GAMMA KNIFE RADIOSURGERY

Edited by **David Mathieu**

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Published by InTech
Janeza Trdine 9, 51000 Rijeka, Croatia

Publishing Process Manager Vana Persen
Technical Editor Teodora Smiljanic
Cover Designer InTech Design Team
Image Copyright Eraxion, 2011. DepositPhotos

First published December, 2011
Printed in Croatia

A free online edition of this book is available at www.intechopen.com
Additional hard copies can be obtained from orders@intechweb.org

Gamma Knife Radiosurgery, Edited by David Mathieu
p. cm.
ISBN 978-953-307-888-5

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Preface

In the past 25 years, gamma knife radiosurgery has evolved from a tool that was seen as a curiosity to a minimally-invasive neurosurgical treatment modality that is now a recognized alternative to conventional microsurgery or fractionated radiation therapy. Radiosurgery training is now implemented in most neurosurgical residency training program. The literature on the subjected has exploded in the past few years, with literally hundreds of papers being published annually on this topic.

As physicians and patients become increasingly aware of the benefits of gamma knife radiosurgery, it is important that information is readily available when it is needed. That is the purpose of this book, which covers some of the most common indications for which gamma knife radiosurgery is performed.

The first section of the book is dedicated to tumor radiosurgery. Brain metastases are now the most common tumors treated by gamma knife radiosurgery. Two chapters are devoted to this topic. Other chapters report the treatment results for meningiomas and vestibular schwannomas, the most frequent benign intracranial tumors treated by radiosurgery, and another is devoted to the treatment of rarer tumors. The second section covers benign non tumoral indications of radiosurgery, with chapters devoted to trigeminal neuralgia, epilepsy, and arteriovenous malformations. Finally, the last chapter reports on the use of the gamma knife as a tool for preclinical research.

I hope that the information provided in the book will improve the knowledge on the many applications and uses of gamma knife radiosurgery, and allow more patients worldwide to benefit from this treatment modality when appropriate.

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Part 1

Neoplastic Disorders

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.