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Review

Current treatment options of brain metastases and outcomes in patients with malignant melanoma

Jadwiga Nowak-Sadzikowska[a,*], *Tomasz Walasek*[b], *Jerzy Jakubowicz*[a], *Paweł Blecharz*[c], *Marian Reinfuss*[b]

[a] *Oncology Clinic, Centre of Oncology, Maria Skłodowska-Curie Memorial Institute, Cracow Branch, Kraków, Poland*
[b] *Radiotherapy Department, Centre of Oncology, Maria Skłodowska-Curie Memorial Institute, Cracow Branch, Kraków, Poland*
[c] *Gynecologic Oncology Clinic, Centre of Oncology, Maria Skłodowska-Curie Memorial Institute, Cracow Branch, Kraków, Poland*

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ABSTRACT

The prognosis for patients with melanoma who have brain metastases is poor, a median survival does not exceed 4–6 months. There are no uniform standards of treatment for patients with melanoma brain metastases (MBMs). The most preferred treatment approaches include local therapy – surgical resection and/or stereotactic radiosurgery (SRS). The role of whole brain radiotherapy (WBRT) as an adjuvant to local therapy is controversial. WBRT remains a palliative approach for those patients who have multiple MBMs with contraindications for surgery or SRS, or/and poor performance status, or/and very widespread extracranial metastases. Corticosteroids have been used in palliative treatment of MBMs as relief from symptoms related to intracranial pressure and edema. In recent years, the development of new systemic therapeutic strategies has been observed. Various modalities of systemic treatment include chemotherapy, immunotherapy and targeted therapy. Also, multimodality management in different combinations is a common strategy. Decisions regarding the use of specific treatment modalities are dependent on patient's performance status, and the extent of both intracranial and extracranial disease. This review summarizes current treatment options, indications and outcomes in patients with brain metastases from melanoma.

1. Introduction

Melanoma gives rise to about 10% brain metastases (melanoma brain metastases – MBMs) and is ranked the third leading cause of brain metastases after lung cancer (30–60%) and breast cancer (15–25%).[1–4] The incidence of brain metastases in patients with loco-regional melanoma ranges from 10% to 13%, in patients with metastatic disease it can exceed 15–50%.[1,5,6] Almost half of patients with malignant melanoma die as a result of MBMs, autopsy data confirm brain metastases in up to 50–75% of such cases.[1,3,5–7]

* *Corresponding author at*: Oncology Clinic, Gastrointestinal and Urological Cancer Unit, Centre of Oncology, Maria Skłodowska-Curie Memorial Institute, Cracow Branch, 11 Garncarska Street, 31-115 Kraków, Poland. Tel.: +48 126348305; fax: +48 126348305.
E-mail address: Z5sadzik@cyfronet.krakow.pl (J. Nowak-Sadzikowska).
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Use of magnetic resonance imaging (MRI) of the brain in the work-up stage IV melanoma and routine screening NMR for clinical trials have yielded increased detection of asymptomatic, small MBMs.[2–6] This subgroup of patients has relatively long time expectancy and preserved performance status.

The prognosis of patients with MBMs is poor, with a median survival time of 4–6 months.[3,8–23] Median survival in patients with no treatment is shorter and is estimated to be only about 1 month,[6,8,14–16] in patients who had palliative corticosteroid therapy it is about 2 months,[1,8,15,16] and in patients who had whole brain radiotherapy (WBRT), 3–4 months.[13,15–17] Many data suggest that selected patients may benefit from surgical resection or stereotactic radiosurgery (SRS) as median survival was reported from a few to even 14 months.[6,14,16,18–21,23,24]

Various modalities currently available for the treatment of MBMs include: neurosurgery, SRS, WBRT, systemic therapy (chemotherapy, immunotherapy, BRAF (B-Raf proto-oncogene, serine/threonine kinase) inhibitors). Also, multimodality management in different combinations is a common strategy.[1,2,5,7,9,10,18,25–29] Generally, both local (surgery or SRS) and regional treatments (WBRT) are preferred; alternatively, combination surgery with radiotherapy is used, whereas systemic therapy is considered and administered as second-line therapy.[2,7,9,18,21]

2. Surgery

In contrast to the infiltrative nature of primary brain tumors (e.g. Glioblastoma multiforme) MBMs tend to have a noninfiltrative growth pattern, very often characterized by pesudoencapsulation.[2] Therefore, surgical resection continues to be the standard of care in selected patients with MBMs.[1,2,9,21,29,30] The best candidates for surgery are patients with:

- only one lesion, located supratentorially, which can be safely and completely resected
- without neurologic deficits,
- with controlled systemic disease.

The resection of a dominant single MBM, causing severe neurologic compromise or life threatening complication, is reasonable in selected groups of patients, even with a significant extracranial disease. Patients with multiple, up to 3, MBMs may also benefit from surgery. It seems that a potential radical excision of all lesions provides similar probability of cure as compared to surgical resection of a single MBM.[32] Even incomplete resection of MBMs may relieve acute neurological symptoms, while facilitating safe administration of subsequent WBRT or SRS targeting the resection cavity. In some cases, surgery provides histological confirmation of diagnosis.[1,21,33]

Three randomized studies have compared neurosurgery followed by WBRT to WBRT alone.[33–35] Only patients with single brain metastasis (BM) from different primary tumors, including melanoma, were eligible for these studies. The studies by Patchell et al. and Vecht et al. reported an improvement in overall survival rate, with median survival of 9–10 months versus 3–6 months, for the combined therapy arm versus WBRT alone.[33,34] In contrast, Mintz et al. did not demonstrate any benefit, probably due to a higher proportion of patients with active systemic disease and lower performance status.[35]

Several retrospective studies showed improvement in outcome of surgery alone compared with WBRT alone in selected groups of patients with MBMs. Cattell et al. emphasized that median survival of patients with MBMs who had undergone surgical resection ranges from 5.4 to 12 months, with survival rates at 1 year and 5 years amounting to 28–36% and 6.6–8%, respectively.[21] Salvati et al. reported, based on data available in 84 patients with single brain metastasis from melanoma who underwent surgery in years from 1997 to 2007, that 1-, 2- and 3-year survival rates were 38.1%, 14.3%, 6%, respectively. None of the patients in whom removal was subtotal survived more than 6 months. The use of adjuvant radiotherapy did not reveal any statistical impact in terms of overall survival in a group of 32 patients when surgical resection was performed alone versus 52 when it was combined with adjuvant WBRT or SRS.[30]

The role of WBRT following a complete surgical resection of brain metastases remains controversial. Some retrospective studies suggest a good outcome following surgery alone without any benefit from adjuvant WBRT.[2,8] In a very large retrospective analysis, by Fife et al., of patients with MBMs, median survival times of 8.9 and 8.7 months were observed with surgery as a primary treatment with or without adjuvant WBRT, respectively.[8] These findings demonstrate very modest additional benefit of WBRT. Sampson et al. reported that median survivals of patients with MBMs who underwent surgical resection alone or with subsequent adjuvant WBRT were in the range of 195 (161–292) and 268 (220–405) days, respectively, but statistical significance was not reached.[36]

Despite that, some authors suggest the advantage of combined therapy (surgery with WBRT) over surgery alone for patients with MBMs.[37]

Postoperative treatment of patients who have a limited number of brain metastases with SRS targeting the resection cavity has been explored.[38,39] The addition of SRS to neurosurgery results in good local control and allows patients to defer or avoid neurocognitive toxicity associated with WBRT. It should be pointed out that in the group of 112 patients with BMs treated with SRS postoperatively, multivariate analysis showed melanoma histology to be associated with statistically higher distant brain failure.[39]

3. SRS

SRS is delivered by high energy X rays from a linear accelerator, γ-rays from a cobalt-60 source (gamma knife), or, rarely due to high costs, protons from a cyclotron. According to RTOG 90-05 protocol, the maximum tolerated doses of single fraction radiosurgery for lesions of 3.1–4.0 cm, 2.1–3.0 cm and <2.0 in maximum diameter are 15 Gy, 18 Gy and 24 Gy, respectively.[40]

SRS has been used for the treatment of MBMs patients with:

- solitary or multiple (up to 10) lesions,
- deep-seated, surgically inaccessible lesions,
- lesions in eloquent areas,

- minimal neurological symptoms,
- stable systemic disease.[1,2,9,21,36]

In such an appropriately selected group of patients, SRS is considered equivalent to surgery; however, this treatment modality has been addressed in only one prospective randomized trial that was terminated at an early stage because of poor recruitment.[41] Nevertheless, most authors consider SRS to be an alternative to surgery in small asymptomatic MBMs.[2,4,9,18–20,23,24,42,43] Although randomized comparisons are not available, linear accelerator-based SRS and gamma knife-based approaches appear to provide comparable outcomes.[9]

Retrospective studies unequivocally validate the efficacy of SRS in treatment of MBMs, with median survival times from 4.8 to 10.6 months, and local control rate from 47% to 84%.[19,20,23,24,42–47] Significant differences in these outcomes may have resulted from various reasons; including differences in the number and size of treated lesions, performance status, status of extracranial disease, dose of administered SRS, entry criteria for trials, and presentation of research results. Despite these dissimilarities, high local control rate and prolongation of survival can be achieved for patients with MBMs treated with SRS.[2] There is no doubt that SRS of multiple MBMs prolongs survival and relieves annoying symptoms.[9,18,20,23]

The role of WBRT in patients with MBMs treated with SRS is controversial. Mori et al. showed that SRS plus WBRT resulted in equivalent survival and local control, compared with SRS alone, with only a reduced number of new brain metastases that develop at a later phase of the disease.[44] Brown et al. showed improvement in local control for a period of 6 months with a decrease in distant brain failure and unchanged overall survival with adjuvant WBRT to SRS.[48] Stone et al. achieved a median survival of 3.6 months for a WBRT-only group compared with 10.9 months in a combined therapy group: WBRT and SRS, or surgery.[49] Selek et al. did not demonstrate any significant differences in survival between patients treated with SRS alone or with adjuvant WBRT, and observed that one year local control rates were worse in the combined therapy group.[47] In a study by Mathieu et al., the addition of WBRT at any point during the course of management did not affect survival and local control.[20] Some authors point out that a combination of WBRT and SRS preclude the use of salvage therapy in case of local failure.[4]

On the other hand, phase III, randomized, prospective trial comparing WBRT with or without SRS boost for patients with 1-3 brain metastases demonstrates significantly improved performance status for all patients and survival for patients with a single brain metastasis in the combine therapy group. Decreased steroid use at 6 months in the SRS boost treatment group was also observed.[50] Secondary analysis of the JROSG99-1 Randomized Clinical Trial comparing SRS alone with WBRT + SRS for up to 4 BMs demonstrates significant prolongation of survival among WBRT patients with non-small-cell lung cancer with favorable prognosis (median survival time of 16.7 months vs. 10.6 months $p = 0.04$).[51] The addition of WBRT to local treatment (neurosurgery or SRS) in patients with brain metastases from solid tumors decreases intracranial relapse and need for salvage therapy without improvement in overall survival and duration of functional efficiency.[9,31,52] Antoni et al., however, recommend adjuvant WBRT, pointing out that its value should be assessed in randomized, prospective multicenter trials.[31]

Chang et al. indicated that WBRT may impair neurocognitive function (NCF), especially among patients with longer survival.[53] A phase III randomized multicenter trial of WBRT in addition to SRS in patients with up to 3 BMs showed an important and prolonged impact of WBRT on NCF.[54] Deterioration in cognitive function, specifically immediate recall (31% vs. 8%, $p = 0.007$), delayed recall (51% vs. 20%, $p = 0.002$) and verbal fluency (19% vs. 2%, $p = 0.02$), was more frequent with the addition WBRT to SRS. Adjuvant WBRT did not improve OS despite a better brain control.

Currently, randomized III phase trial of WBRT vs. observation after local treatment of MBMs is conducted by the Australia and New Zealand Melanoma Trials Group and Trans-Tasman RTOG Trial in hope of improving disease control, and quality of life, while maintaining satisfactory cognitive performance. Patients with 1-3 brain metastases excised and/or stereotactically irradiated and ECOG status of 0-2 are eligible. WBRT prescription is at least 30 Gy in 10 fractions commenced within 8 weeks of surgery and/or SRS.[25]

The neurocognitive decline in patients with brain metastases receiving WBRT is often affected by other factors including: brain tumors; disease progression, both intracranial and extracranial; treatment interventions, such as neurosurgery, chemotherapy, anticonvulsants, steroids, opiates, etc.

Recent clinical studies indicate that radiation-induced damage to the hippocampus plays considerable role in NCF decline of patients after cranial irradiation.[55] In the single arm, phase II, multi-institutional, international clinical trial, conformal avoidance of the hippocampus during WBRT was associated with memory preservation at 4 and 6 months follow up.[56] Hippocampal sparing WBRT warrants consideration, especially that the hippocampus is rarely a site of metastatic spread.[57]

In order to reduce the cognitive effect of WBRT, a Japanese group launched a clinical trial investigating the combination of reduced total dose as well as fraction dose: WBRT – 25 Gy in 10 fractions combined with SRS in patients with BMs.[51]

RTOG conducted a randomized, double-blind, placebo-controlled trial assessing memantine for the prevention of cognitive dysfunction in patients receiving WBRT.[58] Use of memantine during and after WBRT resulted in better cognitive function over time, but the difference was not statistically significant.

4. WBRT

WBRT commonly combined with corticosteroids remains the treatment modality of choice in patients with:

- multiple MBMs,
- contraindications for surgery or SRS,
- poor performance status,
- extensive extracranial disease.

WBRT has a very small impact on survival, the median survival of patients with MBMs who undergo WBRT ranges from

3 to 6 months.[8,18,20,21,31,43,59] Palliative WBRT rapidly relieves neurological symptoms, improves performance status, with prolongation of life with self-care activities.[9,31] The use of adjuvant WBRT to surgery or SRS allows to prevent recurrence at initial site of metastases and decrease the development of new lesions elsewhere in the brain.[2,9]

Regiments of 30 Gy divided into 10 fractions or 37.5 Gy in 15 fractions, have been widely adopted. Nevertheless, according NCCN guidelines, 20 Gy in 5 fractions is a good option in poor performers.

5. Systemic therapy

Only two cytostatic drugs, fotemustine and temozolomide (TMZ), were observed to show a real but very low efficacy in the treatment of MBMs was observed.[1,7,9,21,60–66] In phase III trial conducted by Mornex et al., fotemustine combined with WBR, compared with fotemustine alone, resulted in equivalent survival (median survival 3.4 months vs. 2.8 months) and brain response (7.4% vs. 10.0%).[62] Avril et al. achieved a relatively low percentage of cerebral response after treatment of MBMs with fotemustine – 5.9%, as compared with no brain response following treatment with dacarbazine – 0%.[63] Fotemustine has significant hematologic toxicity and is used in Europe, for example in France, but it is not approved for clinical use in the USA. As in the case of fotemustine, the majority of either prospective or retrospective studies on temozolomide have demonstrated its limited efficacy in the treatment of MBMs.[1,2,7,9,60,61,65–67] In phase II study carried out by Agarwala et al., on previously untreated MBMs patients with TZM achieved 7% of an objective response, with median survival of 3.5 months. Among previously systemically treated patients, median overall survival was 2.2 months.[64] Schadendorf et al. demonstrated limited efficacy of TZM, with less than 5% of objective responses and median survival of 3.5 months in a group of 45 patients with asymptomatic MBMs.[65] In a study by Boogerd et al. including 52 patients with advanced melanoma with MBMs that measured <2 cm and with TZM as a single treatment, the median survival was 5.6 months.[66] Also, adjuvant TZM to WBRT regimen has a very small impact on the MBMs patients outcome.[7,9,60,67] Schild et al. did not observe any benefit from the addition of TZM to WBRT in a group of 53 patients with MBMs. The median survival was 3.8 months with WBRT alone compared to 4.3 months in a WBRT plus TZM group.[7]

There is some evidence that ipilimumab, a monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA-4), can be effective in patients with MBMs.[9,28,29,68] In a small group of 12 patients with MBMS on ipilimumab therapy, Weber et al. reported partial response in 2 cases and stabilization in 3 cases, while the median survival for all groups was 14 months.[68] Margolin et al. enrolled 72 ipilimumab-treated patients with MBMS into two cohorts. Patients in cohort A (52 patients) were neurologically asymptomatic, while those in cohort B (21 patients) were symptomatic and stable on corticosteroids, and the median survival was 7 and 4 months, respectively.[28] Knisely et al. reviewed 77 MBMs patients who underwent SRS between 2002 and 2010, and 35% percent of these patients received ipilimumab. The use of ipilimumab in a supportive treatment of SRS was associated with an increased median survival from 4.9 to 21.3 months, with a 2-year survival rate of 19.7% versus 47.2%.[29] In a retrospective study by Mathew et al., administration of ipilimumab did not improve overall survival, local control and freedom from new brain metastases in patients with limited MBMs who received SRS.[69] It should be pointed out that the efficacy of ipilimumab is limited to asymptomatic patients with MBMS, with good performance status owing to its slow onset of actions. Therapeutic response peak is observed between 12 and 24 weeks, with slow responses continuing up to and beyond 12 months. Ipilimumab is inappropriate for those patients with rapidly progressing or symptomatic BMs.[9]

Du Four et al. presented four melanoma patients with MBMs who developed symptomatic radiation necrosis of the brain (RNB) that was histologically confirmed, following SRT and ipilimumab.[70] These cases represent about 10% of all cases treated with ipilimumab and irradiation. This observation indicates a need for further research to determine whether this problem is the result of longer survival or whether there is some synergy between these two modalities.

PD-1 protein, a T-cell coinhibitory receptor and one of its ligands play a pivotal role in the ability of tumor cells to evade the host's immune system. Nivolumab, an antibody against programmed death 1 (PD-1), produced durable tumor regression and prolonged stabilization of disease in patients with metastatic melanoma in phase I trials.[71] CTLA-4 and PD-1 appear to play complementary roles in the enhancement of immune function. Combined therapy – nivolumab plus ipilimumab – in patients with advanced melanoma, in phase I study results in more rapid and deeper clinical tumor responses as compared with previous experiences with either agent alone.[72] This results form the basis of a further planned trials. Currently, ANZMTG 01.14 ABC Nivo A phase II study of nivolumab and nivolumab in combination with ipilimumab in patient with melanoma brain metastases is being conducted.

Mutation of the BRAF gene is observed in approximately 40–60% patients with melanoma, and the V600E mutation (amino acid substitution at position 600 in BRAF from a valine to a glutamic acid E) comprises about 90% of these cases. Vemurafenib and dabrafenib, which are BRAF inhibitors, have been developed and are available for the first line systemic therapy of advanced melanomas in subpopulations identified by mutation tests.[9] Dummer et al. presented the results from a pilot study of vemurafenib in 5 previously treated metastatic melanoma patients with MBMs. Stabilization of brain metastases occurred in 4 patients and partial remission in one.[73] Rochet et al. described 3 patients with BRAF V600E mutation metastatic melanoma in whom the treatment with vemurafenib resulted in a prompt extracranial disease response, but in a progression of metastatic disease in the brain.[74]

Long et al. in 2010, and Falchook et al. in 2012, reported a marked efficacy of dabrafenib in the treatment of MBMS.[75,76] In a group of patients with untreated, asymptomatic MBMs with BRAF mutations, with size range of 3–15 mm, reductions in the size of brain lesions were seen in nine out of ten.[75] Mittapalli et al. suggested that dabrafenib compared with vemurafenib shows greater brain penetration at a similar dose.[77] The largest multicentre, open-label phase 2 trial (BREAK-MB) assessed dabrafenib in 172 patients with MBMs.[78] Enrolled were

patients with histologically confirmed Val600Glu (often called V600E) or Val600Lys (amino acid substitution at position 600 in BRAF from a valine to a lysine K) BRAF-mutant melanoma and at least one asymptomatic metastasis of 5–40 mm in diameter. Overall intracranial response occurred in 29/74 (39.2%) patients with Val600Glu BRAF-mutant previously untreated for brain metastases and in 20/65 (30.8%) patients with progressive intracranial disease after previous local treatment. Median progression-free survival was longer than 16 weeks and overall survival was greater than 31 weeks in both groups. Disease response and survival were worse in patients with Val600Lys BRAF-mutant melanoma compared with Val600Glu BRAF-mutant melanoma. However, small numbers of patients with Val600Lys BRAF-mutant melanoma in this study limit the interpretation of these results. Treatment was well tolerated and only 2% of patients discontinued dabrafenib because of adverse events.

In summary, BRAF inhibitors probably improve the outcome of patients with MBMs with tumor BRAF mutations, and multicenter translational prospective randomized trials are warranted to determine their real effectiveness. Future clinical trials are also required to test the combination of molecular targeted treatment with local therapy (surgery or SRS) or regional therapy WBRT.[9]

In conclusion, there are no uniform standards of treatment for patients with MBMs. Decisions regarding the use of specific treatment modalities for the management of MBMs are dependent on a patient's performance status, and the extent of both intracranial and extracranial disease. Multidisciplinary team of neurosurgeons, medical oncologists and radiation oncologists should determine the best treatment strategy and participation in a clinical trial is recommended whenever possible. Local therapy – surgical resection and/or SRS – is the preferred treatment option. Radical local treatment surgery or SRS can be used in patients with a good performance status, solitary or a few lesions, and stable systemic disease. The role of WBRT as an adjuvant to local therapy is controversial. WBRT remains a palliative approach for those patients with contraindications for surgery or SRS, and/or a poor performance status or/and very widespread cranial and extracranial metastases. In view of small efficacy of chemotherapy (fotemustine, TZM), the development of immunomodulatory agents and threonine-protein kinase inhibitors creates new possibilities.

Conflict of interest

None declared.

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