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Review

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

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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]

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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,