Brain metastases

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Purpose of review

Brain metastases occur in 10–30% of cancer patients, and they are associated with a dismal prognosis. Radiation therapy has been the mainstay of treatment for patients without surgically treatable lesions. For patients with good prognostic factors and a single metastasis, surgical resection is recommended. The management of patients with multiple metastases, poor prognostic factors, or unresectable lesions is, however, controversial. Recently published data will be reviewed.

Recent findings

Radiation therapy has been shown to substantially reduce the risk of local recurrence after surgical resection of brain metastases, although this does not translate into improved survival. Recently, stereotactic radiosurgery has emerged as an increasingly important alternative to surgery that appears to be associated with less morbidity and similar outcomes. Other potentially promising therapies under investigation include interstitial brachytherapy, new chemotherapeutic agents that cross the blood–brain barrier, and targeted molecular agents.

Summary

Patients with brain metastases are now eligible for a number of treatment options that are increasingly likely to improve outcomes. Randomized, prospective trials are necessary to better define the utility of radiosurgery versus surgery in the management of patients with brain metastases. Future investigations should address quality of life and neurocognitive outcomes, in addition to traditional outcome measures such as recurrence and survival rates. The potentially substantial role for chemotherapeutics that cross the blood–brain barrier and for novel targeted molecular agents is now being elucidated.

Keywords

brain metastases, chemotherapy, stereotactic radiosurgery, surgery, whole brain radiation therapy

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Abbreviations

BBB	blood–brain barrier
KPS	Karnofsky performance status
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
PCI	prophylactic cranial irradiation
RPA	recursive partitioning analysis
RTOG	Radiation Therapy Oncology Group
SRS	stereotactic radiosurgery
WBRT	whole brain radiation therapy

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Introduction

Despite major treatment advances in recent decades, almost 25% of deaths in the United States are cancer-related, and cancer remains the second leading cause of death [1]. Brain metastases are among the most feared complications of cancer because they often cause profound neurologic symptoms that severely impair quality of life [2•]. They represent a common complication, occurring in 10–30% of cancer patients. The prevalence of brain metastases in cancer patients has been rising over the past three decades. Factors contributing to this increase include improved survival of cancer patients as a result of more effective systemic therapy, the aging of the US population, and enhanced detection of clinically silent lesions with magnetic resonance imaging (MRI). Among adults, the most common origins of brain metastasis include lung cancer (50%), breast cancer (15–20%), and melanoma (10%). The next most frequent sources include renal cancer, colorectal cancer, lymphoma, and tumors of unknown primary [2•–4•,5]. Metastases from breast, colon, and renal cell carcinoma are often single, while melanoma and lung cancer have a greater tendency to produce multiple metastases [6•,7•]. MRI studies suggest that single metastases account for one third to one quarter of patients with brain metastases [8••]. This is important because stereotactic radiosurgery (SRS), an increasingly valuable therapeutic modality, is effective only in patients with a limited number of metastases.

Because physical factors contribute to the deposition of tumor cells, the distribution of metastases generally occurs in proportion to blood flow. Thus, about 80% of metastases are located in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem. As a brain metastasis grows and edema develops, the majority of patients present with a progressive focal neurological deficit such as hemiparesis, aphasia, or visual field defect.

Other typical features include headache, seizure, and cognitive dysfunction. Notably, as many as one third of brain metastases may escape detection during life [5,9•].

Treatment goals and options

Brain metastases are associated with a poor prognosis. Depending on the patient's age, functional status, extent of systemic disease, and number of metastases, median survival ranges from 2.3 to 13.5 months [10]. Management consists of supportive care and definitive therapy. Supportive care addresses brain edema, seizures, deep venous thrombosis, gastrointestinal complaints, psychiatric complications, and side-effects of treatment. This important topic is comprehensively reviewed elsewhere [9•]. The remainder of this review will focus on definitive therapy.

Definitive therapy is intended to restore neurological function, improve quality of life, and extend survival. Therapeutic modalities that may be used singly or in combination include surgery, stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), and chemotherapy. The optimal combination of therapies for each patient depends on careful evaluation of various factors including the location, size, and number of brain metastases; patient age, general condition, and neurological status; extent of systemic cancer; and the tumor's response to past therapy and its potential response to future treatments.

Surgery

The goals of surgery are to provide immediate relief of neurological symptoms due to mass effect, to establish a histological diagnosis, to provide local control of the metastasis, and if possible, to prolong survival. Thanks to advances in surgical technique including image-guided surgery and improved localization, surgical morbidity and mortality have improved significantly [6•,11•]. In one large series, overall in-hospital mortality for patients undergoing surgical resection of brain metastases was 3.1%. Data from this series suggest that high-volume surgical centers are associated with substantially lower mortality rates than low-volume centers (1.8% versus 4.4%) [12•].

Single metastasis

In general, surgery should be considered for patients with good prognostic factors when there is a single metastasis in an accessible location, especially if the tumor is producing mass effect. This approach is based on the results of two prospective randomized trials [8••,13]. In both studies, reasonably functional patients with a single brain metastasis and well-controlled extracranial disease were randomized to receive needle biopsy of the metastasis followed by WBRT versus surgical resection followed by WBRT. Patients in the surgery plus WBRT group had fewer local recurrences, improved survival (40 weeks versus 15 weeks, and 10 months versus 6 months), and better Karnofsky performance status (KPS) than patients who received WBRT alone. Studies have been unable to replicate these results in patients with active extracranial disease and lower KPS [14]. A recent meta-analysis published by the Cochrane collaboration concluded that surgery may improve functionally independent survival but has not been shown to have a statistically significant impact on overall survival [15•]. Across multiple studies, a trend toward decreased proportion of deaths due to neurological causes was observed. Small numbers of patients in the published trials, as well as highly selected patient populations, rendered the results difficult for the Cochrane investigators to interpret. Similar results were obtained in a Canadian meta-analysis [16•]. Although these recent studies did not confirm a significant survival benefit, most neuro-oncologists feel that resection of a single metastasis is probably beneficial in carefully selected patients. It deserves mention that the fraction of patients who have a single metastasis on imaging depends on the modality used. As high-resolution MRI techniques continue to advance, one can expect the frequency of single metastases to steadily decline.

Multiple metastases

The role of surgery in patients with multiple brain metastases is usually limited to resection of a large, symptomatic or life-threatening lesion or to obtain a tissue diagnosis. Retrospective trials of WBRT versus WBRT plus surgery for patients with multiple metastases have produced conflicting results that are reviewed elsewhere [11•]. Large retrospective series recently published in the neurosurgical literature suggest that resection is a viable option for patients with good prognostic features and two or three metastases [17,18]. This remains to be assessed in a prospective, controlled study.

Radiation therapy

Many patients are deemed poor surgical candidates because of multiple or inaccessible lesions or poor performance status. In contrast to surgery, radiation therapy can be delivered to most patients with relatively modest morbidity. As such, radiation therapy has been the cornerstone of treatment for brain metastases for more than 50 years. Radiation has traditionally been viewed as a palliative modality intended primarily to relieve neurological symptoms, with only a modest impact on survival.

Whole brain radiotherapy

WBRT produces symptomatic improvement in 75–80% of patients with brain metastases [5]. Only one trial has ever compared WBRT with supportive care, and although median survival was better in the WBRT group, statistical significance of the findings was not reported [19]. A large number of studies performed by the Radiation Therapy Oncology Group (RTOG) and others since

1971 have compared various WBRT dose-fractionation schedules. These uniformly failed to show any significant differences in outcome and are reviewed in detail elsewhere [16•]. At present, the most frequently used regimen delivers 30 Gy in 10 fractions over 2 weeks. Despite interest in improving WBRT outcomes with radiosensitizing agents such as gemcitabine [20], lonidamine, metronidazole, misonidazole, bromodeoxyuridine, motexafin gadolinium, and efaproxiral (RSR-13), most results have thus far been disappointing [16•]. Promising phase II results for efaproxiral [21•] were partially confirmed in an international phase III trial which suggested a possible survival benefit in patients with non-small cell lung cancer (NSCLC) or breast cancer [22]. ENRICH (Enhancing Whole Brain Radiation Therapy In Patients with Breast Cancer and Hypoxic Brain Metastases) is another phase III trial of this agent, which enhances tumor oxygenation by an allosteric effect on hemoglobin, that will enroll up to 360 women with brain metastases from breast cancer; results are expected in early 2006 (NCT-00083304; Allos Therapeutics). Celecoxib, a cyclooxygenase-2 inhibitor, is currently under investigation for its radiation sensitizing properties [23]. A novel agent, motexafin gadolinium, is being tested as a radiation sensitizer and as an anti-tumor agent [24]. In one trial, it appeared to improve cognitive function in patients with brain metastases from NSCLC treated with WBRT [25]. A compelling recent study [26•] suggested that diffusion-weighted MRI may be useful in predicting the response of primary and metastatic brain tumors to radiotherapy.

Palliative whole brain radiation therapy

Some investigators advocate the use of the RTOG recursive partitioning analysis (RPA) prognostic classes in defining WBRT candidates (Table 1) [10,27••]. Recent literature suggests that non-surgical candidates in RPA classes 2 and 3 may not benefit from WBRT [28]. Unfortunately, investigators have not yet succeeded in precisely defining the subset of patients who are likely to die before realizing any benefit of WBRT [29]; this information is relevant because older studies suggest that as many as 40% of high-risk patients live fewer than 2 months [27••]. Furthermore, the acute side effects of WBRT are unpleasant and include hair loss (88%), fatigue (95%), memory impairment (72%), poor concentration (61%), and depression (54%) [30].

Table 1. Recursive partitioning analysis prognostic classes and median survival

Class	Features	Median survival
1	KPS $\geq$70 Age $<$65 years Controlled primary tumor No extracranial metastases	7.1 months
3	KPS $<$70	2.3 months
2	All others	4.2 months

KPS, Karnofsky performance status. Data from Gaspar *et al.* [27••].

Postoperative whole brain radiation therapy

As compared with surgery alone, WBRT after surgical resection of a single brain metastasis leads to a marked reduction in recurrence rate (18% versus 70%) and in the rate of death due to neurologic causes (14% versus 44%). An overall survival benefit has not, however, been demonstrated [31••]. Recent data conclude that the benefits of postoperative WBRT may be realized in patients regardless of RPA prognostic class [32].

Late toxicity

As increasing numbers of patients survive after treatment for brain metastases, late complications are a mounting problem. These include neurocognitive decline, hydrocephalus and its associated symptoms, and neuroendocrine dysfunction. Although few data are available to guide management decisions, patients in a favorable prognostic category are generally treated with daily fraction doses of less than 3 Gy so as to minimize neurotoxicity [3•]. Increasingly, studies are including neurocognitive outcome evaluations as part of the patient assessment [33•].

Prophylactic cranial irradiation

Patients with locally advanced NSCLC have a particularly high incidence of brain recurrence. Current therapy for NSCLC patients includes chemotherapy, radiation, and surgery, and results in median survival rates of 15–25 months. Despite the improving efficacy of treatment for extracranial disease, these modalities are inadequate to prevent central nervous system recurrences, which ultimately develop in 21–54% of patients. A number of investigators have used PCI with various radiation doses and regimens to treat patients with locally advanced NSCLC and no evidence of metastasis. Although a survival benefit has not been demonstrated, the majority of these studies show a decreased incidence of brain metastasis in patients who receive PCI [34•]. A recent Cochrane meta-analysis concluded that PCI should not be used outside of clinical trials until better data regarding efficacy, survival, and quality of life outcomes are available [35]. The RTOG has an ongoing phase III study in which patients are randomized to PCI (30 Gy in 15 fractions) or close observation. The study is powered to demonstrate a survival advantage, and it includes cognitive and quality of life assessments [34•].

Stereotactic radiosurgery

SRS is a technique of external irradiation that utilizes multiple convergent beams to deliver a high single dose of radiation to a discrete treatment volume. Radiosurgery can be performed with high energy x-rays produced by a

linear accelerator, with gamma radiation (gamma knife), and less frequently with charged particles such as protons produced by cyclotrons. All of the stereotactic radiation techniques produce a rapid fall-off of dose at the edge of the target volume resulting in a clinically insignificant radiation dose to normal non-target tissue. Because most metastases are small, spherical, discrete, and sensitive to single fraction radiotherapy, they serve as ideal targets for stereotactic radiotherapy [36••]. Ample data have shown that SRS is responsible for local tumor control rates on the order of 73–94% [5]. Numerous recent analyses indicate that SRS may effectively treat brain metastases [37–41]. Even neoplasms that are resistant to fractionated radiation therapy such as melanoma, renal cell carcinoma, and NSCLC, usually respond to single fraction SRS [42]. Complications of SRS include nausea, brain edema, seizures, and later, radiation necrosis; these are reviewed elsewhere [36••].

Stereotactic radiosurgery versus surgery

There is an emerging view that SRS may serve as an alternative to surgical resection for small metastases not producing mass effect. SRS can also be used to treat lesions in the brainstem or eloquent areas with much less risk than surgery. Additionally, because of the non-invasive, outpatient nature of SRS, it is associated with less morbidity and may be more cost-effective than conventional surgery [43]. There may be a lower risk of leptomeningeal disease dissemination in patients with posterior fossa metastases treated with SRS [44]. As is the case for conventional surgery, careful selection of patients is critical; patients without good prognostic factors are unlikely to benefit [45]. Although the precise role for SRS remains to be defined by a randomized, prospective trial, many retrospective studies suggest that SRS outcomes for appropriately selected patients are equivalent to those achieved with conventional surgery [36••], and long-term survival among patients with good prognostic factors is possible [37]. The most recent of these reviewed the Mayo Clinic experience of 74 patients with solitary brain metastases treated with surgery compared with 23 patients treated with SRS. Outcomes were similar with 1-year survival of 56% for the SRS group and 62% for the surgery group ($P = 0.15$). Local control was significantly better in the radiosurgery group (no recurrences compared with 58% in the surgery group) [46•]. A prospective trial comparing SRS to surgery is much needed. Unfortunately, previous attempts at such a study have been unsuccessful due to poor accrual, primarily as a result of patient or physician preference for one of the treatment modalities.

Stereotactic radiosurgery with or without whole brain radiation therapy

The role of WBRT in patients treated with SRS is controversial, especially for patients with relatively radioresistant tumors. While recent data established that the addition of WBRT to SRS significantly improves local tumor control [47•], an overall survival benefit has not been demonstrated [48•]. Patients report that the addition of WBRT causes more memory impairment, depression, poor concentration, and hair loss than SRS alone [30]. Much needed randomized studies comparing SRS and the combination of SRS and WBRT are underway to assess survival, quality of life, and cost-effectiveness in patients with newly diagnosed brain metastases.

Whole brain radiation therapy with or without stereotactic radiosurgery

In 2004, Andrews *et al.* [49••] published the first randomized trial comparing SRS combined with WBRT to WBRT alone (RTOG 95-08). For patients with a single unresectable metastasis, SRS was found by intention-to-treat analysis to confer a significant survival benefit (mean survival 6.5 months versus 4.9 months; $P = 0.039$). Additionally, the SRS group showed a significant improvement in KPS and decreased steroid use at 6 months. There was no significant survival benefit for patients with multiple metastases. No difference in efficacy was observed between linear accelerator or gamma knife SRS. Trials are needed to further assess the role of SRS for patients with multiple metastases. A study is currently underway to investigate the value of combining temozolomide or the epidermal growth factor receptor inhibitor, gefitinib with SRS to improve its efficacy (RTOG 0320).

Interstitial brachytherapy

This technique involves the implantation of radioactive nuclides into the wall of the surgical cavity to deliver a dose of radiation to the residual tumor while limiting radiation exposure to the surrounding brain. Thus far, brachytherapy remains an experimental treatment modality. GliaSite (Proxima Therapeutics, Alpharetta, Georgia, USA) is a novel brachytherapy system currently under investigation. An inflatable balloon catheter is placed in a resection cavity following debulking or resection of a brain tumor. The balloon is filled with an aqueous solution of ^{125}I that delivers a low, continuous dose of radiation to the margins of the resection cavity. Preliminary results for primary brain tumors are promising [50]. Studies of GliaSite for the treatment of metastases are ongoing.

Chemotherapy

Chemotherapy has generally been used in patients who have failed other treatment modalities. Although chemotherapy may occasionally be useful in patients with chemosensitive tumors such as small cell lung cancer, choriocarcinoma, and breast cancer, the results of most chemotherapy trials have been disappointing. The primary reasons for chemotherapeutic failure include

inability of the agent to cross the blood–brain barrier (BBB) and insensitivity of the tumor to the particular agent. Some of the new chemotherapeutic agents that cross the BBB hold promise as treatment options for brain metastases. Preliminary studies suggest that topotecan, an inhibitor of topoisomerase I that crosses the BBB, may effectively treat brain metastases from small cell lung and breast cancer [51]. Temozolomide, an oral alkylating agent approved for use in the treatment of malignant gliomas, is well-tolerated and also crosses the BBB. It has been studied in phase II trials and appears to have modest activity against brain metastases from lung cancer, breast cancer, and melanoma [52•,53].

Experimental approaches

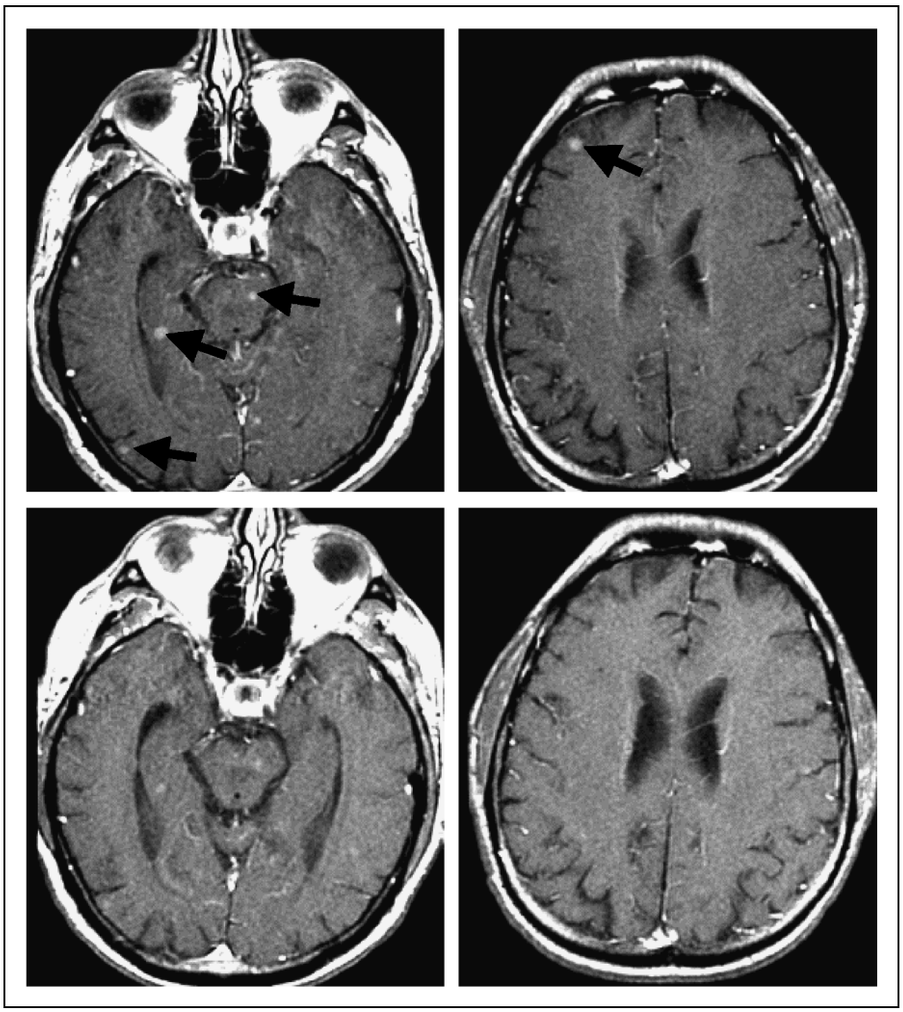
An area of intense research involves targeted molecular agents. A promising recent finding is that gefitinib has activity against brain metastases from NSCLC [54••,55]. Gefitinib is an oral tyrosine kinase inhibitor of the epidermal growth factor receptor, which is effective against a subset of NSCLC. In a prospective trial, gefitinib controlled brain metastases in 27% of patients, with a median duration of 4 months (Fig. 1) [54••]. Additional molecular agents in development are reviewed elsewhere [56]. One provocative idea currently being studied in mice with intracerebral human breast tumors involves the intracarotid administration of a genetically engineered oncolytic virus [57•]. This approach has produced a survival benefit in mice and warrants additional investigation.

Guidelines

Current guidelines published by the National Comprehensive Cancer Network recommend management similar to that which has been detailed herein [58]. For patients with one to three metastatic lesions on brain

Figure 1. Radiological response of metastatic lung cancer to brain with high dose gefitinib

A 54-year-old male with non-small cell lung cancer and multiple small brain metastases (arrows), which progressed through whole brain radiation therapy (August 2004, top row). The patient was then treated with high dose gefitinib with reduction in size of parenchymal nodular lesions (October 2004, bottom row).



MRI, aggressive management is generally recommended so long as systemic disease is limited or controllable. Options include resection and SRS. Either resection or SRS may be followed by WBRT in an attempt to prevent local recurrence. If the lesions are deemed unresectable, WBRT or SRS should be considered. In cases of highly radiosensitive tumors such as small cell lung cancer or lymphoma, or when there is disseminated systemic disease with poor treatment options, WBRT is recommended. In all cases, surgery should be considered for relief of symptomatic mass effect or hydrocephalus. When brain metastases initially present as more than three lesions, surgery is again recommended if a diagnosis has not been established or if there is symptomatic mass effect. Surgery should be followed by WBRT with or without SRS. The same treatment regimen is recommended for patients with multiple metastases who do not have surgery. After treatment for brain metastases, patients should be followed with MRI approximately every 3 months for 1 year and then as clinically indicated. Local recurrences may be treated with surgery, SRS or occasionally chemotherapy. In cases of distant recurrence, multiple treatment modalities can be considered.

Prognosis

The median survival of patients with untreated brain metastases is approximately 1 month. The addition of steroids increases survival to 2 months, while WBRT further improves survival to 3–6 months [5]. Patients with single brain metastases and limited extracranial disease who are treated with surgery and WBRT have a median survival of approximately 10–16 months [8••,13]. Prognostic data for patients treated with SRS or novel chemotherapy is not yet available. In reviewing prognostic information for various treatment modalities, though, one is clearly struck by the degree to which interventions developed in recent decades have had an impact on the survival of patients with brain metastases.

Conclusion

In the last decade, the emergence of SRS as a primary treatment modality for patients with good prognostic factors and one or a few small metastases has been a significant development. Additional data will be necessary to validate the view that SRS is a viable alternative to surgery in certain situations. Future investigations should address quality of life and neurocognitive outcomes in addition to traditional outcome measures such as recurrence and survival rates. Promising therapies currently under investigation include chemotherapeutics that effectively cross the BBB, targeted molecular agents, radiation sensitizing agents, and oncolytic viruses.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 756–757).

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