Chapter 9

Metastatic Brain Tumors

Steven N. Kalkanis and Sanjay Patra

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1. Introduction

The 2008 American Cancer Society Registry data show that approximately 1.4 million Americans are diagnosed with cancer every year of which 40% will go onto to develop brain metastases. Consequently, the incidence of these secondary brain tumors is about four to five times that of primary brain tumors [1, 2].

The past two decades have seen a large increase in treatment options, resulting in longer life expectancy and better quality of life to a point where metastatic lesions are no longer the major cause of mortality in this patient group. This has made decision making on treatment modality more complex. Evidence for local aggressive control through surgery and stereotactic radiosurgery (SRS) [3–5] has resulted in a paradigm shift since the mid 1990's when whole brain radiation therapy (WBRT) was the mainstay of treatment. Now, treatment of metastatic tumors includes a full spectrum of medical providers including neurosurgeons, medical oncologists, radiation oncologists, neurologists, and neuro-oncologists. This Chapter will focus on the contemporary management of metastatic brain tumors using surgery, radiosurgery, conventional radiation therapy, chemotherapy, steroids, anti-epileptics, and emerging modalities. Given the myriad of treatment options and the multiple providers utilizing them, the substantiation for these treatments are vital for the clinician to make an evidence-based decision. The information in this chapter will not only serve to guide the clinician in treatment options, but also to focus the researcher on areas that need further investigation.

2. Radiation Therapy

Historically, whole brain radiation therapy (WBRT) was the mainstay for treatment of metastatic brain tumors. Today, it remains an important part of the treatment regime, although in a more complimentary role.

In the randomized control trial (RTC) of Patchell [6] a total of 48 patients were treated with WBRT and either biopsy or complete surgical resection. The surgical group had a statistically significant increase in survival (40 weeks) compared to the biopsy group (15 weeks) (Ib/A). Freedom from death due to neurologic compromise, duration of functional independence and time to recurrence of a new brain lesion were all increased significantly as well. All patients had a Karnofsky performance score (KPS) of at least 70 and patients with acute neurological deterioration and radiosensitive tumors (SCLC, lymphoma, germ cell tumors, multiple myeloma or leukemia) were excluded from the study.

Another RCT done in Canada done by Mitz et al looked at 84 patients treated with WBRT and surgery or WBRT alone [7]. This trial included patients who spent greater than 50% of day in bed and MRI scans were not mandatory. They did not find any statistically significant difference in causes of death, quality of life, or overall survival. The lack of mandatory MRI scans raised the possibility of patients with multiple lesions being included in the study population.

Finally, a RTC done by Vecht et al [8] in the Netherlands looked at 63 patients and compared surgical resection plus WBRT to WBRT alone. Survival in the surgical group was significantly longer (10 months) compared with the non-surgical group (6 months). The patients included in the trial were younger than 60 years, within 6 months of diagnosis, and without progressive systemic disease.

In total, there are three randomized controlled trials (RCTs) [6-8] and three level II studies [9-11] that show surgical resection plus WBRT is superior to WBRT alone for surgically accessible single brain (verified by MRI) metastatic lesions in patients with limited extra cranial disease who spend less than 50% of the day in bed. Taken together, there is level Ia/A evidence supporting the use of surgical resection plus WBRT rather than WBRT alone.

3. WBRT dosing and fractionation schedule

There are 10 level I studies [12-20] including 9 RCT that have shown deviating from the standard 30Gy in 10 fractions does not significantly change local control, neurocognitive outcome or median survival in newly diagnosed adults with brain metastasis (Ia/A).

4. Surgical Resection

In the previous section we described the evidence for improved mortality outcomes in patients with newly diagnosed single metastatic lesions undergoing surgical resection plus WBRT compared to WBRT alone in terms of overall survival. Various groups have compared the effects of surgery alone to surgery plus WBRT given the known side effects of radio therapy.

Patchel et al [3] studied 95 patients who underwent MRI verified complete surgical resection and randomized them to receive WBRT or no further treatment. Tumor recurrence was 70%

in the surgery alone group compared to 18% in the WBRT group ($p<0.001$). Recurrences were lower for both the resection site and de novo lesions. There were fewer deaths from neurologic causes in the WBRT (14% vs. 44%) but the study was not powered to analyze overall survival. This RCT along with three retrospective cohort studies [21-23] provide level Ib/A evidence for improved tumor control with surgical resection and WBRT compared to surgical resection alone.

With the emergence of high dose single fraction radiotherapy groups have compared surgical resection plus WBRT to stereotactic radiosurgery (SRS) alone. There has been one small multicenter RCT in Germany by Muacevic et al [24] that enrolled a total of 64 patients with KPS scores greater than 70 with single, small (<3cm) metastatic lesion into a surgical resection plus WBRT group and a SRS group. Their primary outcome was overall survival but they also looked at time of freedom from local recurrence. The only outcome that was statistically different between the groups was distant recurrence, which was higher in the SRS alone group.

There have been four retrospective cohort studies [25-28] comparing surgical resection and WBRT to SRS and WBRT. Taken together these studies provide level III/B evidence that surgical resection with WBRT is comparable to SRS with WBRT in terms of survival and local recurrence. These studies also show that lesions larger than 3cm or those with significant mass effect have better outcomes with surgical resection and WBRT.

5. Stereotactic radiosurgery

SRS has emerged as a less invasive focal treatment modality to treat metastatic lesion. There have been two RCTs comparing single dose SRS and WBRT to WBRT alone.

Kondziolka et al [4] evaluated a total of 27 patients (KPS<70) with 2-4 solid metastatic lesions less than 2.5cm in diameter and randomized them to receive SRS and WBRT or WBRT alone. The primary outcome was image-defined local tumor control with median survival being the secondary outcome. The study showed the local failure rate was 8% in the SRS plus WBRT group compared to 100% in the WBRT group. The study was stopped prematurely due to this significant benefit. This did not give the study enough power to look at survival.

The other multicenter RCT [5] looked at a total of 272 patients with 1-3 solid metastatic lesions (<4cm in diameter) and KPS of more than 70. They randomized patients into a group undergoing WBRT plus SRS and WBRT alone. Their primary endpoint was median survival which was statistically improved in the group receiving SRS (6.5 vs. 5.7 months). Superior one year local control and improved KPS was also evident in the group receiving SRS.

There have also been three other retrospective series [29-31] looking at the above comparisons which have supported the findings of the RCTs in regards to improved overall survival, thus providing level Ia/A evidence for using single dose SRS with WBRT rather than WBRT alone for single metastatic lesions in patients with a KPS greater than 70. There is lev-

el IIa/B evidence that SRS plus WBRT is superior in local tumor control and maintaining functional status compared with WBRT alone in patients with less than 4 lesions.

There has been one RCT that compared SRS alone to WBRT plus SRS. This was a multi-institutional study by Aoyama et al [32] that randomized patients with 1-4 solid brain metastatic lesions (diameter <3cm) and KPS greater than 70 to received SRS alone or SRS with WBRT. Median survival, which was the primary end point, was not statistically different between the groups (8vs7.5 months). No difference was found in 1 year local control or neurologic cause of death. Distant brain recurrence and the requirement for salvage therapy were significantly greater in the SRS alone group. There has also been a prospective cohort study [30] along with 9 retrospective cohort studies [33-41] that have addressed this question. Together, there is level IIa/B evidence that SRS alone provides a similar survival advantage to SRS and WBRT. There is also Ia/B evidence that WBRT provides improved distant site control. For this reason patients only undergoing SRS require close monitoring so salvage therapy can be delivered early to a de novo lesion.

A three arm prospective cohort study by Li et al [30] provides a comparison between SRS alone and WBRT alone. The SRS alone group had improved neuroimaging response (87% vs. 38%), median time to progression (6.9 vs. 4 months) and longer median survival (9.3 vs. 5.7) months. Although there have been no RCTs addressing this question data from the Li et al trial and four other retrospective cohorts studies [42-45] provides level II/B evidence for SRS alone being superior to WBRT alone in terms of survival for patients with up to 3 lesions.

6. Chemotherapy

Chemotherapy has remained the primary treatment modality for systemic metastases. However, it is believed that brain metastases are selected to be chemoresistent because only resistant cells are able to survive systemic chemotherapy and make it to the brain. Furthermore, the effectiveness of chemotherapy in the brain has remained a concern due to the blood-brain barrier and active efflux pumps [46] limiting the effective dose in the central nervous system. For this reason, chemotherapy has been less effective in treating CNS metastases. This is evident from a study [47] that involved treatment of metastatic SCLC which showed decreased effectiveness from chemotherapy of CNS compared to system lesions.

There have been four RCTs [48-51] comparing WBRT plus chemotherapy to WBRT alone. A multi-institutional RCT [48] studied patients who had histologically proven NSCLC and a WHO performance status of 0, 1, or two and at least one brain metastasis on CT or MRI. These patients either refused surgery or were deemed inoperable. The patients were randomized to receive WBRT and Carboplatin or WBRT alone and the primary end point was overall survival. The median survival was similar in both groups. The trial was halted for poor accrual and did not show improved survival (Ib/A).

Another RCT was performed by Ushio et al [49] where patients with all lung cancer subtypes and projected survivals of greater than 4 months were randomized to WBRT, WBRT

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plus chloroethyl nitrosourea (CCNU), and WBRT plus CCNU plus tegafur. Patients were excluded if they received any prior chemotherapy. The primary end point of tumor response rates were 36%, 69%, and 74% respectively. The only statistically significant difference was between WBRT and WBRT plus CCNU plus tegafur. The secondary end point of survival showed no statistically significant difference (Ib/A).

The two other RCTs [50, 51] looked at temazolamide (TMZ) and radiotherapy and did not show any statistically significant differences.

Taken together these studies provide level Ia/A evidence that adding chemotherapy to WBRT does not improve survival. However, these trials did not take into account all histologies, focusing on NSCLC and breast cancer and their results cannot be applied to chemo sensitive tumors such as germinomas.

7. Re-treatment

There is very little data on managing recurrent metastasis. Detailed guidelines on this were published by Ammirati et al in 2010 [52].

There have been three retrospective case series looking at the effects of repeating WBRT in patients with brain recurrence following previous therapy. Post WBRT survival was 4-5 months in all series [53-55] (III/B).

Four case series [56-59] evaluated the effects of surgery on patients with recurrent or progressive brain metastases. Median time to recurrence at local and distant sites was 5-8.4 months with survival ranging from 8.9-11.5 months (III/B).

There has been one prospective Phase/II study [59] that investigated the effects of SRS for recurrent brain metastases. Twelve patients with progressive metastatic lesions, with at least 3 months of projected survival and who were previously treated with WBRT were given SRS. The median survival was 6 months.

Currently, there is only enough evidence to give a level III/B recommendation for individualization of care based on functional status, extent of systemic and intracranial disease, previous treatment type, primary cancer type, progression at original or distant site, and enrollment in clinical trials. Taking this into consideration no further treatment of WBRT, SRS or surgical excision can be recommended.

8. Prophylactic anticonvulsants

It is thought that brain metastases are unlikely to be as epileptogenic as primary gliomas due to their less infiltrative nature. However, the role of prophylactic antiepileptic drugs (AEDs) remains unclear. Mikklesen et al [60] has published evidence-based guidelines on this topic in 2010.

Forsyth et al [61] performed a RCT and studied anticonvulsant use in 100 patients with all types of brain tumors and stratified them into primary and metastatic groups. Exclusion criterions were known seizures, life expectancy less than 4 weeks, allergies to AEDs, history of substance abuse, and pregnancy. Most patients were treated with phenytoin. The primary outcome was seizure occurrence at 3 months. The trial was halted early because the anticipated seizure rate in the non AED arm was only 10% and the 3 month mortality was higher than expected (30 vs. 15%). This lowered the power of the study and the authors reported no difference between treatment groups.

Taking into account the known side effects of AEDs there is level III/B evidence for not using them routinely for seizure prophylaxis in patients with newly diagnosed brain metastases. Further studies are needed in this area and are currently underway.

9. Steroids

Steroids have an established role in controlling cerebral edema with dexamethasone typically chosen due to its minimal mineralocorticoid activity. They are however not without side effects including myelopathy, insulin resistance, and gastrointestinal bleeding. The role of steroid use and timing are discussed in this section. Ryken et al [62] has published the evidence based guidelines on this topic in 2010.

Vechet et al [63] performed a RCT in patients with metastatic disease and a KPS of less than 80. This study evaluated the minimal effective dose of oral dexamethasone. The author found no evidence for higher doses in patients who were not in immediate danger of herniation. In moderately symptomatic patients doses of 4-8mg/day were equivalent to 16mg/day.

Given the minimal data, a level III/B recommendation can be made for the use of corticosteroids with dexamethasone (4-8mg/day) as the glucocorticoid of choice, to provide temporary symptomatic relief of elevated intracranial pressure. In patients experiencing severe symptoms of elevated intracranial pressure a dose of 16mg/day can be recommended. Doses should be tapered off over a 2 week period.

10. Emerging and investigational therapies

Plainly, successful control of brain tumors has not been uniformly achieved given the efficacy and toxicity profile of the currently used modalities. Several new treatment modalities are emerging including radiation sensitizers, local irradiation with balloon-based brachytherapy, local chemotherapy with BCNU-impregnated polymers, and molecular targeting. The evidence based guidelines for these modalities have been reviewed by Olson et al [64].

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11. Motexafin gadolinium

Motexafin gadolinium (MGd) is a metallotexaphrin that concentrates within tumors at higher levels than within normal tissues. It is detectable on MRI scanners and although its exact mechanism of action is unclear, it is thought to act as a radiation sensitizer. Two RCTs and one prospective single arm study have studied this agent.

Carde et al studied the dosing of MGd and found 5mg/day with 30Gy of WBRT in 10 fractions to be best tolerated [65]. This led to a RCT of 410 patients that compared WBRT with WBRT plus MGd in patients with brain metastasis [66]. Although the study showed no difference in median survival or tumor response there was a 0.5 month delay in neurologic progression in the MGd group. A Phase III RCT was then conducted that included 554 patients with NSCLC. They were randomized to WBRT or WBRT plus MGd. No statistically significant difference was found in neurologic progression between groups.

12. Efaproxiral

Efaproxiral is a radiation sensitizer that is thought to change the conformation of hemoglobin. This is thought to increased free radical formation by decreasing oxygen binding. The two phase II studies done did not show any benefit in survival. There is level IIa/B evidence that early use of efaproxiral with WBRT does not prolong survival.

13. Interstitial modalities

Interstitial modalities are defined as brachytherapy placed inside or next to the areas being treated. There has been one retrospective cohort study by Ostertab and Kreth who implanted ^{125}I seeds in spherical brain metastases with a diameter of 4cm or less, giving 60Gy to the rim of the lesion [67]. No difference was found between WBRT and ^{125}I to ^{125}I alone. Two other case [68, 69] series supported the feasibility of the modality but did not offer any evidence for increased efficacy.

A phase II study by Rogers et al [70] evaluated the Glia Site Radiation Therapy System in post resection surgical beds in patients with metastatic lesions. The system involved liquid ^{125}I that could be injected via a balloon system from a subcutaneous reservoir. The median survival was 40 weeks at 1 year of follow-up with tumor progression only being involved in 4 of the 35 total deaths. Although the data was prospectively obtained, there was no comparison group.

Two single-arm studies evaluated surgery plus local chemotherapy with or without WBRT. Nakagawa et al [71] used the DNA synthesis inhibitor 5-fluro-d-deoxyuridine (FdUrd) in post resection tumor cavities via an Ommaya reservoir. This study only included 6 patients and no comparative data were given. Ewend et al [72] prospectively studied 25 patients with newly diagnosed solitary brain metastases treated with surgical resection. They used the Gliadel Wafer and WBRT. Median survival was 33 weeks but again there was no comparative data (III/B).

Two case series [73, 74] investigated interstitial radiosurgery with the Photon Radiosurgery System. Neither study had comparative data but showed a median survival of 8 months and 1-year survival of 53% (III/B).

Based on the current data there is no evidence to support the use of interstitial radiation, chemotherapy or other modalities outside of clinical trials.

14. Molecularly targeted therapy

Currently there is no level 1 evidence for the use of molecularly targeted therapies in brain metastasis. Given the promising theoretical advantage of these therapies prospective trials focusing on survival, tumor control, and quality of life are warranted.

There have been a few case reports and single arm prospective studies [75-79] showing tumor response or stabilization in patients with metastatic NSCLC being treated with the receptor tyrosine kinase inhibitor Gefitinib. Angiogenesis inhibitors such as bevacizumab, a monoclonal antibody against vascular epidermal grown factor, is also being vigorously investigated but no evidence based recommendation can yet be made.

15. Conclusion

Current treatment of brain metastasis is complex involving multiple specialists and modalities. Evidence based recommendations can be extremely helpful in making sense of the vast array of treatment modalities when properly understood and utilized. They allow for contemporary treatment regimens affording maximal patient survival and delayed neurologic progression while pointing out gaps in current knowledge to direct future research. A key knowledge gap is in quality of life outcomes. Also, little data exists for creative combination treatments such as post-operative SRS to the operative bed without WBRT with frequent surveillance imaging and for resection of 2+ metastatic lesions. The complete evidence based guidelines [80] for metastatic brain tumors has recently been published and should be reviewed by all clinicians who treat patients with brain metastasis.

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Author details

Steven N. Kalkanis* and Sanjay Patra

*Address all correspondence to: kalkanis@neuro.hfh.edu

Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan, USA

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