Clinical Outcomes of Gamma Knife Stereotactic Radiosurgery for Neurological Disease

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Clinical Outcomes of Gamma Knife Stereotactic Radiosurgery
for Neurological Disease

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# Table of Contents

Introduction: Beginnings of Neurological Surgery and the Metamorphosis of the Neurosurgeon (Page 2)

**Brain Metastases**

Chapter One: Brain Metastases: Clinical Outcomes for Stereotactic Radiosurgery (Method) (Page 6)

Chapter Two: Multimodality Treatment of Brain Metastases: An Institutional Survival Analysis of 275 Patients (Page 34)

Chapter Three: Clinical Outcomes of Stereotactic Radiosurgery in the Treatment of Patients with Metastatic Brain Tumors (Page 63)

**Vestibular Schwannomas**

Chapter Four: Vestibular Schwannoma: Gamma Knife Radiosurgery (Method) (Page 103)

Chapter Five: A Review of Treatment Modalities for Vestibular Schwannoma (Page 116)

Chapter Six: Gamma Knife Radiosurgery for Vestibular Schwannomas: Tumor Control and Functional Preservation in 70 patients (Page 151)

**Functional Neurosurgery**

Chapter Seven: Gamma Knife Radiosurgery for Movement Disorders: A Concise Review of the Literature (Page 171)

Chapter Eight: Gamma Knife Radiosurgery for Essential Tremor: A Case Report and Review of the Literature (Page 186)

Chapter Nine: Feasibility of Multiple Repeat Gamma Knife Radiosurgeries for Trigeminal Neuralgia: A Case Report and Review of the Literature (Page 200)
Abstract

Stereotactic radiosurgery (SRS) is a form of radiation therapy that delivers a focused, highly conformal dose of radiation to a single intracranial volume, while minimizing damage to the adjacent nervous tissue. SRS ensures precise radiosurgical localization by immobilizing the patient’s skull in a specified fixed position and in turn precisely aiming a high dose of radiation at the neurological target. SRS can be delivered to the patient via 3 therapeutic devices: Gamma Knife (GK) radiosurgery, linear accelerator based treatment, and a cyclotron-based proton beam. Published reports have not found statistically significant differences in terms of clinical outcomes when analyzing patients treated with either radiosurgical device. The GK is a cobalt-60-based machine, with 201 separate 4 to 18 mm collimator openings that emits multiple gamma rays that converge on a target specified by computer planning. This thesis describes the clinical outcomes of patients treated with GK radiosurgery at the Gamma Knife of Spokane and Cancer Care Northwest for metastatic brain tumors, vestibular schwannomas, movement disorders, and trigeminal neuralgia. This thesis will not address specific treatment recommendations for other neurological disorders that may be treated using GK radiosurgery.
Beginnings of Neurological Surgery and the Metamorphosis of the Neurosurgeon

Neurological surgery is recognized to be the oldest surgical specialty, with evidence in the form of manipulated human skulls identified from specimens estimated to be over 12,000 years old [1]. Many ancient cultures used incision, cutting, and scraping methods for cranial entry for use in religious, ritualistic, and therapeutic practices [1]. However, the formal birth of neurological surgery was not recognized until 1905, which was the year Harvey Cushing published his findings regarding the establishment of homeostasis, control of intracranial pressure, and effects of special pathologies on specific neurological disorders in the Bulletin of the Johns Hopkins Hospital [2]. Approximately 3 years later in Surgery, Its Principles and Practice, Cushing extended his definition of neurological surgery by describing precise surgical techniques and methods for cranial entry, exploration, and treatment protocols for common neurological disorders [3].

Since the time of Dr. Cushing, the field of neurosurgery has advanced due to the rapid accumulation of scientific knowledge in the fields of molecular biology, computational science, imaging, biomedical engineering, and information processing [1]. One such advance is the advent of stereotactic radiosurgery (SRS). SRS is a form of radiation therapy that delivers a focused, highly conformal dose of radiation to a single intracranial volume, while minimizing damage to the adjacent nervous tissue [4]. SRS is known to be the first accepted form of “biological neurosurgery” due to its ability to
allow the neurosurgeon to operate at a macromolecular level through the “cutting” of nucleic acid strands and performing protein biosynthesis [5]. The applications of SRS in the treatment of malignant and benign neurological diseases are abundant because SRS has the ability to cause differential cellular effects. For example, SRS can prevent tumor cells from undergoing mitosis, prevent neurons with abnormal electrophysiological properties from firing, and cause abnormal blood vessels to occlude [5].

One form of SRS that can be delivered to a patient is through a machine called the Gamma Knife (GK). The GK device is a cobalt-60-based machine, with 201 separate 4 to 18 mm collimator openings that emits multiple gamma rays that converge on a target specified by computer planning [4]. Although GK remains the “gold standard” of brain radiosurgery, published reports by Andrews, et al. [6] and Sneed, et al. [7] concluded that patient prognosis did not differ in terms of the method in which SRS was delivered. SRS using the GK, as well as other devices, has proven to be a valuable tool for the modern neurosurgeon because SRS is a minimally-invasive treatment modality that has the capability to target any region in the brain with accuracy and can irradiate multiple lesions in the same clinical treatment setting [4]. After the introduction of SRS by Professor Lars Leksell in 1968 [8], traditional neurosurgical tools, such as suction, forceps, and scissors, have coincided with modern neurosurgical tools, such as nuclear science and the microprocessor, to ultimately give today’s neurosurgeon the ability to tailor treatment regimens based on the individual patient [1].

This thesis describes the clinical outcomes of patients treated at Cancer Care Northwest and the Gamma Knife of Spokane for metastatic brain tumors (cancerous secondary brain tumors), vestibular schwannomas (benign intracranial tumors that arise
from the myelin sheath about the vestibular nerve), movement disorders, and trigeminal neuralgia (a condition of extreme facial pain caused by malfunctioning of the trigeminal nerve).

References


Chapter One

BRAIN METASTASES: CLINICAL OUTCOMES FOR STEREOTACTIC
RADIOSURGERY (METHOD)

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ABSTRACT

Stereotactic radiosurgery (SRS) is a form of radiation therapy that delivers a focused, highly conformal dose of radiation to a single volume, while minimizing damage to the adjacent nervous tissue. Historically, surgical resection followed by whole brain radiation therapy (WBRT) has offered patients with a single metastatic brain tumor an improved quality of life, as well as an improved longevity, when compared to patients treated with WBRT alone or surgical resection alone. However, tumor resection with WBRT is not always the optimal treatment for all patients. Other clinical factors that impact treatment decisions are tumor location, patients who have multiple brain metastases, and patients who are in a poor medical state and are unable to undergo surgery. Due to the limitations of surgical resection alone and side-effects of WBRT, the efficacy of SRS has been examined in the treatment of brain metastases for multiple clinical scenarios. Stereotactic radiosurgery is capable of targeting any region in the brain and can be utilized to irradiate multiple tumors in the same treatment setting in a non-invasive fashion. For many clinical situations, radiosurgery alone or radiosurgery in combination with WBRT or surgery can be an optimal treatment approach. Although many questions remain unanswered, this chapter reviews current management options for the treatment of brain metastases, along with describing the patient selection criteria, treatment planning, methods, and outcomes associated with SRS.
INTRODUCTION

Brain metastases are the most frequently observed cancerous lesions in the brain. Metastasis to the brain will occur in 20 to 40% of patients with systematic cancer and in each incidence the brain metastases have the potential to pose a serious threat to the patient’s quality of life and longevity (Smedby et al., 2009). Lung cancer is the most common form of primary cancer that has the ability to metastasize to the brain. However, melanoma, breast cancer, colorectal cancer, renal-cell carcinoma, and carcinoma of multiple other origins may also lead to brain metastases (Suh, 2010). Areas of the brain that receive a larger blood supply are more likely to develop one or more metastatic brain tumors, thus, roughly 80% of brain metastases are hemispheric, while only 15% arise within the cerebellum and 5% arise within the brain stem (Delattre et al., 1988; Suh, 2010). Significant improvements in both imaging techniques and the treatment of extracranial cancer have led to early detection and an increase in the overall life expectancy of cancer patients, leaving them more susceptible to the development of brain metastases (Hazard et al., 2005).

Due to the high rate of morbidity and mortality that results from metastatic brain tumors, the efficacy of multiple treatment regimens have been analyzed and compared with one another to determine the most advantageous course of treatment in selected patient groups. In general, patients who suffer from brain metastases have a poor outlook and curative treatment is not achievable in most situations. Patients have an estimated survival time of 1 to 2 months when treated with corticosteroids alone and no radiation therapy or surgery (Andrews et al., 2004). Whole brain radiation therapy (WBRT) is a time-honored treatment protocol that targets rapidly dividing tumor cells in all areas of
the brain with photon beams, while eliciting minimal harmful effects on the healthy surrounding brain tissue. As a result, patients treated with WBRT alone have an average survival time of 4 to 7 months (Hazard et al., 2005). Despite the advantages of WBRT, 50% of these patients will still die from their neurological disease (rather than their extracranial disease) (Delattre et al., 1988). Surgical resection followed by WBRT for appropriate patients with single, surgically accessible brain metastases has proven to be a superior treatment modality in studies comparing WBRT alone and surgical resection alone (Patchell et al., 1990, 1998; Vecht et al., 1993). However, for patients with multiple brain metastases, the relative efficacy and safety of tumor resection followed by WBRT has not been evaluated in a randomized trial, thus, remains a questionable and most experts would argue, an excessive course of treatment (Schackert, 2002).

Stereotactic radiosurgery (SRS) is a highly technical image-guided form of radiation therapy that delivers a focused, highly conformal dose of radiation to a single intracranial volume, thereby minimizing damage to the adjacent nervous tissue. Stereotactic radiosurgery ensures precise tumor localization by immobilizing the patient’s skull in a specified fixed position and in turn precisely aiming a high dose of radiation at the tumor mass. Stereotactic radiosurgery can be delivered to the tumor volume via 3 therapeutic devices: gamma knife (GK) radiosurgery, linear accelerator (LINAC) based treatment, and a cyclotron-based proton beam. Of the 3 modalities, GK radiosurgery and LINAC-based treatment are the most frequent methods utilized (Hazard et al., 2005). Very few institutions use a cyclotron-based proton beam due to the high price of the machine and space requirements (Suh, 2010). As SRS has proven to be a viable course of treatment, numerous studies have been conducted on patient groups with single and
multiple brain metastases to evaluate their treatment-specific outcomes compared with
groups treated with the traditional modalities. As the evidence examining the role of SRS
in the treatment of brain metastases accumulates, it is of utmost importance for
physicians to understand the criteria associated with SRS, so that the optimal course of
treatment for their patients can be prescribed. This chapter reviews the current therapies
for the treatment of brain metastases, along with describing the patient selection criteria,
treatment planning, methods, and outcomes associated with SRS. This chapter will not
address specific treatment recommendations for primary brain tumors.

INDICATIONS AND PATIENT COUNSELING

Patient Selection

Patients with brain metastases are frequently assessed using the Radiation
Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) prognostic
system (Gaspar et al., 1997). This system categorizes patients into 3 different prognostic
groups (classes 1, 2, or 3) based on the age of the patient, presence of extracranial
metastases, Karnofsky Performance Score (KPS), and control of primary cancer.
Statistically, a higher class (class 2 and 3) represents a worse prognosis for the patient.
Phase III evidence suggests that surgical resection followed by WBRT for patients with a
single, surgically accessible brain metastasis who have a good performance status
(functionally independent and spend no more than 50% of their day in bed) is a more
effective treatment modality when compared to WBRT alone or surgical resection alone
(Patchell et al., 1990, 1998; Vecht et al., 1993). However, for patients with multiple brain
metastases, surgical resection of all lesions followed by WBRT is thought to be an extreme course of treatment, usually with unacceptable outcomes, and has not been analyzed in a randomized study. For patients with multiple metastases, a combination of WBRT alone, SRS alone, or a combination of SRS with WBRT can be the optimal approach for select patient subsets.

In addition to the 4 criteria described by the RTOG partitioning analysis, the outcomes of SRS are also influenced by the number, location, and size of metastatic brain tumors the patient possesses at the time of diagnosis. Literature reviews have demonstrated that patients with a KPS ≥ 70 and a single brain metastasis, who receive SRS treatment combined with WBRT survive a longer period of time than patients treated with WBRT alone (Linskey et al., 2010). Surgical resection followed by WBRT for a single brain metastasis is recommended for patients who present with rapid neurologic deterioration due to a dominant brain tumor, a ventricular obstruction, or a tumor of a large diameter of ≥ 40 mm (which many times leads to a mass effect) (Hazard et al., 2005). Stereotactic radiosurgery is warranted when the patient has controlled neurological symptoms (with or without steroids), a tumor/s ≤ 30 mm in diameter, a single brain metastasis, a surgically inaccessible brain metastasis, or multiple brain metastases in specific clinical situations (Hazard et al., 2005). In a review analyzing the role of SRS in the management of patients with newly diagnosed brain tumors, Linskey et al. (2010) found evidence that SRS with WBRT leads to an increased level of local tumor control and functional independence for patients with 1 to 4 brain metastases who have a KPS ≥ 70 and an increased survival time for patients with 2 to 3 brain metastases, when compared to patients treated with WBRT alone.
Whole Brain Radiation Therapy for Single and Multiple Brain Metastases

Whole brain radiation therapy is historically recognized to be the most common treatment utilized for approximately 70 to 80% of patients diagnosed with brain metastases (Kirsch and Loeffler, 2004; Peacock and Lesser; 2006). The aim of WBRT is to destroy metastatic tumor cells, while sparing as much as possible of the neighboring, functional brain tissue from acute and late side-effects from radiation therapy (Peacock and Lesser, 2006). Patients who possess either single or multiple inoperable brain tumors, or brain tumors that are thought to be too large for SRS are often treated with WBRT. Whole brain radiation therapy is an effective treatment modality due to the fact that tumor cells undergo mitosis much more rapidly than nervous tissue, making them more susceptible to radiation cell-kill (Goodhead, 1994). This difference in radiobiology provides an advantageous therapeutic ratio. However, even though radiation therapy has the capability to eradicate tumor cells more frequently than healthy cells, it is still possible for the patient to experience a variety of acute, sub-acute, or late side-effects from treatment. The acute side-effects from WBRT include fatigue, headache, nausea, impaired sense of taste, erythema, alopecia, hair loss, and hyperpigmentation (Kaal et al., 2005; Peacock and Lesser, 2006). The long-term side effects include hearing loss, decrease in neurocognitive function, alopecia, changes in behavior, ataxia, urinary incontinence, necrosis from radiation, and potential somnolence syndrome (Kaal et al., 2005; Peacock and Lesser, 2006). Gaspar et al. (2010) conducted a review evaluating WBRT in the management of patients with brain metastases and concluded that altered dose/fractionation schedules do not exhibit a compelling difference in survival, local
control, or neurocognitive outcomes when compared with “customary” dosing (i.e. biologically effective dose of 30 Gy in 10 fractions).

Surgical Resection with Whole Brain Radiation Therapy for a Single Brain Metastasis

After the diagnosis of a single brain metastasis with magnetic resonance (MR) imaging, neurosurgical intervention in appropriate patients, with open-skull craniotomy or tumor resection followed by WBRT has proven to be a more effective treatment method when compared with WBRT alone. In 1990, Patchell et al. published a study investigating the role of surgical resection followed by WBRT in the treatment of patients with single brain metastases. The authors randomized a total of 48 patients, where 25 were treated with neurosurgery followed by WBRT, while the other 23 were treated with WBRT alone. The prescribed radiation dose for both groups was uniform, with a total of 36 Gy being delivered in 12 daily fractions of 3 Gy each. Patients eligible for the study were able to care for themselves independently, with a KPS ≥ 70. Patients treated with surgery and WBRT experienced a statistically significant increase in median survival time (P < 0.01), living 40 weeks, whereas patients in the WBRT alone group lived a median of 15 weeks following treatment. Also, the addition of surgery substantially increased the time for the brain metastases to reoccur (P < 0.02) and functional independence (P < 0.005).

In 1993, another study was performed by Vecht, et al., which randomized 63 patients with single brain metastases to a surgical resection followed by WBRT group and a WBRT alone group. The authors delivered a novel, but constant, radiation schedule
between the 2 groups. Specifically, a total of 40 Gy were prescribed to the patients, with 2 Gy being delivered twice per day over 10 treatment days. The patients who participated in the study had a moderate quality of life and did not spend more than 50% of their day in bed. It was reported that the surgery and WBRT group survived a median of 10 months, which was a statistically significant (P = 0.04) improvement over the WBRT alone group, which survived a median of 6 months. Although the tendency did not reach full statistical significance (P = 0.06), it was observed that the surgery and WBRT group experienced an increased period of functional independence when compared with the WBRT alone group. Due to these data, surgical resection followed by WBRT was considered to be the benchmark treatment modality for patients with a single brain metastasis.

**Radiosurgery with Whole Brain Radiation Therapy for a Single Brain Metastasis**

After it was demonstrated that surgery combined with WBRT improved outcomes for patients with a single brain metastasis, the role of SRS with WBRT was soon investigated. As discussed earlier, neurosurgical resection followed by WBRT is the suggested course of treatment when the patient experiences a severe neurologic deficit, ventricular obstruction, or a substantial mass effect (Hazard et al., 2005). Since large tumors (≥ 40 mm) tend to cause mass effect, surgery is also the desired modality for patients with metastatic brain tumors of a large volume (Hazard et al., 2005; Suh, 2010). In appropriate patients that exhibit manageable neurocognitive symptoms, have a tumor diameter ≤ 30 mm, or possess an unressectable brain tumor, SRS has proven to be a respected treatment modality. Andrews et al. (2004) evaluated 333 patients with 1 to 3 brain metastases that were treated with either SRS with WBRT or WBRT alone.
Precisely, 167 patients were randomized into the SRS with WBRT group, while 164 patients were randomized into the WBRT alone group. Stereotactic radiosurgery was performed with either GK radiosurgery or LINAC-based treatment. It was found that there was no statistical significance in survival between the 2 treatment groups (P = 0.1356). Even though the 2 groups, when compared as a whole, did not differ in terms of median survival in subset analysis, those patients with single metastatic brain tumors in the SRS with WBRT group experienced a statistically significant (P = 0.0393) increase in survival time (6.5 vs. 4.9 months). Other sub-groups within the SRS with WBRT group which had an increased survival time were patients categorized in the RPA class 1, patients with nonsmall cell lung cancer, or patients with squamous cell lung cancer. Also, the authors observed that patients in the SRS with WBRT group were more inclined to have a stable or improved KPS score at 6 months of follow-up.

**Radiosurgery with Whole Brain Radiation Therapy for Multiple Brain Metastases**

Other clinical research has reported positive results when comparing SRS with WBRT and WBRT alone in patients who suffer from multiple brain metastases. A study published by Kondziolka et al. in 1999 investigated the role of SRS with WBRT versus WBRT alone in patients with 2 to 4 brain metastases. A total of 27 patients with a KPS ≥ 70, 2 to 4 metastatic brain tumors, and tumor diameters ≤ 25 mm were randomized into the SRS with WBRT and WBRT alone groups. Precisely, 13 patients were placed in the radiosurgery group, while 14 patients were placed in the WBRT alone group. All 27 patients received a total radiation dose of 30 Gy delivered in 12 daily fractions of 2.5 Gy each. Stereotactic radiosurgery was performed using GK radiosurgery. The 13 patients that underwent GK radiosurgery received a tumor marginal dose of 16 Gy. Because the
authors witnessed a drastic difference in tumor control between the 2 groups, the study was stopped at the 60% accrual point. The authors observed that the SRS with WBRT group lived a median of 11 months, whereas the WBRT alone group lived a median of 7.5 months. Differences in survival times did not reach statistical significance (P = 0.22) because there were a limited number of patients in the study. The radiosurgery group exhibited a substantially better local failure rate at 1 year (8%) and median time of recurrence (36 months) compared with the WBRT alone group, which had a 100% local failure rate at 1 year and a median time for recurrence of 6 months at the original site.

Sanghavi et al. (2001) evaluated 502 patients treated with SRS with WBRT from databases from 10 institutions. The authors excluded patients who had previously underwent WBRT or surgical resection, those with incomplete follow-up data, those not being treated for all brain metastases with radiosurgery, and those who had treatment after the specified cut-off date. Of the 10 institutions, GK radiosurgery was used in 3, LINAC-based treatment was used in 6, and 1 institution utilized both radiosurgical techniques. Each of the institutions prescribed radiation doses based on preference. The authors concluded that the overall median survival time was 10.7 months. Specifically, patients with a higher KPS (P = 0.0001), a controlled primary cancer (P = 0.0023), the absence of extracranial cancer (P = 0.0001), and a lower RPA class (P = 0.000007) were likely to survive an increased period of time when compared with those who do not possess those characteristics. Although this trial was not randomized, the results indicate that radiosurgery improves patient outcomes in RPA classes 1 through 3. Also, the authors found that the addition of radiosurgery improved survival times when compared
with patients treated with solely WBRT in another study previously performed by the RTOG (Borgelt et al., 1980).

**Surgical Resection or Radiosurgery Alone**

After the efficacy of surgical resection followed by WBRT was demonstrated in patients with single brain metastases, questions arose pertaining to the clinical outcomes of patients treated with solely surgical resection. In 1998, Patchell et al. performed a study where 95 patients with single brain metastases were randomized to either surgical resection followed by WBRT (49 patients) or surgical resection alone (46 patients). The authors reported that patients in the postoperative WBRT group experienced less frequent tumor recurrence at the sight of the original metastasis ($P < 0.001$) and less frequent tumor recurrence anywhere in the brain ($P < 0.001$). In addition, patients who received WBRT were less likely to die from neurological causes when compared with the surgical resection alone group ($P = 0.003$). Interestingly, there was not a statistically significant difference in median survival time and functional independence between the surgical resection with WBRT group and the surgical resection alone group.

Cumulative evidence suggests that SRS alone may provide equivalent levels of survival when compared with patients treated with both SRS and WBRT (Linskey et al., 2010). However, there is conflicting data regarding the 2 treatment modalities when analyzing the risk of both local and distant tumor control. Aoyama et al. (2006) randomized 132 patients into either a SRS with WBRT (65 patients) group or a SRS alone group (67 patients). There were no statistically significant differences in the 2 groups, with respect to survival, death due to neurological causes, and toxicity. It was
observed that the SRS and WBRT group experienced a statistically significant (P < 0.001) lower local and distant 12-month actuarial brain tumor recurrence rate when compared with the SRS alone group.

Sneed et al. (2002) performed a retrospective study evaluating 569 patients from 10 institutions treated with either SRS with WBRT (301 patients) or SRS alone (268 patients). After adjusting median survival time for each RPA class, it was found that there were no statistically significant differences in overall survival between the 2 groups, with the SRS and WBRT group surviving a median of 8.6 months and the SRS alone group surviving a median of 8.2 months. It was documented that only 7% of patients in the SRS with WBRT group required salvage treatment, whereas 37% of patients in the SRS alone group required salvage treatment. This indicates an increase in the local control rate in the SRS with WBRT group.

Li et al. (2000) analyzed 29 patients treated with WBRT alone, 23 patients treated with SRS alone, and 18 patients treated with SRS with WBRT. Only patients with small-cell lung cancer (SCLC) and nonsmall-cell lung cancer (NSCLC), a single metastatic brain tumor ≤ 45 mm in diameter, and a KPS ≥ 60 were eligible for the study. Of the SRS with WBRT group and SRS alone group, the authors reported that there were no statistically significant differences in median survival. In contrast to the previous studies mentioned, adding WBRT to SRS did not improve local control levels when compared to the SRS alone group. Although this combination of data indicates patients who undergo SRS alone require salvage therapy more often than patients treated with SRS with WBRT, patients treated with both modalities should be monitored closely following
treatment so appropriate patients can begin salvage procedures at the earliest possible time.

**Impact of Various Histologic Subtypes**

The influence of primary tumor histology on the effectiveness of SRS is an area of controversy in the treatment of patients with brain metastases. Historically, melanoma and renal cell carcinoma have been identified as “radioresistant” histological types because they have displayed a poor response to standard radiation therapy when compared with cancers of other origins. Nieder et al. (1997) analyzed 108 patients (336 brain metastases) before and after WBRT using contrast-enhanced CT scans. The authors observed that complete response after WBRT occurred in 37% of metastases from small-cell carcinoma, 35% of metastases from breast cancer, 25% of metastases from squamous-cell carcinoma, and 14% of metastases from nonbreast adenocarcinoma. The complete response for melanoma and renal cell carcinoma was found to be 0% for each.

On the contrary, Flickinger et al. (1994) conducted a study where 116 patients from 5 institutions underwent GK radiosurgery for the treatment of solitary brain metastases. It was reported that tumor histology influenced survival time, with breast cancer patients experiencing a statistically significant increase in median survival (P < 0.004). Interestingly, it was also observed that patients with melanoma and renal cell carcinoma primaries exhibited a statistically significant higher local tumor control rate (P < 0.0003) than primary cancers of other histologies. Continued research on the influence of tumor histology on SRS efficacy and the specific radiobiology of tumors will lead to a greater understanding of the outcomes following SRS treatment.
TREATMENT PLANNING & METHODS

Types of Radiosurgery

As previously discussed, there are 3 main modalities by which SRS can be delivered (GK radiosurgery, LINAC-based treatment, and a cyclotron-based proton beam). The cyclotron-based proton beam is rarely used because the machine is extremely expensive and requires a great deal of space (Hazard et al., 2005). The GK device is a cobalt-60-based machine, with 201 separate 4 to 18 mm collimator openings that emits multiple gamma rays that converge on a target specified by computer planning (Suh, 2010). The LINAC device functions by accelerating an electron, which generates high-energy x-ray beams that are focused on a specific target at different angles by micro-multileaf collimators (Suh, 2010). Studies by Sneed et al. (2002) and Andrews et al. (2004) concluded that patient outcome is independent of mode of SRS delivery.

Dose Selection

A study from the RTOG evaluating the maximum tolerated dose of single fraction radiosurgery in patients with metastatic brain tumors (64% of patients) or primary brain tumors (36% of patients) which were previously irradiated, was conducted by Shaw et al. (2000). 156 patients with cerebral or cerebellar solitary non-brainstem tumors which were ≤ 40 mm in diameter participated in the study. The maximum tolerated doses for tumors ≤ 20 mm was 24 Gy, 18 Gy for tumors 21 to 30 mm in diameter, and 15 Gy for tumors 31 to 40 mm in diameter. The authors reported 3 variables associated with grade 3 to 5 toxicity: maximum tumor diameter, KPS, and tumor dose. It was found that compared to tumors < 20 mm, tumors 21 to 40 mm in diameter were 7.3 to 16 times more likely to
encounter grade 3 to 5 toxicity. Grade 3 toxicity was edema, which occurred a median of 4.5 months following treatment. Grade 4 toxicity was radionecrosis, which occurred at an incidence of 5% at 6 months, 8% at 12 months, 9% at 18 months, and 11% at 24 months after SRS was administered. Additionally, risk of local progression was higher in patients with primary brain tumors than in patients with metastatic brain tumors. It was concluded that large tumors (> 20 mm) were more likely to encounter toxicities, while local control was associated with the histologic type of brain tumor.

In 2004, Shehata et al. published a study assessing 160 patients (468 brain metastases ≤ 20 mm in diameter). The SRS dose ranged from 7 to 30 Gy (median of 20 Gy). 240 patients received WBRT (49%), in which the dose ranged from 6.75 to 50.4 Gy (median of 40.5 Gy). Patients who received WBRT in addition to SRS, with a SRS dose of ≥ 20 Gy, had a local control rate of 99%, whereas patients who received a SRS dose < 20 Gy had a local control rate of 91%. Interestingly, SRS doses > 20 Gy did not increase the patient’s local control rates, and increasing doses resulted in a near statistically significant increased level of grade 3 or 4 toxicities (P = 0.078).

Dose Limitations of Adjacent Structures when Performing Treatment Planning

At our institution (the Gamma Knife of Spokane), we follow the RTOG guidelines and adjust the dose range for tumors ≤ 20 mm in size to 20 to 24 Gy, depending on previous SRS and WBRT the patient has undergone in the past. Marginal doses may also be adjusted based on the vicinity of adjacent, healthy brain tissue. The RTOG guidelines (Shaw et al., 2000) for tumors 21 to 30 mm in diameter and tumors 31 to 40 mm are followed, with patients being prescribed a marginal dose of 18 Gy and 15
Gy, respectively. In general, the normal tissue maximum tolerance doses for the brainstem ranges from 12 to 13 Gy, while the optic chiasm can receive a dose of 7 to 9 Gy. A dose of 8 to 10 Gy to the optic chiasm is possible if the patient has not received previous surgical or radiation therapy intervention. After prior external beam radiation therapy (EBRT), the normal tissue tolerance dose for the chiasm is 7 Gy. Alterations may be taken based on the patient history and tumor location. Of course, these general guidelines need to be tailored to each patient’s specific circumstances and cannot be applied safely to every patient or in every clinical situation.

**TREATMENT OUTCOMES**

**Local and Regional Tumor Control**

In the three-arm study already discussed by Li et al. (2000), the SRS with WBRT group did not show an increased local control rate when compared to the SRS alone group, but the SRS with WBRT group did show a statistically significant improvement in local control (P < 0.0001) when compared to the WBRT alone group. The RTOG study performed by Andrews et al. (2004) evaluating the efficacy of WBRT with or without SRS found that the group treated with SRS with WBRT had a statistically significant improvement in local control rate (P = 0.01) when compared to the WBRT alone arm, along with patients having an improved survival time with a single brain metastasis, RPA class 1, NSCLC, or squamous-cell lung cancer. Evidence from the studies by Li et al. (2000) and Andrews et al. (2004), along with the findings already discussed by Kondziolka et al. (1999), who witnessed a substantially improved local control rate (P =
0.0016) in the SRS with WBRT arm, indicates that SRS combined with WBRT produces significantly better local tumor control when compared with patients treated with WBRT alone. This improvement in local tumor control is more pronounced in patients with a KPS ≥ 70 who have 1-4 brain metastases (Linskey et al., 2010).

A subject matter that requires further experience and research is the effect of SRS with or without WBRT on local and distant tumor control. Aoyama et al. (2006) found that patients treated with SRS alone were more likely to have an increased 12-month brain tumor recurrence rate than patients treated with both SRS and WBRT (P < 0.001). However, several retrospective studies have reported that the SRS alone and SRS with WBRT treatment groups do not exhibit compelling statistical differences, with respect to local tumor control (Jawahar et al., 2002; Sneed et al., 1999; Wang et al., 2002). Muacevic et al. (2008) found that patients treated with GK radiosurgery do not differ in terms of survival when compared to patients treated with surgical resection followed by WBRT. The authors did conclude that postoperative WBRT led to less frequent distant tumor recurrences than within the GK radiosurgery alone group (P = 0.04). This finding that WBRT reduces the risk of distant tumor recurrences correlates with those found by Patchell et al. (1990). This data permits the close monitoring of patients treated with either modality following treatment, so that salvage therapy may proceed at the earliest possible time.

**Impact of Treatment on Survival**

The evidence previously examined pertaining to the addition of WBRT to SRS demonstrated an increased median survival for patients with a single metastatic brain
tumor (P = 0.0393) in the RTOG randomized trial by Andrews et al. (2004). For patients
with a single brain metastasis who are treated with SRS with WBRT, survival is more
pronounced if the patient has a KPS $\geq$ 70 (Linskey et al., 2010). The study by Kondziolka
et al. (1999) evaluating patients with 2 to 4 brain metastases showed a trend in survival
that favored the SRS with WBRT group (P = 0.22), but did not reach statistical
significance due to the low number of patients. This data still supports the use of SRS
with WBRT in patients with 2 to 4 brain metastases, but this evidence is still in evolution
when compared to the evidence in treating a single brain metastasis with SRS with
WBRT.

SRS with WBRT and surgical resection with WBRT are known to produce
equivalent survival rates. Schoggl et al. (2000) compared neurosurgery and SRS in the
treatment of single brain metastases. A total of 133 patients were treated, where 67 were
treated with SRS and 66 were treated with neurosurgery. The authors included all patients
treated with WBRT. There was not a statistically significant difference in survival (P =
0.19) between the treatment arms.

Likewise, SRS with WBRT and SRS alone both represent effective treatments,
with respect to patient survival. The studies previously discussed by Aoyama et al.
(2006), Sneed et al. (2002), and Li et al. (2000) all reported no statistically significant
differences in median survival between the 2 treatment arms. Other studies have
demonstrated that SRS alone is a superior treatment modality when compared to WBRT
alone. Rades et al. (2007) investigated the outcomes of 186 patients treated with either
SRS alone (95 patients) or WBRT alone (91 patients). It was found that the SRS
treatment arm exhibited a longer median survival (13 months) than the WBRT alone arm
(7 months), with a P value of 0.045. Even though the groups exhibited similar outcomes in distant brain control and toxicity, it was observed that the SRS alone group had substantially better 1-year local and overall brain control levels.

**Neurological Acute and Late Toxicity**

The most frequent acute side-effects following SRS include headaches after the stereotactic head-frame is removed and screw-site soreness at the areas where the head-frame was attached to the patient’s skull (Suh, 2010). Other acute side-effects that are not as common range from seizures, infection at the screw-site, and the worsening of neurological symptoms for a relatively short period of time (Suh, 2010). Sub-acute and late reactions to radiosurgery are not as commonly observed. Lutterbach *et al.* (2003) analyzed radiosurgery alone in patients with 1 to 3 brain metastases and found that acute side-effects, including seizures and increased severity of pre-existing neurocognitive symptoms, were present in 9% of patients, while late side-effects, paresis and decreased visual awareness, were present in only 4% of patients. In general, late side-effects following radiosurgery include radiation necrosis, edema, the development of new neurological deficits, and the exacerbation of neurological deficits the patient has previously suffered from (Suh, 2010). Patients who are treated with steroids must be closely monitored because steroid therapy puts patients at risk for weight gain, insomnia, diabetes, psychosis, and suppression of the patient’s immune system (Suh, 2010).

**DISCUSSION**
In suitable patients, SRS is a beneficial modality in the treatment of brain metastases. For patients who suffer from a single brain metastasis, the RTOG randomized trial by Andrews et al. (2004) determined that those treated with SRS with WBRT experience a significantly longer period of survival than those treated with WBRT alone. In addition to improving survival time for patients with a single brain metastasis, the RTOG 95-08 trial also demonstrated an enhancement in KPS and local control in patients treated with SRS with WBRT who have 1 to 3 metastatic brain tumors. Although it has shown relatively successful outcomes, the survival rate for patients with \( \geq 2 \) brain metastases \( \leq 30 \text{ mm} \) remains a controversial treatment modality and needs to be evaluated further in a Phase III study with more compelling statistical evidence than reported by Kondziolka et al. (1999). Recent publications have shown that specific patients with \( > 4 \) brain metastases have also benefited from SRS. At our institution, we do advocate treatment of selected patients with \( > 4 \) brain metastases if their performance status is high and they are undergoing active treatment for systematic disease, or are free of known extracranial disease. This decision is based on the lack of other treatment options and because of the encouraging, evolving literature, which shows benefits for select patients.

Despite the fact that the study by Schoggl et al. (2000) found equivalent survival rates for patients treated with surgical resection following WBRT versus SRS with WBRT, it is still unclear which is a superior treatment modality for specific patients with a single brain metastasis who are qualified candidates for both procedures. Investigation into this matter in the form of a randomized trial would provide the best statistical evidence in terms of survival rates to help answer this question.
The most controversial subject matter in the treatment of patients with brain metastases is whether or not the addition of WBRT will provide a favorable patient prognosis when compared to those who are treated with SRS alone. It is now known that the combination of SRS with WBRT does not produce a survival advantage for all patients, however, physicians who support the use of SRS alone emphasize the fact that if tumor recurrence occurs, then salvage treatment, with either SRS or WBRT is warranted and can provide the patient with further tumor control and does impact survival outcomes for specific patients (Suh, 2010). Those who advocate the addition of WBRT to SRS note that patients who undergo SRS alone exhibit local and distant tumor recurrence within the brain more often and that disease progression can produce further neurological deficits (Suh, 2010). These can be more damaging to the patient than the potential side-effects that can occur following WBRT. In conclusion, SRS can be of clinical benefit to specific patient cohorts when utilized after surgery, with WBRT, or in combination with either or both of the treatment modalities. We agree that many questions remain unanswered, and look forward to additional clinical outcome studies, which will further guide us with future clinical treatment decisions.

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knife radiosurgery for brain metastases: do patients benefit from adjuvant


Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone


Chapter Two

Multimodality Treatment of Brain Metastases: An Institutional Survival Analysis of 275 Patients

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Abstract

Whole brain radiation therapy (WBRT), surgical resection, stereotactic radiosurgery (SRS), and combinations of the three modalities are used in the management of patients with metastatic brain tumors. We present the previously unreported survival outcomes of 275 patients treated for newly diagnosed brain metastases at our institution between 1998 and 2008. The effects treatment regimen, age, Eastern Cooperative Oncology Group—Performance Status (ECOG-PS), primary tumor histology, number of brain metastases, and total volume of brain metastases have on patient overall survival were analyzed. Statistical analysis was performed using Kaplan-Meier survival curves, Andersen 95% confidence intervals, approximate confidence intervals for log hazard-ratios, and multivariate Cox proportional hazard models. The median clinical follow-up time was 7.2 months. On univariate analysis, survival statistically favored patients treated with SRS alone, patients < 65 years of age, patients in ECOG-PS class 0, and patients with non-small-cell lung cancer (NSCLC) when compared to patients treated with WBRT alone (p < 0.001), patients ≥ 65 years of age (p = 0.002), patients in an ECOG-PS class of 2 (p = 0.006) or 3 (p = 0.005), and patients in the small-cell lung cancer group (p = 0.04) or other primary tumor histology group (p = 0.002), respectively. On multivariate analysis, survival statistically favored patients treated with SRS alone when compared to patients treated with WBRT alone (p < 0.001), patients treated with resection with SRS when compared to patients treated with SRS alone (p = 0.020), patients in ECOG-PS class 0 when compared to patients in ECOG-PS classes 2 (p = 0.04), 3 (p < 0.001), and 4 (p < 0.001), patients in the NSCLC group when compared to patients in the combined melanoma and renal-cell carcinoma group (p < 0.001), and patients with breast cancer
when compared to patients with NSCLC (p < 0.001). In our analysis, patients benefited from a combined modality treatment approach and physicians must consider patient age, performance status, and primary tumor histology when recommending specific treatments regimens.

**Introduction**

Brain metastases are defined as cancerous lesions in the brain that originate and spread from an extracranial primary cancer. Brain metastases occur in 20 to 40% of patients with systemic cancer and the incidence is growing due to advances in imaging technologies and the treatment of extracranial disease [1]. The site of metastasis often depends on the nearest location of vascular clusters. As a consequence, the most common primary cancers that have the ability to metastasize to the brain are cancers that develop from the lung or breast [2]. However, metastasis to the brain originating from melanoma, colorectal cancer, renal-cell carcinoma, and carcinoma of multiple other origins may also lead to the development of one or more metastatic brain tumors [3]. Due to a large amount of blood flow, the cerebrum accounts for approximately 80% of all brain metastases, while metastases that arise on the cerebellum and brain stem account for the remaining 20% of metastatic tumors [4].

Patients diagnosed with brain metastases have several potential management options and treatment regimens are dependent on the patient’s performance status, age, control of primary cancer, presence of extracranial disease, number of brain metastases, size of brain metastases, and location of brain metastases [1, 5]. In general, patients with brain metastases have a poor outlook and survive an average of 1 to 2 months when
treated with steroid therapy alone [6]. Whole brain radiation therapy (WBRT) has been historically a standard of care for patients with brain metastases. WBRT takes advantage of differences in radiobiology between tumor cells and nervous tissue by targeting rapidly dividing tumor cells in all areas of the brain, while minimizing damage to the adjacent brain tissue [3]. Due to this favorable radiation cell-kill therapeutic ratio, WBRT extends the survival time of patients who undergo treatment to an average of 4 to 7 months [1]. Surgical resection followed by WBRT has proven to be a superior treatment modality than WBRT alone or surgical resection alone for patients with a high performance status (functionally independent and spend no more than 50% of their day in bed) that possess a single, surgically accessible brain metastasis [7-9]. However, surgical resection followed by WBRT is considered an excessive and potentially destructive treatment modality for patients with multiple brain metastases and has not been investigated in a randomized controlled trial [10].

Stereotactic radiosurgery (SRS) is a highly technical form of radiation therapy that delivers a focused dose of radiation to a single volume, while minimizing damage to nearby, critical structures. The patient’s skull is immobilized, allowing a controlled dose of radiation to be delivered to a specified target with sub-millimeter precision. There are currently 4 devices utilized for SRS treatment: Gamma Knife (GK) radiosurgery, linear accelerator (LINAC) based treatment, a cyclotron-based proton beam, and cyberknife technology [3]. Although GK remains the “gold standard” of brain radiosurgery, published reports by Andrews et al. [6] and Sneed et al. [11] concluded that patient prognosis did not differ in terms of the method in which SRS was delivered. The evidence assessing the efficacy of SRS in the treatment of patients with brain metastases
is continuously increasing due to the fact that it is capable of targeting any area in the brain with accuracy and can be utilized to irradiate multiple lesions during the same clinical treatment setting. For specific patient subsets that have newly diagnosed brain metastases, WBRT alone, SRS alone, SRS with WBRT, SRS with surgical resection, or a combination of the three treatments can be the optimal management approach.

We present a retrospective survival analysis of the 275 patients treated for newly diagnosed brain metastases at our institution between 1998 and 2008; including a comprehensive analysis of the effects treatment regimen, age, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), primary tumor histology, number of brain metastases, and total volume of brain metastases have on patient survival.

**Materials and Methods**

We analyzed the patient population baseline characteristics and survival of 275 patients treated for newly diagnosed brain metastases at Cancer Care Northwest and the Gamma Knife of Spokane (Deaconess Hospital, Spokane, WA) between 1998 and 2008. After obtaining approval from IRB Spokane (IRB 1554) and the University of Washington Human Subjects Division (Human Subjects Application 36306), the following pre-treatment factors were recorded from the patient’s medical records: age at first brain metastasis diagnosis, ECOG-PS at first brain metastasis diagnosis, number of brain metastases, primary tumor histology, and total volume of brain metastases at the time of SRS for patients who received SRS, or at an imaging appointment prior to the patients first treatment session for patients who did not receive SRS. Patients were categorized by age at first brain metastasis diagnosis (< 65 years and ≥ 65 years), number
of brain metastases at first diagnosis (1 tumor, 2-4 tumors, > 4 tumors), primary tumor histology (non-small-cell lung cancer, small-cell lung cancer, breast cancer, melanoma, renal-cell carcinoma, other/unknown primary), total volume of brain metastases in cm³ (2.0, 2.0-3.9, 4.0-5.9, 6.0-7.9, ≥ 8.0), and ECOG-PS class (0, 1, 2, 3, 4).

Treatment regimens were prescribed based on the patient’s performance status, age, control of primary cancer, presence of extracranial disease, number of brain metastases, size of brain metastases, location of brain metastases, and at the discretion of the treating physician. Of the 275 patients, 117 were treated with WBRT alone, 65 were treated with SRS alone, 48 were treated with WBRT with SRS, 11 were treated with surgical resection with WBRT, 15 were treated with surgical resection with SRS, and 19 were treated with surgical resection + WBRT + SRS. SRS was performed using the Leksell ⁶⁰Co Gamma Knife (model C). The prescribed SRS dose to the 50% isodose line was completed in a single treatment and was based on the patient’s tumor volume, tumor location, tumor shape, prior radiation treatment, and standard Radiation Therapy Oncology Group (RTOG) guidelines. The median SRS dose was 18 Gy (13 Gy to 22 Gy). For patients receiving WBRT, the median total dose prescribed was 30 Gy (5 Gy to 54 Gy). Length of follow-up was determined as the time interval between the date of first treatment and the date of the most recent clinical encounter or imaging appointment. Period of survival, in months, was based upon the patient’s first treatment session.

Kaplan-Meier survival curves were utilized to compare survival differences between the treatment groups, age groups, ECOG-PS groups, tumor volume groups, primary tumor histology groups, and number of brain metastases groups. Andersen 95% confidence intervals for the median survival times of the groups were constructed. Log-
rank tests were employed to determine statistically significant differences between the survival curves of each group. Approximate confidence intervals for the log hazard-ratio were calculated using the estimate of standard error. Finally, the Cox proportional hazard was used in a multivariate analysis of the treatment groups, age groups, ECOG-PS groups, and primary tumor histology groups. All statistical analyses were performed using StatsDirect Version 2.5.7 (StatsDirect Ltd., Altrincham, UK) and SigmaPlot Version 11.0 (SYSTAT Software, Inc. San Jose, CA). Statistical significance was set at a p value < 0.05.

Results

We identified 275 patients treated at Cancer Care Northwest and the Gamma Knife of Spokane for newly diagnosed brain metastases. The median patient age was 60 years (29 years to 86 years) at the time of diagnosis. Non-small-cell lung cancer (NSCLC) was the most common primary tumor histology. Patients possessing a single brain metastasis were the largest tumor number category. Of the 275 total patients, ECOG-PS class was not recorded in 162 patients and total tumor volume was not recorded in 151 patients. Table 1 shows the number of patients according to treatment regimen, age, ECOG-PS class, primary tumor histology, number of brain metastases, and tumor volume of brain metastases. The median patient clinical follow-up time was 7.2 months (0.20 months to 117 months).

An initial statistical analysis was performed using univariate median survival confidence intervals and hazard ratio confidence intervals. Within each category a reference group was selected (treatment regimen = SRS alone, age = less than 65 years, ECOG-PS = 0, primary tumor histology = NSCLC, number of brain metastases = 1,
tumor volume ≤ less than 2 cm³) and was tested against the other groups’ hazard ratios. Univariate hazard ratio analysis of treatment groups indicated that the survival of the SRS alone treatment group was statistically superior (p < 0.001) to the survival of the WBRT alone treatment group (95% CI, 1.37-2.53). Kaplan-Meier survival curves illustrating overall survival based on treatment modality can be found in Figure 1. Univariate hazard ratio analysis of age groups (95% CI, 1.14-1.98) indicated that survival statistically favored patients < 65 years of age (p = 0.002). Comparison of univariate hazard ratios in relation to ECOG-PS class indicated that survival statistically favored patients categorized in ECOG-PS class 0 when compared to patients categorized in ECOG-PS class 2 (95% CI, 1.57-6.4) and ECOG-PS class 3 (95% CI, 1.12-15.06), with p values of 0.006 and 0.005, respectively. Comparison of univariate hazard ratios in relation to primary tumor histology indicated that survival statistically favored patients with NSCLC when compared to patients with small-cell lung cancer (SCLC) (95% CI, 0.94-2.61) and patients in the other primary tumor histology group (95% CI, 1.14-2.65), with p values of 0.04 and 0.002, respectively. Kaplan-Meier survival curves illustrating overall survival based on primary tumor histology can be found in Figure 2. The analysis of the number of brain metastases groups and tumor volume groups did not yield any statistically significant results. Kaplan-Meier survival curves showing overall survival based on the number of brain metastases and volume of brain metastases are shown in Figures 3 and 4.

The overall patient median survival time was determined to be 7.9 months. The median survival time for patients treated with WBRT alone was 4.3 months (95% CI, 3.30-5.38), 9.4 months (95% CI, 6.41-12.45) for patients treated with SRS alone, 10 months (95% CI, 8.17-12.15) for patients treated with resection with WBRT, 12 months
(95% CI, 8.74-15.98) for patients treated with WBRT with SRS, 13 months (95% CI, 9.70-16.54) for patients treated with resection + WBRT + SRS, and 24 months (95% CI, 1.73-45.55) for patients treated with resection with SRS. Patients < 65 years of age survived a median time of 11 months (95% CI, 8.42-12.88), while patients ≥ 65 years of age survived a median time of 5.7 months (95% CI, 4.29-7.09). The median survival time for patients in ECOG-PS class 0 was 22 months (95% CI, 4.43-39.69), 9.5 months (95% CI, 3.84-15.16) for patients in ECOG-PS class 1, 6.0 months (95% CI, 2.64-9.26) for patients in ECOG-PS class 2, and 1.5 months (95% CI, 0.94-1.96) for patients in ECOG-PS class 3. In regard to primary tumor histology, the median survival time for patients with NSCLC was determined to be 9.78 months (95% CI, 7.90-11.56), 9.2 months (95% CI, 4.04-14.30) for patients with breast cancer, 8.6 months (95% CI, 3.67-13.55) for the combined melanoma and renal-cell carcinoma group, 6.7 months (95% CI, 3.47-10.01) for patients with SCLC, and 5.7 months (95% CI, 2.66-8.72) for patients classified in the other primary tumor histology group.

Further statistical analysis was conducted using multivariate Cox regression analysis with hazard ratio estimates and confidence intervals (Table 2). The multivariate analyses utilized patients treated with SRS alone, patients < 65 years of age, patients in ECOG-PS class 0, and patients with NSCLC as the reference groups. Multivariate hazard ratio analysis of treatment groups indicated that the survival of patients in the SRS alone treatment group was statistically superior (p < 0.001) to the survival of the patients in the WBRT alone treatment group (95% CI, 1.37-2.73) and that the survival of the resection with SRS treatment group was statistically superior (p = 0.020) to the survival of the SRS alone treatment group (95% CI, 0.49-0.94). Comparison of multivariate hazard ratios in
relation to ECOG-PS class indicated that survival statistically favored patients
categorized in ECOG-PS class 0 when compared to patients categorized in ECOG-PS
class 2 (95% CI, 1.02-2.72), ECOG-PS class 3 (95% CI, 4.28-4.91), and ECOG-PS class
4 (95% CI, 5.98-21.2), with p values of 0.04, < 0.001, < 0.001, respectively. Multivariate
hazard ratio analysis of primary tumor histology groups indicated that the survival of
patients in the breast cancer group was statistically superior (p < 0.001) to the survival of
patients in the NSCLC group (95% CI, 0.78-0.96) and that the survival of patients in the
NSCLC group was statistically superior (p < 0.001) to the survival of patients in the
combined melanoma and renal-cell carcinoma group (95% CI, 1.06-1.3). Multivariate
hazard ratio analysis of age groups did not yield any statistically significant results.

Discussion

Patients with metastatic brain disease have a poor prognosis and curative
treatment is not achievable in most clinical situations, with 50% of patients dying from
their neurological cancer rather than their extracranial cancer [12]. Due to this
unfortunate outlook, maximizing patient’s period of survival and comfort level is of great
importance. Although several Phase III studies have been published assessing the
efficacy of different treatment modalities, many questions still remain unanswered and
further randomized evidence is needed not only to prove superior treatments in
comparison studies, but to identify optimal courses of treatment in unique patient subsets
[6-9, 13-17].

Our comprehensive analysis evaluates the clinical effects treatment regimen, age,
performance status, primary tumor histology, number of brain metastases, and total
volume of brain metastases have on patient survival. It is, however, necessary to acknowledge the potential limitations of this study. As mentioned above, ECOG-PS class was not recorded in 162 patients and total tumor volume was not recorded in 151 patients. In addition, our study did not analyze the extent of systematic disease of the evaluated patients. With respect to the WBRT alone treatment arm, tumor number was not recorded in 41% of patients, ECOG-PS class was not recorded in 57% of patients, and tumor volume was not recorded in 99% of patients. It is probable that these unmeasured cofounders can explain the low survival rate of the patients treated with WBRT alone because it is likely that this subset of patients had lower performance scores and extensive systematic disease, which are variables that could cause these patients to succumb to their primary cancer before the effects of their neurological treatment could manifest. Thus, the patients constituting each treatment regimen group are likely different patients who are able to undergo different treatment modalities for their metastases. For example, patients who receive resection in combination with SRS or WBRT or both treatments likely have few brain metastases, or are experiencing neurological deficits due to a dominant brain tumor through mass effect or herniation.

Perhaps the most questionable matter in the management of patients with brain metastases is whether the addition of WBRT to SRS will provide patients with a superior prognosis when compared to patients treated with SRS alone [3]. Our study did not find statistically significant survival differences between the SRS alone treatment group and the SRS with WBRT treatment group in both univariate and multivariate analysis. In the randomized controlled trial published by Aoyama et al. [13], the authors evaluated the clinical outcomes of patients treated with SRS with or without WBRT and also witnessed
no significant (p = 0.4) differences in survival between the two treatment arms. However, the patients treated with WBRT with SRS had a substantially better 12-month brain tumor recurrence rate (p < 0.001) and underwent salvage therapy (p < 0.001) less often than the patients treated with SRS alone, but these increases in tumor control did not affect patient survival. Several retrospective cohort studies published in the last ten years have also reported that the addition of WBRT to SRS does not result in superior levels of patient survival [11, 18-21].

On multivariate analysis, we found that the survival of the SRS alone treatment arm did not statistically differ when compared to the survival of the resection with WBRT treatment arm. These data correlate with the Phase III randomized trial conducted by Muacevic et al. [17]. A total of 64 patients with a single, surgically accessible brain metastasis ≤ 30 mm in diameter, a Karnofsky Performance Score (KPS) ≥ 70, and a controlled primary cancer were randomized into a GK radiosurgery alone group (31 patients) and a surgery with WBRT group (33 patients). The authors reported non-significant differences in survival between the two treatment groups. Rades et al. [22] retrospectively compared SRS alone and surgery with WBRT in 260 patients classified in RPA class 1 or 2 [5] that were diagnosed with 1 to 2 brain metastases and also reported that the two groups did not differ in survival. Our multivariate analysis also found superior levels of survival in patients treated with resection with SRS when compared to patients treated with SRS alone. The body of world literature lacks sufficient studies comparing patients treated with SRS alone against patients treated with resection with SRS. However, survival differences between patients treated with SRS alone and patients treated with resection with SRS was recently reported in another study by Rades et al.
[23]. The authors analyzed the clinical outcomes of 164 patients of advanced age (≥ 65 years). Specifically, 34 patients were treated with WBRT alone, 43 patients were treated with SRS alone, 41 patients were treated with resection + SRS, and 46 patients were treated with resection + WBRT+ SRS boost. In contrast to our results, which favored the resection with SRS treatment group, the authors reported that treatment regimen influenced survival, with the SRS alone treatment group surviving a greater time than the resection + SRS treatment group. The results reported by Rades et al. [23] can be explained when considering the risks of surgery in elderly patients. This data permits the treatment of select patients who are < 65 years of age and are functionally independent with resection in combination with SRS.

In subset analysis, patients treated with WBRT alone at our institution exhibited the shortest period of survival, with each of the other five treatment arms surviving a substantially greater time than the WBRT alone treatment arm. Although it is likely that the treatment arms consisted of very different patient subsets with respect to ECOG-PS class, tumor number, tumor volume, and extent of systematic disease, both univariate and multivariate analysis found statistically significant differences between the hazard ratio of patients treated with WBRT and the hazard ratio of patients treated with SRS alone. No randomized controlled trials have been conducted assessing patients treated with SRS alone compared with patients treated with WBRT alone. However, in a recent literature review, Linskey et al. [12] found level 3 evidence indicating that patients with 1 to 3 brain metastases that are treated with SRS alone have superior levels of survival when compared to patients treated with WBRT alone.
As expected, we found that age and performance status are both significant predictors in determining patient prognosis, as survival statistically favored patients < 65 years old in univariate analysis and patients in a lower ECOG-PS class in both univariate and multivariate analysis. Several comparison studies have reported a survival dependency on patient age and performance status. Sanghavi et al. [24] retrospectively analyzed the outcomes and potential prognostic factors of a total of 502 patients treated with SRS with WBRT and 1200 patients treated with WBRT alone and found that survival was more pronounced in patients with a higher KPS (p = 0.0001), a controlled primary cancer (p = 0.0023), the absence of extracranial cancer (p = 0.0001), and a lower RPA class (p = 0.000007). Kocher et al. [25] compared the efficacy of SRS alone against WBRT alone in 255 patients with 1 to 3 brain metastases and reported statistically significant increases in median survival in patients categorized in RPA class 1 (p < 0.0001) and RPA class 2 (p < 0.04). Frazier et al. [26] retrospectively analyzed 237 patients treated with SRS ± WBRT and also found that survival statistically favored patients that were < 65 years of age (p = 0.008) with a KPS score > 70 (p = 0.034).

The number and volume of brain metastases patients possess at the time of diagnosis are crucial factors in prescribing the most advantageous course of treatment in select patient groups. When evaluating our six treatment arms in univariate analysis, however, the number and size of brain metastases did not influence patient survival. Tumor resection in combination with WBRT and/or SRS in treating patients with a single brain metastasis is recommended for those who present with severe neurologic deficits, a ventricular obstruction, or a tumor of a large intracranial volume (which often produces mass effect) [1]. When the patient has controlled neurological symptoms, a tumor/s of a
small intracranial volume, a single brain metastasis, a surgically inoperable brain metastasis, or multiple brain metastases, SRS alone or in combination with WBRT is often the recommended course of treatment [1]. Questions remain regarding the survival dependency on the number and size of brain metastases patient groups possess. Studies have shown increased survival levels in patients with a single brain metastasis that were treated with radiosurgery [6, 26]. However, other publications have reported that total tumor volume has a greater impact on patient survival than number of brain metastases and primary tumor histology, with patients possessing small tumor volumes surviving a greater period of time [27-30]. Further study and research is needed on how the number and total volume of brain metastases affect patient survival.

The histologic subtype of the primary tumor may be an essential predictor in assessing the survival advantage of specific patient subsets. NSCLC is known to produce the greatest amount of metastatic brain lesions [31, 32]. In univariate analysis, survival statistically favored patients with NSCLC when compared to patients with SCLC and patients classified in the other primary histology group. In multivariate analysis, however, survival statistically favored patients in the breast cancer group when compared to patients in the NSCLC group. Increases in the survival of breast cancer patients when compared to NSCLC patients was also recently reported in the survival analysis of 237 patients treated with radiosurgery by Frazier et al. [26]. These results are likely due to advances in the surgical and chemotherapeutic care of breast cancer patients [33]. It was also observed in multivariate analysis that survival statistically favored patients with NSCLC when compared to the combined melanoma and renal-cell carcinoma group. Traditionally, melanoma and renal-cell carcinoma have been classified as “radioresistant”
tumor histologies because of their negative response to standard radiation treatment. However, several studies have reported positive outcomes when treating patients with melanoma and renal-cell carcinoma primaries with radiosurgery [34-40]. Further study and supporting evidence is needed on the effects SRS and WBRT have on melanoma and renal-cell carcinoma brain metastases, along with the specific radiobiology of those tumors.

Conclusions

We report retrospectively on the effects treatment regimen, age, performance status, primary tumor histology, number of brain metastases, and volume of brain metastases have on the survival of patients diagnosed with brain metastases. Although it is likely that the 6 treatment arms consisted of very different patient subsets with respect to ECOG-PS class, tumor number, tumor volume, and extent of systematic disease, multivariate analysis of treatment regimens showed that survival statistically favored patients treated with SRS alone and patients treated with resection with SRS when compared to patients treated with WBRT alone and patients treated with SRS alone, respectively. Comparison of multivariate hazard ratios in relation to ECOG-PS class indicated that survival statistically favored patients categorized in ECOG-PS class 0 when compared to patients categorized in ECOG-PS classes of 2, 3, and 4. Multivariate analysis of primary tumor histology groups indicated that the survival of patients in the breast cancer group was statistically superior to the survival of patients in the NSCLC group and that the survival of patients in the NSCLC group was statistically superior to the survival of patients in the combined melanoma and renal-cell carcinoma group. In our
analysis, patients benefited from a combined modality treatment approach and physicians must consider patient age, performance status, and primary tumor histology when recommending specific treatment regimens.

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Table 1: Patient Population Baseline Characteristics

<table>
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<tr>
<th>Characteristic</th>
<th>WBRT</th>
<th>SRS</th>
<th>WBRT+SRS</th>
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<td>(n=117)</td>
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ECOG-PS = Eastern Cooperative Oncology Group-Performance Status; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy
Table 2: Multivariate hazard ratios, confidence intervals, and p values

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<th>Treatment Groups</th>
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<td>95% CI</td>
<td>p value**</td>
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<td>reference</td>
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ECOG-PS = Eastern Cooperative Oncology Group-Performance Status; NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy
* Reference group against which other groups’ survival experience are compared
** p value for test if groups’ survival experience is same as reference group
Figure 1: Kaplan-Meier curves illustrating overall survival based on treatment modality
Figure 2: Kaplan-Meier survival curves illustrating overall survival based on primary tumor histology
Figure 3: Kaplan-Meier survival curves illustrating overall survival based on number of brain metastases
Figure 4: Kaplan-Meier survival curves illustrating overall survival based on volume of brain metastases
Chapter Three

The Clinical Outcomes of Stereotactic Radiosurgery in the Treatment of Patients with Metastatic Brain Tumors

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Abstract

Background: Stereotactic radiosurgery (SRS) is a form of radiation therapy that delivers a focused, highly conformal dose of radiation to a single volume, while minimizing damage to the adjacent nervous tissue. The efficacy of SRS has been examined in the treatment of patients diagnosed with brain metastases due to the fact that it is capable of targeting any region in the brain and can irradiate multiple tumors in the same treatment setting in a non-invasive fashion.

Methods: Modern literature was reviewed for studies on SRS in the treatment of patients with brain metastases.

Results: 1. After assessing patient age, Karnofsky Performance Score (KPS) score, control of primary cancer, presence of extracranial metastases, number of brain metastases, location of brain metastases, and size of brain metastases, SRS offers suitable patients a viable, less-invasive treatment option.

2. In patients with 1 to 4 brain metastases who have a KPS ≥ 70, the addition of SRS to whole brain radiation therapy (WBRT) produces increased levels of survival and local tumor control when compared to patients treated with WBRT alone.

3. The available evidence suggests that specific patients treated with SRS alone exhibit superior levels of survival and tumor control when compared to patients treated with WBRT alone. Further evidence in the form of a randomized trial is needed to confirm this observation.

4. Questions remain regarding survival and tumor control in patient groups treated with SRS with or without WBRT. Recently published randomized evidence reported a survival advantage in patients treated with SRS alone. This data differs from other
previously published randomized evidence, as well as several prospective and retrospective studies, which reported non-significant survival differences. Contrasting evidence also exists pertaining to local and distant tumor control, which warrants further investigation into this matter.

5. The available evidence suggests that in patients with 1 to 2 brain metastases, both SRS alone and SRS with WBRT offer equivalent levels of survival when compared to patients treated with surgery with WBRT. Research has been conducted which reports a survival advantage in patients with 1 to 3 brain metastases that were treated with SRS with WBRT.

**Conclusion:** SRS can be an advantageous course of treatment in specific patient groups when utilized alone, after surgery, with WBRT, or in combination with either or both of the treatment modalities. Although treatment approaches have been refined, many questions remain unanswered and further clinical evidence is needed to guide physicians in their future treatment decisions regarding treating patients in specific clinical scenarios.

**Abbreviations:** CNS, central nervous system; GK, gamma knife; KPS, Karnofsky Performance Score; LINAC, linear accelerator; NSCLC, non-small-cell lung cancer; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group; SCLC, small-cell lung cancer; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy
1. Introduction

As advances in imaging technologies and the treatment of extracranial disease allow the longevity of cancer patients to increase, the incidence of brain metastases has grown (occurring in up to 40% of cancer cases) (12). Regions of the brain that receive a larger blood supply are more at risk in developing one or more metastatic brain tumors than other areas of the brain (7). As a consequence, 80% of brain metastases are hemispheric, while 15% arise within the cerebellum and 5% arise within the brain stem. Cancers originating from the lung are responsible for approximately 30 to 60% of brain metastases (40). However, metastasis to the brain originating from melanoma, breast cancer, colorectal cancer, renal-cell carcinoma, and carcinoma of multiple other origins are also frequently observed (40).

Patients who suffer from brain metastases have a poor prognosis and are estimated to survive 1 to 2 months when treated with solely corticosteroids (1). Whole brain radiation therapy (WBRT) is considered to be a mainstay of treatment for approximately 70 to 80% of patients diagnosed with brain metastases (14, 27). WBRT is capable of eliminating rapidly dividing tumor cells in all regions of the brain. Because of the differential susceptibility to radiation therapy between tumor cells and nervous tissue, WBRT is one effective treatment modality, which can extend the patient’s life an average of 4 to 7 months, with no surgical or radiosurgical treatment (12, 40). Studies have demonstrated that surgical resection followed by WBRT provides patients with a single, surgically accessible brain metastasis a better prognosis when compared to patient groups treated with WBRT alone or surgical resection alone (25, 26, 42). However, many
physicians believe neurosurgical intervention for patients with multiple metastatic tumors is a drastic and potentially harmful course of treatment (35).

Stereotactic radiosurgery (SRS) is a form of radiation therapy that is capable of delivering a highly conformal dose of radiation to a target specified by computer planning in a single treatment. The patient’s skull is immobilized, allowing a high dose of radiation to be delivered to the tumor volume with precision, while sparing the adjacent nervous tissue. Unlike the traditional neurosurgical modalities, SRS is a non-invasive treatment regimen that has the ability to precisely target any region in the brain and can irradiate multiple lesions in the same treatment setting. Due to those advantages, the role of SRS in the treatment of patients with brain metastases is continuously increasing.

Recently, Linskey et al. (20) published a clinical practice guideline on the role of SRS in the management of patients with newly diagnosed brain metastases in an evidence-based fashion from 1990 to 2008. The authors addressed the need of WBRT in patients where SRS is prescribed and the role of WBRT when SRS is delivered following surgical resection, as well as comparing single-dose SRS with multi-dose SRS.

The goal of this paper is to provide a modern review of the literature thoroughly analyzing the efficacy of SRS alone or in a multi-modality management approach compared to the traditional courses of treatment for patients who present with single or multiple metastatic brain tumors. In addition, this paper will also discuss the specific treatment planning and patient results associated with SRS, as well as evaluating the randomized controlled trials analyzing patients treated with WBRT with or without surgical resection and patients treated with surgical resection with or without WBRT to
ultimately show the extent in which SRS has evolved in the treatment of patients with brain metastases.

2. Review and Comparison of Treatment Modalities

2.1. Literature Search Strategy

To identify contemporary comparative studies assessing the clinical outcomes of patients treated with SRS for brain metastases, a PubMed search from 2000 to June 2010 was performed. Keywords for search included “stereotactic radiosurgery OR radiosurgery brain metastases OR brain metastasis.” Comparative studies analyzed in this review included randomized controlled trials, prospective cohort studies, and retrospective cohort studies with ≥ 8 evaluated patients. Studies published only in abstract form and studies assessing patients treated with multi-dose SRS were excluded. Due to our broad search strategy and the vast amount of world literature, references from existing review articles were also selected and analyzed for study inclusion eligibility. In addition, randomized controlled trials assessing patients treated with WBRT with or without surgical resection and patients treated with surgical resection with or without WBRT published from 1990 to June 2010 were included in this review to ultimately show the evolving nature of SRS in the treatment of patients with metastatic brain disease and were identified based on citations in existing review articles found from our initial PubMed search.

2.2. Whole Brain Radiation Therapy ± Surgery

Due to the fact that neurosurgical tumor resection for patients with multiple brain tumors is considered to be an excessive course of treatment, surgery combined with
WBRT is only recommended for patients with a single, surgically accessible brain metastasis or for patients who have a dominant metastasis causing focal neurological symptoms due to intracranial pressure or mass effect. Three randomized trials have been conducted evaluating the efficacy of surgical resection followed by WBRT compared to WBRT alone for patients with a single brain metastasis (Table 1). The first was published in 1990 by Patchell, et al. (26). A total of 48 patients with a single brain metastasis were randomly assigned to a surgical resection followed by postoperative WBRT group (25 patients) or a needle biopsy followed by WBRT group (23 patients). The total prescribed radiation dose for both groups was 36 Gy, which were delivered in 12 daily fractions of 3 Gy each. Patients who did not require urgent focal treatment for an acute neurological deficit, with a Karnofsky Performance Score (KPS) ≥ 70 were eligible for the study. It was reported that the surgical resection with WBRT group lived a statistically significant (P < 0.01) amount of time longer than the WBRT alone group (median of 40 weeks vs. 15 weeks). Patients in the surgical arm also experienced less frequent tumor recurrence (P < 0.02) at the original site of metastasis, along with a longer time of functional independence (P < 0.005) compared with the WBRT alone arm (median of 38 weeks vs. 8 weeks).

In 1993, Vecht, et al. (42) published the second randomized trial analyzing WBRT ± surgical resection. The authors randomized 63 evaluable patients with a single brain metastasis to a surgical resection with WBRT group and a WBRT alone group. Patients were ineligible if they spent more than 50% of their day in bed. A total radiation dose of 40 Gy were delivered in 2 fractions per day of 2 Gy each. Similar to the results of Patchell, et al. (26), it was found that the addition of surgery offered patients with an
increased period of survival (P = 0.04), living a median of 10 months, whereas the
WBRT alone group lived a median of 6 months. Functional independence reached near
statistical significance (P = 0.06), favoring the surgical resection with WBRT arm.

The third and most recent randomized trial was conducted by Mintz, et al. (22) in
1996. A total of 84 patients with a single cerebral metastasis, who were < 80 years old,
and had a KPS score of ≥ 50, participated in the study. Specifically, 41 patients were
assigned to the surgical arm and 43 patients were assigned to the WBRT alone arm. The
total radiation schedule delivered was 30 Gy given in 10 daily fractions of 3 Gy each. In
contrast to the 2 prior studies, it was reported that the surgical resection with WBRT
group and the WBRT alone group did not differ in terms of survival (P = 0.24), where the
surgical arm survived a median of 5.6 months and the WBRT alone arm survived a
median of 6.3 months. This study, however, contained a greater number of patients with
lower KPS scores and progressive extracranial cancer, which could have resulted in a
higher proportion of patients succumbing to their primary cancer before the effects of
surgery could manifest (11).

2.3. Whole Brain Radiation Therapy ± Stereotactic Radiosurgery (Table 2)

After it was shown that surgical resection followed by WBRT provided patients
with a single brain metastasis an improved longevity when compared to patient groups
treated with WBRT alone, the outcomes of patient groups treated with SRS with WBRT
were soon analyzed and compared with the traditional treatment modalities. Patients with
a single, surgically accessibly brain metastasis who have a severe neurologic deficit, a
ventricular obstruction, a tumor ≥ 40 mm, or a significant mass effect are often treated
with neurosurgery followed by WBRT (12). SRS has shown success in patients who have
manageable neurological symptoms, a tumor/s diameter \( \leq 30 \text{ mm} \), a surgically inaccessible brain metastasis, or multiple brain metastases.

Two randomized trials have been published evaluating the addition of SRS to WBRT. The most recent, which was conducted by the Radiation Therapy Oncology Group (RTOG), was published in 2004 (1). A total of 333 patients were randomized into a SRS with WBRT (167 patients) arm and a WBRT alone arm (164 patients). Eligible patients possessed 1 to 3 brain metastases, a KPS score \( \geq 70 \), and a maximum tumor diameter of 40 mm for the largest lesion and a diameter of \( \leq 30 \) mm for the remaining lesions. The author’s main outcome was patient survival, while the other variables assessed were local tumor control, overall brain tumor control, KPS score, and cause of death. There were no statistically significant differences in terms of survival between the 2 groups. However, patients that were treated with SRS with WBRT who possessed a single brain metastasis survived a median of 6.5 months, whereas the other patients survived a median of 4.9 months (\( P = 0.0393 \)). In addition, patients with 1 to 3 brain metastases were likely to have an increased local control level (\( P = 0.01 \)) at 1-year of follow-up and an increased KPS score (\( P = 0.03 \)) at 6 months of follow-up.

The other randomized trial of WBRT ± SRS was performed by Kondziolka, et al. (16) in 1999. Only 27 patients participated in the study, where 13 patients were randomized into the SRS with WBRT group and 14 patients were randomized into the WBRT alone group. All patients had a KPS \( \geq 70 \), 2 to 4 metastatic brain tumors, and tumor diameters \( \leq 25 \text{ mm} \). In contrast to the RTOG study by Andrews, et al. (1), the main outcome assessed was local tumor control. Other variables analyzed were median survival time and tumor recurrence at the original site. The authors stopped the study at
the 60% accrual point because they witnessed a drastic difference in tumor control between the 2 treatment arms. Median survival favored the radiosurgery arm, but was not statistically significant due to the fact that there were a relatively small number of patients in the study (11 months vs. 7.5 months). It was also observed that the SRS with WBRT group had a better local failure rate at 1 year (8% vs. 100%) and median time of recurrence (36 months vs. 6 months) when compared to the WBRT alone group.

In addition, we evaluated two retrospective cohort studies (34, 43) and one prospective cohort study (19), all of which were published in the last 10 years. All studies reported a statistically significant increase in median survival in patient groups treated with SRS with WBRT compared to patient groups treated with WBRT alone. The three-arm prospective study by Li, et al. (19) limited patients suffering from non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) with a single brain metastasis ≤ 45 mm in diameter, while the four-arm retrospective cohort study by Wang, et al. (43) included patients with 1 to 6 brain metastases, who had a KPS ≥ 40, and tumor/s < 40 mm in diameter. The other retrospective cohort study by Sanghavi, et al. (34) evaluated 502 patients from databases of 10 institutions. Survival was more pronounced in patients with a higher KPS (P = 0.0001), a controlled primary cancer (P = 0.0023), the absence of extracranial cancer (P = 0.0001), and a lower RPA class (P = 0.000007). While Li, et al. (19) found that patients in the radiosurgery arm had an increased local tumor control rate (P < 0.0001) and median time of tumor recurrence (P < 0.00001), Wang, et al. (43) found comparable 1 month local tumor control rates between the 2 treatment arms. However, since the data by Wang, et al. (43) was collected at only 1-month following treatment, it is possible that the clinical outcomes observed with the addition of SRS to WBRT did not
have enough time to manifest, which explains the non-significant difference in local control between the 2 treatment arms. Sanghavi, et al. (34) did not report tumor control and recurrence data.

2.4. Surgery ± Whole Brain Radiation Therapy

Surgical resection followed by WBRT was proven to be a superior treatment modality when compared to WBRT alone; however, questions arose pertaining to the relevance of WBRT in the treatment regimen. The only randomized trial evaluating the efficacy of surgical resection followed by WBRT compared to surgical resection alone was performed by Patchell, et al. (25) in 1998. A total of 95 patients were randomized into a surgical resection with WBRT arm and a surgical resection alone arm. Specifically, 49 patients had WBRT in addition to surgery, while the other 46 patients did not. There was not a statistically significant difference in median survival and functional independence between the 2 treatment arms. It was reported, however, that the surgical resection followed by WBRT group exhibited less frequent tumor recurrence at the sight of the original metastasis (P < 0.001), less frequent tumor recurrence anywhere in the brain (P < 0.001), and were less likely to die from neurological causes (P = 0.003) than the surgical resection alone treatment arm.

2.5. Stereotactic Radiosurgery + Whole Brain Radiation Therapy Compared with Surgery + Whole Brain Radiation Therapy

Once SRS with WBRT and surgical resection with WBRT proved to be effective treatment modalities for patients with brain metastases, several studies have been published comparing the 2 treatment therapies. No randomized trials have been published
comparing SRS with WBRT to surgical resection with WBRT. We reviewed 4 retrospective cohort studies all published in the last 10 years (24, 30, 31, 36) (Table 3).

In 2009, Rades, et al. (30) performed a matched-pair analysis evaluating a total of 94 patients with 1 or 2 brain metastases. Specifically, 47 patients were treated with SRS with WBRT and another 47 patients received surgical resection with WBRT. The authors reported that there was not a statistically significant difference between the 2 treatment arms in 1-year survival rates, 1-year intracerebral control rates, and 1-year local control rates. In the same year, Rades, et al. (31) published another matched-pair analysis comparing the 2 treatment modalities in patients with 1 to 3 brain metastases. 52 patients were placed in each treatment arm, respectively. In contrast to patients with 1 to 2 brain metastases, patients with 1 to 3 brain metastases that underwent SRS with WBRT exhibited a statistically significant increase in 1-year survival rates (P = 0.034), 1-year intracerebral control rates (P = 0.003), and 1-year local control rates (P = 0.006).

O’Neill, et al. (24) evaluated a total of 97 patients with a single brain metastasis treated with either SRS ± WBRT (23 patients) or surgical resection ± WBRT (74 patients). One-year survival favored the surgery group (62% vs. 56%), but did not reach statistical significance (P = 0.15). Additionally, the authors observed that the 2 groups did not differ in terms of toxicity, neurological cause of death, and median time of tumor recurrence. This study could be criticized due to the large difference in the number of patients between the 2 treatment arms.

Similarly, Schoggl, et al. (36) conducted a study where 133 patients with a single brain metastasis underwent SRS with WBRT (67 patients) or surgical resection with WBRT (66 patients). Median survival favored the surgical resection group (12 vs. 9
months), but did not reach statistical significance (P = 0.19). However, it was reported that patients in the SRS group exhibited an improved local control rate (P < 0.05) and a decreased neurological death rate (12.5% vs. 21.8%) when compared to the surgery group.

2.6. Stereotactic Radiosurgery Alone Compared to Whole Brain Radiation Therapy Alone

No randomized trials have been published comparing patient groups treated with SRS alone against those treated with WBRT alone. We reviewed a three-arm prospective cohort study (19) and 6 retrospective cohort studies (6, 15, 18, 32, 33, 43), all of which were published in the last 10 years (Table 4). The three-arm prospective cohort study by Li, et al. (19) evaluated patient groups treated with SRS alone, WBRT alone, or SRS with WBRT. One of the retrospective cohort studies by Rades, et al. (33) was a four-arm study that evaluated elderly patients treated with SRS alone, WBRT alone, surgical resection with WBRT, or surgical resection + WBRT + SRS boost. The retrospective cohort study by Wang, et al. (43) was also a four-arm study that compared patients treated with SRS alone, WBRT alone, surgical resection alone, and SRS with WBRT.

The most recent of these studies was that of Rades, et al. (33) in 2008. Patients ≥ 65 years of age who were diagnosed with 1 to 2 metastatic brain tumors were treated with WBRT alone (34 patients), SRS alone (43 patients), surgical resection with WBRT (41 patients), or surgical resection + WBRT + SRS boost (46 patients). The SRS alone treatment arm had an increased 1-year survival rate (40%) when compared to the WBRT alone treatment arm (17%). The one-year intracerebral control rate (55% vs. 17%) and 1-year local control rate (68% vs. 19%) also favored the SRS alone treatment group.
In 2007, Rades, et al. (32) published a study analyzing the role of SRS in 186 patients with 1 to 3 brain metastases ≤ 40 mm in diameter, who were classified in either RPA class 1 or class 2. 91 patients who received a total WBRT dose of 30 to 40 Gy and 95 patients who received a SRS dose of 18 to 25 Gy were eligible candidates for the study. The authors reported that the SRS alone group exhibited a statistically significant (P = 0.045) increase in median survival compared to the WBRT alone group (13 months vs. 7 months). In addition, the SRS alone treatment arm had a substantially improved 1-year local and overall brain control rate when compared to the WBRT alone treatment arm. These results correlate with those found by Kocher, et al. (15) in 2004, who reported statistically significant increases in median survival in RPA class 1 (P < 0.0001) and RPA class 2 (P < 0.04) in 255 patients with 1 to 3 brain metastases. Patients in the 2 treatment arms classified in RPA class 3 did not exhibit compelling differences in median survival. Increases in median survival in the SRS alone group was also reported by Lee, et al. (18) (29 months vs. 6 months) and Wang, et al. (43) (67 weeks vs. 37 weeks).

All patients who participated in the three-arm prospective cohort study by Li, et al. (19) had a single brain metastasis ≤ 45 mm in diameter, a KPS score ≥ 60, and either SCLC or NSCLC. 23 patients were placed in the SRS alone treatment arm, while 29 patients were placed in the WBRT alone treatment arm. The authors reported that median survival was higher in the SRS alone treatment group (9.3 months vs. 5.7 months). Also, a greater proportion of patients exhibited either partial or complete tumor response in the SRS alone arm compared to the WBRT alone arm (87% vs. 48%).

Datta, et al. (6) compared the overall survival rate in patients with brain metastases who were treated with gamma knife (GK) SRS ± WBRT (22.6% of patients)
or WBRT alone. Specifically, 53 patients were treated with GK radiosurgery and 67 patients were treated with WBRT. The 1-year survival rate for the WBRT group was 26.3% (mean of 7.8 months) and 22.6% (mean of 6.7 months) for the GK group. Based on the given data, there was no statistical significance between the GK and WBRT groups in survival time. However, the authors concluded that 89% of patients treated with GK radiosurgery had lesions that were reduced, stabilized, or disappeared, but this high level of tumor control did not produce longer periods of survival.

2.7. Stereotactic Radiosurgery ± Whole Brain Radiation Therapy

An area of controversy in the treatment of patients with metastatic brain tumors is whether or not the addition of WBRT to SRS will provide patient groups with a better prognosis when compared to patient groups treated with SRS alone. We evaluated 2 randomized trials (2, 3), 1 prospective cohort study (19), and 10 retrospective cohort studies (4, 5, 8, 9, 13, 17, 29, 39, 41, 43) to investigate this question (Table 5). Studies by Li, et al. (19) and Fokas, et al. (8) are three-arm studies, assessing patient groups treated with SRS alone, WBRT alone, and SRS with WBRT. The study by Wang, et al. (43) was a four-arm study that compared patients treated with SRS alone, WBRT alone, surgical resection alone, and SRS with WBRT. All 13 of these studies have been published since the year 2000.

The first randomized trial was published in 2006 by Aoyama, et al. (2). A total of 132 patients with 1 to 4 brain metastases ≤ 30 mm in diameter who had a KPS score ≥ 70 were eligible for the study. Precisely, 67 patients were randomized into the SRS alone treatment arm and 65 patients were randomized into the SRS with WBRT treatment arm. The median time of survival for the SRS alone group and SRS with WBRT group was 8
months and 7.5 months, respectively (P = 0.42). It was reported that the 12-month brain
tumor recurrence rate (P < 0.001) and the frequency in which patients underwent salvage
therapy (P < 0.001) statistically favored the SRS with WBRT treatment arm. The 2
groups did not differ in terms of death from neurological causes, toxicity, and functional
preservation.

The most recent randomized trial, published in 2009, by Chang, et al. (3) investigated whether the potential tumor control benefits of the addition of WBRT to
SRS compensated for the potential toxicity associated with WBRT. The author’s primary
objective was to assess neurocognitive differences between the 2 treatment arms via the
Hopkins Verbal Learning Test-Revised Scale at 4 months following treatment. There was
a total of 58 patients with 1 to 3 brain metastases that were randomly assigned to a SRS
alone group (30 patients) and a SRS with WBRT group (28 patients) using a standard
permutated algorithm. The study was stopped prematurely due to a very high probability
(96%) that patients in the SRS with WBRT treatment arm would exhibit worse
neurocognitive deficits than the SRS alone treatment arm at 4 months of follow-up (mean
posterior decline probability of 52% vs. 24%). It was reported, however, that only 27% of
patients in the SRS alone group were free from central nervous system (CNS) tumor
recurrence, while 73% of patients in the SRS with WBRT group were free from CNS
tumor recurrence (P = 0.0003). Interestingly, patients in the SRS alone treatment arm
exhibited an increased period of survival, with a 1-year survival rate of 63% compared to
21% in the SRS with WBRT treatment arm (P = 0.003).

In the retrospective cohort study by Frazier, et al. (9), the authors compared
survival in 237 patients who were treated with either SRS alone or SRS with WBRT. It
was reported that survival did not statistically differ between the 2 groups. However, patient groups that were < 65 years of age ($P = 0.008$) with a KPS score > 70 ($P = 0.034$) were more inclined to survive a greater period of time than those who do not possess those characteristics. In the three-arm prospective cohort study by Li, et al. (19), 23 patients underwent SRS alone, while 18 patients were treated with SRS with WBRT. Similar to the studies above, the authors found that the 2 treatment arms did not exhibit compelling statistical differences, with respect to survival and tumor recurrence.

Of the 9 other retrospective cohort studies we reviewed, 6 found no statistically significant differences in survival between patient groups treated with SRS alone and those treated with SRS with WBRT (4, 5, 8, 13, 39, 41). Wang, et al. (43) reported that the SRS with WBRT treatment arm had a survival advantage, living a median of 91 weeks, while patients treated with SRS alone survived a median of 67 weeks. In contrast, Chidel, et al. (4) found a non-significant trend in survival ($P = 0.07$) that favored the SRS alone treatment arm. Kong, et al. (17) reported a statistically significant advantage in survival ($P = 0.042$) and local control ($P = 0.021$) in patients classified in RPA class 1 who were treated with SRS with WBRT, but this trend did not extend into patients classified in RPA class 2 or 3. Increased local control levels in the SRS with WBRT treatment groups were also reported in studies by Chidel, et al. (4), Varlott, et al. (41), and Rades, et al. (29). Improvements in distant brain control with the addition of WBRT were not as prevalent. Chidel, et al. (4) ($P = 0.06$) and Varlott, et al. (41) ($P = 0.0657$) both witnessed non-significant trends in distant brain control favoring the SRS with WBRT treatment arm. Clarke, et al. (5) reported that 55.6% of patients in their study exhibited distant brain failure. Two of the 9 studies (8, 29) found increased intracerebral control
levels with the addition of WBRT to the SRS treatment regimen. This data permits the close monitoring of patients treated with either modality following treatment, so that salvage therapy may proceed as soon as possible.

2.8. Stereotactic Radiosurgery Alone Compared to Surgery + Whole Brain Radiation Therapy

We reviewed one randomized trial and one retrospective cohort study comparing patient groups treated with neurosurgical resection with WBRT and patient groups treated with SRS alone. The randomized trial was conducted by Muacevic, et al. (23) in 2008. A total of 64 patients with a single, surgically accessible brain metastasis ≤ 30 mm in diameter, a KPS ≥ 70, and a stable primary cancer were randomly assigned to a surgery with WBRT group (33 patients) and a SRS alone group (31 patients). Unfortunately, the study was stopped at the 25% accrual point. The authors did report, however, that the 2 treatment arms did not show statistically significant differences in survival, death due to neurological causes, and freedom of local tumor recurrence. The SRS treatment arm experienced a larger amount of distance tumor recurrences (P = 0.04), but this difference diminished after salvage therapy was conducted. It was also observed that patients encountered toxicities more frequently in the surgery with WBRT group (P ≤ 0.01).

Rades, et al. (28) analyzed 260 patients classified in RPA class 1 and 2 who possessed 1 to 2 metastatic brain tumors ≤ 40 mm in diameter. 94 patients were treated with SRS alone, while 112 patients were treated with surgical resection followed by WBRT. The authors reported that the 2 treatment arms did not exhibit statistically
significant differences in terms of survival, overall brain control, and local tumor control. Data regarding death from neurological causes was not assessed.

3. Stereotactic Radiosurgery Treatment Planning

3.1. Modes of Deliverance

There are 3 devices currently used for SRS deliverance: GK radiosurgery, linear accelerator (LINAC) based treatment, and a cyclotron-based proton beam. The cyclotron-based proton beam is used by very few institutions because it is very expensive and requires a great deal of space and maintenance (12). The LINAC machine functions by accelerating an electron at a metal target, which produces an x-ray beam that is focused on a precise target by micro-multileaf collimators (40). The GK device’s main functional unit is cobalt-60, which is used to emit photon energy through 201 separate 4 to 18 mm collimator openings that ultimately converge on a focal point specified through computer planning (40). GK radiosurgery and LINAC-based treatment are known to produce equivalent patient outcomes. Published reports by Andrews, et al. (1) and Sneed, et al. (39) both concluded that mode of SRS delivery did not influence patient prognosis.

3.2. Dosing

In 2000, the RTOG published a study investigating the maximum tolerated dose of single-fraction radiosurgery, which was lead by Shaw, et al. (38). A total of 156 patients with recurrent brain metastases (64%) and primary brain tumors (36%) were assessed. The authors concluded that the maximum tolerated doses for tumors \( \leq 20 \) mm was 24 Gy, 18 Gy for tumors 21 to 30 mm in diameter, and 15 Gy for tumors 31 to 40 mm in diameter, respectively. Patients with tumors > 20 mm in diameter were 7.3 to 16 times more likely to encounter grade 3 to 5 toxicities when compared with patients who
possess tumors ≤ 20 mm in maximum diameter. At the Gamma Knife of Spokane, we follow the guidelines diagrammed by the RTOG and prescribe a maximum dose of 20 to 24 Gy for metastatic tumors ≤ 20 mm in diameter, based on previous radiation therapy the patient has undergone and the proximity of critical structures. For tumors 21 to 30 mm in diameter and 31 to 40 mm in diameter, maximum doses of 18 Gy and 15 Gy are prescribed. These doses may be altered, thus, each specific patient’s treatment is unique.

3.3. Variables Influencing Patient Advantage

The most common method in categorizing patients who suffer from metastatic brain tumors is the RTOG recursive partitioning analysis (RPA) prognostic system (10) (Table 6). The patient’s age, KPS score, control of primary cancer, and presence of extracranial metastases are all taken into account to assign the patient into 1 of 3 RPA classes, with a higher class statistically indicating a worse prognosis for the patient in question. Patient outcomes following SRS are influenced by the 4 criteria diagrammed by the RTOG, as well as 3 other factors: the number, location, and size of the patient’s metastases. With the numerous combinations of treatment modalities that exist today for patients with brain metastases, these 7 variables must be assessed together to prescribe the optimal course of treatment in desired patients.

3.4. Toxicity (Table 7)

The most common acute side-effects following SRS are caused not by the radiation, but by the stereotactic head-frame which is attached to the patient’s skull. These include headaches after the stereotactic head-frame is removed and screw-site soreness at the areas where the head-frame was attached to the patient’s skull (40). Acute toxicities that result from the radiation are seizures and the worsening of neurological
symptoms for a relatively short period of time (37). Studies by Aoyama, et al. (2) and Lutterbach, et al. (21) both concluded that long-term side-effects following SRS are less common in treated patients than acute toxicities. However, a small fraction of patients will experience long-term side-effects that range from radiation necrosis, edema, the development of new neurological deficits, and the exacerbation of neurological deficits the patient has previously suffered from (40). Caution must be taken with the use of steroids because they are also known to come with a variety of side-effects.

4. Conclusion

1. After assessing patient age, KPS score, control of primary cancer, presence of extracrani al metastases, number of brain metastases, location of brain metastases, and size of brain metastases, SRS offers suitable patients a viable, less-invasive treatment option.

2. In patients with 1 to 4 brain metastases who have a KPS ≥ 70, the addition of SRS to whole brain radiation therapy (WBRT) produces increased levels of survival and local tumor control when compared to patients treated with WBRT alone.

3. The available evidence suggests that patients treated with SRS alone exhibit superior levels of survival and tumor control with less cognitive side-effects when compared to patients treated with WBRT alone. Evidence in the form of a Phase III randomized trial is needed to confirm this published evidence.

4. Many unanswered questions remain regarding survival and tumor control in patient groups treated with SRS with or without WBRT. Recently published randomized evidence reported a survival advantage in patients treated with SRS alone. This data
differs from previously published randomized evidence, as well as several prospective and retrospective studies, which reported non-significant survival differences. Contrasting evidence also exists pertaining to local and distant tumor control, which warrants further investigation into this controversial matter.

5. The available evidence suggests that in patients with 1 to 2 brain metastases, both SRS alone and SRS with WBRT offer equivalent levels of survival when compared to patients treated with surgery with WBRT. Research has been conducted which reports a survival advantage in specific patient subsets with 1 to 3 brain metastases that were treated with SRS with WBRT. Inconsistent results have been reported for these groups regarding local and distant tumor control levels. Further analysis and research must be conducted for this patient group and for patients with ≥ 3 brain metastases.

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### Tables

Table 1: Randomized Trials of WBRT ± Surgery in the Treatment of Patients with a Single Brain Metastasis

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients in Treatment Arms</th>
<th>Median Survival Time</th>
<th>Median Time of Functional Independence</th>
<th>Patients with Local Tumor Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell <em>et al.</em> (26) (1990)</td>
<td>WBRT: n = 23 WBRT/Surgery: n = 25</td>
<td>WBRT: 15 weeks WBRT/Surgery: 40 weeks (P &lt; 0.01)</td>
<td>WBRT: 8 weeks WBRT/Surgery: 38 weeks (P &lt; 0.005)</td>
<td>WBRT: 12 WBRT/Surgery: 5 (P &lt; 0.02)</td>
</tr>
<tr>
<td>Vecht <em>et al.</em> (42) (1993)</td>
<td>WBRT: n = 31 WBRT/Surgery: n = 32</td>
<td>WBRT: 6 months WBRT/Surgery: 10 months (P = 0.04)</td>
<td>WBRT: 15 weeks WBRT/Surgery: 33 weeks (P = 0.06)</td>
<td>NR</td>
</tr>
<tr>
<td>Mintz <em>et al.</em> (22) (1996)</td>
<td>WBRT: n = 43 WBRT/Surgery: n = 41</td>
<td>WBRT: 6.3 months WBRT/Surgery: 5.6 months (P = NS)</td>
<td>WBRT: 9 weeks WBRT/Surgery: 8 weeks (P = NS)</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported; NS = non-significant; WBRT = whole brain radiation therapy
### Table 2: WBRT ± SRS in the Treatment of Patients with Single or Multiple Brain Metastases

<table>
<thead>
<tr>
<th>Author/Study Type (year)</th>
<th># BM</th>
<th>Study Endpoints</th>
<th>WBRT</th>
<th>WBRT/SRS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews et al. (1) / Randomized (2004)</td>
<td>1-3</td>
<td>overall MS 1 BM MS 1-yr local control rate 6-month KPS rate</td>
<td>6.5 months 4.9 months 71% 27%</td>
<td>5.7 months 6.5 months 82% 43%</td>
<td>NS 0.0393 0.01</td>
</tr>
<tr>
<td>Kondziolka et al. (16) / Randomized (1999)</td>
<td>2-4</td>
<td>MS 1-yr local failure rate median local recurrence time</td>
<td>7.5 months 100% 6 months</td>
<td>11 months 8% 36 months</td>
<td>NS 0.0005 0.0016</td>
</tr>
<tr>
<td>Li et al. (19) / Prospective Cohort (2000)</td>
<td>1</td>
<td>MS tumor response rate median local recurrence time median distant recurrence time</td>
<td>5.7 months 48% 4 months 4.1 months</td>
<td>10.6 months 89% 8.6 months 8.6 months</td>
<td>&lt; 0.0001* 0.004* 0.0000*</td>
</tr>
<tr>
<td>Wang et al. (43) / Retrospective Cohort (2002)</td>
<td>1-6</td>
<td>MS 1-month local tumor control rate</td>
<td>37 weeks 88%</td>
<td>91 weeks 96%</td>
<td>&lt; 0.00001** NR**</td>
</tr>
<tr>
<td>Sanghavi et al. (34) / Retrospective Cohort (2001)</td>
<td>BM</td>
<td>MS RPA Class1 MS RPA Class2 MS RPA Class3</td>
<td>7.1 months 4.2 months 2.3 months</td>
<td>16.1 months 10.3 months 8.7 months</td>
<td>&lt; 0.05 &lt; 0.05 &lt; 0.05</td>
</tr>
</tbody>
</table>

BM = brain metastases; KPS = Karnofsky Performance Score; MS = median survival; NR = not reported; NS = non-significant; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy

*Data includes SRS alone treatment arm
Data includes SRS alone and surgery alone treatment arms

**Table 3: SRS + WBRT vs. Surgery + WBRT in the Treatment of Patients with Single or Multiple Brain Metastases**

<table>
<thead>
<tr>
<th>Author/Study Type (year)</th>
<th># BM</th>
<th>Study Endpoints</th>
<th>SRS/WBRT</th>
<th>Surgery/WBRT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rades <em>et al.</em> (30) / Retrospective Cohort (2009)</td>
<td>1-2</td>
<td>1-yr survival rate</td>
<td>65%</td>
<td>63%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr IC rate</td>
<td>70%</td>
<td>78%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr LC rate</td>
<td>84%</td>
<td>83%</td>
<td>NS</td>
</tr>
<tr>
<td>Rades <em>et al.</em> (31) / Retrospective Cohort (2009)</td>
<td>1-3</td>
<td>1-yr survival rate</td>
<td>56%</td>
<td>47%</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr IC rate</td>
<td>66%</td>
<td>50%</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr LC rate</td>
<td>82%</td>
<td>66%</td>
<td>0.006</td>
</tr>
<tr>
<td>O'Neill <em>et al.</em> (24) / Retrospective Cohort (2003)</td>
<td>1</td>
<td>1-yr survival rate</td>
<td>56%</td>
<td>62%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>local recurrence rate</td>
<td>0%</td>
<td>17%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>overall recurrence rate</td>
<td>29%</td>
<td>30%</td>
<td>NR</td>
</tr>
<tr>
<td>Schoggl <em>et al.</em> (36) / Retrospective Cohort (2000)</td>
<td>1</td>
<td>MS local recurrence rate</td>
<td>12 months</td>
<td>9 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5% local recurrence rate</td>
<td>4.9 months</td>
<td>3.9 months</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% distant recurrence rate</td>
<td>4.4 months</td>
<td>3.7 months</td>
<td>NS</td>
</tr>
</tbody>
</table>

BM = brain metastases; IC = intracerebral control; LC = local control; NR = not reported; NS = non-significant; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy
Table 4: SRS alone vs. WBRT alone in the Treatment of Patients with Single or Multiple Brain Metastases

<table>
<thead>
<tr>
<th>Author/Study Type (year)</th>
<th># BM</th>
<th>Study Endpoints</th>
<th>SRS</th>
<th>WBRT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rades et al. (33) / Retrospective Cohort (2008)</td>
<td>1-2</td>
<td>1-yr survival rate</td>
<td>40%</td>
<td>17%</td>
<td>0.043***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr IC rate</td>
<td>55%</td>
<td>17%</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr LC rate</td>
<td>68%</td>
<td>19%</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Rades et al. (32) / Retrospective Cohort (2007)</td>
<td>1-3</td>
<td>MS</td>
<td>13 months</td>
<td>7 months</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr LC rate</td>
<td>64%</td>
<td>26%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr DC rate</td>
<td>61%</td>
<td>66%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-yr OC rate</td>
<td>49%</td>
<td>23%</td>
<td>0.005</td>
</tr>
<tr>
<td>Kocher et al. (15) / Retrospective Cohort (2004)</td>
<td>1-3</td>
<td>MS: RPA class 1</td>
<td>25.4 months</td>
<td>4.7 months</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS: RPA class 2</td>
<td>5.9 months</td>
<td>4.1 months</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MS: RPA class 3</td>
<td>4.2 months</td>
<td>2.5 months</td>
<td>NS</td>
</tr>
<tr>
<td>Lee et al. (18) / Retrospective Cohort (2008)</td>
<td>1-12</td>
<td>MS</td>
<td>29 months</td>
<td>6 months</td>
<td>0.0061</td>
</tr>
<tr>
<td>Wang et al. (43) / Retrospective Cohort (2002)</td>
<td>1-6</td>
<td>MS</td>
<td>67 weeks</td>
<td>37 weeks</td>
<td>&lt; 0.0001**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-month LC rate</td>
<td>93.3%</td>
<td>88.3%</td>
<td>NR**</td>
</tr>
<tr>
<td>Author/Study Type (year)</td>
<td>#BM</td>
<td>Study Endpoints</td>
<td>SRS</td>
<td>SRS/WBRT</td>
<td>P Value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----</td>
<td>----------------</td>
<td>-----</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Li et al. (19) / Prospective Cohort (2000)</td>
<td>1</td>
<td>MS</td>
<td>9.3 months</td>
<td>5.7 months</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumor response rate</td>
<td>87%</td>
<td>48%</td>
<td>0.004*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local recurrence time</td>
<td>6.9 months</td>
<td>4 months</td>
<td>0.0000*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distant recurrence time</td>
<td>6.7 months</td>
<td>4.1 months</td>
<td>0.0000*</td>
</tr>
<tr>
<td>Datta et al. (6) / Retrospective Cohort (2004)</td>
<td>BM</td>
<td>1-yr survival rate</td>
<td>22.6%</td>
<td>26.3%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mean survival</td>
<td>7.8 months</td>
<td>6.7 months</td>
<td></td>
</tr>
</tbody>
</table>

BM = brain metastases; DC = distant control; IC = intracerebral control; LC = local control; MS = median survival; NR = not reported; NS = non-significant; OC = overall control; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy
* Data includes SRS with WBRT treatment arm
** Data includes surgery alone and SRS with WBRT treatment arms
*** Data includes surgery with WBRT and surgery + WBRT + SRS boost treatment arms

Table 5: SRS ± WBRT in the Treatment of Patients with Single or Multiple Brain Metastases
<table>
<thead>
<tr>
<th>Study</th>
<th>Geographical Location</th>
<th>Type</th>
<th>Follow-up</th>
<th>OS 1-year IC Rate</th>
<th>OS 2-year IC Rate</th>
<th>OS Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frazier et al. (9) / BM</td>
<td>BM</td>
<td>MS</td>
<td>8.3 months</td>
<td>8.5 months</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Li et al. (19) / BM</td>
<td>BM</td>
<td>MS</td>
<td>9.3 months</td>
<td>10.6 months</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sneed et al. (39) / BM</td>
<td>BM</td>
<td>MS</td>
<td>8.2 months</td>
<td>8.6 months</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Jawahar et al. (13) / BM</td>
<td>BM</td>
<td>MS</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Varlotto et al. (41) / BM</td>
<td>BM</td>
<td>MS</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Fokas et al. (8) / BM</td>
<td>BM</td>
<td>OS</td>
<td>12 months</td>
<td>16 months</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

(2009)
1-year LC rate 67% 100% 0.012
1-year DC rate 45% 73% 0.02
1-year CNS freedom recurrence rate
27% 73% 0.0003

Retrospective Cohort (2010)
Retrospective Cohort (2010)
Retrospective Cohort (2000)
Retrospective Cohort (2002)
Retrospective Cohort (2005)
Retrospective Cohort (2010)
<table>
<thead>
<tr>
<th>Study</th>
<th>Recurrence Type</th>
<th>Median Local Recurrence Time</th>
<th>Median Distant Recurrence Time</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kong et al. (17) / Retrospective Cohort (2010)</td>
<td>MS</td>
<td>272 days</td>
<td>351 days</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>MS: RPA class 1</td>
<td>426 days</td>
<td>854 days</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>MS: RPA class 2</td>
<td>380 days</td>
<td>351 days</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>MS: RPA class 3</td>
<td>94 days</td>
<td>161 days</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>median local recurrence time:</td>
<td>336 days</td>
<td>701 days</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>RPA class 1</td>
<td>325 days</td>
<td>295 days</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>median local recurrence time:</td>
<td>RPA class 2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>median local recurrence time:</td>
<td>RPA class 3</td>
<td>336 days</td>
<td>967 days</td>
</tr>
<tr>
<td></td>
<td>median distant recurrence time:</td>
<td>RPA class 1</td>
<td>292 days</td>
<td>311 days</td>
</tr>
<tr>
<td></td>
<td>median distant recurrence time:</td>
<td>RPA class 2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>median distant recurrence time:</td>
<td>RPA class 3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rades et al. (39) / Retrospective Cohort (2008)</td>
<td>OS rate</td>
<td>53%</td>
<td>56%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>IC control rate</td>
<td>51%</td>
<td>66%</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>LC rate</td>
<td>66%</td>
<td>87%</td>
<td>0.003</td>
</tr>
<tr>
<td>Clarke et al. (5) / Retrospective Cohort (2010)</td>
<td>OS</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>local failure rate</td>
<td>22.7%</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>distant failure rate</td>
<td>68.2%</td>
<td>0%</td>
<td>NR</td>
</tr>
<tr>
<td>Wang et al. (43) / Retrospective Cohort (2002)</td>
<td>MS</td>
<td>67 weeks</td>
<td>91 weeks</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1-month LC rate</td>
<td>93%</td>
<td>96%</td>
<td>NR</td>
</tr>
<tr>
<td>Chidel et al. (4) / Retrospective Cohort (2000)</td>
<td>MS</td>
<td>10.5 months</td>
<td>6.4 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>median local recurrence time</td>
<td>NR</td>
<td>NR</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>median distant recurrence time</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>median overall recurrence time</td>
<td>9.2 months</td>
<td>35.1 months</td>
<td>0.027</td>
</tr>
</tbody>
</table>
BM = brain metastases; CNS = central nervous system; DC = distant control; DF = distant failure; IC = intracerebral control; LC = local control; MS = median survival; NR = not reported; NS = non-significant; OS = overall survival; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole brain radiation therapy
*Data collected on multivariate analysis

Table 6: RPA Categorization (10)

<table>
<thead>
<tr>
<th>RPA Class 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS ≥ 70</td>
<td></td>
</tr>
<tr>
<td>controlled 1° cancer</td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years of age</td>
<td></td>
</tr>
<tr>
<td>extracranial disease is not present</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RPA Class 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS ≥ 70</td>
<td></td>
</tr>
<tr>
<td>uncontrolled 1° cancer and/or</td>
<td></td>
</tr>
<tr>
<td>≥ 65 years of age and/or</td>
<td></td>
</tr>
<tr>
<td>extracranial disease is present</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RPA Class 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS &lt; 70</td>
<td></td>
</tr>
</tbody>
</table>

KPS = Karnofsky Performance Score; RPA = recursive partitioning analysis
Table 7: Toxicities Associated with SRS

<table>
<thead>
<tr>
<th>Acute Side-Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>headaches</td>
</tr>
<tr>
<td>screw-site soreness</td>
</tr>
<tr>
<td>seizures</td>
</tr>
<tr>
<td>infection at screw site</td>
</tr>
<tr>
<td>worsening of neurological symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-Term Side-Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>radiation necrosis</td>
</tr>
<tr>
<td>edema</td>
</tr>
<tr>
<td>new neurological deficits</td>
</tr>
<tr>
<td>worsening of existing neurological deficits</td>
</tr>
</tbody>
</table>
Chapter Four

VESTIBULAR SCHWANNOMA: GAMMA KNIFE RADIOSURGERY (METHOD)

ABSTRACT

Vestibular schwannomas are benign intracranial tumors that may be managed using watchful waiting, surgical resection, or radiation. Gamma Knife radiosurgery has been a continually evolving technique for managing such tumors. Over the past two decades, improvements in imaging technology, treatment planning software, and lower dose protocols have helped radiosurgery become a highly efficacious and safe alternative to microsurgical resection. We review the indications that may help patients make an informed decision to choose Gamma Knife for their vestibular schwannoma. The current methods for treatment using the Gamma Knife are discussed, including a description of selecting an isodose line and marginal dose. Follow-up strategies are outlined, for tracking treatment success as well as for patient-centered outcomes such as hearing preservation and monitoring for facial neuropathy. Finally, we describe the best available evidence regarding the efficacy of Gamma Knife radiosurgery for vestibular schwannomas, including the rates of hearing preservation and facial neuropathy being encountered using current treatment protocols.
INTRODUCTION

Vestibular schwannomas (VSs) are benign intracranial tumors arising from those cells that myelinate the vestibular nerve. Most occur within the internal acoustic canal (intracanalicular) and expand to include a significant extracanalicular portion. These extracanalicular masses lie within the cerebellopontine angle, and the resulting mass effect may prove injurious to adjacent cranial nerves, brainstem nuclei, or the cerebellum. Vestibular schwannomas therefore manifest by a spectrum of ipsilateral signs and symptoms including hearing loss, tinnitus, disequilibrium, vertigo, dizziness, facial numbness, and facial paresis. The most common presentation includes gradual sensorineural hearing loss, occurring in 95% of cases according to Matthies and Samii (1997).

Patients diagnosed with a VS may be candidates for several management options. Watchful waiting involves serial magnetic resonance imaging to track tumor growth and regular follow-up to evaluate symptoms and signs of tumor progression. Treatment options include microsurgery, stereotactic radiosurgery, and fractionated radiotherapy. Unfortunately, evidence based guidelines for choosing a management strategy are relatively weak as reviewed by Pollock (2008). Most data on treatment outcomes arose from retrospective studies, as there have been few prospective comparative studies and no randomized controlled trials. At this point, treatment selection is commonly based on the size of the tumor, associated symptoms and signs, and characteristics of the patient, including age, health, and personal preferences.

Stereotactic radiosurgery using the Gamma Knife (GK) is a promising treatment modality for many patients with VSs. The precise administration of a single dose of
radiation, limited to the tumor margin, seeks to arrest growth. Absence of intracranial manipulation may reduce post-operative morbidity and mortality, compared to invasive microsurgery. Therefore, GK radiosurgery may be particularly appealing to patients with smaller VSs and higher functionality prior to treatment. This may be particularly true now, as radiosurgical techniques have evolved considerably over the past decade and the use of lower doses is proving efficacious and safe for treating VSs. In this chapter we attempt to outline the current evidence on the indications, methods, and outcomes associated with the managing VSs using the GK.

**TREATMENT INDICATIONS & PATIENT COUNSELING**

The indications for selecting a particular management strategy for a VS are multifactorial. The lack of robust comparative studies means evidence based guidelines are not available to assist such decisions. Pogodzinski et al. (2004) identified a trend suggesting the strongest predictor of treatment choice was the specialty of the attending physician. The authors of this chapter advocate a patient-centered approach to selecting an approach. This should be based on the tumor size, tumor growth rate, and the patient’s age, health, and personal preferences. Patients should be fully informed of the efficacy and risks associated with each option, but in presenting this evidence the physician should be conscious of their own biases and the limited availability of comparative studies in the literature on VS management. Ultimately, each patient should be made aware of all available options, which may be facilitated by discussions with a radiation oncologist, neurosurgeon, and neuro-otologist prior to treatment.

Watchful waiting offers the least invasive approach to VS management. It is appropriate due to the slow-growing nature of these tumors and the risks associated with
the available interventions. On average, most VSs will grow at a rate of 1.9 mm per year in their greatest dimension according to papers by Smouha et al. (2005) and Yamakami et al. (2003). According to their meta-analyses, on average 20% of those managed conservatively will require treatment. This is typically indicated upon additional tumor growth or progression of symptoms.

The greatest challenge in selecting patients for watchful waiting is the unpredictable behavior of a given tumor. Some may grow rapidly, at rates 10-fold greater than average according to Fucci et al. (1999), while others may spontaneously regress. In a large meta-analysis by Smouha et al. (2005), there were few predictors associated with growing VSs. Those identified include previous growth, extracanalicular projections, and younger patients. Separate studies by Battaglia et al. (2006) and Hajioff et al. (2008) identified statistically significant differences in growth rates depending on tumor magnitude, with larger and extracanalicular tumors having greater average growth rates. Furthermore, symptoms do not necessarily correlate with tumor size or growth, and quality of life may diminish even in the case of a static tumor. Smouha et al. (2005) recommend considering watchful waiting for patients over 45 years old and with small tumors, less than 25 mm in largest dimension. With tumor growth, greater than 2 mm per year in any dimension, or progression of symptoms, patients should consider treatment.

Microsurgery is a highly efficacious treatment for VSs. For patients with large tumors, 30 mm or greater in greatest dimension, surgical removal is strongly indicated and Nikolopoulos and O'Donoghue (2002) have suggested that alternative management “would be unethical.” In general, fewer than 2% of patients who undergo resection of their tumor will require additional treatment, according to reviews by Kaylie et al. (2000)
and Yamakami et al. (2003). Due to the invasive nature of intracranial surgery, resection is also associated with significant morbidity and a very small risk of mortality (< 1%). Hearing preservation was achieved in 49% of patients with tumors smaller than 30 mm, according to a meta-analysis by Yamakami et al. (2003). Postoperative facial neuropathy is a common complication of microsurgery, due to the proximity of the facial nerve to the site of resection. In two comparative studies of microsurgery and radiosurgery, one by Pollock et al. (2006) and another by Myrseth et al. (2005), facial neuropathy was experienced in 17 and 20 percent of surgical patients, respectively. The only clear indication for microsurgery, as opposed to radiation treatments, is large tumor size. Otherwise, patients should be counseled regarding microsurgery’s strong efficacy and associated risks, and an informed decision should be made taking into account their preferences.

Gamma Knife radiosurgery offers a strong alternative to microsurgery for patients with smaller tumors (< 30 mm). The goal of radiosurgical treatment is to arrest tumor growth, rather than diminish the tumor volume. However, since it can be accomplished without dissecting into the cranium, it may provide less risk of morbidity than surgery. This is especially true with the adoption of improved imaging and planning techniques, as well as lower dose protocols. We will outline the evidence for the efficacy and safety of GK radiosurgery for VSs below in TREATMENT OUTCOMES. In general, the paucity of comparative studies between radiosurgery and alternative treatments make it difficult to identify strong indications for preferentially using the GK. Its use may be well suited for patients with smaller tumors (< 30 mm) and those with good hearing function prior to treatment. It is a good option for patients who are not considering surgical resection,
either because of health problems or personal preference. As the body of comparative evidence grows, the ability of radiosurgery to provide better patient-oriented outcomes, including functional preservation, will become clear and stronger indications may be identified.

TREATMENT PLANNING & METHODS

Gamma Knife radiosurgery is a well-established method for treating intracranial lesions using a single dose of radiation concentrated at a precise intracranial location. It is accomplished by utilizing a hemispherical array of 201 fixed Cobalt-60 sources, whose concentric radiation beams sum to a considerable dose at the focus point. The patient’s head is immobilized within a frame, defining a precise coordinate system. Gadolinium enhanced magnetic resonance imaging of the head within the coordinate frame allows the tumor volume to be defined in three dimensions. Treatment planning software allows the neurosurgeon or radiation oncologist to map the tumor margin and define the treatment fields. The radiation dose is prescribed such that the 50% isodose line corresponds to the tumor margin. During planning, care should be taken to minimize the dose to adjacent structures of the inner ear or cerebellopontine angle.

The primary goal when using the GK to treat a VS is to permanently arrest tumor growth while preserving cranial nerve function and limiting treatment associated morbidity. Achieving this balance of efficacy and safety requires the administration of a significant dose of radiation to the tumor volume while minimizing the exposure to surrounding tissues. Technological advances in the past decades have been instrumental in accomplishing this goal. These come in the form of high-resolution imaging and more powerful treatment planning software, allowing more precise mapping of the 50%
isodose line to the tumor margin. Additionally, there has been a trend towards using lower marginal doses to treat VSs, therefore decreasing dose dependent toxicity to surrounding structures. Marginal doses below 13 Gy have been utilized with similar efficacy as higher doses, as reported by Flickinger et al. (2004), thereby justifying the trend towards using low dose protocols. The use of improved technologies and lower marginal doses has been instrumental in the improving rates of hearing preservation and reducing post-treatment morbidities, such as facial neuropathy.

In planning a GK treatment for a VS, care should be taken to avoid doses to certain intracranial structures. Irradiating structures of the inner ear and brainstem have been implicated in post-operative hearing loss in a dose-dependent fashion. This association has been identified by Linskey (2008), Paek et al. (2005), and Timmer et al. (2009). Specifically, Linskey (2008) explained that exposure to the cochlea has been postulated to cause high-frequency hearing deficits, while exposure to cochlear nuclei may cause low-frequency deficits. Therefore, avoiding doses to the cochlea and brainstem should be a priority in order to facilitate a good functional outcome. It may be appropriate to demarcate these volumes using the planning software in order to record the dose to these structures. Avoiding additional structures within the cerebellopontine angle can be accomplished by planning a highly conformal dose to the tumor margin.

Selecting a dose is another important aspect to treatment planning. Early on, VSs were treated with marginal doses greater than 15 Gy. Current treatment protocols commonly use 12 to 13 Gy, which has been shown to offer tumor control as well as improved functional outcomes, particularly hearing preservation. In a recent comparison of low and high doses, published by Yang et al. (2009 a, b), there was a statistically
significant improvement in hearing preservation and post-treatment facial neuropathy in patients treated with 13 Gy or less. Therefore, the best available evidence suggests that to maximize patient-oriented outcomes, GK radiosurgery should be implemented using a marginal dose of 12-13 Gy, corresponding to the 50% isodose line.

FOLLOW-UP

Patients treated with GK radiosurgery for VS should be subject to close follow-up. This is important to verify the efficacy of the treatment, for early referral for additional interventions (microsurgery or additional radiation) if treatment fails, and to manage treatment associated morbidities. Follow-up records may also be useful for performing retrospective studies and contributing to the body of knowledge on VSs.

The efficacy of radiosurgery is best followed by periodic gadolinium enhanced magnetic resonance imaging. Tumors are typically characterized by linear dimensions, or by volume, which is more typical in the radiosurgical literature. Treatment success is defined by the cessation of growth after radiosurgery. Growth is typically defined as a change in any dimension by more than 1 or 2 mm, providing some margin of error for differences in contrast uptake or image resolution. Transient growth during the first year following GK, followed by cessation of enlargement or tumor regression, has been observed by Nagano et al. (2008). Therefore, minor growth within the first year may not indicate failed radiosurgery, and should prompt close monitoring rather than secondary treatments.

One of the main advantages of GK radiosurgery is the ability to preserve hearing function. Many patients will have been subject to audiometric evaluations prior to radiosurgery, and these should continue to be part of their regular follow-up. For those
with vestibular symptoms, formal vestibular testing may also be indicated. Hearing function can be tracked using a variety of statistics. Speech recognition threshold (SRT), which can be approximated by averaging the pure tone hearing function at 500, 1000, and 2000 Hz, and speech discrimination scores (SDS) are commonly tracked. In the VS literature, these two statistics are combined to yield a Gardner-Robertson score, first described in Gardner and Robertson (1988), allowing patients to be grouped into 5 categories of hearing function. Serviceable hearing is defined as a pre-treatment score of 1 or 2, corresponding to an SRT \( \leq 50 \text{ dB} \) and SDS \( \geq 50\% \), and hearing preservation is defined as maintaining such a score following treatment. Tracking pure tone hearing loss may be useful for the purpose of research, especially when combined with pre-treatment data regarding the radiation dose to the cochlea and brainstem nuclei. This may be useful in clarifying the magnitude of dose-dependent toxicity associated with GK radiosurgery.

Similar to hearing function, facial nerve function may be compromised following radiosurgery and should be followed closely. Signs of facial neuropathy are commonly followed using the House-Brackmann grading system, based on the work of House and Brackmann (1985), a somewhat subjective categorization scheme based on a combination of symptoms and signs. Grades range from I to VI, with good facial nerve function commonly defined by having a grade of I or II. A small fraction of patients will experience a permanent decline in facial nerve function from grades I or II to grade III or higher (see TREATMENT OUTCOMES below). Some other patients may experience transient symptoms of facial paresis in the acute period following radiosurgical treatment, which has been described in case reports, such as those by Tago et al. (2000) and Pollack et al. (2005).
During follow-up patients may also experience a variety of other treatment-related morbidities, which should be evaluated for during follow-up. Other commonly reported side effects of GK treatment include trigeminal neuropathy and hydrocephalus. Patients may also experience minor morbidities that significantly impact quality of life. These include tinnitus, dizziness, and post-operative headache. Historically, the literature has rarely reported such quality of life measures, and it would be useful to record such data to provide patients a more informed perspective on the experience associated with undergoing GK treatment for their VS. This void in the literature is discussed in depth in the paper by Myrseth et al. (2007). Finally, as with any radiation exposure, there is a small risk of secondary neoplasm after treatment with the GK. Patients and physicians should be aware of this risk, both before treatment and during long-term follow-up.

TREATMENT OUTCOMES

There are a number of retrospective studies and a few prospective studies on the use of GK radiosurgery for treating VSSs. There have been several large meta-analyses of this data to provide a strong summary of the functional outcomes attained using the GK. These include Kaylie et al. (2000), Shin et al. (2003), Weil et al. (2006), Yamakami et al. (2003), Battaglia et al. (2006), Yang et al. (2009 a, b). As described previously, despite the abundance of data, there are only a handful of comparative trials between radiosurgery and alternative treatments, and there have been no randomized trials. Therefore, definitive guidelines have not been established and the reader should be careful not to over-interpret the results below. However, the authors feel that it is appropriate to describe some of the outcomes currently being realized using the GK, with respect to both tumor control and functional preservation.
Radiosurgery for VSs has proven highly efficacious. Tumor control, defined as the cessation of growth, is accomplished in between 91 and 95 percent of cases based on available meta-analyses. In two studies reporting 10-year actuarial rates, Chopra et al. (2007) and Hasegawa et al. (2005), control was achieved in 91 and 92 percent of cases. In a retrospective study of 70 patients treated at our center with a mean dose of 12.7 Gy, control was achieved in 94% after an average of 26 months follow-up, as published in Arthurs et al. (2010).

While tumor control, as defined above, remains the traditional measure of success in the radiosurgical literature, greater clinical value may be placed in knowing the fraction of patients who go on to require secondary treatment. This statistic is commonly cited as the outcome in the literature on watchful waiting and microsurgery. For radiosurgery, between 2 and 4 percent will require additional treatment, based on Yamakami et al. (2003) and Battaglia et al. (2006). This is slightly higher than the 1-2% reported in the microsurgical literature, but the significance of this comparison is limited without additional studies that directly compare the two modalities.

Hearing preservation rates with GK radiosurgery have improved along with improvements in treatment planning and the movement towards lower marginal doses. In the meta-analysis data, between 44 and 63 percent of patients with serviceable hearing prior to treatment retained function with follow-up. Individual studies published during the past five years have achieved rates above 50%. These papers include Arthurs et al. (2010), Lasak et al. (2008), Chopra et al. (2007), Pollock et al. (2006), and Hasegawa et al. (2005).
The GK has also provided good preservation of facial nerve function. In all meta-
analyses published after 2000, the average rate of post-operative neuropathy was less
than 10%. The cited rates have been from 0-5% in a selection of recently published
studies by Arthurs et al. (2010), Lasak et al. (2008), Chopra et al. (2007), Pollock et al.
(2006), Hasegawa et al. (2005), and Myrseth et al. (2005).

Finally, we will discuss the results of two recently published comparative studies
of GK radiosurgery and microsurgical resection. It should be noted that these studies
represent small numbers of patients and the results were subject to some confounding
based on differences between the treatment cohorts. In a prospective comparison,
Pollock et al. (2006) reported that 4% of patients undergoing radiosurgery required
additional treatment, as opposed to 0% in the surgical cohort. On the other hand, hearing
preservation was achieved in 63% versus 5% and post-operative facial neuropathy in 0%
versus 17% in the radiosurgery and microsurgery cohorts, respectively. Myrseth et al.
(2005) observed, retrospectively, nearly identical rates of additional treatment (5 versus 6
percent) and a significant difference in facial neuropathy (5 versus 20 percent) between
radiosurgery and microsurgery, respectively. Both trials favored GK radiosurgery over
microsurgery due to the high rate of efficacy and improvements in patient-oriented
outcomes. This data alone is insufficient to suggest that radiosurgery is superior to
microsurgery, but it does represent an early indication that there may be some patients for
whom radiosurgery might be ideal. We hope this will encourage stronger comparative
studies in the future and that better evidence will come available to help patients and their
physicians make informed decisions regarding the treatment of their VSs.
Chapter 5

A review of treatment modalities for vestibular schwannoma

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Abstract

Vestibular schwannomas are benign intracranial tumors arising from the vestibular nerve. Treatment options include observation, stereotactic radiosurgery, fractionated radiotherapy, and microsurgery. We review the evidence describing efficacy and side-effect profiles of each of these modalities. This was accomplished by outlining the results of published meta-analyses and performing a systematic search of the literature for individual studies published between 2004 and June 2009. Without intervention, 29-54% of tumors will grow and 16-26% of patients require additional treatment, with 54-63% preserving functional hearing. With radiosurgery only 2-4% require additional treatment and hearing preservation is accomplished in 44-66% of cases. Reviewing contemporary studies, it appears that reduced marginal doses may have decreased morbidity risks associated with radiosurgery without sacrificing efficacy. With fractionated radiotherapy 3-7% will require additional treatment, and hearing preservation is reported at 59-94% of patients, although long-term outcomes are not known. Microsurgery is an alternative for eligible patients, with fewer than 2% requiring additional treatment; however, the risk of hearing loss, facial neuropathy, and other morbidities is relatively high. There are significant limitations with comparing the efficacy and morbidity rates across interventions because of selection bias and confounding factors. Additional prospective comparative trials and randomized studies are needed to improve our understanding of the relative benefits of each modality.
Introduction

Vestibular schwannomas (VSs), also called acoustic neuromas, are benign intracranial neoplasms arising from Schwann cells, which myelinate the vestibular portion of the eighth cranial nerve. Incidence of these tumors is approximately one per 100,000 person-years, a rate that has increased over time [29]. While advances in diagnostic capabilities offer a logical explanation for this trend, incidence of similar tumors remains static suggesting an undetermined etiology may be at play.

Patients with VS experience dysfunction of structures sharing anatomical proximity with their tumor. Typically, a VS originates within the internal acoustic meatus. Tumors confined within this structure are dubbed intracanalicular, while those extending beyond the petrous portion of the temporal bone are designated extracanalicular. Mass effect of extracanalicular VSs, which project into the cerebellopontine angle, may compromise function of additional cranial nerves, brainstem nuclei, or the cerebellum. Therefore, unilateral VS can present with a spectrum of ipsilateral symptoms and signs.

Matthies and Samii provide a summary of typical clinical presentations associated with VS based on the experiences of 1000 patients [19]. Hearing loss was the most common problem, affecting 95% of patients based on subjective assessment. The next most common was tinnitus, affecting over 60% of patients. Notably, nearly half of deaf patients experienced tinnitus. Symptoms associated with vestibular function also caused problems for a significant number of patients. Vertigo reportedly occurred in 28%, dizziness in 22%, and disequilibrium in 40%. The unsteadiness experienced may also be attributable, in part, to compression of the cerebellum, especially in those with very large
extracanalicular tumors. Finally, some patients experienced dysfunction of additional cranial nerves. Signs of trigeminal neuropathy occurred in 12-19%, although only 7-9% complained of symptoms of reduced facial sensation. Facial neuropathy was exhibited by 17% of patients, with 5% noting symptoms of paresis. Caudal cranial nerves (IX-XII) were rarely involved, identified in 3% of patients with VS.

The presence of symptoms and signs caused by VSs is indicative of an intracranial lesion, which should provoke physicians to perform a more thorough evaluation. Patients with hearing loss often undergo audiometric evaluation, and those with vestibular disturbances may undergo vestibular testing. Confirmation of asymmetric sensorineural hearing loss, or defects in other cranial nerves, indicates the need for imaging workup. Gadolinium enhanced magnetic resonance imaging (MRI) of the internal acoustic meatus remains the standard method for diagnosing VS. Diagnosis typically occurs in the 5th or 6th decade of life, with a median age at diagnosis of 50 years in a large epidemiological study [29].

Following diagnosis with VS, patients have several options for managing their tumor. These include observation by MRI, stereotactic radiosurgery (SRS), fractionated radiotherapy (FRT), and microsurgery (MS). Selection of a treatment modality depends on tumor size, associated symptoms and signs, patient age, patient health, and patient preference. Unfortunately, some evidence suggests that a predictor of treatment choice is the discipline of the attending physician [25]. This may be attributed partly to the limited evidence-based guidelines for treating VS. There remains no level-1 evidence comparing the modalities, and the majority of data is level-3 or worse, coming from retrospective studies [23, 28]. Until additional prospective comparisons or randomized trials can be
accomplished, systematic meta-analysis of the available literature offers the most powerful guidance for clinical decisions. However, such data must be interpreted with caution when comparing modalities, as there is a strong potential for selection bias in the different treatment categories.

We present a summary of the available evidence describing the efficacy and side-effect profiles of the major treatment modalities for VS. Specifically, we tabulated the outcomes from existing meta-analysis published in the literature. Additionally, we performed a systematic search to identify individual studies published in the past 5 years, some of which may not have been included in published meta-analyses. These represent the most current data on VS treatment, reflecting the impact of evolving treatment techniques over the past decade. Our goal is to provide a comprehensive and contemporary review of observation, radiosurgery, radiotherapy, and MS as options for managing patients with VS. This review also offers a concise presentation of the available evidence for guiding patients and practitioners in clinical decision-making.

Methods

Literature search for systematic meta-analyses

Seeking existing meta-analyses examining the treatment modalities used in VS management, we searched PubMed using the Clinical Queries service (http://www.ncbi.nlm.nih.gov/corehtml/query/static/clinical.shtml). We used the query “acoustic neuroma OR vestibular schwannoma” in the Find Systematic Reviews field. This search yielded 84 articles. Papers were selected which included systematic reviews of observation, SRS, FRT, or MS. Only those that described treatment outcomes were included in this review.
**Literature search for studies published in the past 5 years**

In order to identify contemporary studies describing VS treatment modalities, we performed a systematic *PubMed* search. The following query was used, incorporating appropriate headings from the *MeSH database*; “"Neuroma, Acoustic/prevention and control"[Majr] OR "Neuroma, Acoustic/radiotherapy"[Majr] OR "Neuroma, Acoustic/surgery"[Majr] OR "Neuroma, Acoustic/therapy"[Majr]”.’ Limits on the article type, used to pair down the results, were “Clinical Trial, Randomized Controlled Trial, Comparative Study, Evaluation Studies, Validation Studies.” This yielded 91 studies for further analysis.

For inclusion, studies must have been published in English after 2003, have a study size ≥ 25 patients, have a mean follow-up ≥ 24 months, and have reported a measurement of treatment success. When multiple articles meeting our criteria were published from the same center, we included data from the most recent study. If appropriate, we included multiple studies from the same center because they described different outcomes. Finally, for SRS we only included studies that used Gamma Knife, and for FRT we omitted studies on hypofractionation.

We also sought to identify articles not found in our initial *PubMed* query. First, references cited in papers already selected for inclusion were evaluated. Second, we searched for additional articles from identified study centers, using the city name paired with “AND acoustic neuroma” in a *PubMed* query. Those additional manuscripts identified in this fashion were evaluated using our inclusion criteria.
Data analysis

Appropriate data was captured from studies, which were identified using the search criteria above. Extracted data points included measurements of treatment success and permanent morbidities, such as hearing preservation rates and facial neuropathy rates. Treatment success was identified as the fraction of patients requiring additional treatment during the follow-up period, in the form of radiation or surgery. Outcomes specific to observation included the number of tumors growing and the mean growth rate. In the radiosurgery and radiotherapy categories, tumor arrest was defined as no growth or regression at last follow-up, based on post-treatment MRI measurements. Growth was not uniformly defined across studies, but typically represented a net increase in tumor dimension $> 2$ mm at last follow up. Serviceable hearing was based on audiometric data and the Gardner-Robertson scale, defined as a pure tone average or speech reception threshold $\leq 50$ dB and speech discrimination score $\geq 50\%$ [10]. Hearing preservation refers to the retention of serviceable hearing at last follow-up in those patients with serviceable hearing prior to treatment. Facial neuropathy rate was defined as the permanent loss of good facial nerve function following treatment. Good facial nerve function corresponds to House-Brackmann grade of I or II [12]. In some cases, data extracted from the literature had to be recalculated to obtain the outcomes described above, because of differences in reporting summary statistics across studies. For meta-analyses, this included calculating weighted means, weighted by study size (N), for those papers that presented overall outcomes as a simple mean. Data from individual studies was summarized in a similar fashion, using weighted means.
Discussion of treatment modalities

Observation

Slow growth rates of some VSs suggest that some patients may be managed conservatively, without active intervention aimed at controlling the size of their tumor. Patients undergoing this approach are monitored using MRI until progression of symptoms or tumor growth warrants more invasive treatment. This allows patients freedom from the potential adverse effects of radiation treatments or surgery.

Observation is not without risks, however, because growth rates vary with time and some VSs have been observed to increase in size at rates 10-fold faster than the average tumor [9]. Few variables are predictive of the magnitude of future growth [36]. Previous growth, large size, and young age are the only indicators identified [22]. Furthermore, even small, static, or slowly growing tumors may eventually cause symptom progression and require additional treatment [22]. Regular follow-up is a key component to this strategy, but evidence suggests patient compliance may not be ideal [36].

The efficacy of observation is measured by tumor growth rate, freedom from additional intervention, and preservation of normal cranial nerve function. We present evidence on these subjects from currently available meta-analyses in Table 1 [2, 34, 36, 37, 42, 45]. No individual studies were identified in our search that both met our inclusion criteria and were not already included within those meta-analyses. Therefore, we did not tabulate individual studies describing observation. The mean follow-up times reflected in the observation literature were typically just over three years. Patients included in this cohort had a mean tumor size hovering around 10 mm in diameter.
During observation, tumor growth was identified in 29-54% of patients, with a mean growth rate between 1 and 3 mm per year. Of patients who underwent observation, 16-26% eventually required treatment in the form of radiation or MS. The two systematic reviews that objectively measured hearing preservation report rates of 54 and 63% [37, 42].

Observation offers a low-risk option for some patients with VS. Patients considering this management strategy should be informed that many tumors continue to grow, and approximately 1 in 5 people ultimately require intervention. Furthermore, progression of symptoms remains a possibility regardless of tumor size or growth. For those presenting with serviceable hearing, preservation rates are over 50%. Notably, these outcomes are witnessed over a mean follow-up of 3 years, and in the long term additional patients may experience worsening symptoms and require intervention. This option may be indicated for older patients, those with small, intracanalicular tumors, and those committed to undergoing regular following up with serial MRI. Progression of symptoms or signs of tumor growth should prompt evaluation for additional treatment.

**Stereotactic radiosurgery**

SRS is an alternative intervention to surgical resection for VSs. It involves the precise administration of a single dose of radiation to the tumor volume, with the goal of arresting tumor growth. This is accomplished by immobilizing the patient’s head, defining a coordinate system to the cranium, and mapping the tumor volume within this frame of reference. Multiple beams of ionizing radiation are oriented such that they sum to a highly conformal dose at the tumor margin. Gamma Knife radiosurgery accomplishes this feat using 201 fixed Cobalt-60 sources, while the linear accelerator
(LINAC) uses a single source rotated about the target in radiation arcs. In this review we focus on the efficacy of Gamma Knife radiosurgery. Since no intracranial manipulation is required, radiosurgery offers minimal invasiveness compared to MS.

While radiosurgery is less invasive than surgery by nature, radiation exposure comes with related risks. With the treatment of VSs, dose profiles may overlap structures adjacent to the tumor, potentially resulting in dysfunction of cranial nerve or brainstem structures. For instance, post-operative hearing loss has been associated with increased dose to the cochlea or associated brainstem nuclei [16, 24, 40]. Post-treatment hydrocephalus is another adverse outcome experienced by some patients. Radiation exposure also poses a small risk of secondary malignancy, however follow-up times reported in the literature are likely too short to deduce the true risk to patients treated for VS.

Over the past two decades, side effect profiles associated with radiosurgery have improved along with treatment techniques. Advances in radiosurgical treatment come in the form of high-resolution MRI and treatment planning software [7, 16]. These allow physicians the ability to achieve more precise dose conformality about the tumor volume. Additionally, the dose prescribed to the tumor margin has been gradually reduced, with similar efficacy being reported with doses below 13 Gy [8]. Evidence suggests that minimizing the radiation exposure to extraneous cranial structures, achieved by modern treatment techniques and reduced doses, minimizes morbidity rates associated with SRS without sacrificing efficacy [7, 8, 20]. In recent meta-analyses, statistically significant improvements in hearing preservation and facial neuropathy rates were identified, with doses ≤ 12.5 and ≤ 13 Gy respectively [43, 44].
The efficacy of Gamma Knife radiosurgery has been the subject of several meta-analysis identified by our search [2, 13, 35, 41-44]. Table 2 reports key measures of treatment outcome captured from those reviews, measured at a mean follow up of 25-60 months. The radiosurgical literature typically reports tumors by volume rather than diameter, and those treated in this cohort had mean sizes between 2.7-4.0 cm³. As mentioned previously, doses have gradually decreased since the first use of radiosurgery for treating acoustic neuromas, so the mean doses reported in the meta-analyses range from 12-17 Gy. Arrest of tumor growth was achieved in 91-95% of cases. The fraction of patients needing additional treatment after SRS was 1.6 and 4.2 percent from the data in two meta-analyses [2, 42]. Hearing preservation rates with radiosurgery range from 44-63%. Permanent facial neuropathy was experienced by 4-19% of patients; however, in all meta-analyses published after 2000 the rate was below 10%. In reviews that evaluated permanent trigeminal neuropathy following radiosurgery rates ranged from 11-16%, and hydrocephalus occurs in only 2-3% of patients treated (not shown in Table 2).

Evaluating contemporary studies on Gamma Knife radiosurgery for VS may reflect the advantages offered by lower marginal doses and improved radiosurgical techniques. We present the data identified in our literature search in Table 3, including mean statistics weighted by study size (N) [4, 11, 15, 21, 26, 27, 30, 31]. A total population of 1850 patients was included in the analysis, with a mean tumor volume of 2.3 cm³. They were treated with a mean dose of 12.6 Gy and half of the patients underwent a mean follow up of just under 6 years. Tumor arrest was observed at rates comparable to, but not within the range of those reported in existing meta-analyses (mean 89%). Two studies determined 10-year actuarial rates of tumor arrest slightly over 90%
[4, 11]. The mean number of patients requiring additional treatment was 3.9 percent, based on data from 6 of the 7 studies. Hearing preservation was achieved in 60% of 411 patients who presented with serviceable hearing. The rates of facial and trigeminal neuropathy were lower than those reported in other systematic reviews, 1.5 and 1.2% respectively (data for trigeminal neuropathy is not shown in Table 3). This may reflect a reduction in cranial nerve toxicity as a result of lower doses and more precise treatment planning. However, determining a quantitative association will require more robust examination. Finally, hydrocephalus was observed in 2.7% of patients following treatment (not reported in table 3), which doesn’t deviate from the range of values reported in Table 2.

Given the available evidence, SRS is an effective alternative to surgery for the treatment of VS. Physicians can confidently advise patients that radiosurgery will arrest tumor progression in approximately 90% or more cases and only about 4% will require additional treatment. While it remains possible that with longer follow-up this may prove an overestimation, 10-year actuarial rates of arrested growth are reported at greater than 90%. For patients with serviceable hearing prior to treatment, preservation of function is reported at between 44 and 63%. Patients should be informed that major adverse outcomes associated with radiosurgical intervention include trigeminal neuropathy (1-17%), facial neuropathy (2-19%), and hydrocephalus (2-3%). It appears that current treatment protocols, which typically prescribe below 13 Gy, these side effects will be limited to fewer than 1 in 10 patients, and likely closer to 1 in 50. The risk of radiation-induced neoplasm has not been determined in patients treated for VS; however, patients should be informed that it is a possibility. This modality may be well suited for patients
exempt from surgical intervention, those with small tumors (<30 mm diameter), those with serviceable hearing, and those who prefer not to undergo surgical resection because of preference or anxiety.

**Fractionated radiotherapy**

FRT is akin to SRS in that it uses ionizing radiation to treat intracranial tumors in a minimally invasive fashion. Similar to radiosurgery, the patient’s head is immobilized and assigned a coordinate system, allowing for the orientation of external radiation beams to achieve a conformal dose encompassing the tumor volume. The primary difference is that radiotherapy involves the sequential administration of numerous dose fractions over a series of weeks, which ultimately sum to one large dose. The goal is to administer significant dose to the tumor, while the surrounding tissue, which receives minimal dose with each fraction, will be capable of healing between treatments. However, questions exist as to whether FRT will offer long-term efficacy comparable to radiosurgery [16].

We identified no systematic reviews evaluating the efficacy of FRT, although a number of individual studies published in the last 5 years were available. The data captured is outlined in Table 4, and includes 6 studies and 404 patients [1, 3, 5, 14, 18, 39]. As summary statistics we calculated weighted means, weighted by study size (N). Patients treated in this cohort had a mean tumor volume of 4.1 cm³ and received a mean total dose of 52 Gy, administered in fractions of 1.8 or 2.0 Gy. Overall, a mean follow-up of 53 months was reported. The mean rate of tumor arrest was 96%. Based on four studies, the 5-year actuarial rate was 94% [3, 5, 14, 18]. From three reporting studies, the rate of additional treatment was 5.4% [3, 18, 39]. Hearing preservation was achieved in 79% of 261 patients with serviceable hearing prior to intervention and facial neuropathy
was experienced by 1.0%. Adverse events also included trigeminal neuropathy (1.8%) and hydrocephalus (3.8%) (not shown in Table 4). It should be noted that two centers preferentially guided patients with serviceable hearing to receive FRT, potentially confounding the results and limiting comparison of radiotherapy to other modalities [1, 39].

While long-term outcomes are yet to be evaluated, available results indicate FRT is an efficacious option for treatment of VS. The major downside is that FRT requires the administration of more than 25 treatments over a period of weeks. Patients should be made aware of this treatment modality as an alternative to radiosurgery. While it may offer a similar success rate and improved hearing preservation relative to SRS, the results in this review are not sufficient to prove or disprove a significant difference in relative outcomes. Such conclusions can only come from prospective comparative studies or randomized trials, which limit confounding and provide adequate power to elucidate differences between SRS and FRT. Results in the FRT literature should also be evaluated with the awareness that they represent a mean follow-up period of just over four years and the long-term outcomes are yet to be determined. FRT may appeal to patients with small tumors, similar to those well suited for radiosurgery, who desire to maximize the possibility of preserving of cranial nerve function. However, at this point there is inadequate evidence to recommend it over SRS in the treatment of vestibular schwannomas.

**Microsurgery**

Surgical intervention for VSs was first performed over a century ago. Unfortunately early efforts involved significant mortality rates, as reviewed in [23]. The
advent of the surgical microscope and improvement in surgical practices has eliminated much of that risk. Today, surgery offers the possibility of excellent tumor control. Also, since this intervention seeks to remove all or part of the tumor, while SRS or FRT only seek to prevent additional growth, surgery is appropriate for use in treating larger tumors. Furthermore, despite its invasiveness, microsurgical approaches can offer some patients the chance to preserving serviceable hearing. Unfortunately, even technological and procedural advances have not eliminated the risk of adverse events associated with surgical resection. Damage to cranial nerves, cerebrospinal fluid (CSF) leak, and infection occur in a significant fraction of patients. There is also a significant learning curve associated with VS resection, and small tumor size and the surgeon’s experience have been associated with facial nerve preservation [22]. Whether this site-specific variability is specific to surgical approaches, as opposed to SRS or FRT is not clear. Despite its invasiveness, surgery remains a mainstay in VS treatment.

Two meta-analyses were identified evaluating the use of surgery in over 7500 patients with VS [13, 42]. Data collected from the studies is compiled in Table 5. These reviews represent a population with a range of tumor sizes who were treated with a variety of surgical approaches. Surgery offers excellent efficacy, with additional treatments utilized in 1.4 and 1.8 percent of the cohort. The preservation of serviceable hearing is accomplished in 36-44% of cases. Notably, hearing preservation was 49% in a cohort of 926 patients with tumors smaller than 30 mm in diameter, which more closely aligns with the population typically treated with radiation. The most prevalent side effect is facial nerve injury or transection, with permanent facial neuropathy occurring in 13-19% of patients treated, and 10% of those with tumors smaller than 30 mm. CSF leak is
the most common complication of surgery, affecting 6-11% of patients (not shown in Table 5). Mortality associated with VS resection occurs 0.3-0.6% of cases.

Our search for individual studies published after 2003 yielded 5 papers consisting of 813 patients total treated with a variety of surgical approaches [6, 21, 27, 32, 33]. Results, including means weighted by study size (N), are presented in Table 6. Tumor size was not consistently reported, but it should be noted that a significant portion of patients had large tumors compressing the cerebellum or brainstem, which would not typically be treated with radiation. With a mean follow-up of just over 5 years, the mean fraction of patients requiring additional treatment was 1.1% with MS. Hearing preservation was only reported in two studies, one of which involved a more lenient criteria for serviceable hearing (see Table 6 footnotes), and the mean rate was 44% out of 148 patients eligible for preservation. Permanent facial neuropathy was experienced by 29% of patients. The most common acute morbidity was CSF leak in 7% of cases on average (not shown in Table 6). Similar to the data presented in existing meta-analyses, mortality was rare, occurring in 0.4% of surgeries.

MS remains an efficacious treatment for acoustic neuromas. It offers patients excellent efficacy, with approximately 1% requiring additional treatment. Patients and physicians must weight this against the risks associated with surgical intervention. For patients with serviceable hearing, preservation is achieved in 32-44% of cases, although the rate may approach 50% for those with smaller tumors. While advances in surgical technique have reduced the risk of death to 0.3-0.6%, morbidity rates remain significant. Between 14-29% of patients experience permanent facial neuropathy and 6-11% will have post-operative CSF leak. For patients with VS who are candidates for surgery,
microsurgical resection is indicated for those whose tumors progress after previous intervention, those with large tumors (> 30 mm diameter).

**Comparative Studies**

Of the studies included in this review, five involved direct comparison of VS treatment modalities. Three meta-analyses evaluated historical outcomes (see Table 7) [2, 13, 42]. Kaylie et al. represented early outcomes in the field of radiosurgery, the reason that the mean marginal dose was 17 Gy, which was likely the reason the authors favored microsurgical resection until results of low-dose treatment strategies were available [13]. Battaglia et al. reviewed more recent data and drew no clear conclusion regarding the efficacy of radiosurgery relative to conservative management with observation [2]. Yamakami et al. also failed to identify any clear guidelines for implementing observation, radiosurgery, or microsurgery in vestibular schwannoma treatment [42]. Similar to results of this review, existing meta-analyses clearly organize the outcomes of many individual studies but suffer from the inability to draw comparative conclusions from such results (see Limitations of this Review below).

Two studies included in this review represent comparative studies of radiosurgery versus microsurgery in patients treated at a single institution (see Table 8) [21, 27]. Pollock et al. represents the only prospective cohort study, and the highest quality evidence encountered using our inclusion criteria [27]. The studies favored SRS because similar efficacy and greater freedom from treatment associated morbidity. Both studies include a relatively small cohort of patients and involve statistically significant confounders such as patient age and pre-treatment hearing status, the latter present only in the Myrseth et al. study [21]. Therefore, the strength of their conclusions remains
limited. However, the reader should be aware that the only comparative studies identified in our review of the literature suggest that SRS offers greater functional outcomes compared to surgical resection of vestibular schwannomas.

**Limitations of this Review**

This review seeks to present a summary of the recent literature describing VS management. It is necessary to acknowledge inherent biases in our methods and the limitations of our review. For example, our search for publications on this topic was relatively narrow and convergent. We utilized a number of restrictions in our search criteria, including omitting primary studies published prior to 2003 and restricting our search to PubMed’s MeSH headings or the Clinical Queries database. Our goal was to provide a comprehensive yet concise review of the current literature, yet there are certainly selection biases present by neglecting additional resources.

There are also significant problems with comparing the evidence associated with individual modalities. The patient population undergoing each treatment modality suffers from selection biases, making it impossible to compare the outcomes associated with each one. For instance, patients undergoing observation had mean tumor sizes around 10 mm. Although a poor estimation, if we assume a spherical volume then the mean diameter of tumors treated with SRS or FRT were 16 and 20 mm, respectively. MS, on the other hand, includes many large tumors greater than 30 mm, which are rarely considered for management with another option. Therefore, comparing modality-specific rates of treatment success reported in this review is challenging and should be performed with significant skepticism.
Evaluating the relative probability of hearing preservation for each modality is equally troublesome. While it may be postulated that those with serviceable hearing prior to treatment may be relatively homogenous across cohorts, this is not always the case. For instance, surgical series typically involve larger tumors than radiosurgical data, and meta-analysis by Yamakami et al. identified a large difference in hearing preservation even among those treated with MS when the entire patient population was compared with a subset of those with tumors smaller than 30 mm (see Table 5) [42]. Additionally, hearing preservation rates in the surgical and FRT literature often reflect a population of patients selected with the specific goal of hearing preservation, based on age, symptom profile, or tumor characteristics such as size. In this review, it was not always possible to clearly differentiate which results may have been subject to this confounder, although it was clearly present in two studies [1, 39]. Such results would be more appropriately compared with others reflecting a matched cohort of patients treated with alternative modalities. For instance, several recently published studies of SRS have evaluated hearing preservation in select patients, however these were not identified using our search criteria and therefore have not been included in our data [17, 38]. Since hearing preservation statistics do not necessarily measure the same outcome across studies or represent similar cohorts of patients, it remains difficult to draw sound conclusions by cross-examining the results tabulated in this review. It would be most appropriate to compare hearing preservation rates across matched populations, with respect to age, tumor size, and pre-treatment hearing status, a feat that may be accomplished in a future review or comparative studies.
We hope the reader will recognize that this review seeks to present the evidence in a concise fashion for use in clinical decision-making, but that it does not have sufficient capacity to facilitate comparative conclusions or treatment guidelines with regard to VS management. Problems exist with selection bias and different ways of reporting outcomes in the observation, microsurgery, and radiosurgical literature. Surgeon experience has been identified to impact microsurgical outcomes, so that even comparisons between different study centers reporting on the same treatment modality must be evaluated carefully [22]. Experience likely also plays a role in radiosurgical outcomes between different treatment centers. For these reasons, the information provided throughout this paper and within the tables should be utilized judiciously, for confounders are undoubtedly present that weaken conclusions that might be formed regarding the relative efficacy and safety of each treatment modality.

Higher quality evidence is the only means to develop more robust set of treatment guidelines for VS. This comes in the form of prospective studies, prospective comparisons, and ultimately randomized controlled trials with regards to the treatment modalities. Better guidelines will also be facilitated by uniformly reporting precise measures of tumor volume, treatment success, and morbidity rates. Furthermore, outcomes must be measured at greater follow-up intervals, such as a minimum of 5-years post-treatment, as conclusions are limited when they represent the experience after an average follow-up of similar duration. We hope that this compilation of currently available evidence will encourage VS treatment centers to engage in more powerful, well-designed studies.
Summary

In Tables 1-6 we outline the existing evidence, from meta-analyses and contemporary studies, describing the modalities used for treating VS. Observation offers the least risk to patients, but 29-54% of tumors will grow and 16-26% of patients require treatment at approximately 3 years. Gamma Knife radiosurgery arrests growth in 89-95% of tumors after an average of 6 years following treatment. Only 2-4% of patients will require additional treatment, hearing preservation is achieved in 44-66% of treatments, and fewer than 2% of patients experienced facial neuropathy or trigeminal neuropathy in recent studies. The adoption of lower doses may yield even better morbidity rates, and our center has adopted a standard marginal dose of 12 Gy to the 50% isodose line. FRT has not been evaluated with follow-up as long as radiosurgery, but the available data suggests that 3-7% will require additional treatment after 4 years follow-up and associated morbidity rates are similar to SRS. MS is an efficacious treatment for VSs, and fewer than 2% of patients are likely to require additional treatment at 5 years average follow-up. It remains a primary option for patients with very large tumors and those who have failed previous intervention. Despite the invasiveness of intracranial surgery, hearing preservation can be achieved in 32-44% of cases, and higher in those with smaller tumors. However, rates of facial neuropathy and other morbidities are significant.

Comparative studies and randomized trials are lacking, and conclusions regarding the relative efficacy and safety of each modality based on data in this review should are limited. Our center advocates counseling patients with VS using the best available evidence for all treatment modalities, but at this point there are no clear treatment
guidelines. Choice of intervention is multifactorial, depending on tumor size, tumor
growth rate, symptoms, health status, and the personal preference of the patient. Patients
and physicians should be aware of the risks and benefits offered by each modality.
Furthermore, it is important to be aware of how advancements in treatment protocols are
impacting treatment success and side effect profiles, especially in the rapidly evolving
fields of radiosurgery and radiotherapy. With the development of more powerful studies,
we may identify more conclusive guidelines for the treatment of VS. Until then we hope
that this comprehensive review will provide a convenient means to evaluate currently
available data and help to guide decision making for physicians, radiation oncologists,
neuro-otologists, and neurosurgeons in the management of their patients with VS.
Acknowledgements

Funding for this project was provided by Gamma Knife of Spokane and a grant from the University of Washington School of Medicine’s Medical Student Research Training Program (MSRTP). We would like to acknowledge Rachel Garman and Michelle Osso as well as the entire Cancer Care Northwest research staff for their contributions to this manuscript.
References


Table 1: Observation, meta-analyses. Data points include weighted mean, the range (square brackets), and the sample size (italics). For hearing preservation, the sample size represents the number of patients with functional hearing prior to observation.

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Studies (Patients</th>
<th>Follow-Up (mos)</th>
<th>Tumor Size (mm)</th>
<th>Tumors Growing (%)</th>
<th>Growth Rate (mm/yr)</th>
<th>Additional Treatment Rate (%)</th>
<th>Hearing Preservation Rate (%)</th>
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<td>16</td>
<td>54</td>
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<tr>
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<td>54</td>
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<td>26</td>
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</tr>
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</table>

aData not available to calculate weighted means
bUnspecified criteria for hearing preservation
Table 2: Stereotactic radiosurgery, meta-analyses. Data points include weighted mean, the range (square brackets), and the sample size (italics). For hearing preservation, the sample size represents the number of patients with functional hearing prior to observation.

<table>
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<tr>
<th>First Author (Year)</th>
<th>Studies (Patients)</th>
<th>Tumor Volume (cm³)</th>
<th>Dose (Gy)</th>
<th>Follow-Up (mos)</th>
<th>Tumor Control Rate (%)</th>
<th>Additional Treatment Rate (%)</th>
<th>Hearing Preservation Rate (%)</th>
<th>Facial Neuropathy Rate (%)</th>
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<td></td>
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^a Unspecified criteria for facial neuropathy
^b Data not available to calculate weighted means
^c Includes transient hypesthesia
d Linear measurement of tumor size

Table 3: Stereotactic radiosurgery, contemporary studies. Data points include weighted mean, the range (square brackets). For hearing preservation, the sample size (italics) represents the number of patients with functional hearing prior to observation.

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<thead>
<tr>
<th>First Author (Year)</th>
<th>N</th>
<th>Tumor Volume (cm³)</th>
<th>Dose (Gy)</th>
<th>Follow-Up (mos)</th>
<th>Tumor Control Rate (%)</th>
<th>Additional Treatment Rate (%)</th>
<th>Hearing Preservation Rate (%)</th>
<th>Facial Neuropathy Rate (%)</th>
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<td>90</td>
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<td>1.9</td>
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<td>46</td>
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<td>9</td>
<td>58</td>
<td>1.6&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>[&lt; 30 mm]&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>71</td>
<td>89.2</td>
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**Weighted Mean**

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<th>71</th>
<th>89</th>
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<td>1817</td>
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<td>715</td>
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* Median
** 10-year actuarial rate
<sup>a</sup> Unspecified criteria for facial neuropathy
<sup>b</sup> Facial neuropathy defined as House-Brackmann grade > 1
<sup>c</sup> Linear measurement of tumor size
Table 4: Fractionated radiotherapy, contemporary studies. Data points include weighted mean, the range (square brackets). For hearing preservation, the sample size (italics) represents the number of patients with functional hearing prior to observation.

<table>
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<tr>
<th>First Author (Year)</th>
<th>N</th>
<th>Tumor Volume (cm³)</th>
<th>Dose (Gy)</th>
<th>Fractions (Gy)</th>
<th>Follow-Up (mos)</th>
<th>Tumor Control Rate (%)</th>
<th>Additional Treatment Rate (%)</th>
<th>Hearing Preservation Rate (%)</th>
<th>Facial Nerve Rate</th>
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</thead>
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<tr>
<td>Andrews (2009) [1]a</td>
<td>89</td>
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<td>97.8</td>
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<td>73.3</td>
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<td>32 [6-107]</td>
<td>96.7</td>
<td>96.2**</td>
<td>77.3</td>
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<tr>
<td>Thomas (2007) [39]a</td>
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<td>94.1</td>
<td>2.9</td>
<td>59</td>
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</tr>
<tr>
<td>Maire (2006) [18]</td>
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<td>80</td>
<td>88.9 [4-227]</td>
<td>6.7</td>
<td>86**</td>
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<td>Combs (2005) [5]</td>
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<td>6.6 [2.7-31]</td>
<td>57.6*</td>
<td>1.8</td>
<td>48.5 [3-172]</td>
<td>95.3</td>
<td>93**</td>
<td>94.0</td>
<td>2.3</td>
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<td>Chan (2005) [3]</td>
<td>70</td>
<td>4.5 [0.05-21]</td>
<td>54*</td>
<td>1.8</td>
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Weighted Mean

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<th>95.8</th>
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<td>149</td>
<td>261</td>
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</table>

* Median
** 5-year actuarial rate
a Patients with serviceable hearing selectively assigned to FRT treatment
b Unspecified criteria for facial neuropathy
c Hearing preservation based on subjective assessment

Table 5: Microsurgery, meta-analyses. Data points include weighted mean, the range (square brackets), and the sample size (italics). For hearing preservation, the sample size represents the number of patients with functional hearing prior to observation.
Table 6: Microsurgery, contemporary studies. Data points include weighted mean, the
range (square brackets). For hearing preservation, the sample size (italics) represents the
number of patients with functional hearing prior to observation.
<table>
<thead>
<tr>
<th>First Author (Year)</th>
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<th>Patients (n)</th>
<th>Follow-Up (mos)</th>
<th>Additional Treatment Rate (%)</th>
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<td>20</td>
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</table>

Table 7: Results from within comparative meta-analyses. Data points represent weighted means. For hearing preservation, the sample size (italics) represents the number of patients with functional hearing prior to observation.

NC = Non-compressing with respect to cerebellum
C = Compressing with respect to cerebellum
RS = Retrosigmoidal
MF = Middle fossa
TL = Translabyrinthine
SO = Suboccipital
RL = Retrolabyrinthine

* Functional hearing defined as SRT < 60 dB & SDS > 40%
* House-Brackmann grade IV or V (excludes III)
Table 8: Results from within comparative prospective trials. Data points represent weighted means. For hearing preservation, the sample size (italics) represents the number of patients with functional hearing prior to observation.
Chapter Six
Gamma Knife radiosurgery for vestibular schwannomas: tumor control and functional preservation in 70 patients

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6Spokane Ear Nose & Throat Clinic, Spokane, WA, USA
7Carroll College, Helena, MT, USA
8DataWorks Northwest, LLC, Coeur D'Alene, ID, USA

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Abstract

Object: We present the previously unreported outcomes of 70 patients treated with Gamma Knife radiosurgery for vestibular schwannoma (VS), including comprehensive analysis of clinical outcomes and the effects of lower marginal doses.

Methods: We performed a retrospective study of patients treated for VS at Gamma Knife of Spokane between 2003 and 2008. Endpoints measured include tumor control, hearing preservation, and facial nerve preservation, including the impact of tumor size and marginal dose. Statistical analysis was performed with Wilcoxon’s signed-rank test, paired Student’s t-test, Mann-Whitney U test, Kendall’s rank correlation, Fischer’s exact test, and Liddell’s exact chi-squared test for matched pairs.

Results: With a mean follow-up of 26 months, 93.8% of tumors either shrank or remained static after receiving a mean marginal dose of 12.7 Gy. Tumor control was independent of marginal dose or tumor size. Hearing preservation was achieved in 64% of patients with serviceable function prior to treatment. Hearing changes were independent of dose or tumor size. Preservation of good facial nerve function was achieved in 95% of patients. Post-treatment hydrocephalus occurred in 4.4% of patients, but no other significant morbidities were elucidated.

Conclusions: In the treatment of VS, contemporary radiosurgical techniques and the use of marginal doses below 13 Gy offer excellent tumor control, at high rates relative to surgical intervention. These findings are independent of marginal dose and tumor size. Patients should be informed about the benefits and risks of radiosurgery and microsurgery prior to choosing an intervention. Further analysis of post-treatment...
outcomes should be encouraged as follow-up times increase and the treatment protocols continue to evolve.

**Introduction**

Vestibular schwannomas (VSs) are benign tumors arising within the internal acoustic meatus about the vestibulocochlear nerve (CN IX). Incidence is approximately 1 per 100,000 person years and diagnosis occurs with a median age of 50 years.¹ Because of projecting into the cerebellopontine angle and mass effect, VS commonly cause symptoms of adjacent cranial nerves, brainstem nuclei, and the cerebellum. The most common ipsilateral symptoms are hearing loss, tinnitus, disequilibrium, vertigo, dizziness, facial numbness, and facial paresis.²

Patients diagnosed with VS have several management options. Ultimately, selection of a treatment modality may depend on tumor size, symptom profile, comorbidities, and patient preference. Choices include observation with serial magnetic resonance (MR) imaging, surgical resection, stereotactic radiosurgery (SRS), and fractionated radiotherapy (FRT). Conservative observation is non-invasive; however, up to 20% of patients will eventually require intervention, because of tumor growth or symptom progression.³⁻⁷ Surgery offers the greatest rate of tumor control (>98%) but it is also the most invasive, offering the lowest preservation rates of cranial nerve function.⁶,⁸ The use of external beam radiation, in the form of radiosurgery or radiotherapy, seeks to arrest tumor growth while minimizing morbidity rates. Reported rates of tumor control are above 90% for both SRS and FRT, and side effect profiles appear better than microsurgery.⁶,⁸⁻¹⁶
The use of SRS in the treatment of VSs has been the subject of several meta-analyses. Reported rates of tumor control range from 91-95%.\textsuperscript{3,6,8,16-18} The risk of morbidity associated with Gamma Knife (GK) treatment has also been assessed. Serviceable hearing, defined by the maintenance of a speech recognition threshold (SRT) below 50 dB and speech discrimination score (SDS) above 50%, has been maintained in 44-63% of patients following SRS.\textsuperscript{6,8,15,17} Toxicity to the trigeminal and facial nerves has resulted in neuropathy rates reported between 9-17% and 4-19%, respectively.\textsuperscript{6,8,16,17} Finally, post-treatment hydrocephalus occurs in rarely, affecting 2-3% of patients.\textsuperscript{6,8,17}

There is a small risk of radiation-induced malignancy, but definitive incidence rates have not been identified in patients treated for VS. The risk of mortality due to radiosurgery is essentially absent.

Over the past decade, protocols for treating VSs using GK radiosurgery have evolved considerably. Changes come in the form of improved MR resolution and more powerful planning software for the Gamma Knife, which ultimately allow greater precision in defining a conformal dose to the tumor volume.\textsuperscript{19,20} Additionally, doses prescribed to tumor margins have been lowered with the goal of minimizing morbidity rates.\textsuperscript{19,21,22} Most recently, marginal doses of 12-13 Gy have been indicated for the treatment of VSs.\textsuperscript{21} Yang et al. reviewed the impact of such protocols finding a statistically significant difference between low dose (≤ 13 Gy) and high dose groups with respect to hearing preservation rates (59% versus 53%, p = 0.0285) and facial neuropathy rates (1.5% versus 5.3%, p < 0.001).\textsuperscript{15,16} As additional data becomes available, we will be able to determine more definitively whether technique improvements and lower doses affect tumor control or morbidity rates.
Contributing to the available evidence evaluating contemporary radiosurgical techniques, we present the previously unreported results of 70 patients treated for VS at Gamma Knife of Spokane. These patients were treated between 2003 and 2008, with a mean marginal dose of 12.7 Gy. We report retrospectively on tumor control, hearing preservation, facial neuropathy, and additional morbidity rates. Additionally, we provide statistical analysis, shedding light on the impact of radiation dose and tumor size on outcomes. These results will be valuable for guiding clinical decisions and for the purpose of future systematic review of VS treatments.

**Materials and Methods**

We examined the pretreatment factors and clinical outcomes of 70 patients treated for VS at Cancer Care Northwest and Gamma Knife of Spokane (Deaconess Hospital, Spokane, WA) between 2003 and 2008. The following patient variables were captured from medical records: age at treatment, laterality of tumor, diagnosis of neurofibromatosis type 2, and previous intervention. Pre-treatment records were examined for the presence of relevant symptoms or signs. These were also evaluated from post-treatment records, along with the incidence of morbidities. Follow-up length was determined as the difference between the date of treatment to the date of most recent clinical encounter (clinical follow-up), most recent imaging (imaging follow-up), and most recent audiogram (audiometric follow-up).

Efficacy of GK was determined based on the response of the tumor to treatment. Tumors were followed based on direct measurements, or values reported in radiology reports if images were not available for our review. Tumor size was defined as the largest linear dimension. Tumors growing in size by more than 1 mm in any direction
were classified as growing. This accounts for the precision of tumor measurements, which are at best +/− 1 mm as a result of differences in contrast uptake and the resolution offered by the 2.5-5 mm slice thickness used in most imaging studies. Transient tumor enlargement during the first year following GK has been well documented, so overall outcomes were based on comparison of the most recent study to the pre-treatment MRI. Tumor control (GK success) was defined as the absence of growth.

The impact of radiation on hearing loss was quantitatively analyzed using audiometric records available for 41 patients. Pure tone hearing loss was evaluated at 250, 500, 1000, 2000, 4000, and 8000 Hz. Additionally, we recorded SRT, approximated from the average of pure tone hearing loss at 500, 1000, and 2000 Hz when appropriate, and SDS. Gardner-Robertson (GR) scores were used as an assessment of overall hearing function, assigned based on SRT and SDS. Serviceable hearing was defined as a GR score of 1 or 2, corresponding to a SRT ≤ 50 dB and SDS ≥ 50%, as has been the standard in the literature. Hearing preservation was defined as the maintenance of serviceable hearing following GK treatment.

Facial nerve outcomes were defined using the House-Brackmann (HB) system for grading facial nerve function. Scores were captured from pre-treatment and post-treatment records, or estimated retrospectively based on the symptoms and signs described when necessary. Good facial nerve function was defined as normal or mild dysfunction, a HB score of I or II.

Statistical analysis was performed using StatsDirect (Version 2.7.3) and Microsoft Excel. We utilized the following tests to identify dependent relationships amongst variables: Wilcoxon’s signed-rank test, paired Student’s t-test, Mann-Whitney U test,
Kendall’s rank correlation, Fischer’s exact test, and Liddell’s exact chi-squared test for matched pairs. Statistical significance was arbitrarily set as a p-value of less than 0.05. Summary statistics are presented as a mean, with one standard deviation when appropriate, unless otherwise noted.

This study was performed in accordance with ethical standards guiding retrospective chart reviews. Our study and protocol were approved by IRB Spokane (IRB #1554) and the University of Washington Human Subjects Division (Human Subjects Application #36306).

**Results**

We identified 70 patients treated for VS at our institution. A summary of the clinical data for these patients can be found in TABLE 1. Of our study population, one patient was diagnosed with neurofibromatosis type 2, and 12 patients had been subject to previous intervention for their tumors.

Pre- and post-treatment imaging records were available for 65 patients, who were included in the analysis of tumor control. The mean imaging follow-up was 26 ± 18 months (range 0.3 - 72). Treatment data and outcomes are summarized in TABLE 2. At most recent follow-up, 93.8% of tumors had been controlled by GK radiosurgery (FIGURE 1). Tumor control rates were also calculated as a function of tumor size, as shown in FIGURE 1. Wilcoxon’s signed ranks indicated a statistically significant difference between the tumor diameters pre- and post-treatment (p < 0.0001). The difference in tumor size, including an approximate 95% confidence interval (CI), was -1.65 mm (-2.05 to -0.85 mm). Mann-Whitney U tests failed to identify significant
relationships between marginal dose, tumor size, and tumor volume with respect to tumor control.

Hearing outcomes were evaluated for 41 patients with pre- and post-treatment records, with a mean audiometric follow-up of 17 ± 16 months (range 0.2 - 65). Pure tone hearing loss data is shown in FIGURE 2. Prior to GK, the mean SRT was 51.6 ± 25.5 dB, and SDS was 45.5 ± 36.0 %. These were 68.8 ± 28.1 dB and 34.4 ± 36.8 % following GK radiosurgery, respectively. Wilcoxon’s signed ranks test showed a significant change in SRT and SDS following GK (p < 0.0001 and p = 0.0216, respectively), shown in TABLE 3. Kendall’s rank correlation tested the dependence of SRT changes and SDS changes with respect to marginal dose, tumor size, and tumor volume. Those relationships were found to be independent, and an approximate two-side test adjusted for ties indicated that any correlation was not statistically significant. Hearing preservation rates in 14 patients with pre-GK serviceable hearing and audiometric follow-up are shown in TABLE 3.

The preservation of good facial nerve function (HB class I or II) was achieved in 95.3% of the 64 patients with good function prior to treatment. A Liddell’s exact chi-squared test for matched pairs yielded a two-sided test statistic of 1.5 (p = 0.5078), indicating there was not a significant difference in facial nerve function following radiosurgical treatment. Identical tests performed for other symptoms and signs associated with VS, suggest that any changes were statistically insignificant. These included trigeminal neuropathy (p = 0.6875), tinnitus (p = 0.6250), disequilibrium (p = 0.9999), vertigo (p = 0.6072), and headaches (p = 0.7905). The rate of post-GK
hydrocephalus was 4.4%. There were no cases of secondary malignancy or mortality. At last follow-up, two patients had died of unrelated causes.

**Discussion**

Several papers have identified the need for phase III clinical trials evaluating the efficacy of current radiosurgical or microsurgical techniques in the treatment of VSs.\(^3\,8\,21\) There exists little prospective evidence on the topic, so for the moment, systematic meta-analysis of retrospective data remains the most powerful tool for basing clinical decisions. Contributing to the available evidence for such reviews, we present the previously unreported outcomes of 70 patients treated for VS with the GK at our center. Our comprehensive study evaluated tumor control, hearing preservation, facial nerve preservation, and other functional outcomes. Additionally, we evaluate the dependence of such outcomes on tumor size and radiation dose.

Characteristics of our patients prior to treatment (TABLE 1) are similar to existing studies.\(^6\,8\,15\,18\) Patients presented with a spectrum of symptoms and signs related to dysfunction of the vestibulocochlear nerve and anatomically adjacent structures. The incidence rates identified for hearing loss, tinnitus, vertigo, trigeminal neuropathy, and facial neuropathy (see TABLE 1) were similar to those reported by Matthies et al.\(^2\) These facts suggest that our study population does not consist of a unique demographic of patients with VS.

Patients in this study were treated according to standard American Society of Therapeutic Radiation Oncology (ASTRO) guidelines, using a mean marginal dose of 12.7 Gy. The majority of patients (55, 79\%) were prescribed a marginal dose of 13 Gy or less. Flickinger et al. reported that 12 to 13 Gy offers tumor control and greater hearing
preservation, and this has remained an arbitrary cutoff point for low-dose classification in the field. Therefore, our study results are relevant for evaluating the efficacy of lower doses in the radiosurgical treatment of VSs.

Patients in our study were followed up clinically, with MR imaging, and with audiometry. Results are based on a mean clinical follow-up of 27.6 months, imaging follow-up of 26.2 months, and audiometric follow-up of 17.1 months. This magnitude of follow-up is appropriate for determining the efficacy of GK radiosurgery for treating patients with VS. However, longer-term endpoints are required to fully evaluate the benefits and risks of SRS, especially risks of tumor recurrence and secondary malignancy. These outcomes should be the objective of future studies at our center.

GK radiosurgery provided tumor control for 94% of patients, with a 95% CI of 88-100%. This fits well with control rates published in existing systematic reviews (91-95%). We identified a statistically significant decrease in tumor size following GK intervention and determined that tumor control was determined independent of marginal dose. These result indicates that treating patients with lower doses of 12-13 Gy continues to offer significant control of VSs, as reported elsewhere.

When grouped by tumor size, similar control rates were achieved in tumors smaller than 30 mm in diameter (see FIGURE 1). Only five patients with tumors over 30 mm existed in our patient population, so the significance of results for that group is limited. However, it is noteworthy that radiosurgical treatment of tumors above this size is rare, and it has been suggested that surgery should be the sole option for such patients. Statistical tests identified an independent relationship between tumor control and either tumor size or volume, suggesting that the efficacy of GK radiosurgery not
dependent on such factors. Future studies may seek to elucidate whether this trend is equally relevant to patients treated with tumors greater than 30 mm in size.

Hearing function decreased on average following radiosurgery. Mean pure tone hearing loss was worse at all frequencies tested when compared to pre-treatment levels (see FIGURE 2). It has been previously postulated that dose margins overlapping the cochlear nuclei in the brainstem would preferentially cause low-frequency hearing deficits, whereas exposure to the cochlea would cause high-frequency deficits.20 We see a similar magnitude of loss at all frequencies, which may be attributable to the exposure to both the brainstem and cochlea. Dose dependent toxicity beyond the tumor margin has been reported previously.27 In order to determine what doses are toxic, future studies should seek to examine relationships between pure tone hearing loss and dose to the brainstem or cochlea.

As a summary of overall hearing function, we also evaluated changes in SRT and SDS (see TABLE 3). SRT increased by a mean value of 17 dB (95% CI of 8 to 21), corresponding to a decrease in function. SDS also exhibited a statistically significant trend towards worse function, changing by -11% (95% CI of -20 to -2). Marginal dose, tumor size, and tumor volume had no impact on the changes in SRT or SDS upon statistical analysis.

In the treatment of VS, preservable hearing function is typically defined using the GR scoring system, where SRT < 50 dB and SDS > 50% correspond to good function. Prior to treatment we had 17 patients who fit this criteria, with GR scores of 1 or 2. Audiometric outcomes were available for 14 of the patients, and hearing was preserved in 64% of that population (95% CI of 38 to 90). In assuming that patients without follow-
up lost function, the preservation rate drops to 53%. These values fit well with the preservation rates elucidated in large meta-analyses published since 2003 (54-63%).6,15,17 In an older meta-analysis by Kaylie et al. hearing was preserved in only 44% of patients using a significantly higher mean dose (17.3 Gy). Furthermore, a 2009 review by Yang et al. identified a statistically significant difference in preservation rates in those patients treated with 12.5 Gy or less (p = 0.0285).15 Our study contained too few candidates for hearing preservation to perform meaningful analysis on the impact of dose. However, we achieve a preservation rate comparable to other studies using a mean marginal dose of 12.7 Gy, supporting the conclusion that low-dose therapy offers lower risk of hearing loss.

In patients with good facial nerve function, defined as a HB score of I or II, we achieved a preservation rate of 95%. Contemporary meta-analyses quote control rates of 93 to 96%.6,16,17 Notably, a study published in 2000 identified a facial nerve preservation rate of 81% in patients treated with an mean of 17 Gy.8 We did not analyze the impact of dose on facial nerve preservation, but doses below 13 Gy have been indicated to offer lower risk (p < 0.0001).16 Current radiosurgical techniques appear to offer the greatest benefits with respect to facial nerve preservation as compared to alternative interventions, as meta-analyses of surgical outcomes have identified facial preservation rates much lower (81-86%).6,8

Treating VSs with radiation also poses potential risks of toxicity to other intracranial structures. However, we found no statistically significant difference between pre-treatment and post-treatment status for the following symptoms and signs: facial neuropathy, trigeminal neuropathy, tinnitus, disequilibrium, vertigo, and headaches. Risk
of hydrocephalus was 4.4%, which is slightly higher than the 3% identified elsewhere. Treatment posed no risk of mortality or secondary malignancy; however, definitive risks of radiation-induced neoplasm will require longer follow-up in future studies.

**Conclusions**

We retrospectively evaluated the outcomes of 70 patients treated for VS with Gamma Knife radiosurgery. Our study population represents a cohort of patients treated since 2003 using low marginal doses (mean 12.7 Gy) and modern radiosurgical techniques. Radiosurgery offered excellent tumor control, with 94% of tumors shrinking or remaining static after a mean follow-up of 26 months. Control was independent of dose or tumor size. A statistically significant decrease in hearing function was observed; however, in those patients with serviceable hearing prior to treatment, 64% preserved function at last follow-up. Changes in audiometric parameters were also independent of dose and tumor size. Facial nerve function was preserved in 95% of patients following treatment. These results support the conclusion that lower marginal doses, adopted over the past decade, offer excellent tumor control and functional preservation. In the future, prospective studies and meta-analysis of contemporary data, such as that published here, will offer more robust evidence for guiding clinical decisions. For now, our results reveal that GK radiosurgery is a viable option for all patients with VSs less than 30 mm in diameter, and we feel that further study is needed to quantify the efficacy of treatment for patients with larger tumors. Practitioners should inform their patients of the benefits and risks associated with radiosurgery, as well as those of alternatives like observation, microsurgery, and fractionated radiotherapy.
Acknowledgements:

Funding for this project was provided by Gamma Knife of Spokane and a grant from the University of Washington School of Medicine’s Medical Student Research Training Program (MSRTP). We would like to acknowledge Rachel Garman and Michelle Osso as well as the entire Cancer Care Northwest research staff for their contributions to this manuscript.
References


Figures

FIGURE 1: Tumor control rates grouped by tumor size. Error bars represent 95% confidence intervals.

![Graph showing tumor control rates grouped by tumor size.](image)

FIGURE 2: Pure tone hearing loss as a function of frequency, including pre- and post-treatment data. Error bars represent one standard deviation.

![Graph showing hearing loss as a function of frequency.](image)
# Tables

TABLE 1: Summary of study population and pre-treatment characteristics (mean ± one standard deviation, range in parenthesis where appropriate).

<table>
<thead>
<tr>
<th>Study Population</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>70</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59 ± 14</td>
</tr>
<tr>
<td></td>
<td>(18 – 88)</td>
</tr>
<tr>
<td>Clinical Follow-Up (mos)</td>
<td>27 ± 18</td>
</tr>
<tr>
<td></td>
<td>(1 - 72)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-Treatment Tumor Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size (mm)</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>Tumor volume (cm³)</td>
<td>1.70 ± 2.17</td>
</tr>
<tr>
<td>Tumors growing (%)</td>
<td>61</td>
</tr>
<tr>
<td>Growth rate (mm/yr)</td>
<td>2.9 ± 4.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting Symptoms &amp; Signs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective hearing loss (%)</td>
<td>94</td>
</tr>
<tr>
<td>Tinnitus (%)</td>
<td>71</td>
</tr>
<tr>
<td>Disequilibrium (%)</td>
<td>80</td>
</tr>
<tr>
<td>Vertigo (%)</td>
<td>39</td>
</tr>
<tr>
<td>Trigeminal neuropathy (%)</td>
<td>23</td>
</tr>
<tr>
<td>Facial neuropathy (%)</td>
<td>19</td>
</tr>
<tr>
<td>Headaches (%)</td>
<td>38</td>
</tr>
</tbody>
</table>
TABLE 2: Summary of gamma knife treatment outcomes in 65 patients (mean ± one standard deviation, range in parenthesis where appropriate).

<table>
<thead>
<tr>
<th>Gamma Knife Treatment Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal dose (Gy)</td>
<td>12.7 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>(10 – 16)</td>
</tr>
<tr>
<td>Maximum dose (Gy)</td>
<td>26.2 ± 6.9</td>
</tr>
<tr>
<td>Tumor covered by marginal dose (%)</td>
<td>96.3 ± 4.7</td>
</tr>
<tr>
<td>Post-treatment tumor size (mm)</td>
<td>17 ± 7</td>
</tr>
<tr>
<td>Static tumors (%)</td>
<td>45</td>
</tr>
<tr>
<td>Shrinking tumors (%)</td>
<td>59</td>
</tr>
<tr>
<td>Growing tumors (%)</td>
<td>6</td>
</tr>
</tbody>
</table>

TABLE 3: Median hearing preservation outcomes following gamma knife treatment.

<table>
<thead>
<tr>
<th>Hearing Outcome</th>
<th>Result (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in SRT(^b) (dB)</td>
<td>17.2 (7.5 - 21)</td>
</tr>
<tr>
<td>Change in SDS(^c) (%)</td>
<td>-11 (-20 - -2)</td>
</tr>
<tr>
<td>Hearing preservation (%)(^*)</td>
<td>64.3 (38.2 - 90.3)</td>
</tr>
</tbody>
</table>

* Based on outcomes in 14 patients with serviceable hearing prior to treatment.

\(^a\) Confidence interval

\(^b\) Speech recognition threshold

\(^c\) Speech discrimination score
Chapter Seven
Gamma Knife Radiosurgery for Movement Disorders: A Concise Review of the Literature

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171
Abstract

Medication is the predominant method for the management of patients with movement disorders. However, there is a fraction of patients who experience limited relief from pharmaceuticals or experience bothersome side-effects of the drugs. Deep brain stimulation (DBS) and surgical lesioning of the thalamus and basal ganglia are respected neurosurgical procedures, with valued success rates and a very low incidence of complications. Despite these positive outcomes, DBS and surgical lesioning procedures are contraindicated for some patients. Stereotactic radiosurgery with the Gamma Knife (GK) has been used as a lesioning technique for patients seeking a non-invasive treatment alternative and for medication-intolerable patients, who are unable to undergo DBS or lesioning due to comorbid medical conditions. Tremors of various etiologies are treated using GK thalamotomy, which targets the ventralis intermedius nucleus. GK thalamotomy produces favorable outcomes when treating tremors, with success rates ranging from 80-100%. In contrast, GK pallidotomy targets the internal globus pallidus, and is used in treating bradykinesia, rigidity, and dyskinesia. Although radiosurgery has proven beneficial for tremors, radiosurgical pallidotomy for bradykinesia, rigidity, and dyskinesia remains questionable, with mixed success rates in the literature that ranges from 0-87%. We suggest that GK thalamotomy be offered along with other neurosurgical approaches as a feasible treatment option to patients who prefer the non-invasive nature of radiosurgery and to those who are unqualified candidates for the neurosurgical alternatives. Also, we advise that patients with bradykinesia, rigidity, and dyskinesia be educated about the variability in the literature pertaining to GK pallidotomy before proceeding with treatment.
Background

Pharmacotherapy is the general treatment method for patients who suffer from movement disorders. Even though a large proportion of patients are able to manage their condition with medication, there is still a small amount of patients who do not experience significant relief from pharmaceuticals, thus, seek out other treatment modalities. Deep brain stimulation (DBS) and surgical lesioning of the thalamus and basal ganglia are respected and well-studied neurosurgical procedures that come with a low incidence of potential side-effects. However, there is a subset of patients with movement disorders who are not qualified candidates for invasive neurosurgery. This population of patients consists of those who use anticoagulants, those who have advanced cardiac or respiratory disease, those who are known to be noncompliant, those who are of advanced age, and those who elect to not proceed with neurosurgery. Despite the fact that radiofrequency (RF) neurosurgical lesioning has shown success in many patients, there is still a possibility for patients to encounter a wide array of side-effects. These include intracerebral or extracerebral hemorrhage, seizures, infection, brain displacement, tension pneumocephalus, and direct injury from probe placement [1]. Stereotactic radiosurgery using the gamma knife (GK) is a non-invasive alternative modality for lesioning intracranial structures.

The first cobalt-60-based GK device dates back to Sweden in 1968, where Professor Lars Leksell’s intention was to create precisely located, well-circumscribed lesions in the brain in a minimally-invasive fashion [2]. Between 1968 and 1982, a total of 762 patients underwent treatment with the cobalt-based GK unit. Only 5 of the 762 patients were treated for Parkinsonism, but this historic study shows that the idea of
treating movement disorders using radiosurgical techniques is not a recent advance and has evolved considerably over the past four decades.

In recent years, thalamotomy and pallidotomy with the GK have been used to treat a variety of movement disorders. Specifically, GK thalamotomy targets the ventralis intermedius nucleus (VIM) of the thalamus, and is used in treating essential, Parkinsonian, and other types of tremors. Evidence suggests that GK thalamotomy produces favorable results when treating tremors, offering a safe alternative to RF thalamotomy and DBS [1, 3-9]. GK pallidotomy targets the internal globus pallidus (Gpi) of the basal ganglia, and is used in treating bradykinesia, rigidity, and dyskinesia. However, a variety of outcomes have been reported when using radiosurgical pallidotomy, thus, it remains a controversial procedure [1, 3, 10, 11].

We present a brief modern review of published data on the effectiveness of GK thalamotomy and pallidotomy in the treatment of patients with movement disorders.

**Review**

*GK thalamotomy for tremor treatment* (See table 1 for data summary)

In 2010, Young et al. [9] published a study analyzing 161 patients who were treated for ET with GK thalamotomy. The main clinical scale utilized to assess tremor control was the Fahn-Tolosa clinical rating scale. The authors reported statistically significant (P < 0.0001) differences in both drawing scores (81% of patients showed improvements) and writing scores (77% of patients showed improvements), with a mean follow-up of 44 ± 33 months. Overall, 14 (8.4%) patients suffered from post-operative complications, which included limited sensory loss contralateral to the side of the
procedure, motor impairments, and difficulties with speech. In the same year, Lim et al. [12] investigated the role of GK thalamotomy in 18 patients with disabling tremor from either ET or Parkinson’s disease (PD). The authors utilized the clinical Fahn-Tolosa scale and the United Parkinson’s Disease Rating Scale (UPDRS) to assess potential tremor improvements. Follow-up ranged from 7 to 30 months (mean of 19.2 months). It was reported that patients significantly improved (P = 0.03) in activities of daily living scores. However, 3 (16.7%) patients encountered toxicities from the procedure. The observed complications from radiosurgery included edema, hemorrhage, dysarthria, hemiparesis, and lip and finger numbness.

In 2008, Kondziolka et al. [5] performed a study where 31 patients with ET were treated with thalamotomy using GK radiosurgery. All patients were considered unqualified candidates for neurosurgery. The Fahn-Tolosa tremor scale was used to provide an objective measurement of response to treatment. The authors reported statistically significant improvements in both the mean tremor score (P < 0.000015) and mean handwriting score (P < 0.0002) following radiosurgery (median follow-up of 36 months). Of the evaluated patients, 18 (69%) exhibited improvements in their action tremor and handwriting scores, 6 (23%) exhibited improvements in only their action tremor, and 3 (12%) did not exhibit compelling improvements in either variable. One patient suffered from transient mild right hemiparesis and dysphagia, while a separate patient also developed mild right hemiparesis and difficulties in their speech following radiosurgery.

An initial review on movement disorders was performed in the past by Duma et al. [3]. Over a seven year period, 38 patients with disabling tremor from PD underwent
thalamotomy using the GK. Patients were assessed using the UPDRS. 42 thalamic lesions were created in these 38 patients, and 90% were deemed successful, with respect to tremor control. Young et al. [1] also performed a study that evaluated the safety and efficacy of GK thalamotomy in the treatment of tremors. The UPDRS and Hoehn and Yahr ratings determined by trained specialists were utilized. Overall, an 88.9% success rate was reported in their 27 patients suffering multiple types of tremors. More specifically, 16 patients were treated for Parkinsonian tremor, 8 were treated for ET, 2 were treated for tremor following cerebral infarctions, and 1 patient was treated for a tremor following a bout of encephalitis. After a mean follow-up of 22.2 months, 19 patients experienced complete or nearly complete resolution of tremor and 5 patients were nearly tremor free. Young et al. [8] also completed an additional study investigating the long-term effects of GK thalamotomy for disabling tremor and obtained favorable results. Patients were evaluated by blind evaluations, the UPDRS, and the Fahn-Tolosa tremor scale. After a mean follow-up of 52.5 months, 88.3% of PD patients became fully or nearly tremor free. At 12 months post-operation, 92.1% of ET patients were fully or nearly tremor free. 88.2% of these ET patients maintained excellent tremor control 48 months or more following radiosurgery. Only 50% of patients with other forms of tremor experienced notable improvements.

To compare the surgical approaches for the management of tremor, Niranjan et al. [7] analyzed the outcomes of patients treated with GK thalamotomy, RF thalamotomy, and DBS. Out of the 13 patients that underwent RF thalamotomy, 5 (39%) had complete arrest of tremor, 6 (46%) had a significant reduction, and 2 (15%) had approximately 50% tremor reduction. All 11 DBS patients experienced excellent tremor control
immediately after surgery, and it was reported that only 2 (18.2%) of those patients’ tremor reoccurred. 10 (83.3%) noted excellent tremor relief and 2 (16.7%) experienced good relief. Niranjan’s results with GK thalamotomy correlates with studies done by Jankovic et al. [13] and Fox et al. [14] with RF thalamotomy. Their reported success rates were 90% and 91%, respectively.

GK thalamotomy is also a worthy treatment option to consider for patients who struggle with tremors caused by Multiple Sclerosis (MS). Mathieu et al. [6] created radiosurgical thalamic lesions in six patients with MS-related tremors and recorded advantageous results. Patient results were assessed using the Fahn-Tolosa tremor scale. After a median follow-up time of 27.5 months, it was documented that radiosurgery was beneficial to every patient. Niranjan et al. [15] explored the role of GK thalamotomy in the management of ET and MS-related tremor in 12 patients of advanced age (median of 75 years). Patient outcomes were also assessed using the tremor scale diagrammed by Fahn-Tolosa. Of the 11 evaluable patients, 9 (81.8%) reported excellent tremor control and 2 (18.2%) announced a satisfactory improvement with their tremor.

Two issues pose potential challenges with radiosurgical thalamotomy: the time interval between treatment and effect and the variability of the thalamic reaction, and inability to predict the potential subsequent side-effects for specific patients. Both of these issues were demonstrated in a study done to evaluate the survival of neurons adjacent to the thalamic lesion after GK thalamotomy by Ohye et al. [16]. They performed a total of 36 thalamotomies in 31 patients and analyzed the treatment outcomes. It was noted in this analysis that in the majority of patients, tremor reduction started approximately one year after irradiation. The delay in treatment effect may not be
desired by some patients. Based on MRI data, two types of tissue reactions were observed: a simple oval lesion and one of a complex irregular shape. There was no correlation between the tissue reaction and tremor outcome. Unlike DBS and stereotactic lesioning, where subsequent side-effects can be predicted by neurological physiological responses during the procedure, there are no predictors prior to GK radiosurgery for the type of resultant lesion observed. In some patients, the lesion may extend into the internal capsule or medial thalamic region, causing a variety of delayed-onset complications months after GK radiosurgery that cannot be anticipated [16].

*GK pallidotomy for bradykinesia, rigidity, and dyskinesia treatment* (See table 2 for data summary)

In contrast to radiosurgical thalamotomy, controversy exists regarding the effectiveness of GK pallidotomy for bradykinesia, rigidity, and dyskinesia. Duma et al. [3] performed a study investigating outcomes of GK pallidotomy. In contrast to the prior section on thalamotomy, they reported a lack of faith in the procedure which targets the basal ganglia. Similar to the prior section on GK thalamotomy, the authors used the UPDRS to assess patient outcomes. A total of 18 patients underwent stereotactic lesioning in the basal ganglia for bradykinesia, rigidity, and dyskinesia related to PD. Only 6 (33%) patients showed transient improvement in rigidity and dyskinesia. Three (17%) patients displayed no changes, and 9 (50%) were worsened by the treatment. The complications from treatment included homonymous visual field cuts, dysphagia, dysasthria, hemianesthesia, hemiparesis, and a worse gait. As with GK thalamotomy, the size of the lesions, thus observed complications, created by GK pallidotomy cannot be anticipated. Also, to explain the high complication rate, the authors hypothesized that
lesion creation in the basal ganglia is more difficult than in the thalamus due to a greater likelihood of perforating arteries [3] In addition to arterial infarction, the authors hypothesized that there is a differential sensitivity to radiation between the VIM and Gpi. This is because the pallidum has previously been known to show an increased sensitivity to hypoxia [3]. Also, because the iron concentration in the pallidum tends to increase with age, it has been thought that the excess iron catalyzes undesirable reactions, thus, leading to the formation of free radicals [3]. Friedman et al. [10] witnessed outcomes with GK pallidotomy comparable to that of Duma et al. [3] Only four patients participated in the study, and none of them exhibited compelling improvements. Complications were seen in one patient, who became psychotic and demented following radiosurgery.

Conversely, additional research studies from single institutions have reported positive outcomes in radiosurgical pallidotomy. Young et al. [11] performed a study comparing the outcomes of RF pallidotomy and GK pallidotomy for patients with PD. The UPDRS and Hoehn and Yahr ratings were utilized. In 29 patients, the pallidotomies were performed radiosurgically, and 22 patients had the open-skull RF method performed. Before surgery, 15 of the 29 radiosurgery patients experienced dyskinesias, and 13 (86.6%) had complete or nearly complete relief of that symptom postoperatively. Out of the 22 RF patients, 12 experienced dyskinesia preoperatively, and 10 (83.3%) of those patients had complete or nearly complete relief after surgery. Bradykinesia and rigidity were present in every patient preoperatively, and 19 (65.5%) of the GK patients and 14 (63.6%) of the RF patients had significant improvement in those symptoms. One patient in the GK group developed a homonymous hemianopsia nine months after treatment and five RF patients became transiently confused after surgery.
Conclusions

The goal of this report is to provide a concise review of the literature on the efficacy and potential side-effects of GK radiosurgery in the treatment of patients with movement disorders. As seen in the reported research, thalamotomy with the GK is an effective and non-invasive alternative in treating tremors, with success rates ranging from 80-100%. Additionally, because of the non-invasive lesioning technique associated with radiosurgical thalamotomy, the procedure comes with a different risk profile than the open-skull neurosurgical methods. On the contrary, GK pallidotomy has shown mixed outcomes in the treatment of bradykinesia, rigidity, and dyskinesia. The inconsistency of radiosurgical pallidotomy is demonstrated in the available literature, with success rates that range from 0-87%. However, studies on radiosurgical pallidotomy have not been as extensive as those on radiosurgical thalamotomy, so less is known about the procedure and there remains room for continued research and improvements. We suggest that GK thalamotomy should be mentioned as a viable treatment option to tremor patients who prefer the non-invasive aspects of radiosurgery and to the fraction of medication-intolerable patients, who are ineligible to undergo RF thalamotomy or DBS. We also recommend that patients should be educated about the variability in the literature pertaining to GK pallidotomy and need for further study before proceeding with radiosurgery treatment.

Competing Interests

The authors declare that there are no competing interests.
Authors’ Contributions

ALE and CML reviewed relevant literature for this review and drafted the manuscript. BJA, WTL, JJD, ARM, RFK, DRG, and BSC provided expertise relevant to this review and helped draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements
We would like to acknowledge Rachel Garman and Michelle Osso, as well as the entire Gamma Knife of Spokane and Cancer Care Northwest research staff for their contributions to this manuscript.

References


### Tables

**Table 1: GK thalamotomy for tremor treatment**

<table>
<thead>
<tr>
<th>1st Author (Year)</th>
<th># Patients (Age Range)</th>
<th>Radiation Dose (Gy)</th>
<th>Follow-up (Range)</th>
<th>Improvement Rate</th>
<th>Complications Observed</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young [9] (2010)</td>
<td>161 (18-93 yrs)</td>
<td>141-152</td>
<td>Mean: 44 ± 33 months</td>
<td>Drawing: 81%  Writing: 77%</td>
<td>sensory loss, motor impairments, dysarthria</td>
<td>8.4%</td>
</tr>
<tr>
<td>Lim [12] (2010)</td>
<td>18 (64-83 yrs)</td>
<td>130-140</td>
<td>Mean: 19.2 months (7-30 months)</td>
<td>NR</td>
<td>edema, hemorrhage, dysarthria, hemiparesis, lip and finger numbness</td>
<td>16.7%</td>
</tr>
<tr>
<td>Kondziolka [5] (2008)</td>
<td>31 (52-92 yrs)</td>
<td>130-140</td>
<td>Median: 36 months (4-96 months)</td>
<td>92%</td>
<td>hemiparesis, dysphagia, dysarthria</td>
<td>7.7%</td>
</tr>
<tr>
<td>Duma [3] (1999)</td>
<td>38 (60-84 yrs)</td>
<td>120-160</td>
<td>Median: 30 months (6-72 months)</td>
<td>90%</td>
<td>dysarthria</td>
<td>2.6%</td>
</tr>
<tr>
<td>Young [1] (1998)</td>
<td>27 (73.3 ± 7.2 yrs**)</td>
<td>120-160</td>
<td>Mean: 22.3* months (12-44* months)</td>
<td>89%</td>
<td>none</td>
<td>0%</td>
</tr>
<tr>
<td>Young [8] (2000)</td>
<td>PD: 102 (71.3 ± 8 yrs) ET: 52 (73.8 ± 9.4 yrs) Other: 4</td>
<td>120-160</td>
<td>&lt;12-96 months</td>
<td>PD: 88.3 % ET: 92.1% Other: 50 %</td>
<td>balance disturbance, paresthesias, weakness, dysphasia</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
(64.3 ± 7 yrs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range</th>
<th>Duration</th>
<th>Incidence</th>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niranjan [7] (1999)</td>
<td>12 (38-78 yrs)</td>
<td>130-150</td>
<td>Median: 24 months (4-40 months)</td>
<td>100%</td>
<td>dysarthria, weakness</td>
</tr>
<tr>
<td>Niranjan [15] (2000)</td>
<td>11 (38-92 yrs)</td>
<td>130-150</td>
<td>Median: 6 months (2-11 months)</td>
<td>100%</td>
<td>dysarthria, weakness</td>
</tr>
<tr>
<td>Mathieu [6] (2007)</td>
<td>6 (31-57 yrs)</td>
<td>130-150</td>
<td>Median: 27.5 months (5-46 months)</td>
<td>100%</td>
<td>hemiparesis</td>
</tr>
<tr>
<td>Friedman [4] (1999)</td>
<td>15 (37-84 yrs)</td>
<td>120-140</td>
<td>3 months</td>
<td>93.3%</td>
<td>edema, incoordination, action tremor</td>
</tr>
</tbody>
</table>

ET = essential tremor; NR = not reported; PD = Parkinson’s disease
*Data includes pallidotomy patients
**Data includes only patients assessed by an independent team
Table 2: GK pallidotomy for bradykinesia, rigidity, and dyskinesia treatment

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; Author (Year)</th>
<th># Patients (Age Range)</th>
<th>Radiation Dose (Gy)</th>
<th>Follow-up (Range)</th>
<th>Improvement Rate</th>
<th>Complications Observed</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duma [3] (1999)</td>
<td>18 (59-85 yrs)</td>
<td>120-160</td>
<td>Median: 8 months (6-40 months)</td>
<td>33.3%</td>
<td>homonymous visual field cut, dysphagia, dysarthria, hemiparesis, hemianesthesia, worse gait</td>
<td>50%</td>
</tr>
<tr>
<td>Friedman [10] (1996)</td>
<td>4 (61-74 yrs)</td>
<td>180</td>
<td>18 month interval</td>
<td>0%</td>
<td>dementia, psychosis</td>
<td>25%</td>
</tr>
<tr>
<td>Young [1] (1998)</td>
<td>28 (68.2 ± 10.2 yrs**)</td>
<td>120-160</td>
<td>Mean: 22.3* months (12-44* months)</td>
<td>Bradykinesia/ Rigidity rate: 64.3% Dyskinesia rate: 85.7%</td>
<td>homonymous hemianopsia</td>
<td>3.6%</td>
</tr>
<tr>
<td>Young [11] (1998)</td>
<td>29</td>
<td>120-140</td>
<td>Mean: 20.6 months (6-48 months)</td>
<td>Bradykinesia/ Rigidity rate: 65.5% Dyskinesia rate: 86.6%</td>
<td>homonymous hemianopsia</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

*Data includes thalamotomy patients
**Data includes only patients assessed by an independent team
Chapter Eight
Gamma Knife Radiosurgery for Essential Tremor: A Case Report and Review of the Literature

Ameer L Elaimy [1,2], John J Demakas [1,4], Benjamin J Arthurs [1,3], Barton S Cooke [1], Robert K Fairbanks [1,5], Wayne T Lamoreaux [1,5], Alexander R Mackay [1,6], David R Greeley [7], Christopher M Lee [1,5]

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Abstract

Approximately 5 million people in America are affected by essential tremors (ET), which are classified as a type of benign movement disorder. This disease manifests as tremors that usually occur in the hands, but they may also be present in the head, face, tongue, and lower limbs. Radiofrequency thalamotomy (RF) and deep brain stimulation (DBS) are common invasive procedures with proven track records that are used to treat ET. Although these procedures have high success rates, they still put patients at risk of potential side effects and are invasive by nature. Thalamotomy using the gamma knife (GK) also produces favorable outcomes in treating tremors, without the complications associated with invasive neurosurgery procedures. This report describes the presenting symptoms and extended treatment outcome for a patient with an advanced case of ET, who received GK thalamotomy treatment six years ago. Because of this non-invasive treatment, she regained the ability to paint and live with an improved quality of life. We also discuss and review the relevant literature regarding the risks and benefits of this treatment modality. GK thalamotomy is one effective option for the treatment of ET, and due to its noninvasive nature, it has a different risk profile than neurosurgery. We suggest that GK thalamotomy should be presented as one viable treatment option to all ET patients, and should be recommended to those who would be best served by less invasive treatment techniques.
Background

Essential tremor is a common type of movement disorder that normally affects people over the age of 65; however, this illness can occur in younger patients as well. In recent years, ET has been categorized as a heritable condition, which can be transferred to family members in an autosomal dominant fashion [1]. The primary symptom of ET involves shaking of the hands during voluntary movements, but it may also present with movements of the head, face, tongue, and lower limbs [1-3]. Other than tremors, there are no other direct medical symptoms associated with ET and it does not decrease life expectancy. However, many patients with ET have difficulties accomplishing their daily tasks or other activities that affect quality of life, which is how this disorder elicits a negative impact on the social and mental wellness of the patients who bear this illness [1, 4].

There are multiple treatment options for ET patients. The most common medications utilized are beta-blockers. Unfortunately, these are contraindicated for many patients with asthma, diabetes, and certain heart conditions. Anti-seizure medications and botulinum toxin injections are also used, but they are known to cause unwanted side effects. Stereotactic RF thalamotomy is the most common neurosurgical procedure for treating ET. It involves MR imaging of the thalamic target (ventralis intermedius nucleus), placement of an electrode neurosurgically, stimulation of the target, and creation of a lesion through tissue ablation [5]. DBS is also an invasive surgical procedure performed as an alternative to RF thalamotomy. DBS involves the implantation of a device that utilizes electrical impulses to block abnormal nerve signals [5, 6].
Even though surgical treatments such as RF thalamotomy and DBS are effective in many patients with ET, there are those who are not qualified candidates for invasive neurosurgery because of comorbid medical conditions. These include patients who use anticoagulants, who have advanced cardiac or respiratory disease, who are known to be noncompliant, and who are of advanced age. An alternative for such patients is thalamotomy using GK radiosurgery. GK thalamotomy is a safe alternative to invasive neurosurgery, and evidence shows it is successful in the treatment of ET and similar movement disorders [5, 7-11]. Also, because this disorder often occurs at a late age, and pharmaceuticals can have significant side effects, GK can be the only treatment option for this population of medication-intolerable patients.

We present an inspiring case of an ET patient, whose daily life was drastically modified by the severity of her hand tremors, until GK thalamotomy treatment restored her ability to control movement and pursue her passion of painting.

**Case Presentation**

**Case Report**

The patient was a 65 year-old right-handed female, who reported a history of right-handed tremors for approximately one to two years before her GK consultation in 2003. The tremors involving her right arm were fine postural tremors, as well as intentional tremors. She did not experience resting tremors. Also, the patient experienced fine tremors in her left arm. She found that the tremors were more pronounced with stress. Eventually, the patient’s handwriting worsened to the point where she was no longer able to write legibly (See Fig. 1). The patient worked as a nurse, and said certain aspects of her job became difficult to accomplish (e.g. administering IVs) because of her
tremor. The patient was initially treated medically for her tremor, but she did not experience significant relief and thus sought out other treatment options.

She consulted with a neurosurgeon, with the goal of learning the risks and benefits of the available surgical procedures. In her case, DBS was felt to be a better option than RF thalamotomy. She was educated about the risks and benefits of DBS and GK thalamotomy and opted to proceed with GK treatment. After an MRI was obtained and GK planning was complete, the patient underwent a left VIM thalamotomy, with a prescribed maximum dose of 140 Gy. The dose administered was 70 Gy to the 50% isodose line, with a 4 mm gamma knife shot. Following the procedure, the patient was monitored closely and had serial follow-up appointments with a neurosurgeon. We have included an illustration of her treatment fields (See Fig.3).

The patient did well post-operatively and experienced no side effects or focal neurological problems. The patient first observed tremor improvement within two weeks of radiosurgery. Tremor control continued to improve over the next eight months. At that point, the patient’s tremors completely dissipated (See Fig. 2). Because of her profound improvement, the patient painted a beautiful picture for her treating neurosurgeon out of gratitude for her ability to regain this hobby (See Fig. 4). United Parkinson’s Disease Rating Scale (UPDRS) scoring and the Fahn-Tolosa clinical rating scale were utilized to provide an objective measurement of response to treatment [12, 13]. We compared scores from pre-treatment with scores eight months after treatment to demonstrate her clinical improvements. Assessment by the treating neurosurgeon revealed that the patient’s scoring improved from a grade of 3 to 0, with respect to handwriting and tremor control in both the UPDRS and the Fahn-Tolosa scales. It was also concluded that the patient’s
drawing capability improved from a grade of 4 to 0 by Fahn-Tolosa grading. A post-
treatment MRI eight month after radiosurgery showed an 11 mm enhancing ring-like
lesion consistent with the treatment.

Unfortunately, the patient did experience complications one year after GK
surgery. She developed numbness in the first three fingers of her right hand and her
tongue, which led to dysarthria. The patient also reported balance problems at this time.
An MRI showed increased signal in the thalamus, but no new lesions were found. The
lesion measured about 10 mm in circumference, with a vertical diameter of 7 mm. A
Medrol Dosepak was prescribed to the patient for the inflammation. She saw
improvements in her speech and balance when she began the medication, but those issues
returned shortly after completion of the dose pack. She was then placed on a Decadron
taper for seven weeks, and responded quite well following that course of treatment. She
saw a definite improvement in her speech and balance; however, she occasionally
experienced transient numbness in her lips and the first two fingers of her right hand. The
patient’s status continued to improve from there on. At 72 months post treatment, her
tremors have not returned and she is living a happy and fulfilling life. She still enjoys
painting as a hobby.

**Review of Relevant Literature**

We have reached a point in the field of neurosurgery where minimally-invasive
procedures exhibit outcomes comparable to open-skull surgery. Young, et al.
[11] performed a study where 27 patients with a variety of tremor causes (Parkinson’s
disease, ET, cerebral infarctions, and encephalitis) underwent GK thalamotomy for
tremor treatment. Out of these 27 patients, 24 (88.9%) saw positive results. Specifically,
19 of these patients experienced complete tremor resolution and the other 5 had nearly complete tremor resolution, with a mean follow-up of 22.2 months. There were no complications observed. Friedman, et al. [8] conducted 15 thalamotomies using the GK. Out of these 15 patients, 14 (93.3%) experienced complete absence or a slight residual tremor three months after surgery. Similar to our patient in this case presentation, it was reported that two patients in this study exhibited severe edema three months following radiosurgery. Both of these patients underwent steroid therapy, and it was found that one of these patients significantly improved, while the second patient experienced moderate improvement, with a slight residual deficit. Plowman [14] classified post- radiation reactions into categories based on the timeframe following radiosurgery in which they occur. This is an example of a subacute tissue reaction, due to the fact that the edema occurred 3-10 months after radiosurgery. Subacute reactions are many times either completely or partially reversible. Acute reactions, occurring 12-48 hours after surgery, are rarely seen in thalamotomies with the GK because the effects of radiosurgery take time to manifest clinical symptoms.

GK thalamotomy is also an accepted treatment for tremors caused by PD. Duma, et al. [7] created 42 radiosurgical thalamic lesions in 38 PD patients with GK thalamotomy and obtained promising results. The tremor was eliminated completely in 10 thalamotomies (24%). Excellent improvement was seen in 11 (26%), good improvement was seen in 13 (31%), and mild improvement was seen in 4 (9.5%). GK treatment did not affect 4 (9.5%) patient’s tremors. Therefore, 38 out of the 42 (90%) thalamotomies were deemed successful. However, one patient reportedly suffered a mild acute dysarthria one week after treatment.
Both RF thalamotomy and DBS have excellent reported control rates, but a varied side effect profile. Fox, et al. [15] reported a 91% success rate and Jankovic, et al. [16] reported a 90% success rate with open RF thalamotomy. Despite the high success rates, RF techniques put the patient at risk for intracerebral or extracerebral hemorrhage, seizures, infection, brain displacement, tension pneumocephalus, and direct injury from probe placement [11]. Unemura, et al. [6] performed a thorough review that evaluated the morbidity and mortality related to DBS. They noted 16 serious adverse events related to surgery in 14 (12.8%) of 109 patients. These included pulmonary embolism, subcortical hemorrhage, chronic SDH, venous infarction, seizure, infection, cerebrospinal fluid leak, skin erosion, and death.

A study done to compare GK thalamotomy, RF thalamotomy, and DBS by Niranjan, et al. [5] displayed confidence in all three methods, with respect to tremor control rates. DBS systems were implanted in 11 patients, who all had excellent control of their tremors immediately after surgery. Long-term follow up showed that 9 out of 11 patients maintained excellent tremor control. Out of the 15 patients that underwent GK thalamotomy, the 12 who had more than six months of follow-up showed positive results. There were no immediate complications after radiosurgery. Although, one patient who had experienced a reduction in her ET 2 months after GK treatment noted mild weakness in the contralateral arm and leg, along with dysarthria 8 months after surgery.

Fortunately, the patient was managed on corticosteroids and showed incremental improvements over time, with regard to those clinical symptoms. Immediately after surgery, all 13 RF thalamotomy patients experienced improvements, but 6 of those patient’s tremors reoccurred. Young, et al. [10] monitored GK thalamotomy patients for a
longer period of time. At one year, 92.1% of their ET patients were completely or nearly
tremor free. At four years, 88.2% maintained their radiosurgical success.

Even though invasive surgery approaches show immediate results, the amount of
risk associated with treatment appears to be greater than radiosurgery using the GK.
However, GK thalamotomy has its own challenges. Ohye, et al. [17] reported that in most
of their 31 GK thalamotomy patients, the reduction of tremor started approximately one
year after irradiation. That time period may not be preferred by some patients. Another
challenge is variability of the thalamic reaction and subsequent side effects between
patients. They concluded that there are two types of thalamic lesions formed by GK
radiation. The first type is simple, showing a round punched-out lesion, consisting of an
oval, low signal area surrounded by a ring-like high signal area. The second type is an
irregular-shaped high signal zone that is large and amorphous. There was no correlation
between the two types of lesions and the clinical effect on tremor. The type and volume
of a thalamic lesion cannot be predicted before radiosurgery. In some cases, the lesion
may extend into the internal capsule or medial thalamic region, which is usually
accompanied by streaking, thus, can cause severe delayed-onset complications.

Conclusions

We described a patient successfully treated for ET with the GK. Six years after
treatment, this patient is still exceptionally happy with her results. She has recently
reported that her tremors are completely controlled; allowing her to live an active
lifestyle. This patient, who previously could not write her own name legibly, is now an
avid painter. The published data, as reviewed in this manuscript, indicates that GK
thalamotomy is an effective procedure in the treatment of tremors and that the risk profile
is different and in many cases preferable to open-skull surgery. We suggest that GK thalamotomy should be presented as an acceptable treatment option to all ET patients before making a decision to undergo invasive neurosurgery. We look forward to continued research and evolution of this exciting treatment option for patients suffering from tremors.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Competing Interests**

The authors declare that there are no competing interests.

**List of Abbreviations**

- DBS= deep brain stimulation; ET= essential tremor; GK= gamma knife; PD= Parkinson’s disease; RF= radiofrequency; UPDRS= United Parkinson’s Disease Rating Scale; VIM= ventralis intermedius nucleus

**Acknowledgments**

We would like to acknowledge Rachel Garman, as well as the entire Cancer Care Northwest research staff for their contributions to this manuscript.
References


Figures

Figures 1 and 2: Handwriting sample before and after radiosurgery
Figure 3: GK Treatment Fields
Figure 4: Painting patient gave to her treating neurosurgeon
Chapter Nine

Feasibility of Multiple Repeat Gamma Knife Radiosurgeries for Trigeminal Neuralgia: A Case Report and Review of the Literature

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Abstract:

Objective and Importance:

It is essential that treatment options for trigeminal neuralgia (TN) be customized for the individual patient, and physicians must be aware of the medical, surgical, and radiation therapy treatment modalities to prescribe the optimal course of treatment for specific patients. The following case illustrates the potential for Gamma Knife Radiosurgery (GKRS) to be repeated multiple times for the purposes of achieving facial pain control in cases of TN that have been refractory to other medical and surgical options, as well as prior GKRS treatment.

Clinical Presentation:

The patient in this case failed to achieve pain control with initial GKRS, as well as medical and surgical treatments. He experienced significant pain relief for a period of time with a second GKRS procedure and later underwent a third procedure to again attain relief. Three months after the procedure, the patient had significant relief of his pain and reported no facial numbness or other new symptoms.

Intervention:

The patient underwent an initial GKRS 20 months previously, after pharmacotherapy failed. He underwent percutaneous radiofrequency ablation 13 months previously, a second GKRS procedure 10 months previously, and a third GKRS procedure 3 months previously. The first 2 GKRS procedures targeted the trigeminal nerve root entry zone, while the 3rd procedure targeted the nerve root a few millimeters distal to the prior targets.

Conclusion:
To date, only a small reported subset of patients have reportedly undergone more than two GKRS for TN, thus further research and long-term clinical follow-up will be valuable in determining its usefulness in specific clinical situations.

**Introduction:**

Trigeminal neuralgia (TN), also known as *tic douloureux*, is a disorder of the sensory nucleus of cranial nerve V, which causes severe episodic shooting pains in one or more of its three divisions (V1-V3). TN is most commonly idiopathic, but may be caused by pressure from a structure, such as a blood vessel compressing or pulsating on the trigeminal nerve or its vasculature. This condition affects females twice as often as males, with a peak incidence at 60 years of age (7). Triggers for episodes of pain vary greatly among individuals, with patients commonly reporting pain with brushing teeth, chewing, talking, touching the face, and cold sensations on the face or teeth. Options for management of TN include medical, surgical, and radiation approaches. This report describes a rare and unique course of treatment for TN due to the refractory nature of the disease process and because the patient received three separate Gamma Knife radiosurgery (GKRS) treatments. This course of treatment may prove useful in a select group of patients with a similar clinical situation.

**Case Report:**

A 72 year old man was referred to a community oncology center by his neurologist due to complaints of a recurrence of lancinating, “shock-like” pain in the left side of his face from the pre-auricular area into the left side of his upper and lower jaw. The patient stated that the pain was intermittent, 10/10 in intensity (on a scale of 1 to 10, with 10 being the worst), and was triggered by several actions, including eating, brushing
gums, cold sensations, and touching his face. The patient stated that the pain was accompanied by tenderness and sensitivity to touch around the outside margin of his left eye, but he denied numbness or other change in sensation in the affected area.

The patient stated that his symptoms began as an “annoyance” approximately 4.5 years prior and progressed slowly to the current state approximately 19 months ago, at which time he was diagnosed with TN by his dentist. An MRI of the brain performed at the time of diagnosis demonstrated a tortuous basilar artery abutting the left trigeminal nerve. He was initially started on Gabapentin, which provided only mild relief. Carbamazepine was added later, but it caused him to become excessively drowsy, which resulted in a significant fall and concussion. Due to his fall, the medications were discontinued.

The patient underwent initial GKRS 20 months prior with a Leksell Model C Gamma Knife to the trigeminal nerve root entry zone with 201 cobalt sources (4 mm shot size) to a dose of 42 Gy prescribed to the 50% isodose line for a maximum point dose of 84 Gy (see Figure 1). Shortly after the procedure, the patient experienced mild relief of pain, but had a sudden recurrence in the second division of the trigeminal nerve within 2 months. In hopes of achieving further pain relief, the patient underwent a radiofrequency gangliotomy procedure at a major university medical center 13 months ago, which provided temporary relief. However, the patient’s pain recurred and became debilitating leading him to again seek treatment. A second GKRS procedure was performed 8 months previously (approximately 11 months after the first one), with the same proximal nerve root entry zone targeted to a dose of 27 Gy to the 50% isodose line for a maximum dose of 54 Gy at the center point. At that point, the patient had a maximum dose of 138
Gy to the nerve. Shortly after the procedure, the patient experienced nearly complete resolution of his pain for the next 6.5 months and was able to discontinue all oral pain medications. However, approximately 3 months prior to the writing of this report, the patient began to experience gradual recurrence of the pain in his left upper and lower jaw and again sought evaluation for further pain control.

Medical, surgical, and radiosurgical pain management options were discussed with the patient. He stated that he would prefer to avoid surgery and had difficulty tolerating pain medications, which he reported made him feel drowsy and disoriented. The patient stated that he would prefer to have a 3rd GKRS procedure because it was the only treatment that had provided him extended and significant pain relief. The patient underwent his 3rd GK treatment approximately 3 months ago. The 3rd treatment was delivered a few millimeters distal from the previous target and was prescribed (with 4 mm shots) to 20 Gy to the 50% isodose line (see Figure 2). The patient did well post-operatively and experienced no side-effects or focal neurological problems. Nine weeks after the procedure, the patient stated that he had experienced significant relief of his pain and no new facial numbness or complications of treatment. He will continue to be followed closely by his treating physicians in the future and understands that with retreatment his risks of permanent side-effects are increased.

Discussion:

Optimal treatment of TN remains challenging, as each clinical situation can vary significantly. This case illustrates a unique approach to the management of TN in that this patient has received 3 separate GKRS treatments to the same nerve root for refractory
disease. Patients who suffer from TN have a number of treatment modalities to consider and treatments should be tailored to the individual situation.

Medication in the form of anticonvulsants, such as Gabapentin and Carbamazepine, as well as antidepressants, is the predominant method in treating TN related facial pain. However, there are a fraction of patients who experience only limited relief from pharmacotherapy or are unable to endure the side-effects of the prescribed drugs, and thus, seek other treatment alternatives (3).

Neurosurgical intervention is often the next line of treatment for patients where pharmaceuticals have failed. Microvascular decompression (MVD) is a procedure that involves a craniotomy to locate and separate veins or arteries in contact with the trigeminal nerve, while preserving its function (2). Despite the fact that MVD has proven to provide patients with TN pain relief, it is the most invasive treatment regimen and puts patients at risk for a variety of neurosurgical complications (15). Percutaneous rhizotomies are another set of neurosurgical procedures that create a permanent lesion at the trigeminal root or ganglion by thermal or chemical means (2). Although these approaches are preferred in many clinical situations and are effective treatments, rhizotomy procedures are also invasive by nature and can come with a number of unwanted side-effects such as nerve damage (2, 15) and vascular injury.

GKRS has been shown to be safe and effective in patients with medically (12) and surgically (6) refractive TN. On an increasing number of occasions, GKRS is attempted a second time and in only a handful of cases have outcomes been reported in the literature where a 3rd treatment was performed, making it largely uncharted territory. Repeat GKRS in cases where it has previously been effective have reported similar rates of
complete pain control as with the initial procedure (9). However, successful retreatment of patients in whom the initial GK treatment fails is also feasible (4), as was illustrated in this case with the second GKRS. Overall, repeat GKRS has been shown to provide significant pain relief in more than 2/3 of patients (5, 13), with some studies showing similar (8, 11) and others showing better (13) overall facial pain outcomes than primary radiosurgery. Lack of a prior neurosurgical procedure was also predictive of better pain control (1).

Pollock et al investigated the effect of different treatment modalities for idiopathic TN in patients who had undergone three or more previous operations of any kind. This study found that posterior fossa exploration resulted in better facial pain outcomes than SRS or percutaneous techniques in this group of patients, however, this paper acknowledges selection bias in their choice of treatment (14). Based on the fact that the patient in this report had at least 3 interventions for pain relief, with the most recent being GKRS, the Pollock study would predict that he has a 36% chance of complete pain relief after 3 years and a 45% chance of new facial numbness or dysesthetic pain. It should be noted that the study did not mentioned whether any patient in this study underwent 3 GKRS making it difficult to stratify the likely outcome. Another study by Gellner et al also reports that two patients each had four GKRS operations, but gives few details about those specific cases or their outcomes (5).

Studies disagree about the incidence of complications in primary versus repeat GKRS, with some showing no significant increase in incidence of complications beyond that observed in the initial procedure (9), and others showing a significant difference for side effects, such as facial numbness (4, 10, 11, 13). Huang et al suggested that the
incidence of facial numbness was significantly increased above a cumulative dose of 115Gy (10). Dvorak et al showed a dose-response relationship for both pain control and development of side effects, with doses above 130Gy more likely to result in a new dysfunction, as well as improved pain control (4). Another study notes that at cumulative doses above 163Gy, the rate of bothersome numbness was in the range of 16% (13).

The radiosurgery target area may also play a significant role in both maximizing pain control and limiting side effects. Zhang et al showed that increasing the isocenter distance between the two radiosurgeries was associated with improved pain relief (16). Although this study found no relationship between distance between isocenters (in first and second radiosurgeries) and occurrence of dysesthesias, only five patients with dysesthesias were included in this segment of the study.

**Conclusion:**

This report highlights a case of TN refractory to medical and surgical management, non-responsive to an initial GKRS procedure, responsive to a second GKRS procedure, and having undergone a 3rd course of GKRS due to refractory pain after a pain free interval. This is one of very few reported cases of a patient undergoing three GKRS procedures for TN. Further research will be valuable in determining its usefulness in clinical practice.

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References:


14. Pollock BE, Stein KJ: Surgical management of trigeminal neuralgia patients with recurrent or persistent pain despite three or more prior operations. *World Neurosurg* 73:523-528.


Figures

Figure 1. Axial section through the brainstem at the nerve root entry zone of the left trigeminal nerve with an illustration of the location of the 50% isodose line for Gamma Knife radiation treatment planning. This is the treatment location for the first and second Gamma Knife procedures.
Figure 2. Axial section through the brainstem at the nerve root entry zone of the left trigeminal nerve with an illustration of the location of the 50% isodose line for the Gamm knife radiation treatment planning. This is the location of treatment for his third course of treatment.