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1

Outcomes Following Gamma Knife for Metastases

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1. Introduction

Brain metastases occur in approximately 20-40% of all cancer patients, with an annual incidence of 170,000-200,000 cases, outnumbering primary brain tumors by a factor of ten to one (Gavrilovic, 2005; Posner, 1992). The management of brain metastases has evolved significantly in the past 10-20 years. These changes are attributable not only to improvements in the fields of neurosurgery and radiation oncology but also to refinements in diagnostic imaging and systemic therapy. Management of brain metastases requires a multidisciplinary approach. In this chapter, we will explore the evolving role of radiosurgery in the treatment of brain metastases and the controversies that have surrounded this promising therapeutic modality, especially in the context of evolving systemic management protocols.

2. Whole brain radiation therapy

While up to 20% of patients can present with brain metastases as their first sign of cancer, most typically occur later in the course of disease. The finding of a brain metastasis in a cancer patient has historically indicated a continued progression of systemic disease, portending a poor prognosis and shifting the primary goal of treatment to relief of symptomatology. Treatment of brain metastases was therefore, by definition, palliative. Prior to the availability of computerized axial tomographic scanning (CT scan) and magnetic resonance imaging (MRI), brain metastases were diagnosed when they caused symptomatology, including seizures, the effects of increased intracranial pressure, or focal neurological deficits from mass effect on critical structures. Without treatment, the survival rate after diagnosis averaged approximately 4-6 weeks (Al-Shamy & Sawaya, 2009) despite the use of glucocorticoids and ongoing systemic therapy.

This dismal view of brain metastases outcomes began to change with the introduction of whole brain radiation therapy (WBRT). One of the first reports of radiation therapy for brain metastases was by Lenz & Fried (1931) for the palliation of breast cancer patients with intracranial metastases. The initial reasoning behind WBRT was to treat clinically symptomatic metastatic disease, and the ability to control presumed, clinically silent, and

radiographically occult metastatic lesions was a bonus. With the advent of megavoltage, skin-sparing radiotherapy equipment that could deliver treatment rapidly, efficiently, and with acceptable acute morbidity, WBRT became accepted as a standard management approach. More recent retrospective studies have documented WBRT to be effective at reducing brain metastasis growth (Cairncross, 1980; Coia, 1992), improving neurologic symptom relief (Lassman & DeAngelis, 2003), and prolonging median survival to 3-6 months (Berk, 1995; Mintz, 1996; Order, 1968; Patchell, 1990; Vecht, 1993).

Despite the rapid adoption of WBRT, it was soon recognized that there were limitations to its use. Patients undergoing WBRT experienced the acute effects of hair loss, scalp irritation, nausea, debilitating fatigue, anorexia and sometimes worsening neurological function due to increased cerebral edema for possibly up to a month after starting treatment. In addition, in patients living beyond the 3-6 month expected survival duration, two main problems arose. The first was that it was possible for brain metastases to regrow either at previously treated sites or in new locations in the brain (Patchell, 1998). While there are reports of salvage repeat WBRT (Son, 2011; Wong, 1996), the cognitive consequences of radiation-induced leukoencephalopathy were not insignificant. Second, cerebral leukoencephalopathy can also be seen after a single course of WBRT in patients surviving longer than 12 months. A report from the Memorial Sloan-Kettering Cancer Center reported an 11% rate of progressive dementia, ataxia, and urinary incontinence among WBRT patients who survived for at least one year (DeAngelis, 1989a, 1989b). The current relevance of this study has been questioned, however, since hypofractionated regimens of 3-6 Gy to a total dose of 25-39 Gy were used, while smaller fractions are used more commonly today. Multiple phase III RTOG clinical trials evaluating numerous potential WBRT schedules from 10-54 Gy in 1-34 fractions have shown that many fractionation schemes are equivalent in overall survival, neurologic improvement, and overall toxicity, though neurocognitive toxicities have often not been well evaluated (Borgelt, 1980; Borgelt, 1981; Komarnicky, 1991; Kurtz, 1981; Murray, 1997; Sause, 1990).

Several other factors besides WBRT treatment may also contribute to a decline in neurocognitive function in brain metastasis patients, including the tumor itself, neurosurgical procedures, chemotherapy, medical therapy like corticosteroids and anticonvulsants, systemic progression, and paraneoplastic effects. It has been difficult for investigators to resolve these contributing factors (Khuntia, 2006). Though the evidence is limited and sometimes conflicting, the risks of long-term cognitive deficits due to WBRT have raised the controversial possibility that it may be reasonable to delay upfront WBRT when focal therapy is applied for selected patients.

3. Neurosurgery and diagnostic imaging

Neurosurgical resection of apparently isolated brain metastases was one of the first areas in which brain metastasis management standards changed over the past several decades and was a direct result of improved lesion detection with cross-sectional imaging. Beginning in the 1970s, advances in imaging facilitated an increasingly clear visualization of the lesions themselves. Based on early CT scans, retrospective case series began to report a survival benefit following neurosurgical resection of single brain metastases in selected patients. The role of surgical resection remained controversial until the early 1990s, when two randomized controlled studies validated the advantage of the use of resection for single

brain metastasis management. The first study enrolled 48 patients with KPS scores ≥70, including 25 for surgical resection followed by WBRT and 23 with biopsy followed by WBRT (Patchell, 1990). Compared to patients receiving WBRT alone, patients receiving surgical resection with WBRT had longer median overall survival (40 vs. 15 weeks, $p<0.01$), longer median duration of functional independence (38 vs. 8 weeks, $p<0.005$), lower rates of local intracranial recurrence (20% vs. 52%, $p<0.01$), and lower rates of mortality due to neurologic causes (26 vs. 62 weeks, $p<0.001$).

A second randomized trial by Vecht et al. (1993) of 63 patients (with resection+WBRT vs. WBRT alone) confirmed the findings of overall survival benefit for the surgical group (10 vs. 6 months, $p=0.04$), with a non-significant trend of functionally independent survival benefit for the surgical group (7.5 vs. 3.5 months, $p=0.06$). Interestingly, a novel twice-a-day fractionation scheme was used (2 Gy bid x 10 days to a total of 40 Gy), and none of the nine long-term survivors developed late neurological side effects, though detailed neuropsychological assessments were not performed. The subgroup receiving the largest benefit from surgical resection was comprised of patients without active extracranial disease (median overall survival 12 vs. 7 months, functionally independent survival 9 vs. 4 months).

These two studies demonstrated the benefit of focal therapy in appropriately chosen individuals, i.e. those with good performance status (KPS>70) and good extracranial disease control. A third trial by Mintz et al. (1996) failed to show a survival advantage, but the impact of the first two trials established the indispensible role of surgical resection in the management of single brain metastases. Surgical resection can achieve tissue diagnosis, relieve mass effect, improve intracranial hypertension, and rapidly decrease the need for corticosteroids, especially for tumors that are large, radioresistant, or located in the posterior fossa (Vogelbaum & Suh, 2006). However, multiple craniotomies have been rarely offered for multiple brain metastases, given the excessive risk of morbidity.

Gadolinium-enhanced magnetic resonance imaging (Gd-MRI) has further revolutionized the detection and management of brain metastases in several ways. First, many patients who appear to have a single visible intracranial lesion on computerized tomography (CT) have subsequently been found to have multiple lesions on Gd-MRI (Bronen & Sze, 1990; Davis, 1991). Further, increased gadolinium dose and increased MRI scan resolution results in the detection of further additional lesions in 30-40% of patients (Engh, 2007; Hanssens, 2011; Patel, 2011b). The finding of multiple lesions may alter plans for potential surgical management. Second, surveillance use of Gd-MRI allows for the detection of lesions long before the development of symptomatology. Treatment of these lesions is therefore prophylactic and therefore must carry a low-risk profile. Finally, Gd-MRI allows the neurosurgeon to visualize the presence or absence of gross residual tumor after resection. For patients in whom gross total resection is achieved for a truly single brain metastasis, it may be reasonable to avoid further therapy, including WBRT, unless tumor were to recur locally or at a distant intracranial site.

To address this last issue, the role of postoperative WBRT was evaluated by a randomized, controlled trial (Patchell, 1998). This study of 95 patients demonstrated that patients receiving postoperative WBRT had a reduction in local recurrence (10% vs. 46%, $p<0.001$), distant intracranial recurrence (14% vs. 37%), and neurologic cause of death (14% vs. 44% of patients who died, $p=0.003$). The trial did not show a significant difference in overall

survival (48 vs. 43 weeks) or the length of time patients remained independent, though this may have been due to the early death by systemic progression in the majority of patients that prevented definitive determination of brain metastasis control. In addition, 61% of patients in the resection-only group crossed over to receive delayed WBRT, and so the impact of withholding WBRT altogether could not be adequately assessed.

With the frequent findings of multiple asymptomatic brain metastases and of lesions too small to warrant craniotomy in cancer patients when scanned with Gd-MRI, a tool superior to craniotomy that could treat small lesions (either single or multiple) was required. Despite the effectiveness of WBRT and the temporary nature of its acute side effects, the risk of subacute and delayed neurologic sequelae of WBRT remain concerning. Furthermore, timing of the use of WBRT has become an issue. One of the fundamental radiobiological principles states that the likelihood of tumor control decreases with increasing number of tumor cells, i.e. tumor size. This means that brain metastases would be best treated at their smallest size, earlier in the course of their disease. However, early treatment with WBRT puts patients at risk for cognitive decline long before onset of symptomatology from metastases as well as leaving them with no other good options for treatment when new small brain metastases develop later along their course. Therefore, the ideal treatment would occur when tumors are small and asymptomatic, but distinguishable from normal brain tissue, and would optimally spare normal brain from unnecessary irradiation.

4. The changing face of cancer care

Advances in the management of solid organ cancers have occurred alongside the advances in neurosurgery and radiation oncology.

The most common primary sources of brain metastases in descending frequency are: lung cancers, breast cancers, colon cancers, melanoma, and renal cell carcinomas. Over the past few decades, it has become increasingly recognized that outcome is affected not only by the cancer histopathology itself but also by subtypes within each histopathology and by therapies targeted specifically at each histopathology type. It has been shown repeatedly that the identification of HER2/Neu receptor positivity in a breast cancer patient is associated with a survival advantage and that targeted systemic agents such as trastuzumab can result in long-term control of breast cancer. Epidermal growth factor receptor (EGFR) inhibition in non-small cell lung cancer has also been shown repeatedly to improve survival in a subset of patients whose tumors have EGFR mutations. Small molecule tyrosine kinase inhibitors such as sorafenib and sunitinib have also been found to be very effective in some patients with renal cell cancer, while immunomodulation agents such as interleukin-2 and ipilimumab are prolonging survival in melanoma patients. Furthermore, the identification of patients whose tumors have specific genetic markers for responsiveness to targeted treatment has improved survival for a subset of patients with stage IV disease. Median survival durations of 1-3 years have been reported in the literature for these patients (Bafford, 2009; Eichler, 2010; Robert, 2011; Sperduto, 2011; Webber, 2011).

With the improved ability of medical oncologists to control systemic disease, the previously nihilistic approach to brain metastases has also changed. As an example of changing

medical oncology practices, one publication compared 103 patients with brain metastases treated from 1983-1989 with a similar cohort treated from 2005-2009 in 3 institutions in Germany and Norway (Nieder, 2010). Compared with the historical group, contemporary patients were more likely to present with brain metastases simultaneous to their cancer diagnosis (30% vs. 18%) or have an increased time from cancer diagnosis to brain metastasis diagnosis (8 vs. 3 months). Additionally, contemporary patients typically had more frequent findings of multiple brain metastases (61% vs. 29%) and extracranial metastases (52% vs. 23%). This reflects an increased use of MRI resulting in an improved ability to detect metastases over the 20-year period. With regards to cancer therapy, the authors reported concomitantly increased use of focal treatments such as surgery or SRS for brain metastases and decreased use of WBRT. Compared to the 1980s, when it was common to cease administration of systemic treatments after the diagnosis of brain metastases (76%), 55% of contemporary patients received systemic therapy after brain metastasis diagnosis and 13% of contemporary patients (vs. 0% in the historical group) received third line chemotherapy. One-year survival was doubled in the contemporary group compared to the historical group (34% vs. 15%).

Because some stage IV cancer patients may enjoy a prolonged survival, it has now become essential to identify these patients and to offer treatments that carry minimal side effects with the most durable cancer control to provide optimal quality-of-life. It is also increasingly important to offer treatment options that do not interfere with systemic therapy in order to maintain the best systemic control possible, thereby decreasing the chance of developing metastases.

5. Patient selection and prognostic indices

There has been a growing recognition that pre-treatment patient variables may play a major role in determining patient prognosis. One of the most important variables is patient functionality and activity, otherwise known as performance status. Two classifications are widely used (Table 1): the Karnofsky performance status (KPS) and the Eastern Cooperative Oncology Group (ECOG) performance status (PS), the latter of which was adopted by the World Health Organization (WHO) (Karnofsky & Burchenal, 1949; Oken, 1982).

In an attempt to determine patient prognosis following WBRT, Gaspar et al. (1997) published a seminal prognostic index for patients with brain metastases, known as the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA). Using data from 1,200 patients in three consecutive clinical trials (RTOG 7916, 8528, 8905), an interactive, nonparametric statistical method was used to classify patients in three groups depending on four criteria. Patients younger than 65 years with good performance status (KPS≥70), a well-controlled primary tumor, and no extracranial metastases were assigned to RPA Class I (median survival 7.1 months), those with KPS<70 were assigned to RPA Class III (median survival 2.3 months), and all others to Class II (median survival 4.3 months). Despite its widespread validation and adoption, one of the major criticisms of the RPA system was the inhomogeneity of Class II and III, which are based primarily on the KPS, which may not be an entirely objective measure of functionality. Thus, several other research groups have created indices to try to more accurately and reproducibly classify patients into prognostic categories (Table 2).

KPS	Description	ECOG / WHO PS	Description
100	Normal, no signs of disease	0	Fully active, able to carry on all pre-disease performance without restriction
90	Capable of normal activity, few symptoms or signs of disease		
80	Normal activity with some difficulty, some symptoms or signs	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
70	Caring for self, not capable of normal activity or work		
60	Requiring some help, can take care of most personal requirements	2	Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
50	Requiring help often, requiring frequent medical care		
40	Disabled, requiring special care and help	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
30	Severely disabled, hospital admission indicated but no risk of death		
20	Very ill, urgently requiring admission and supportive measures or treatment	4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
10	Moribund, rapidly progressive fatal diseases processes		
0	Dead	5	Dead

Table 1. Descriptions of the Karnofsky performance status (KPS) and the Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) performance status (PS).

Most recently, the Graded Prognostic Assessment (GPA) was developed using data from 1,960 patients from RTOG trials 7916, 8528, 8905, 9104, and 9508 (Sperduto, 2008). It was the first index to remove primary tumor control and systemic disease stability as prognostic indicators, due to subjectivity in the assessment of these factors, which may vary widely based on type, technique, and timing of restaging studies. Additionally, the GPA added number of intracranial metastases as a prognostic factor, due to the findings of RTOG 9508 showing a survival advantage for patients with 1 vs. 2-3 metastases (Andrews, 2004). This study showed that across all histopathology types, patients with age<50 years, KPS 90-100, a single brain metastasis, and no evidence of extracranial metastases survived a median of 11.0-21.7 months, while patients with age>60 years, KPS<70, >3 brain metastases, and evidence of extracranial metastases had median survivals of 2.6-3.0 months.

Prognostic index	Prognostic factors	Score
RTOG Recursive Partitioning Analysis [**RPA**] (Gaspar, 1997)	4 (age, KPS, systemic disease status, extracranial metastases)	-Class I: Age<65, KPS≥70, no extracranial metastases, primary tumor controlled -Class III: KPS<70 -Class II: all others
Rotterdam Index (Lagerwaard, 1999)	3 (ECOG PS, systemic disease status, response to steroids)	-"good": ECOG 0/1, no/limited systemic tumor activity, good steroid response -"poor": ECOG 2/3, limited/ extensive systemic tumor activity, little steroid response -"moderate": all others
Score Index for Radiosurgery [**SIR**] (Weltman, 2000)	5 (age, KPS, systemic disease status, number of metastases, volume of largest lesion)	Summation of individual scores (0, 1, 2) to total score of 0-10
Basic Score for Brain Metastases [**BSBM**] (Lorenzoni, 2004)	3 (KPS, systemic disease status, extracranial metastases)	Summation of individual scores (0, 1) to total score of 0-3
Graded Prognostic Assessment [**GPA**] (Sperduto, 2008)	4 (age, KPS, extracranial metastases, number of metastases)	Summation of individual scores (0, 0.5, 1) to total score of 0-4
Diagnosis-Specific Prognostic Assessment [**DS-GPA**] (Sperduto, 2010)	-Lung: 4 (age, KPS, extracranial metastases, number of metastases) –Breast: 3 (age, KPS, cancer subtype) -Melanoma/Renal: 2 (KPS, number of metastases) -GI: 1 (KPS)	-Lung: Summation of individual scores (0, 0.5, 1) to total score of 0-4 -Melanoma/Renal: Summation of individual scores (0, 0.5, 1) to total score of 0-2 -Breast/GI: Summation of individual scores (0, 1) to total score of 0-4
RTOG = Radiation Therapy and Oncology Group; KPS = Karnofsky Performance Status; GI = gastrointestinal		

Table 2. Summary of major prognostic indices for brain metastases in the past 15 years.

Subsequently, a retrospective, multi-institutional database of 5,067 patients was then undertaken to identify histology-specific prognostic factors to create the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) (Sperduto, 2010). For non-small cell and small cell lung cancer, all four of the original GPA prognostic factors remained significant. For breast cancer, 3 factors determined prognosis: age, tumor subtype and KPS but not number of brain metastases. However, for melanoma and renal cell cancer, only KPS and number of metastases remained significant, while for gastrointestinal cancer, only KPS remained significant. For every histology, a DS-GPA score of 3.5-4.0 was associated with median survival durations of >12 months (13.2 months for melanoma to 18.7 months for breast

cancer). This data emphasizes yet another layer of heterogeneity of patients with brain metastases, in that not all of the prognostic factors were significant for tumors of different histologies and different prognostic factors carried different weights in the prediction of outcome. More importantly, it showed that studies investigated results of treatment must take these varying prognostic indicators into account.

6. Stereotactic radiosurgery and the gamma knife

With the increasing duration of survival in cancer patients, the overall incidence of brain metastases will likely continue rising, making improved therapies for treating brain metastases even more valuable. As discussed previously, WBRT is associated with transient but often not insignificant acute side effects, and may be associated with significant delayed cognitive side effects. It is essentially used only once during the course of a patient's disease, and the appropriate time to intervene with this therapy is still debated in many clinical settings. If WBRT has been used previously, it cannot be repeated with any expectation of significant efficacy for most tumors at the time of intracranial disease recurrence, and most radiation oncologists are hesitant to deliver a second full dose of radiation because of fears of cumulative toxicity. Craniotomy carries significantly higher morbidity and mortality risks than any radiation-based procedure and is also limited by the inability to treat multiple lesions at the same time.

The marriage between the neurosurgical and radiation oncology specialties resulted in the development of stereotactic radiosurgery (SRS), which is a method to deliver a single, high-dose fraction of ionizing radiation treatment to a precisely defined focal target volume. Gamma Knife radiosurgery (GK-SRS), initially developed by Lars Leksell and Borje Larsson (Leksell, 1951), delivers treatment using multiple gamma radiation beams from Cobalt-60 sources that simultaneously converge on a single focus point known as an isocenter. Stereotaxis is achieved with a fixed alignment of the patient to a physical coordinate system, via stereotactic head frame for GK-SRS. GK-SRS is the gold standard system for delivery of stereotactic radiosurgery to the brain, and the latest version of the Gamma Knife, the Perfexion, was specifically designed to facilitate radiosurgical treatment of multiple metastases.

Advantages of GK-SRS include its non-invasiveness, except for the application of the head frame, and association with excellent tolerability. It can be used to treat lesions in any region of the brain and is better tolerated than surgery in eloquent cortical areas (Dea, 2010; Elliott, 2010). Small and multiple lesions can be treated in one setting, minimizing the need for interruption from systemic therapy, unlike WBRT or surgery. GK-SRS treatments are also highly conformal, sparing radiation effects to much of the normal brain.

Disadvantages of SRS treatment include its inability to treat lesions >3 cm in diameter, a relative delay in symptomatic relief from mass effect, and the possibility of inducing a delayed leukoencephalopathic process that is often difficult to distinguish from tumor recurrence (Rauch, 2011). In addition, neither SRS nor surgical resection address the risk of developing further metastases outside the focused field of therapy that WBRT can achieve, though SRS can be used repeatedly for salvage therapy. The delivery of GK-SRS treatment itself is also expensive and labor-intensive compared with standard WBRT.

For brain metastases, SRS was first evaluated for potential effectiveness as a salvage treatment for inoperable, recurrent, and/or persistent lesions. One of the earliest publications reported data from 12 patients with solitary, deep, and radioresistant brain metastases treated with LINAC in Heidelberg (Sturm, 1987). Patients received 20-30 Gy to the 80% isodose surface, and all patients had an arrest in tumor growth and a marked improvement in clinical condition beginning a few days after irradiation, with all but one of these patients being free from side effects at last follow-up. Another study from the Dana-Farber Cancer Institute analyzed data from 18 patients with 21 recurrent or persistent metastases treated with 9-25 Gy to the 70-90% isodose surface with LINAC (Loeffler, 1990). After a median follow-up of 9 months (range 1-39 months), all lesions were well-controlled, and rapid clinical and radiographic improvement was observed with no cases of radiation necrosis despite previous exposure to radiotherapy. One of the first reports of GK-SRS for brain metastases was a case study from the Karolinska Institute of a patient with a solitary recurrent renal cell carcinoma metastasis treated with 25 Gy to the 35% isodose surface without WBRT (Lindquist, 1989). Shrinkage of this growth was observed and no regrowth was evident when the patient expired from his systemic disease 11 months later.

Since these original studies, several authors have reported superior metastasis control rates using SRS or SRS+WBRT when compared with WBRT alone. One-month local control rates of 93-96% have been reported for SRS with or without WBRT compared with 88% for WBRT, while 1-year local control rates of 80-90% have been reported for WBRT+SRS vs. 65-75% for SRS alone vs. 0-30% for WBRT alone (Elaimy, 2011). Two multi-arm studies showed a significant survival advantage for SRS alone and SRS+WBRT over WBRT alone (Li, 2000; Wang, 2002). One large retrospective study of 1,702 patients comparing SRS+WBRT to WBRT alone also reported a significant survival benefit for patients receiving SRS for all three RPA classes (Sanghavi, 2001). Three other studies comparing SRS alone to WBRT alone found that SRS patients lived significantly longer (Kocher, 2004; Lee, 2008; Rades, 2007b), while one found no significant survival difference (Datta, 2004).

Factors that have been shown to affect lesional responses to SRS include lesion volume, 10-12 Gy treatment volumes, marginal treatment dose, histopathology, and time since SRS (Hasegawa, 2003; Hatiboglu, 2011; Shehata, 2004; Yang, 2011), although lesion volume has been the only factor consistent among the varying studies. Typically, lesions <2 cm diameter respond well to 20 Gy of SRS. However, doses have varied from 16 to 24 Gy depending on lesional size and location. One of the additional advantages of SRS over WBRT is the relative uniformity of response of different histopathological tumors to the same SRS treatment dose (Kim, 2011; Powell, 2008, Varlotto, 2003; Wegner, 2011).

Time since SRS has also been shown to play a role in lesion control rates, falling from 93-96% at 1 month to 80-90% at 1 year to 69% at 3 years and 5 years in a study by Varlotto et al. (2005). Local control rates are determined by serial imaging, and local control failure is typically defined as an increase in the size of lesion after SRS. One of the difficulties with interpreting local control has been the demonstration that up to one third of lesions can transiently increase in size following SRS but if followed, many will regress again without further treatment (Patel, 2011a). This study reported that while a significant number of lesions showed transient enlargement 9-18 months following SRS, 2-3 year follow-up showed a local control rate of 99%. This suggests that in previous studies, a significant number of patients may have been classified incorrectly as having local failure.

The first randomized clinical trial to examine the potential benefit of SRS boost for brain metastasis patients was conducted in Pittsburgh (Kondziola, 1999). A total of 27 patients (13 with SRS+WBRT vs. 14 with WBRT alone) with 2-4 brain metastases (all ≤2.5 cm in diameter) and KPS≥70 were enrolled in the study. GK-SRS was utilized for all patients receiving SRS. Compared to WBRT alone, patients receiving SRS+WBRT had significantly lower local failure rates (8% vs. 100%, p=0.002), longer median time to local failure (36 vs. 6 months, p<0.001), and longer median time to any brain failure (34 vs. 5 months, p=0.002). There was also a non-significant trend favoring the patients receiving SRS boost in terms of median overall survival (11 vs. 7.5 months, p=0.02). No neurologic or systemic morbidity related to SRS was noted.

A larger, multi-institutional trial (RTOG 9508) was then undertaken to define the role of SRS boost for a limited number of metastases (Andrews, 2004). A total of 333 patients with 1-3 brain metastases (≤4 cm in diameter for the largest lesion and ≤3 cm for the remainder) and KPS≥70 were randomized to SRS+WBRT (167 patients) and WBRT alone (164 patients). Overall, there was no significant difference in median overall survival between the two arms (6.5 months for SRS+WBRT vs. 5.7 months for WBRT alone, p=0.14) or overall intracranial disease control (p=0.13), although SRS was associated with superior local control (p=0.013), stability or improvement of KPS score at 6 months follow-up (p=0.033), and decrease in steroid requirement (p=0.016). Among patients with single brain metastases, however, those receiving SRS+WBRT had a higher median overall survival than those receiving WBRT alone (11.6 vs. 9.6 months, p=0.045).

One of the major criticisms of the RTOG 9508 trial includes the lack of follow-up neuroimaging review on 43% of the patients. Another was the large bilateral crossover rate, as 19% of patients in the SRS+WBRT arm (mostly in RPA Class II) did not receive their planned SRS, while 17% of patients in the WBRT arm received salvage SRS. Despite these limitations, the superiority of SRS in survival for selected patients with 1 brain metastasis and in local control and KPS maintenance for 1-3 metastases shown by the RTOG 9508 trial, combined with the benefit in local control for 2-4 metastases demonstrated by the Pittsburgh trial, have provided level I evidence for the use of SRS as standard-of-care treatment for patients with a limited number of metastases and KPS≥70.

7. Controversies related to stereotactic radiosurgery

7.1 SRS vs. surgical resection for single metastases

Given that both surgery and SRS can treat single metastases effectively, the question has arisen as to which focal therapy might result in a better outcome. In choosing a focal therapy to use with or without WBRT, SRS and surgical resection each have their own advantages. As described previously, surgical resection is effective in single, large, and surgically accessible lesions, can rapidly relieve mass effect, and obtain tissue diagnosis. However, SRS requires no general anesthesia, is minimally invasive and can be used for small lesions located in nearly any area of the brain, including deep or highly functional regions. Nevertheless, for patients with overlapping indications (i.e. single, accessible lesions without an emergent need for resection in patients who are reasonable surgical candidates), the question of which focal therapy would yield better outcomes continues to be debated.

Several retrospective studies have been performed to evaluate this question. When comparing SRS+WBRT vs. resection+WBRT, a significant survival advantage for SRS+WBRT patients was found in three studies (Garell, 1999; Rades, 2011; Schoggl, 2000), for resection+WBRT patients in one study (Bindal, 1996), and for neither group in one study (O'Neill, 2003). Median time to local recurrence was longer for SRS+WBRT in two studies (Rades, 2011; Schoggl, 2000) and for resection+WBRT in one study (Bindal, 1996). For SRS alone vs. resection+WBRT, no significant survival or local recurrence difference was found in two studies (Muacevic, 1999; Rades, 2007a), while resection+WBRT was favored in survival and local recurrence in one study (Shinoura, 2002).

Given the contradictory conclusions of these retrospective studies, one prospective, randomized clinical trial was performed comparing SRS alone vs. resection+WBRT (Muacevic, 2008). Sixty-four patients (31 SRS alone vs. 33 resection+WBRT) with a single surgically accessible brain metastasis ≤3 cm in diameter and KPS≥70 were enrolled in the study. Between the patients receiving SRS alone vs. resection+WBRT, there was no significant difference in median survival (10.3 vs. 9.5 months, $p=0.8$), neurologic death rates (11% vs. 27%, $p=0.3$), and 1-year local control (97% vs. 82%, $p=0.06$). An increased rate of distant intracranial recurrence was initially observed among SRS patients (26% vs. 3%, $p<0.05$), but this difference no longer persisted following salvage SRS treatment. SRS was also associated with fewer grade 1 or 2 early or late radiation complications ($p<0.01$). Although the study was likely underpowered or biased from poor accrual (25% of target), it appears that SRS, even without WBRT but with the availability of future SRS salvage treatments, is not inferior to surgery with WBRT for highly functional patients with a single operable brain metastasis, and may be preferred due to the shorter hospital stay, less frequent and shorter duration of steroid application, and lower frequency of complications. Patients with stage IV cancer are often reluctant to undergo major surgical procedures and it may not be realistic to design a study to answer this question.

7.2 Omission of WBRT from SRS treatment for limited metastases

Given the previously discussed side effects of WBRT, the possibility of prolonged survival in patients with a limited number of brain metastases, and the demonstrated ability of SRS to provide equivalent local control of brain metastases compared with WBRT, the question of deferring WBRT at initial time of brain metastasis treatment has been raised. Despite their inherent biases, retrospective studies have raised the possibility that the SRS-alone approach may be viable for a limited number of metastases. When first proposed, many studies demonstrated that freedom from intracranial disease progression at 1 year, predominantly at sites distant than those treated with SRS, was significantly worse for SRS alone than SRS+WBRT (Chidel, 2000; Hoffman, 2001; Noel, 2003; Pirzkall, 1998). A single-institution review of 105 patients with 1-4 brain metastases, however, showed that the addition of WBRT to SRS did not result in improvement in survival or local control if salvage therapy was available for recurrence after SRS alone (Sneed, 1999). This lack of a statistically significant difference in overall survival was confirmed by seven other retrospective cohort studies (Chidel, 2000; Hoffman, 2001; Jawahar, 2002; Noel, 2003; Pirzkall, 1998; Sneed, 2002; Varlotto, 2005) and one prospective cohort study (Li, 2000), while one study showed a survival benefit for SRS alone (Combs, 2004) and another showed a survival benefit for SRS+WBRT (Wang, 2002). Among these 10 retrospective cohort studies, only one reported a

statistically significant worsening in local tumor control for patients treated with SRS alone compared to SRS+WBRT (Varlotto, 2005). Despite the excellent outcomes demonstrated by these retrospective studies, their potential for selection bias increased the need for randomized trials to compare SRS alone to SRS+WBRT.

The first randomized trial comparing SRS alone vs. SRS+WBRT was a multi-institutional phase III study (JROSG 99-1) from Japan (Aoyama, 2006). A total of 132 patients (67 SRS alone vs. 65 SRS+WBRT) with KPS scores ≥70 and 1-4 newly diagnosed brain metastases <3 cm in maximum diameter were accrued. Median follow-up was 7.8 months for all patients and 49.2 months for survivors. Overall survival for all patients was not significantly affected by the addition of WBRT (median survival 8 months for SRS alone vs. 7.5 months for SRS+WBRT, p=0.42). Intracranial failure rates, however, were considerably higher in those patients who did not receive WBRT compared with those who did (1-year distant intracranial recurrence 63.7% vs. 41.5%, p=0.003; 1-year overall intracranial recurrence 76.4% vs. 46.8%, p<0.001) as was the use of salvage treatment (43.3% vs. 15.4%, p<0.001). Death attributable to neurologic cause and 1-year systemic functional preservation as defined by a decrease in KPS score to ≤70 were not significantly different between the two arms.

To determine if the increased rate of distant intracranial failure or WBRT affected cognitive function, a secondary analysis was performed for 82 patients for whom baseline Mini-Mental Status Examination (MMSE) scores were >27 and who also had follow-up MMSE testing (Aoyama, 2007). The 1-year, 2-year, and 3-year actuarial MMSE preservation rates were 59.3%, 51.9%, and 51.9% for SRS alone, and 76.1%, 68.5%, and 14.7% for SRS+WBRT, respectively (p=0.73) suggesting that the addition of WBRT resulted in better control of central nervous system (CNS) disease and therefore improved cognitive function. The mean time to 3-point MMSE deterioration was also shorter for SRS alone compared to SRS+WBRT (7.6 vs. 16.5 months, p=0.005). MMSE recovery, however, was observed after successful salvage treatment in patients who had SRS alone and whose MMSE had deteriorated with the development of new brain metastases. Similar improvements were not seen for MMSE deterioration in patients who had received SRS+WBRT and who required protracted steroid therapy for CNS symptoms. These results suggest that progression of CNS disease as seen at time of intracranial distant failure can result in a reversible cognitive decline if successfully treated, compared with an irreversible decline following WBRT.

A second phase III trial at the M.D. Anderson Cancer Center was conducted to further evaluate the neurocognitive effects of SRS vs. SRS+WBRT (Chang, 2009). A total of 58 patients (30 SRS alone vs. 28 SRS+WBRT) with 1-3 newly diagnosed brain metastases and KPS scores ≥70 were accrued, before the trial was stopped early because planned interim analysis indicated that patients randomized to SRS+WBRT were significantly more likely to have learning and memory function deficits at 4 months post-treatment. Baseline characteristics between the two groups were similar, as were the median prescription target volume ratio and median prescription isodose. Median follow-up was 9.5 months for all patients. Patients receiving WBRT were significantly more likely to show a decline in cognitive function as measured by learning and memory function at 4-month follow-up compared to those treated using SRS alone, particularly in Hopkins Learning Test-Revised (HVLT-R) total recall (mean posterior probability of decline 24% for SRS alone vs. 52% for SRS+WBRT) and delayed recall and recognition. The decline in total recall was also found to persist at 6 months. As a secondary finding, median survival was also found to be

significantly higher for patients with SRS alone compared to SRS+WBRT (15.2 vs. 5.7 months, p=0.003), despite their having significantly lower 1-year local tumor control (67% vs. 100%, p=0.012), distant tumor control (45% vs. 73%, p=0.02), and freedom from CNS recurrence (27% vs. 73%, p=0.0003). Salvage therapy was necessary in 87% of patients receiving SRS alone (33% surgical resection, 20% SRS, 33% WBRT), compared to only 7% of those receiving SRS+WBRT. There was no difference between the two groups in neurological cause of death or rate of treatment toxicities. The difference in survival reported in this study is contrary to most other previous studies and was possibly explained by post-hoc analysis showing that patients who received SRS alone underwent systemic therapy over one month earlier and received a median of two cycles more systemic therapy than patients who received additional WBRT. This finding will need further study for validation.

A third randomized clinical trial, EORTC 22952-26001, was performed in Europe to evaluate functional independence and quality-of-life, which are not adequately captured by neurocognitive function alone (Kocher, 2011). A total of 353 patients with 1-3 brain metastases ≤3.5 cm (≤2.5 cm each for multiple metastases), stable extracranial disease, and WHO PS scores of 0-2 were recruited into the study. They were then randomized into two treatment arms: one without WBRT (100 patients SRS alone vs. 79 resection alone) and one with WBRT (99 SRS+WBRT vs. 81 resection+WBRT). There were no significant differences in baseline characteristics between patients not receiving WBRT vs. those receiving WBRT. Median follow-up for surviving patients was 40 months for those not receiving WBRT and 49 months for those receiving WBRT. The median time to decline in functional independence to a WHO PS>2 was not significantly different between patients without WBRT vs. patients with WBRT (10.0 months vs. 9.5 months, p=0.71), nor was overall survival significantly different between the two groups (10.7 months vs. 10.9 months, p=0.89). While median progression-free survival was slightly shorter for the no WBRT group compared to those undergoing WBRT (3.4 months vs. 4.6 months, p=0.02), overall intracranial progression at 2 years was significantly higher for the non-WBRT arm (78% vs. 48%, p<0.001), as was having intracranial failure as a component of cause of death (44% vs. 28%, p<0.002). No differences in toxicity rates were seen.

Several limitations of these trials have been noted by the authors and other observers. Though two of the three major randomized trials showed no difference in overall survival, they may have been underpowered to do so (Patchell, 2006). The increased survival for patients treated with SRS only compared to SRS+WBRT despite increased rates of intracranial recurrence with the omission of WBRT shown in the M.D. Anderson trial (Chang, 2009) may have been due to a much higher utilization of salvage therapies overall (87%), and particularly surgical salvage (33% of patients treated with SRS alone and 0% of patients who also underwent WBRT) as well as a possible difference in chemotherapeutic treatment.

The neurocognitive outcomes in the M.D. Anderson trial have also been called into question for two reasons. First, patients with terminal cancer are known to experience profound neurocognitive dysfunction (Lawlor, 2000; Pereira, 1997); thus, since overall survival was decreased in the arm receiving WBRT, the decreased neurocognitive function could itself be partially explained by the decreased overall survival and not by the additional WBRT the patients received. What may ultimately impact patient survival and function is the decrease

in delay of effective systemic therapy that SRS-only treatment affords – a factor that has not been studied to date. Second, the choice of a single time point for assessment of neurocognitive function at 4 months post-treatment as the primary outcome in the Chang et al. study is controversial. Previous studies have shown that neurocognitive function often reaches its nadir at 2-4 months post-treatment but subsequently rebounds in patients who survive beyond 4 months, and recurrence of intracranial disease tends to affect neurocognitive function more profoundly (Armstrong, 2000; Li, 2007). It is possible to postulate that while WBRT may cause a worsened subacute neurocognitive decline, its ability to control disease recurrence in long-term survivors may ultimately be superior if there is neurocognitive recovery.

Lastly, all three studies are limited by their choice of neurocognitive and functional assessment tools. While the MMSE and HTLV-R tests may be excellent screening tests for neurocognitive dysfunction, the MMSE has been criticized for having low sensitivity and specificity, while the HTLV-R can produce abnormal results in patients with focal neurological deficits that may not accurately reflect neurocognitive dysfunction (Meyers, 2003). Along the same lines, the WHO performance status has also not been validated as a measure of functional independence in patients with brain metastases and has been noted to be subject to inter-observer and intra-observer bias and variability, particularly in a non-blinded setting (Mehta, 2011). In addition, none of these tests have been specifically validated for patients with brain metastases.

In summary, for patients presenting with 1-4 newly diagnosed brain metastases, all three clinical trials discussed above appear to indicate a lack of detriment in neurocognition or quality-of-life with the omission of WBRT despite significantly worsened intracranial tumor control that would require additional salvage therapy (additional SRS, WBRT, or resection) in almost all patients. While the addition of WBRT clearly and reproducibly results in improved local and distant brain disease control, there is insufficient data to conclude definitively if this improved control translates into long-term improved neurocognitive function, functional independence, and quality of life. Thus, the use of SRS alone for the initial treatment of patients with 1-4 newly diagnosed brain metastases in a patient with KPS>70 may be a reasonable strategy in conjunction with frequent serial surveillance and the availability of salvage treatments, though further validation is needed to answer these questions more definitively.

7.3 SRS with or without WBRT for extensive metastases

In patients presenting with ≥5 brain metastases, the evidence for using SRS while deferring WBRT is scarce and primarily limited to retrospective data that mostly use GK-SRS. Two publications reported that patients with 1-10 and 2-20 brain metastases, respectively, treated with GK-SRS only without WBRT had longer overall survival than those treated with WBRT only (Serizawa, 2000; Park, 2009), with the first study also showing improved neurological and qualitative survival (interval from date of initial diagnosis to date of impaired quality-of-life) in those treated with GK-SRS only. Moreover, in patients with ≥10 brain metastases, two other studies reported that the use of GK-SRS alone allowed the achievement of "acceptable" tumor control with low morbidity, and high patient-reported satisfaction with regards to brain metastasis-related symptom management and quality-of-life (Kim, 2008; Suzuki 2000). Another study noted that GK-SRS treatment of 10-43 lesions in 80 patients

with ≥10 brain metastases resulted in acceptable WBRT doses on the order of 2.16-8.51 Gy (Yamamoto, 2002).

Recently, retrospective studies have begun to report that the number of brain metastases does not necessarily predict survival. One study retrospectively compared 130 patients with 1-3 vs. ≥4 brain metastases in patients receiving GK-SRS, and found that only RPA class and neither multiplicity of brain metastases nor receipt of WBRT affected survival (Nam, 2005), while another showed that for 205 patients with ≥4 brain metastases receiving a single SRS procedure, it was the total treatment volume and not the number of metastases that was associated with survival (Bhatnagar, 2006). The largest series to date showed that in their 1,885 patients undergoing 2,448 total GK-SRS treatment, no significant differences were found in median survival among patients with 2, 3-4, 5-8, or ≥9 brain metastases (Karlsson, 2009). Similarly, two other studies showed no significant difference in survival or intracranial recurrence among 778 patients who received GK-SRS without prophylactic WBRT with 1, 2, 3-4, 5-6, or 7-10 brain metastases (Serizawa, 2010) or among 323 patients with 1-5, 6-10, 11-15, and 16-20 brain metastases (Chang, 2010), though in the second study, patients with ≥16 metastases appeared to have an increased risk of distant intracranial recurrence.

For ≥5 brain metastases, no publications were found that specifically address direct comparisons of SRS only vs. SRS+WBRT. It appears that in patients with up to 10-20 metastases, the number of metastases may not be a factor that independently predicts survival. A recent survey of radiosurgeons at two major international meetings revealed that 55-83% of respondents considered it "reasonable" to extend the use of SRS as an initial treatment for ≥5 brain metastases, though there was no clear consensus regarding a reasonable maximum number of brain metastases to treat with SRS alone (Knisely, 2010). However, prospective analyses specifically studying SRS vs. SRS+WBRT for ≥5 brain metastases are still needed to validate this approach.

7.4 SRS as post-resection tumor bed consolidation

Another area of controversy surrounds the use of SRS as a consolidative tool to the tumor bed after microneurosurgical resection of a brain metastasis as an alternative to WBRT. As discussed previously, Patchell et al. (1990) demonstrated the value of resection of a single brain metastasis in improving survival, local control, and functional independence compared with WBRT alone. In a subsequent study, WBRT following resection resulted in superior intracranial metastasis control relative to resection alone (Patchell, 1998), and resection+WBRT has since been the standard approach for patients with single metastases. Despite WBRT, tumor bed recurrences can still occur, and Patchell's studies observed a 10-20% local and distant failure rate with a median follow-up of less than one year. Roberge et al. (2009) reported that an SRS boost with a 10 Gy marginal dose to the area recurring after resection+WBRT could be delivered safely with a 94% local control rate at 2 years.

Due to the potential delayed neurocognitive side effects of WBRT, investigators suggested the use of SRS in lieu of WBRT for consolidation of surgical resection cavities reserving WBRT for salvage therapy. Mathieu et al. (2008) reported on the use of SRS alone following surgical resection of single metastases. In 80% of the cases, a gross total resection was

achieved and GK-SRS was administered a median of 4 weeks after surgery. Median margin dose administered was 16 Gy and this resulted in a local control rate of 73% at 13 months follow-up. At the time of SRS, 33% of patients had additional non-resected lesions treated using GK-SRS at the time of surgical bed GK-SRS. Ultimately, only 16% of patients needed salvage WBRT. Similarly, Jagannathan et al. (2009) reported post-resection GK-SRS to 47 patients, all of whom had gross total resection. Mean marginal doses of 19 Gy were administered for a mean of 14 days after surgery, and local control rate was 94% at 14 months. The most recent series by Jensen et al. (2011) in 106 patients reported an 80% 1-year local control rate when marginal doses of 17 Gy were administered for a mean of 24 days after surgery.

Both Jensen et al. and Jagannathan et al. reported that increased size of resection cavity resulted in decreased local control. Several factors varied within these studies, however. First was marginal dose; unlike most other radiosurgical targets, the post-operative resection bed has its highest tumor burden peripherally where radiosurgical dose is lowest. Thus, it would seem reasonable that the higher the marginal dose, the more effective the local control, as suggested by the previously described three studies and one additional study (Iwai, 2008), which reported superior local control when doses ≥18 Gy were used. Second was time from surgery to SRS; it has been documented that rim enhancement of non-neoplastic resection cavities can show enhancement for 30 days after surgery (Sato, 1997). While this rim enhancement is typically thin and linear in the first 5 days post-operatively, it may become thick and nodular until at least 30 days post-operatively. It may therefore be difficult to determine which parts of the resection cavity are merely post-operative change and which are areas needing treatment for tumor. This may explain why larger lesions are more difficult to control and why two non-GK-SRS studies by Soltys et al. (2008) and Do et al. (2009) in fact recommend adding a 1-3 mm margin around the enhancing lesion to decrease conformality and improve local control. Third was extent of surgical resection; the highest local control rate was seen in the study by Jagannathan et al., in which all the lesions had gross total resection, compared with the other two studies which included subtotal resection cases also. Thus, it is important to determine if differing treatment protocols are required to maximize outcome based on extent of resection. No publications have addressed this question to date.

Only one retrospective study directly comparing resection+SRS with resection+WBRT has been published (Hwang, 2010). For the 43 patients (25 GK-SRS vs. 18 WBRT) treated at Tufts following tumor resection, there were non-significant trends towards superior survival for patients receiving GK-SRS (15 vs. 7 months, p=0.008) and local control (100% vs. 83%). Though the groups were well-balanced in histology, mean number of metastases, and resection extent, the study was severely limited by the lack of other important clinical variables, including performance status, measures of neurological function, cause of death, and control of systemic disease.

Despite these somewhat promising results regarding local tumor control following SRS post-resection boost without initial WBRT, distant intracranial failures appear to occur frequently, requiring high rates of salvage SRS or WBRT. Additional evidence from both retrospective and prospective studies demonstrating noninferiority in survival and preferably overall intracranial control is needed before the substitution of SRS for WBRT as initial post-resection consolidation becomes standard treatment.

8. Conclusions

Several conclusions can be drawn from this chapter. First, WBRT remains the cornerstone of treatment for most patients with brain metastases, since it is highly effective in the palliative setting, and since many patients with brain metastases present in poor functional condition and would not likely benefit from aggressive focal therapy. Second, the addition of focal therapy with either surgical resection or SRS confers benefit in local control, neurologic symptoms, functional independence, and survival for selected patients with good functional status, good systemic control, and a single brain metastasis (and possibly for those with a limited number of multiple metastases). Third, several other questions remain controversial, including the role of SRS in substituting for surgical resection for operable single metastases, serving as definitive treatment without upfront WBRT for a limited number of multiple metastases, complementing or substituting for WBRT for an extensive number of multiple metastases, and substituting for WBRT in the post-resection setting. The key to some of these questions would be clarifying whether or not WBRT truly plays an independent role in contributing to permanent neurocognitive deficits, and if so, whether or not survival and local control outcomes would allow its deferral in various settings. There continues to be a need for well-designed prospective and retrospective studies to evaluate these controversial topics further.

The outcome of treatment of brain metastases using SRS cannot be studied in isolation and must be interpreted in the context of changing systemic cancer care and evolving prognostic indicators. Clinical trials of combined modality approaches with SRS and agents capable of penetrating the blood-brain barrier will likely be mounted in the future. These studies may include chemotherapy, radiation sensitizers, monoclonal antibodies, and other tumor-specific targeted agents, as researchers and clinicians obtain a deeper understanding of the molecular drivers of different subtypes of cancers that metastasize to the brain. As these therapies continue to develop and improve, the potential for more durable systemic control and overall survival may warrant an increase in the utilization of SRS, making a more thorough understanding of its potential indications even more critical.

9. References

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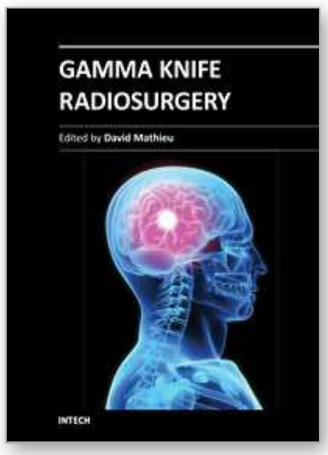

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Gamma knife radiosurgery is a minimally-invasive treatment alternative for intracranial disorders, including tumors, vascular malformations, facial pain and epilepsy. This book will allow the reader to learn when gamma knife radiosurgery is appropriate and what to expect as treatment results.

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