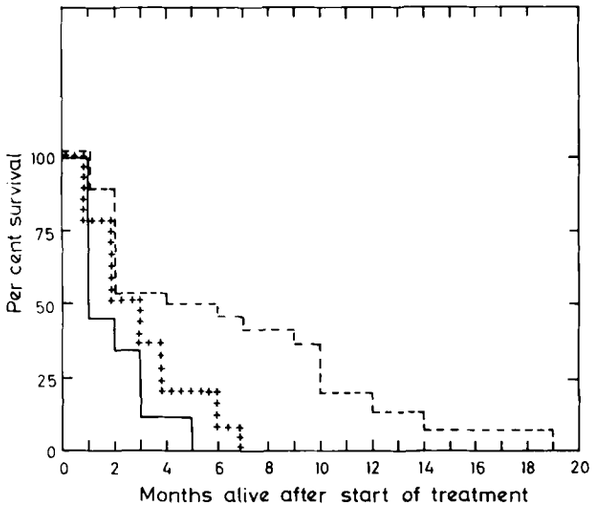

Fig. 2. Survey of survival for all patients who completed a course of irradiation for brain metastases from malignant melanoma. The patients are divided into three groups, according to modality of treatment and to whether they received chemotherapy or not. Group I (– –): 4.8 Gy × 7 + DTIC + CCNU, n=16, median survival 6 months, mean 6.4 months. Group II (——): 4.8 Gy × 7 without chemotherapy, n=9, median survival 1 month, mean 2.0 months. Group III (++): other modes of treatment, n=14, median survival 2 months, mean 3.1 months.

are shown in Table 4, compared with the 9 patients with 4.8 Gy×7 without chemotherapy, and the group receiving irradiation according to other fractionation schedules.

Table 4

Main characteristics of the patients who received 4.8 Gy × 7 and chemotherapy with DTIC and CCNU (group I), the patients having 4.8 Gy × 7 without chemotherapy (group II) and the patients having other modes of treatment (group III)

Brain metastases	Group I (n=16)		Group II (n=9)		Group III (n=14)	
	No.	Per cent	No.	Per cent	No.	Per cent
Unknown	1	6	1	11	0	0
Single	12	75	3*	33	3	21
Multiple	3	19	5	56	11	79
No extracerebral metastases	6	37	5	56	9	64
Extracerebral metastases	10	63	4	44	5	36

Results

Among the 39 patients who completed the planned treatment median survival was 2 months, and the mean survival 4 months. Only 3 patients survived for more than one year. The longest survival time was 19 months after the start of brain irradiation (Fig. 1).

The 25 patients treated with daily doses of 4.8 Gy seemed to have a somewhat longer median survival time (5 months). The 7 patients who lived for more than 8 months all had this fractionation.

The 6 patients who completed irradiation of up to 50 Gy in 4 to 6 weeks were all dead within 8 months.

Twenty-one patients achieved an obvious clinical improvement of consciousness or motor ability, or both, during or after radiation therapy. A few others reported symptomatic improvement of headache and sickness.

Six patients were able to return to part-time or full-time work for a while after completion of radiation therapy.

Twelve patients underwent brain scintigraphy or a CT scan both before and after completion of treatment. Six of them had objective reduction of the brain metastases.

Five of 10 evaluated patients with the fractionation of 4.8 Gy × 7 showed some regression, as did the single patient examined with the fractionation of 4.5 Gy × 10. no change was observed in one patient who received 3 Gy × 9 to 12.

The 24 patients given chemotherapy during or

after radiation therapy had a somewhat longer survival than those not given chemotherapy.

A subgroup of 16 patients who received 4.8 Gy in 7 fractions over 9 to 14 days, and concomitant DTIC and CCNU chemotherapy, with or without VCR, may be of special interest as the survival in this group seemed to be somewhat better than in the other patients (Fig. 2).

A long latency period between the primary diagnosis and the findings of brain metastases did not seem to indicate a better prognosis. The survival of the 5 patients who developed brain metastases more than 10 years after the primary diagnosis, and the finding of brain metastases, was almost the same as for the other patients. However, 4 out of 10 patients who developed brain metastases less than 18 months after the primary diagnosis died of cerebral disease before the end of the planned treatment.

This may indicate that a short latency period carried an extremely poor prognosis for patients with brain metastases from malignant melanoma.

All patients developed total alopecia, otherwise the radiation was well tolerated. However, the side effects may have remained undetected in comparison with the serious symptoms of the illness itself and with the side effects of chemotherapy.

Late CNS damage usually becomes clinically manifest only after a year or more, and few of the patients treated for melanomatous brain metastases survive for so long. All 8 patients in the present investigation who survived for 6 months after radiation therapy and showed deterioration of CNS function had evident progression of their brain metastases, which probably was the cause of the CNS symptoms.

Discussion

Patients with brain metastases from malignant melanoma have a very serious prognosis, as the present investigation also demonstrated. For patients with solitary brain metastases and limited or no evident extracerebral disease, neurosurgical removal should always be considered. If extracerebral disease clearly is beyond therapeutic control, only symptomatic therapy and corticosteroids are indicated.

There remains, however, a subgroup of patients with brain metastases from malignant melanoma who are considered unfit for neurosurgery (multiple metastases) but could benefit from active therapy of the brain metastases.

Whether radiation therapy for inoperable brain metastases from malignant melanoma really improves survival or quality of life as compared with treatment with only corticosteroids and optimal symptomatic therapy remains unclear. The present group of treated patients is too small and heterogeneous to clarify the role of radiation therapy and the effects of dose and fractionation with or without concomitant chemotherapy.

The overall results in this investigation are comparable to other reports on radiation therapy of brain metastases from malignant melanoma.

AMER et coll. (1) gave 40 to 60 Gy during 4 to 6 weeks to 56 patients, who lived for 0.1 to 47 months after the start of irradiation, with a median survival of 2 months. CARELLA et coll. (5) reported on 60 patients who were treated with various doses and fractionation schedules. The median survival time was 3 months (range ½–15 months). The authors did not state whether different fractionation schedules gave any differences in survival.

Up to 10 Gy in one single treatment has been given to patients with brain metastases (8, 10). Such a dosage seems to give considerable side effects without yielding better results. However, this fractionation has not been systematically tested for patients with malignant melanoma. In the present series, the 25 patients treated with 33.6 Gy in 7 fractions during 9 to 14 days had a survival as good as that in patients treated with a more protracted dose of radiation.

Higher fractions of irradiation seem to be more effective in palliative therapy of melanoma metastases in other parts of the body (11). This dose and fractionation is probably near the limit of what can result in late damage to the central nervous system (13).

The subgroup of 16 patients who received both 7 fractions of 4.8 Gy and concomitant chemotherapy with DTIC and CCNU (with or without VCR) possibly had improved survival as compared with the other patients. This may be due to selection of patients with less advanced disease for such active therapy, these patients having a much less severe intracerebral tumour burden than the rest (Table 4). But at least it indicates that such combined treatment is tolerable. The subjective side effects of the chemotherapy did not hamper quality of life considerably, giving the patients at most some hours of sickness for a few days every 6th week. In all patients, progression of disease, and not side effects

such as bone marrow, liver and nephrotoxicity, was the reason for stopping cytotoxic treatment. These patients with brain metastases from malignant melanoma are also often candidates for chemotherapy of extracerebral disease.

Conclusion. Radiation therapy for brain metastases from malignant melanoma seems to be of limited benefit for most patients. Probably, comparatively few, but high fractions of irradiation are as effective as more prolonged therapy to higher total doses, at least for patients with less extensive intracranial disease.

Under cover of dexamethazone, 7 fractions of 4.8 Gy in 9 to 14 days is well tolerated, at least for the expected life time for these patients. This schedule of whole-brain irradiation may be combined with chemotherapy with DTIC and CCNU in the usual therapeutic doses without considerable side effects.

Radiation therapy with 7 fractions in 9 to 14 days occupies little of the remaining life time of the patient, and represents a limited load on the treatment facilities. Fewer and higher fractions might also be considered, and might prove to be more efficient.

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