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Brain metastasis from melanoma*

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Summary

Eighty-one patients with brain metastasis from melanoma were identified at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1978 and 1980. Of 78 evaluable patients, 51 (65%) had multiple brain metastases. Of 64 patients with non-contrast CT scans, 29% had hemorrhagic metastases. Leptomeningeal metastases were found in 15 patients. Patients were grouped into three categories: Group 1, multiple brain metastases treated with radiation therapy (RT) (n = 49); Group 2, single brain metastasis treated with RT (n = 17); Group 3, single brain metastasis treated with surgery with or without RT (n = 9). Median survivals for Groups 1, 2 and 3 were 11, 9 and 41 weeks, respectively. Eighty-six percent, 65% and 33% of patients in Groups 1, 2 and 3, respectively, were steroid-dependent until death. Seizures occurred in 38 patients (48%). In 17 (21%), seizures were the first manifestation of metastasis. Of 51 patients not receiving prophylactic anticonvulsants, 37% had seizures. Of 12 patients treated prophylactically, 17% developed seizures. Surgical extirpation should be considered in highly selected patients with brain metastasis from melanoma. Prophylactic anticonvulsants are recommended if there is no contraindication.

Introduction

Metastasis to the brain is a common complication of malignant melanoma. Of patients dying of melanoma, 70–90% harbor intracranial metastases at autopsy (1, 2). Many of the brain metastases encountered at autopsy have been symptomatic in life and responsible for the patient's death. Some investigators have reported that radiation therapy (RT) effectively palliates brain metastases from melanoma, but median survivals in these series (2–4) are only a few months, and long-term survivals are uncommon. Because of this poor response to RT, other investigators have recommended surgical resection of the metastasis in selected individuals (2, 3, 5, 6). We reviewed the experience with brain metastases from melanoma at Memorial Sloan-Kettering Cancer Center (MSKCC) in an attempt to define the clinical picture and the efficacy of therapy.

Methods

We reviewed the hospital records of all patients with both a histological diagnosis of melanoma and a metastatic brain tumor, confirmed by CT scan or radionuclide brain scan, and treated at MSKCC between 1/1/78 and 12/31/80. Patients with meningeal seeding of tumor but without intraparenchymal brain metastasis were excluded. We sought information regarding age, sex, number of brain metastases, extent of systemic disease, interval

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from initial diagnosis to brain metastasis, the presence of meningeal carcinomatosis and seizure history. The seizure prevalence in patients receiving prophylactic anticonvulsants was analyzed separately from those not receiving anticonvulsants.

We also analyzed the outcome of treatment by dividing the patients into three groups: Group 1: multiple brain metastases treated with whole-brain RT; Group 2: solitary brain metastasis treated with whole-brain RT (this group is considered separately from Group 1 because they might have been candidates for surgery); Group 3: solitary metastasis treated with surgery either with or without RT. All patients received corticosteroids. Two RT schedules were used during this period: 3 900 rad in 11 fractions (36 patients, 500 rad daily for 3 days; 4 day rest; 300 rad daily for 8 days – biological dose equivalent 5 200 rad over 5 weeks), and 3 000 rad in 6 fractions (40 patients, 600 rad daily for 3 days; 400 rad daily for 3 days – biological dose equivalent 5 000 rad over 5 weeks) (7). Patients were included in the analysis of RT response if they received at least one dose of RT. A patient was considered a clinical responder to RT or surgery only if corticosteroids could be discontinued. Survival was measured from the time of diagnosis of the brain metastasis.

Results

There were 81 patients. Although only 68 were followed at MSKCC until death, the outcome of treatment of the brain metastasis could be determined in all. There were 51 males and 30 females, ranging in age from 21 to 83 years, with a median of 48 years (Table 1). The median interval between the initial diagnosis of melanoma and the diagnosis of brain metastasis was 29 months (range 0–196 months). At the time of diagnosis of brain metastasis, 96% of patients had recurrent or metastatic melanoma elsewhere (Table 1). Although leptomeningeal seeding of melanoma was confirmed by CSF cytology in 15 patients (19%), it was suspected in other patients, but increased intracranial pressure precluded safe lumbar puncture.

Table 1. Brain metastasis from melanoma: clinical findings.

Age at neurologic presentation	21–83 years (median 48)
Sex	Male 51; female 30
Interval from initial diagnosis of melanoma to neurologic presentation	0–196 months (median 29)
Evidence of systemic disease elsewhere at neurologic presentation	Present 96%
Number of brain metastases on CT scan	Solitary 35%, multiple 65%

The diagnosis of brain metastasis was confirmed by CT scan (79 patients) or radionuclide brain scan (two patients). These studies were available for review in all but three patients. Of the 78 evaluable patients, 51 (65%) had multiple brain metastases and 27 had a solitary metastasis. Of the 64 patients in whom non-contrast CT scans had been performed, 19 (29%) were dense prior to contrast and interpreted as hemorrhagic metastases.

Seizures

One patient had a pre-existing seizure disorder and was excluded from further analysis. Of the remaining 80 patients, 38 (48%) had at least one focal and/or generalized seizure (Table 2). A seizure was the presenting manifestation of brain metastasis in 17 of 80 patients (21%). Of the remaining 63 patients at risk for developing seizures, 21 (33%) did so. Of 51 patients not receiving prophylactic anticonvulsants, 19 (37%) developed seizures, whereas only two of 12 (17%) patients receiving prophylactic anticonvulsants subsequently developed seizures.

Table 2. Brain metastasis from melanoma: incidence of seizures

Total number of patients with seizures	38/80 (48%)
Presenting manifestation of brain metastasis	17/80 (21%)
Subsequent development of seizures	21/63 (33%)
Among patients not receiving prophylactic anticonvulsants	19/51 (37%)
Among patients receiving prophylactic anticonvulsants	2/12 (17%)

Clinical course

In Group 1, there were 49 patients with multiple brain metastases who underwent whole-brain RT with corticosteroids (Table 3). Survival from the time of neurological presentation ranged from 1 to 55 weeks (median 11 weeks). In only seven patients (14%) could corticosteroids be tapered and then completely discontinued. These seven are consi-

Table 3. Treatment outcome.

	Survival[d]		Steroid-dependent until death	Improved follow-up CT scans
	Median	Range		
Group 1[a]	11 w	1 w–55 w	42/49 (86%)	3/21 (14%)
Group 2[b]	9 w	2 w–43 w	11/17 (65%)	1/10 (10%)
Group 3[c]	41 w	8 w–51 + m	3/9 (33%)	1/4 (25%)

[a] Multiple brain metastases treated with radiation therapy (RT) (n = 49).
[b] Single brain metastasis treated with RT (n = 17).
[c] Single brain metastasis treated with surgery with or without RT (n = 9).
[d] w = weeks; m = months.

dered responders to RT. In three of 21 patients, post-treatment CT scans, off steroids, showed shrinkage of the contrast-enhancing tumors (Figure 1).

In Group 2, there were 17 patients with a solitary brain metastasis treated with whole-brain RT and corticosteroids. The median survival of this group was 9 weeks (range 2–43 weeks). Of the 17 patients, 11 (65%) were steroid-dependent until death. Of the ten patients who had follow-up CT scans, one (10%) showed improvement.

Group 3 consisted of nine patients with solitary brain metastasis who underwent craniotomy and resection of the tumor. Of these, eight received RT after surgery. The median survival of the nine patients was 41 weeks (range 8 weeks to 51+ months). One patient is alive, neurologically normal and free of disease at 51 months after surgical resection of a hemorrhagic metastasis followed by whole-brain RT. In each patient undergoing surgical therapy, the pathological diagnosis confirmed the presence of metastatic melanoma. Three of the nine patients

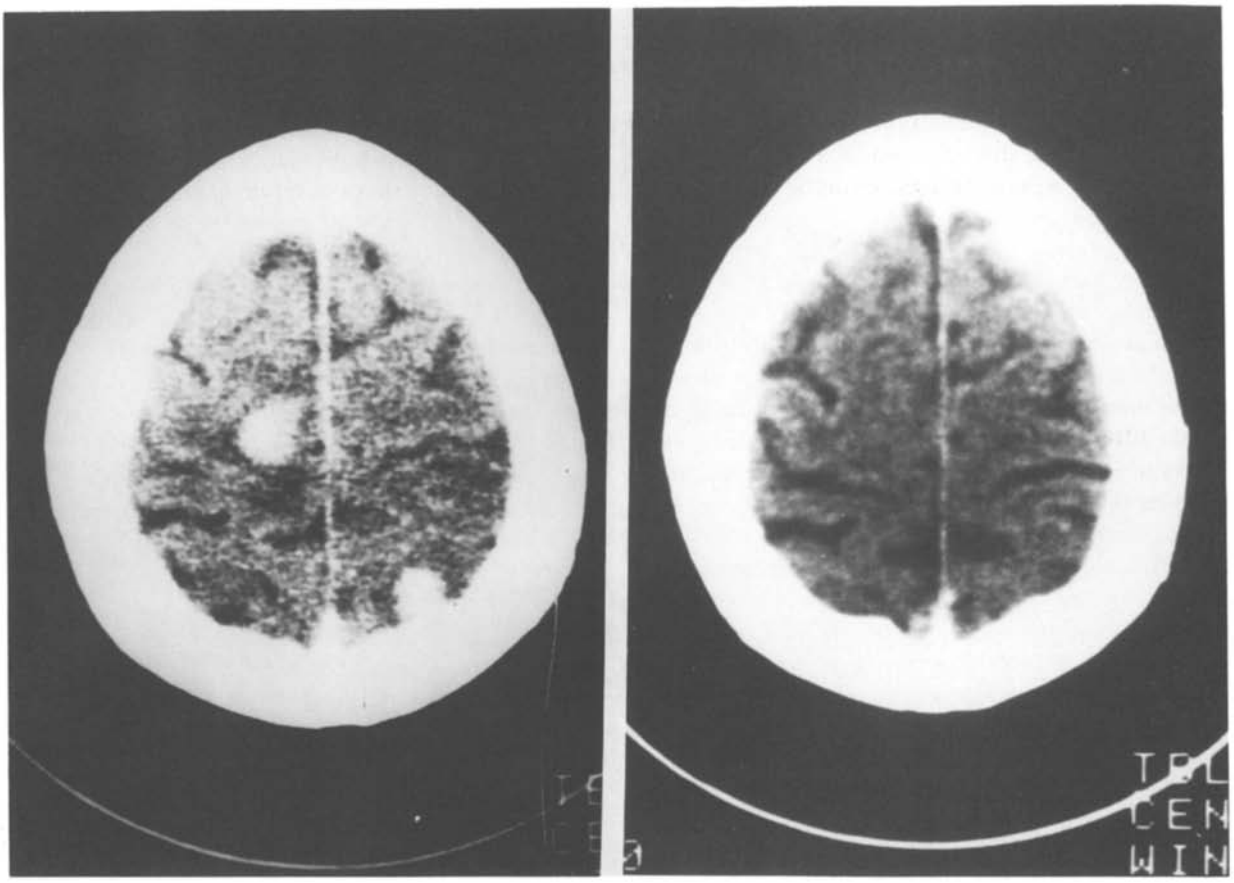

Fig. 1. Left: A 65-year-old woman with melanoma and multiple cerebral metastases. After this scan, she received 3000 rad whole-brain radiation therapy;
Right: Follow-up CT scan 10 weeks later showed complete resolution of metastases.

(33%) were steroid-dependent until death.

There were only three patients in the entire series of 81 who had no evidence of other systemic disease at the time of the brain metastasis presentation; they were all in Group 3. Their survival times were 12 weeks, 41 weeks and 51+ months. The patient who survived only 12 weeks died of rapidly progressive systemic disease which only became apparent after the craniotomy.

The cause of death was determined in 38 patients dying at MSKCC using the criteria of Cairncross (8). Seventeen (45%) died of systemic disease; 13 (34%) died of combined neurological and systemic causes. Nine (21%) died from progressive neurological deterioration alone. The cause of death could be determined in five patients in Group 3. Three died of systemic disease and 2 due to combined neurological and systemic deterioration. No correlation could be found between the time interval from initial diagnosis to brain metastasis and from brain metastasis to death (linear correlation coefficient = 0.04). The one patient who is alive and well at more than 51 months after brain metastasis had a 12-month interval between initial diagnosis and brain metastasis.

Discussion

Malignant melanoma is an unusual tumor. Usually highly malignant and rapidly fatal when it metastasizes, the tumor has been known to lie dormant for years and even at times undergo spontaneous regression (9). Similarly, although it is among the most intractable of metastatic brain tumors, most large neurosurgical series report a few melanomas among their long-term survivors after surgical extirpation of a single metastatic tumor (10, 11). Curiously, one of the longest reported survivors of a metastatic brain melanoma is a patient whose metastatic tumor was only subtotally resected and who was well 11 years at most recent report (11).

There are other peculiarities of melanoma metastatic to the brain that differentiate it from the more common metastases of breast and lung cancer. Melanomas are much more frequently multiple rather than single, it being not unusual to find hundreds of discrete small metastases scattered throughout the brain. At autopsy, the incidence of leptomeningeal spread of melanoma is much higher than that of other tumors (12). Melanomas have a greater tendency to bleed than any metastatic brain tumors except perhaps choriocarcinoma and testicular metastases, and intracranial hemorrhage is often the mode of death in patients with melanoma. Observations at autopsy suggest that when melanoma metastasizes to the brain, it often invades the vasovasorum of blood vessels in the brain (13), perhaps accounting for the high incidence of hemorrhage. Similar invasion of blood vessels has been encountered in testicular tumors metastatic to the brain. Melanoma also, unlike other metastatic tumors, has a curious predilection to metastasize to grey matter (cerebral cortex and basal ganglia) more frequently than do other cancers which typically deposit at the grey matter/white matter junction (14).

Several of the factors that make melanoma an atypical tumor when it metastasizes to the brain may be responsible for the high incidence of seizures encountered in this study (53% of patients not placed on anticonvulsant therapy). Among the characteristics of melanoma that may account for the high incidence of seizures are: 1) the multiplicity of tumors, leading to more involvement of the nervous system and a greater tendency therefore to involve epileptogenic structures; 2) the tendency to involve grey matter rather than white matter; and 3) the tendency of melanomas to bleed. Cerebral hemorrhage is associated with a higher incidence of seizures in cerebrovascular disease (15), and small hemorrhages into metastases may in part account for the high incidence of seizures as the presenting symptom of metastatic melanoma. As a result of the high incidence of seizures, we recommend prophylactic anticonvulsants in patients known to have malignant melanoma metastatic to brain unless there is a specific contraindication. The presence of seizures may indicate that the tumor has bled.

Evaluating the clinical response of metastatic brain tumors to RT, surgery or chemotherapy is difficult. The failure of other organ systems may mimic progressive neurological disease even when treatment has been effective. (The change in CT scan after therapy is thus an important marker of response.) Furthermore, the marked salutary effect of corticosteroids on brain tumors makes it difficult to measure the clinical response to other modalities of therapy while steroids are being administered. Serial measurements of the area of contrast en-

hancement is one criterion by which to measure therapeutic efficacy since in an animal model of brain tumor the region of contrast enhancement corresponded closely to the size of the tumor (16). Many patients, however, in our series did not have follow-up CT scans. We, therefore, chose the discontinuation of steroids as the criterion to measure response to RT or surgery, recognizing that by this criterion many patients who were clinically well and even working full-time while taking steroids were considered non-responders.

Because 86% of patients with RT for multiple brain metastases (Group 1) were steroid-dependent until death, it appears that by this criterion RT has only a modest effect on this population of patients. For patients with a solitary metastasis treated with RT (Group 2), the response rate was 35% using this criterion. However, the median survival times for Groups 1 and 2 were essentially the same, 11 and 9 weeks, respectively. These survival results for RT are comparable to those obtained in other series (2–4).

The patients in Group 3 were selected as good operative risks with apparently stable systemic disease at the time of surgery. In fact, three patients in this group had no evidence of systemic disease at the time of craniotomy. The median survival of this group, 41 weeks, is comparable to that reported in other surgical series (2, 5, 6). Furthermore, as noted, six of nine patients could be tapered off steroids. However, as in Groups 1 and 2, the diagnosis of brain metastasis frequently was associated with the rapid progression of systemic disease. Of interest is the fact that in two patients the chest radiographs were negative at the time of diagnosis of brain metastasis but within 2 weeks there was extensive pulmonary involvement. The observation that the diagnosis of brain metastasis frequently heralds the progression of systemic disease further restricts the indications for surgical therapy.

Our current approach to the treatment of brain metastases from melanoma is as follows:

1) Patients with multiple brain metastases are considered candidates for steroids and whole-brain RT.

2) Patients with solitary brain metastasis undergo an extent-of-disease evaluation; steroids and whole-brain RT are delivered. If after 6–8 weeks the patient remains symptomatic and is considered a surgical candidate, the patient undergoes a second extent-of-disease evaluation and a double-dose contrast CT scan. If the patient's systemic disease appears quiescent and only one brain metastasis is found on the double-dose CT scan, we would consider surgical resection of the lesion.

While few patients will be candidates for surgical therapy under these guidelines, we believe that surgery will be avoided in those with rapidly progressive systemic disease and restricted to those who are most likely to benefit.

References

1. Chason JL, Walker FB, Landers JW: Metastatic carcinoma in the central nervous system and dorsal root ganglia: a prospective autopsy study. Cancer 16:781–787, 1963.
2. Amer MH, Al-Sarraf M, Baker LH et al: Malignant melanoma and central nervous system metastases: incidence, diagnosis, treatment and survival. Cancer 42:660–668, 1978.
3. Katz HR: The relative effectiveness of radiation therapy, corticosteroids, and surgery in the management of melanoma metastatic to the central nervous system. Int J Rad Oncol Biol Phys 7:897–906, 1981.
4. Carella RJ, Gelber R, Hendrickson F et al: Value of radiation therapy in the management of patients with cerebral metastases from malignant melanoma. Cancer 45:679–683, 1980.
5. Hafstrom L, Jonsson P-E, Stromblad L-G: Intracranial metastases of malignant melanoma treated by surgery. Cancer 46:2088–2090, 1980.
6. Fell DA, Leavens ME, McBride CM: Surgical vs nonsurgical management of metastatic melanoma of the brain. Neurosurgery 7:238–242, 1980.
7. Orton OG, Ellis F: A simplification in the use of the NSD concept in practical radiotherapy. Brit J Radiol 46:529–537, 1973.
8. Cairncross JG, Kim J-H, Posner JB: Radiation therapy for brain metastases. Ann Neurol 7:529–541, 1980.
9. McCarthy WH, Shaw HM, Milton GW: Spontaneous regression of metastatic malignant melanoma. Clin Oncol 4:203–207, 1978.
10. Ransohoff J: Surgical therapy of brain metastases. In: Weiss L, Gilbert HA, Posner JB (eds) Brain Metastasis. GK Hall, Boston, 1980, pp 380–389.
11. Bauman ML, Price Y: Intracranial metastatic malignant melanoma. South Med J 65:344–346, 1972.
12. Posner JB, Chernik NL: Intracranial metastases from systemic cancer. In: Schoenberg BS (ed) Neurological Epidemiology: Principles and Clinical Applications. Advances in Neurology series, Vol 19. Raven Press, New York, 1978, pp 579–592.
13. Nielsen SL: Personal communication.
14. Russell DS, Rubenstein LJ: Pathology of the Nervous System. Williams & Wilkins, Baltimore, 1971.
15. Aring CD, Merritt HH: Differential diagnosis between cerebral hemorrhage and cerebral thrombosis. Arch Int Med 56:435–456, 1935.
16. Groothius DR, Mikhael MA, Fischer JM et al: Computed tomography of virally induced canine brain tumors: a preliminary report. J Comp Ass Tomo 5:538–543, 1981.