15 Intracranial Stereotactic Radiosurgery in High Risk Patients with Metastases from Radioresistant Primary Tumors

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Abstract

Traditionally radioresistant brain metastases including melanoma, renal cell carcinoma, and sarcoma have poor outcomes with supportive care and whole brain radiotherapy (WBRT) alone. Although recent advances in biologic and targeted agents have improved systemic disease control in some patients with melanoma and renal cell carcinoma, such agents have poor penetration and are relatively ineffective in controlling brain metastases. Nevertheless, the ability to provide biologically ablative doses of radiotherapy by radiosurgery still can yield excellent local control similar that found in classically non-radioresistant brain tumors. Although conventional radiobiological models suggest that these patients will not respond to conventionally fractionated radiation therapy treatment, stereotactic radiosurgery allows high doses of radiation to be delivered to the target, while minimizing dose to normal tissue. Here we present treatment strategies and clinical outcome data in the management of such patients. Given the excellent local control following radiosurgery in this group of patients we propose that radiosurgery provides a clinical benefit to this group of patients. The use of whole brain radiation therapy should be considered to improve local control, although can be omitted in selected groups of patients.

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Introduction

As a whole, brain metastases represent the most common intracranial tumor and continue to be a significant problem in the multidisciplinary management of cancer patients. Particularly challenging are tumors that are thought to be radioresistant including: melanoma, renal cell carcinoma, and sarcoma, as lesions not amenable to surgical resection have historically poor outcomes when treated with whole brain radiation therapy alone. Although non-small cell lung cancer and breast cancer are the most common malignancies to result in brain metastases, melanoma may account from 4 to 16 % of brain metastases, while metastases from renal cell carcinoma range from 0.3 to 7 % (Lassman and DeAngelis, 2003). According to a population-based cohort study, Schouten et al. (2002), found that the cumulative incidence of brain metastases was 7.4 % of patients with melanoma, and 9.8 % in patients with renal cell carcinoma. Although these tumors are thought to be radioresistant to standard radiation fractionation schemes, intracranial stereotactic radiosurgery allows a high dose of radiation therapy in a single fraction to optimize the therapeutic ratio.

The importance of intracranial disease control is not only important in terms of palliation of symptoms, but the use of local therapy has been shown to translate into a survival benefit. Patchell et al. (1990), showed a survival benefit when surgical resection was added to whole brain radiation therapy in patients who had a single metastatic lesion in the brain. While surgical resection provides the benefit of more immediate resolution of symptoms as well as a histological diagnosis, surgical resection may become difficult depending on the number and location of the lesions.

Stereotactic radiosurgery, which provides a biologically ablative radiotherapy dose, has been shown to be effective in providing local intracranial disease control. In general, it is believed that radiosurgery provides equivalent local control compared to open surgery, although a randomized clinical trial looking at this question had to be closed early due to poor patient accrual (Muacevic et al., 2008). The Radiation Therapy Oncology Group (RTOG), performed a randomized clinical trial randomizing patients with one to three brain metastases to either whole brain radiation therapy alone or whole brain radiation therapy in combination with stereotactic radiosurgery. Patients randomized to the radiosurgery arm have a preserved longer functional independence, and patients with a single metastatic lesion were found to have a benefit in overall survival (Andrews et al., 2004). Another randomized clinical trial performed through the University of Pittsburgh randomized patients with 2–4 metastatic lesions to whole brain radiation therapy alone compared to whole brain radiation therapy plus stereotactic radiosurgery showed 100 % local failure with whole brain radiation therapy alone, compared with 8 % in the stereotactic radiosurgery arm. The investigators noted that the histology of the primary lesion did not have an impact on local failure rate (Kondziolka et al., 1999). Although these trials included patients with radioresistant tumors, the overall number of patients in these trials with such tumors was small.

As improvements in systemic therapy lead to improved systemic disease control and overall survival in patients with traditionally radioresistant tumors, it is possible that patients may derive a greater benefit to disease control in the brain than thought previously.

Radiobiology of Radioresistant Tumors

The rationale for use of fractionated radiotherapy is based on the concept that normal tissue can undergo repair of sublethal damage, while tumor cells can undergo reassortment to a more radiosensitive phase of the cell cycle and reoxygenation which results in increased radiosensitivity ultimately yielding a therapeutic window. This is based on early experiences when fractionated courses of radiotherapy could result in a better side effect profile, yet similar tumor control (Fowler, 1989). Melanoma, sarcoma, and renal cell carcinoma are classically thought to be radioresistant based on historical data that

these tumors do not respond well to standard fractionated radiotherapy.

Various models have been proposed to explain cell killing during a particular course of radiotherapy, although a common model that is frequently applied to the clinic is the linear quadratic model. Using this model, it is possible to quantitate how a given tumor may respond to radiation therapy. This model presumes that there are two components of a radiotherapy dose that contribute to cell death, one that is proportional to the dose, and the other that is proportional to the square of the dose. Based on this model, the surviving fraction of cells (S) following a dose (D) is based on the following formula, where alpha represents the magnitude of cell kill proportional to the dose beta represents the magnitude of cell kill proportional to the dose squared (Hall and Giaccia, 2006).

$$S = e^{-\alpha D - \beta D^2}$$

Based on the equation above, if one wanted to determine the dose at which both components of cell killing contribute equally to cell death, the equation above can be reduced to the following equation.

$$\alpha D = \beta D^2$$

$$D = \alpha/\beta$$

A large alpha-beta ratio means that the linear portion dominates in terms of cell killing, while a smaller alpha-beta ratio means that the quadratic portion dominates. Normal cells are believed to have a low alpha beta ratio, and therefore greatest therapeutic benefit to fractionation is achieved when a tumor cell has a large alpha-beta ratio (Fig. 15.1). Therefore, in general it is believed that low doses of radiation per day will selectively kill tumor cells, while sparing normal cells.

However, it is believed that radioresistant tumors have smaller alpha-beta ratios, making the benefit to standard fractionation less pronounced. However, it does not imply that these tumors are radioresistant, and higher doses of radiotherapy may still be able to control the disease.

Radioresistance of tumor cells is governed by a number of factors. In part it is believed that radioresistant cells containing high percentages

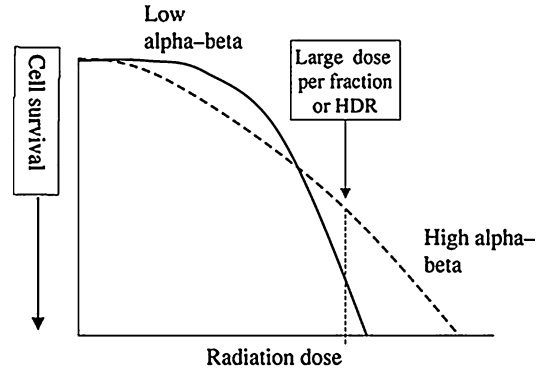

Fig. 15.1 Cell survival curve depicting survival parameters for cell lines with low alpha-beta rations and high alpha beta ratios. In general, it is thought that tumor cells have a high alpha beta ratio compared to normal tissues which have a low alpha-beta ratio. At low radiation doses, there is enhanced cell killing in cells with high-alpha beta ratio (tumor cells), with decreased cell killing in with cells of a low-alpha beta ratio (normal cells). On the other hand, since it is believed that radioresistant tumors have a low alpha beta ratio, it would be expected that cell killing would be enhanced with higher dose per fraction (Figure from Morton, 2005)

of hypoxic cells, which ultimately results in decreased oxygen dependent cell killing. Other factors include variations in gene expression, the presence of cells which are able to divide in an uncontrolled fashion, and distribution of cells in radioresistant phases of the cell cycles (Zhivotovsky et al., 1999). Despite the term radioresistant tumors, even a given histology may show wide variations in cell death patterns. *In vitro* studies attempting to determine the alpha/beta ratios for melanoma cells have been shown to have a wide degree of variation (Rofstad, 1994).

There is a controversy regarding whether or not the linear quadratic model is applicable to the high doses used in stereotactic radiosurgery treatments as outlined by Kirkpatrick et al. (2008) and Brenner (2008). It is believed by some that the biological effect of ablative doses of radiotherapy is underestimated from the linear quadratic model, as the damage may involve alternative mechanisms of cell killing including damage to the vasculature and stroma that is not well explained by the linear quadratic model (Kirkpatrick et al., 2008). Nevertheless, even if one accepts the linear quadratic model, hypofractionation using high

dose per fraction either with stereotactic radiosurgery or stereotactic radiation therapy is expected to result in enhanced cell killing compared to standard fractionation alone making it at least feasible theoretically to treat radioresistant tumors (Hall and Brenner, 1993). Nevertheless, the use of modern stereotactic radiosurgery systems allows a high dose of radiotherapy to be provided to a tumor, with preservation of normal brain tissue. While these tumors may not respond to lower-dose per fraction radiation therapy, it does not imply that radiosurgery doses are ineffective.

Radioresistant Tumors – Overview

Despite the fact that renal cell, melanoma, and sarcomas have distinct disease biology, several series have evaluated these groups of tumors as a whole. If one extrapolates that radioresistance of these tumors to standard fractionation applies to radiosurgery doses, an initial presumption is that these patients may most benefit from surgical resection. Nevertheless, the ability to perform a surgical resection is often believed to be limited to patients who have a solitary lesion with controlled systemic disease. The use of stereotactic radiosurgery in general is popular as it allows for a minimally invasive procedure that is able to target multiple, even surgically inaccessible lesions (Sin et al., 2009).

Part of the interest in treating patients with radioresistant tumors developed from the common situation where surgical resection is not feasible, and that these patients have been found to have poor outcomes with whole brain radiation therapy alone. Patients with radioresistant tumors treated with whole brain radiation therapy alone have survival ranging from 10 to 20 weeks for patients with melanoma primary tumors compared to 8–37 weeks for patients with renal cell primary tumors. The recursive partitioning analysis (RPA) class, which takes into account age, performance status, and status of extracranial disease, has been found to be an important predictor of overall survival from many different studies (Brown et al., 2002). Additionally, uncontrolled metastatic disease to the brain can result in significant morbidity for patients making local control of importance.

The Mayo clinic experience reported by Brown et al. (2002) reported a series of 41 patients who were treated using a GammaKnife stereotactic radiosurgery system. Patients were treated with a median dose to the tumor margin of 18 Gy (range: 12–25 Gy). The reported local control for patients in this series was 88 %, and overall survival was 14.2 months. These survival rates were improved compared to historical controls treated with whole brain radiotherapy alone (Brown et al., 2002).

At our own institution, Powell et al. (2008), at the State University of New York Upstate Medical University reviewed 76 patients, 50 patients with melanoma, 23 patients with renal cell carcinoma, and 3 patients with sarcoma. Patients were treated to a median margin tumor dose of 18 Gy (range 8–30 Gy). Similar to other reports, we also found that predictors of survival included KPS score, RPA class, and having a single metastatic lesion were all predictors of overall survival. The freedom from local progression was 77.7 % for all patients in the series, with local control for patients with melanoma was found to have 63.0 % compared to 93.6 % for patients with renal cell carcinoma.

Our series also evaluated dosimetric parameters that appeared to improve overall local control. The percent coverage of the prescribed dose to the target volume was also associated with improvements in local control. If the target volume received 90 % or greater of the prescribed dose, then the freedom from local progression was 71 %, compared to 0 % of patients receiving less than 90 % total coverage (Powell et al., 2008).

The largest reported experience of patients with radioresistant primaries is from the University of Texas MD Anderson Cancer Center (Chang et al., 2005). This series included 189 patients with 264 radioresistant metastases. Based on their review, patients with three or fewer metastases each less than 3 cm in diameter were generally considered candidates for stereotactic radiosurgery. They utilized dose constraints for critical structures based on the RTOG 90–05 guidelines. Lesions less than 2 cm were prescribed 20–24 Gy, lesions 2–3 cm 18 Gy, and for lesions

>3 cm, 15 Gy was prescribed. The median minimal peripheral dose was 18 Gy, and the median dose to the isocenter was 21 Gy. The reported local failure for all patients in the study was 27.3 %, with a 1 year overall survival of 30.7 %. Patients with smaller tumors less than 1 cm in diameter had a significantly better probability of local control, even when higher doses utilized to treat smaller metastases are accounted for.

Although most of the experience regarding the treatment of radioresistant primaries is based on retrospective data, prospective data does exist as well. A Phase II study from the Eastern Cooperative Oncology group evaluated patients with 1–3 metastases with renal cell carcinoma in a prospective fashion. In this trial, patients with tumors less than 2 cm in greatest diameter were given a prescription dose of 24 Gy, between 2 and 3 cm a dose of 18 Gy was prescribed, and lesions greater than 3 cm were given 15 Gy, with the dose prescribed to the periphery of the tumor. The investigators found a median survival of 8.3 months was similar to retrospective data, with 19 % of patients dying of intracranial disease progression. However, interestingly local control rates in this study appeared to be worse compared to retrospective data. While many retrospective studies have reported local failure in the 10–20 % range, the 3 and 6 month intracranial disease progression within the original radiosurgery field was 19 and 36 % respectively. The investigators attributed the difference in local control due to possible differences in patient selection, the difficult distinction in tumor necrosis and recurrence, and variations in disease biology (Manon et al., 2005).

A natural question that arises involves the question regarding the use of whole brain radiation therapy in addition to radiosurgery. Whole brain radiation therapy and stereotactic radiosurgery are not mutually exclusive entities, and these treatments can be used in combination with each other. Although in general it appears as if patients who receive whole brain radiation benefit from both local control of the known disease, as well a reduction in failure in remainder of the brain, the addition of whole brain radiation therapy does not result in a survival benefit.

From the surgical literature, it is known that whole brain radiotherapy provides a local control benefit, as well as a reduction in neurological deaths (Patchell et al., 1998). Similar to other reports evaluating whole brain radiotherapy in combination with stereotactic radiosurgery, the Mayo clinic experience in radioresistant tumors suggests that the addition of whole brain radiotherapy improves local control, and neurological progression free survival. However, with extended follow-up in this series it did not appear that there was a reduction in death attributed to neurological causes (Brown et al., 2002). However, in a Phase II prospective study Manon et al. (2005), found that tumor recurrence in the brain was 70 % without whole brain radiation therapy, compared to 18 % with whole brain radiation therapy. Based on their findings, the investigators recommended that if whole brain radiation therapy is omitted, it must be done so cautiously.

Melanoma

Brain metastases continue to pose a significant problem in patients with metastatic melanoma. It is estimated that approximately 50 % of patients found to have metastatic melanoma will eventually develop brain metastases. Various factors have been implicated with an increased risk of brain metastases in patients with melanoma, including patients with ulcerated tumors, mucosal, head and neck, or truncal primaries, and BRAF or NRAS mutations. Factors that are associated with overall poor prognosis include multiple brain metastases, uncontrolled extracranial disease, and elevated lactate dehydrogenase levels (Carlino et al., 2012).

Recent advances in systemic therapy with vemurafenib (Chapman et al., 2011), and ipilumimamb (Hodi et al., 2010), have resulted in a survival benefit in patients with metastatic melanoma. Nevertheless, there is poor penetration of systemic treatments into the central nervous system still necessitates the use of alternative modalities regarding treatment to the central nervous system. Avril et al. (2004) showed a maximum response rate of brain metastases in patients with metastatic melanoma of approximately 10 % to fotemustine. A phase II study with 151 patients evaluating the use of temozolomide

in metastatic melanoma to the brain showed at least a partial response in 6 % of patients, and stabilization in 29 % (Agarwala et al., 2004).

Another alternative compared to chemotherapy is the use of whole brain radiotherapy in patients with metastatic melanoma. An RTOG analysis looking at the use of whole brain radiation therapy in metastatic melanoma showed symptomatic improvement in 76 % patients, and complete resolution of symptoms in 31 % of patients (Carella et al., 1980). Despite symptomatic improvement, local control and overall survival is still poor with metastatic melanoma. A retrospective analysis performed by the Cleveland clinic showed survival rates of 1.1, 2.3, 4.8, 8 months for patients who had no treatment, whole brain radiation therapy alone, aggressive local therapy with radiosurgery or open surgery, and combined aggressive local therapy with whole brain radiation therapy respectively (Buchsbaum et al., 2002).

In the Brown et al. (2002) Mayo clinic experience, patients with melanoma had a worse overall survival of 9.7 months compared to renal cell carcinoma where survival was 17.8 months. A series from the University of Pittsburgh reported a 90 % local control rate following GammaKnife radiosurgery. It was also noted that there was a decreased incidence of new brain metastases by nearly 50 % when whole brain radiation therapy was added to GammaKnife radiosurgery (Mori et al., 1998).

At the University of Southern California, researchers reviewed 45 patients who received stereotactic radiosurgery using the GammaKnife radiosurgery unit. The investigators reported a 98 % local control, and 28 % radiographic resolution following radiosurgery. The complications were acceptable especially compared to open surgery, with a 6 % incidence of seizures, 3 % incidence of nausea and vomiting, and a 3 % incidence of worsening muscle strength. All the patients who were found to have seizures had subtherapeutic levels of antiseizure medications, and the patient who had paresis responded to steroid therapy (Lavine et al., 1999). Patients at this institution were treated to a median dose of 20 Gy (range: 14–24 Gy), depending on the size and location of the metastases. Death was attributed to neurological causes in 34 % of patients. Local control rates following GammaKnife radiosurgery was 90 %, and 1 year survival was 26 %. The strongest predictors of survival were found to be volume of intracranial disease burden and systemic disease burden (Yu et al., 2002).

In the MD Anderson experience, the of radioresistant metastases the investigators found that the rates of hemorrhage were found to be the highest in patients with melanoma (10.5 %), although it is not clear if radiosurgery itself contributes to this or if this is related to the treatment itself (Chang et al., 2005).

Overall it appears that stereotactic radiosurgery for metastatic melanoma improves overall survival. While it is difficult to directly compare the benefit of open surgical resection, WBRT, and stereotactic radiosurgery due to variations in selection of these patients, all of these treatments can be combined with the clinical context of the situation. Patients who have control of systemic disease will benefit more from aggressive treatment of brain metastases. Surgical resection provides the most immediate palliation, and whole brain radiation therapy can be added to improve local control.

Nevertheless based on the retrospective data that we have available, as well as our clinical experience suggest that aggressive treatment to the brain yields a clinical benefit. While surgical resection is indicated for accessible, large lesions, and provides a more immediate relief of symptoms, the more common situation is that many patients may not be candidates for surgery given the location and or number of lesions. The survival benefit is roughly 10 weeks with conservative treatment with WBRT and steroids, however, the survival improves to 6–10 months for a single metastases following stereotactic radiosurgery (Lavine et al., 1999).

Renal Cell Carcinoma

Similar to melanoma, patients with renal cell carcinoma have also been found to have poor outcomes with whole brain radiotherapy alone. A retrospective series of 200 patients from The University of Texas MD Anderson Cancer Center reviewing outcomes for patients who received

whole brain radiation therapy from brain metastases showed that 76 % of patients died of neurological causes, and patients had a 1 year survival of 16.8 %. The authors concluded that based on poor rates of local control with standard whole brain radiation therapy, more aggressive therapy including either surgical resection or radiosurgery may improve patient outcomes (Wrónski et al., 1997). An older series published prior to the more common use of radiosurgery reviewed 34 patients with metastatic renal cell carcinoma. Prognostic factors associated with improved survival were good performance status, and surgical resection. While patients who received surgery did better than patients who did not, all patients who received surgery had good performance status. Nevertheless, the investigators concluded that the data supported surgical resection followed by radiotherapy was associated with improved outcomes (Decker et al., 1984).

Compared to other radioresistant tumors, it appears as if patients with metastatic renal cell carcinoma to the brain have a longer overall survival. In the Mayo clinic series, patients with renal cell carcinoma had the longest overall survival 12.6 months compared to approximately 7 months for both melanoma and sarcoma (Brown et al., 2002). In the MD Anderson experience, patients with renal cell carcinoma had the best overall survival rates with a 1 year survival of 40 %, Patients with renal cell carcinoma are less likely to die of neurological causes (31 %) compared to patients with melanoma (66 %) or sarcoma (60 %) (Chang et al., 2005). Similar to melanoma, as new systemic therapies such as sorafenib emerge (Escudier et al., 2007), providing improved local control to the brain may become even more important. A series by Cochran et al. (2012) evaluated outcomes of GammaKnife radiosurgery in the era of target agents including tyrosine kinase inhibitors, rapamycin inhibitors, and bevacizumab. Patients who received targeted agents had an improvement in overall survival of 16.2 months compared to 7.2 months for patients who were not receiving targeted therapy.

A series from the University of Pittsburgh evaluated patients with metastatic renal cell carcinoma reviewed 69 patients with metastatic renal cell carcinoma with a total of 146 metastases. The authors reported an overall survival of 15 months following GammaKnife radiosurgery. The investigators identified prognostic factors on multivariate analysis that were associated with improved survival following radiosurgery included pre-operative KPS score, radiosurgical dose to the margin as well as to the center, time of initial diagnosis to the time of diagnosis of brain metastases. The overall rate of tumor control was 96 % (Sheehan et al., 2003).

A possible criticism regarding many of the series evaluating the use stereotactic radiosurgery is that better performance status patients are selected, and these patients would do better regardless of the modality chosen. Hernandez et al. (2002), reviewed 29 patients with 92 brain metastases from renal cell carcinoma at Wayne State University. In this series, however, it was found that patients treated with combined whole brain radiotherapy and radiosurgery had survival of 18, 8.5, and 5.3 months for RPA class I, II, and III respectively. Patients who had WBRT alone had survival of 7.1, 4.2, and 2.3 months respectively in this same group.

Based on historical series, untreated brain metastases have a poor survival of 1–2 months, which is improved to 3–6 months followed by conventional radiotherapy techniques, and over 12 months with radiosurgery. Overall patients with metastatic renal cell carcinoma tend to be good candidates for radiosurgery since the metastatic lesions are typically less than 3 cm in greatest dimension, are typically spherical in location, and tend to be well-visualized on imaging studies. The morbidity and mortality of the treatment are low, and treatment tends to preserve quality of life in most of the patients who were treated (Sheehan et al., 2003).

Sarcoma

Brain metastases from sarcoma develop in 1–8 % of patients with sarcoma (Flannery et al., 2010). Additionally, even in series evaluating patients with radioresistant metastases, sarcoma is the most infrequent histology noted. In the Phase II ECOG trial evaluating patients with radioresistant brain metastases, 3/31 (10 %) patients had

metastatic sarcoma (Manon et al., 2005). Even the largest reported series on radioresistant tumors from MD Anderson Cancer Center, only 9 out of 189 patients (5 %) were patients with metastatic sarcoma. Nevertheless, the local control for these patients was 42 % at 1 year, and the 1 year survival of these patients was 22 %. Despite the poor local control, five of these patients who had solitary brain metastases had a median survival of 11 months (Chang et al., 2005). One possibility is that the radiographic appearance of sarcomas following radiosurgery may mimic tumor progression, a phenomena called pseudoprogression. Nevertheless, the small number of patients with sarcoma in these series makes any definitive conclusions difficult.

A series from the University of Pittsburgh reviewed 21 patients with a total of 60 metastases from a sarcomatous primary. In their analysis it was pointed out that patients with metastatic sarcoma to the brain were often in the final stages of their illness, yet there appeared to be a clinical benefit to GammaKnife radiosurgery. In general, patients were considered for stereotactic radiosurgery if the patient has less than 5 total lesions, the individual lesions were less than 3 cm in diameter, and the patient had a Karnofsky performance status greater than 60. Local control following radiosurgery was 88, and 33 % of patients developed new brain metastases. Overall, patients had a median survival of 16 months (Flannery et al., 2010).

Conclusions

The concept of radioresistant metastases is coined from historical data that tumors from patients with melanoma, renal cell carcinoma, and sarcoma do not respond well to standardly fractionationated radiotherapy. Although many mathematical models have been utilized to explain the biology of such tumors, one possibility is that such metastases likely have a lower alpha/beta ratio and therefore, hypofractionation using high radiation dose per fraction is expected to yield a clinical benefit. The precision and high doses that can be provided with modern radiosurgery techniques allows a high level of disease control, while sparing normal brain, thus yielding an overall clinical benefit.

The benefits of stereotactic radiosurgery allows the treatment of multiple, surgically inaccessible lesions. While much of the data regarding the benefit of radiosurgery in this group of patients is based on retrospective data, and good performance status of patients may be a confounding variable, even when controlled for, it still appears that radiosurgery provides a local control, and possibly a survival benefit. Furthermore, controlling intracranial disease provides a palliative benefit and improves overall quality of life.

In general, the approach to patients with brain metastases from a radioresistant primary tumor is that patients should be considered for surgical resection. From a medical standpoint, patients can be placed on steroids if there are neurological symptoms, and anti-seizure medications can be used if the patient develops seizure activity. The role of surgical resection is not only to improve a patient's quality and length of life, but also provides the most immediate relief of symptoms compared to other forms of management. In patients with small metastatic lesions of melanoma, renal cell carcinoma, and sarcoma that are not amenable to surgery, we do recommend stereotactic radiosurgery with or without whole brain radiation therapy. The decision to provide whole-brain radiation therapy should involve a discussion between the patient and the oncologist and the side effects of whole brain radiation therapy should be weighed against the higher rates of local relapse when omitted.

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