1994

Radiosurgery for Malignant Brain Tumors

Michael Jino Yun

Virginia Commonwealth University
School of Medicine

This is to certify that the thesis prepared by Michael Jino Yun entitled "Radiosurgery for Malignant Brain Tumors" has been approved by his committee as satisfactory completion for the thesis requirement for the degree of Master of Science.

[redacted]

Randall E. Merchant, Ph.D., Director of Thesis

[redacted]

John W. Bigbee, Ph.D., School of Medicine

[redacted]

William C. Broaddus, M.D., Ph.D., School of Medicine

[redacted]

William P. Jollie, Ph.D., Department Chairman

[redacted]

Hermes A. Kontos, M.D., Ph.D., Dean, School of Medicine

[redacted]

William L. Dewey, Ph.D., Dean, School of Graduate Studies

November 17, 1994

Date

Radiosurgery for Malignant Brain Tumors

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

By

Michael Jino Yun, B.S.
University of Vermont
1992

Director: Randall E. Merchant, Ph.D.
Professor, Department of Anatomy

Virginia Commonwealth University
Richmond, Virginia
December 1994

Acknowledgements

I would like to thank Dr. Randall E. Merchant for all of his guidance, patience, and generosity. I am indebted to Dr. William C. Broaddus for all of his expertise, support, and many words of wisdom. Also, I would like to express my deep gratitude to Dr. George R. Leichnetz for establishing the Pre-Professional Master's Degree Program and for all of his support, encouragement, and sound advice. I extend my appreciation to Dr. John W. Bigbee for all of his patience and help. Thanks are also in order to Dr. Stanley H. Benedict of the MCV Department of Radiation Oncology, Mr. Robert Nekoroski of Radionics Inc., and Ms. Nicola Kinrade of Elekta Radiosurgery. To my friends and classmates: Rebekka Christie, Jerry Quirk, Jim Christian, Kelly Zacharias, Hasan Ahmed, Graham Bundy, Robin Obenchain, Dorthy Fedis, Tourage Rafeei, Jiepei Zhu, and Erin Duecy, I will never forget your kindness. Most importantly, I must thank my family for their love and support during all of my ups and downs. I don't know how you put up with me. I love you all very much.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Anaplastic Astrocytoma	AA
Arteriovenous Malformation	AVM
Basic Fibroblast Growth Factor	bFGF
Bovine Capillary Endothelial Cell	BCE
Brown Roberts Wells	BRW
Centi-Gray	cGY
Centimeter	cm
Cobalt	Co
Cobalt-60	^{60}Co
Computed Tomography	CT
Cubic Centimeter	cc
Curie	Ci
Deoxyribonucleic Acid	DNA
Giga-Hertz	GHz
Gill Thomas Cosman	GTC
Glioblastoma Multiforme	GBM
Gray	Gy
Iodine	I
Iodine-125	^{125}I
Karnofsky Performance Score	KPS
Kilo-Dalton	KDa
Kilo-Electron Volt	kEV
Linear Accelerator	LINAC

Magnetic Resonance Imaging	MRI
Maximum Dosage	d_{max}
Mega-Electron Volt	MeV
Mega-Volt	MV
Mili-Curie	mCi
Millimeter	mm
Radiation Absorbed Dose	rad
Total Dose Inhomogeneity	TDI
Vascular Endothelial Growth Factor	VEGF
World Health Organization	WHO

Introduction

In 1990, there were approximately 505,000 cancer related deaths in the United States (Boring et al., 1994). In the same year, there were 20,500 new cases of primary brain tumor and 20,700 new cases of metastatic brain tumor. The estimated number of deaths in the United States due to primary brain tumors is approximately 11,000 (Prados and Wilson 1993). The estimated number of 1992 cancer deaths due to metastases from: lung, breast, colon and rectum, and skin was 41,600 (Wright et al., 1993). Gliomas, tumors of transformed glial cells, comprise 50% of all primary brain tumors (Radhakrishnan et al., 1994). The most common forms of glioma are astrocytoma, oligodendroglioma, and glioblastoma multiforme (Laws and Thapar 1993).

Glioblastoma multiforme (GBM) is at the extreme scale of malignant astrocytic tumors. There is a slight proclivity for the disease to occur in males (Schiffer 1993). The mean age for a patient who is diagnosed with GBM is 54 years (Prados and Wilson 1993). In addition to endothelial proliferation, hypercellularity, pleomorphism, and atypical mitotic figures, GBM is characterized by large areas of necrosis which distinguishes it from anaplastic astrocytoma. The tumor is usually located in the white matter of the cerebral hemispheres. They occur in many different regions of the cerebral hemispheres including the: frontolateral,

temporolateral, parietodorsal, and occipitodorsal regions. GBM can also occur in the corpus callosum, basal ganglia, and the thalamus. GBM is also characterized by their infiltrative nature, as they are known to actively invade the cortex and white matter (Schiffer 1993). GBM has been classified by the World Health Organization (WHO) as a Grade IV tumor (Kleihues et al., 1993). Over a ten year period, Salcman et al. (1994) treated 289 patients (73.7% Grade IV and 26.3% Grade III) who had gliomas. Fifty-three patients received only surgery and radiation therapy, and an additional 74 patients were also given some form of nitrosourea chemotherapy. In 113 cases, the patients were administered some form of experimental drug therapy, surgery, and radiation therapy in addition to or in place of nitrosourea. Thirty-seven patients were given interstitial implants in addition to surgery, radiation therapy, and chemotherapy. Also, 58% of the patients underwent repeated surgery at some point during their clinical course. Of the patients who underwent surgery and radiation therapy, those that were less than 40 years of age had a median survival of 20 months, and patients who were older than 40 years had a median survival of 7 months. Patients under the age of 40 who were given nitrosourea chemotherapy in addition to surgery and radiation therapy had a mean survival of 26 months, and the patients who were older than 40 had a median survival of 11 months. In the group of patients who underwent experimental drug therapy, patients under the age of 40 had a median survival of 24 months, and

those that were over 40 years had a median survival of 14 months. Of the 37 patients who also underwent interstitial implants, patients under the age of 40 had a median survival of 29 months, and patients over the age of 40 had a median survival of 14 months. In this study, patients with Grade III tumors who were younger than 40 years (n=27) had a median survival of 37 months, and those who were older than 40 years (n=49) had a median survival of 15 months. Patients with Grade IV tumors who were younger than 40 years (n=62) had a median survival of 24 months, and those who were older than 40 years (n=151) had a median survival of 12 months. Those patients who underwent repeated surgery had an additional survival time of 9 months.

Anaplastic astrocytoma (AA) is a malignant brain tumor that has been classified as a Grade III tumor by the WHO (Kleihues et al., 1993). The median age for individuals diagnosed with anaplastic astrocytoma is 45 years (Prados and Wilson 1993). As with GBM, there is a slight tendency for AA to occur more often in males (Zülch 1986). Compared to lower grade astrocytomas (Grade I and II), AA is more infiltrating, and they show a greater propensity to invade the cortex (Schiffer 1993). AA is characterized by moderate hypercellularity and moderate pleomorphism. They also undergo vascular proliferation which is inversely related to the length of survival. AA lacks necrosis (Jellinger 1987).

For patients with GBM or AA, surgery is usually performed in order to remove as much of the tumor as safely

possible, to alleviate symptoms, to make a diagnosis, and to preserve life. However, due to the infiltrative nature of these tumors, surgery is not able to remove 100% of the tumor. In patients with GBM and AA, surgical resection is usually followed by radiation therapy (Prados and Wilson 1993). Different radiation therapy regimens have been studied. Some investigators favor whole brain radiotherapy while others prefer partial brain irradiation. Conventional radiotherapy has been defined as a tumor dose of 50-60 Gray (Gy) given in single fractions of 1.8-2.0 Gy per day, 5 days per week (Sheline 1990). A Gray is the unit by which the quantity of radiation is expressed. One Gray is equal to 1 Joule/kilogram which is also equal to 100 rad.

Dosimetry is the determination of how much dose should be deposited within different biological tissues. It is both a crucial and a complex aspect of radiotherapy. Many variables are considered when determining dosage. The target volume is an import factor used to determine the radiation dosage. Also, there are many different sources of radiation in use. Some of the sources produce radiation by decay; therefore, the half-life of the source whether it is iodine-125 (60.2 days) or cobalt-60 (5.3 years) is an important element of dosimetry.

Computed tomography (CT) and magnetic resonance imaging (MRI) produce anatomic images in multiple planes using x-rays and high frequency radio waves respectively (Khan 1994). Computed tomography relies upon the attenuation of x-rays

within tissue. Attenuation is the removal of x-ray photons from the beam. There are many different attenuation properties within tissue. Regions of brain edema and necrosis are areas of low attenuation and hypodensity. Compared to edema and necrosis, gliomas are regions of greater attenuation. By their very nature, they are hypercellular; therefore, they appear as regions of hyperdensity on CT (Lee et al., 1992).

Magnetic resonance imaging relies upon the abundance of protons within the body. The protons are present in the form of water. At equilibrium, there is a net magnetization of the proton nuclei in a parallel direction. Excitation in the form of a radio wave provides torque to the longitudinal magnetization vector. There is a decrease in the longitudinal magnetization and an increase in the transverse magnetization. Once the radio wave is turned off, there is a loss of the excitation energy to the overall thermal environment, termed spin-lattice interactions. The time course associated with the recovery of longitudinal magnetization is T1. Also, there is an exchange of energy between neighboring nuclei termed spin-spin interactions. The time course for the loss of transverse magnetization is T2. In tumors and areas of edema, water is widely dispersed; therefore, the ability of the protons to impart energy to their environment is poor. This is manifest as a slow decay of the excited state and a low signal. Subsequently, tumors and edematous tissue appear dark on T1 weighted MRI. Solid

tissues are able to give up energy more rapidly because there is a more direct coupling between molecules. This results in: a rapid decay of the excited state, a high signal, and the appearance of solid tissue as lighter areas on T1 weighted MRI. On T2 weighted MRI, tumors and edematous tissue appear as lighter regions while solid tissues appear darker (Lee et al., 1992).

Contrast enhancing substances such as iodine and gadolinium are used in CT and MRI respectively. The presence of contrast enhancement indicates a disturbance in the blood brain barrier. Normal brain vasculature has an intact blood brain barrier composed of tight junctions between endothelial cells, a surrounding basement membrane, and an investment of astrocytic foot processes. Regions of the brain where there is GBM or AA usually tend to contrast enhance, corresponding to endothelial proliferation and neovascularization (Woodruff 1993).

Determining the microscopic margins of the target is impossible even with the best CT and MRI available; therefore, the radiation therapy target must include a margin beyond the target defined by CT or MRI. At the University of California San Francisco, the target volume includes at least 3 cm beyond that indicated by CT and 2 cm beyond what is determined by MRI. There are many prognostic factors of success related to the radiation therapy of GBM and AA including: tumor necrosis, age, Karnofsky performance status, extent of resection, and decrease in tumor size after

radiotherapy (Sheline 1990).

Metastasis is defined as a migration in the blood and lymphatic system of tumor cells that gives rise to tumors elsewhere in the body (Mahadevan and Hart 1990). The incidence of cerebral metastases varies from 2.8 to 11.1 per 100,000 (Schiffer 1993). Autopsy studies have shown that up to 50% of people dying of cancer will possess intracerebral metastases, of these 40% are single lesions (Pickren et al., 1983). Tumors of the skin, breast, lung, kidney, and the digestive tract are responsible for 95% of cerebral metastases. Metastases from lung cancer are the most prevalent, representing more than 50% of all cerebral metastases. There is a tendency for cerebral metastases to occur in males; the incidence is 9.7 per 100,000 for males and 7.1 per 100,000 for females. Approximately 80%-86% of cerebral metastases are localized supratentorially within the frontal, temporal, and parietal regions (Schiffer 1993).

Metastases from melanoma and renal cell carcinoma are considered to be radioresistant, while those from adenocarcinoma and squamous cell carcinoma are classified as radiosensitive (Loeffler et al., 1991). The median survival of patients with a cerebral metastasis is usually only a few months if left untreated. During this period there is a progressive neurological deterioration (Engenhart et al., 1993). Maor et al. (1988) treated 39 patients who had renal cell carcinoma metastatic to the brain with whole brain irradiation (30 Gy in ten fractions). Of the 33 patients who

were followed-up, 23 patients did not respond or deteriorated. Ten patients responded to the radiotherapy and had a median survival of 17 weeks. The entire treatment group had a median survival of 8 weeks. Vecht et al. (1993) treated 31 patients who had a single metastasis to the brain with whole brain irradiation (2 fractions per day of 2 Gy each for a total of 40 Gy). The origin of the metastases were: lung (n=16), breast (n=6), renal cell (n=1), melanoma (n=4), and others (n=4). The patients had a median survival of 6 months.

Patchell et al. (1990) conducted a randomized trial of surgery and radiotherapy in the treatment of single metastases to the brain. One group underwent a treatment of surgical removal of the brain tumor followed by whole-brain radiation therapy (surgical group). The second group of patients underwent needle biopsy and whole-brain radiation therapy (radiation group). The results indicated that the recurrence at the site of the original metastasis was less frequent in the surgical group than in the radiation group (5 of 25 [20%] versus 12 of 23 [52%]. The overall length of survival was significantly longer in the surgical group (median 40 weeks versus 15 weeks in the radiation group; $P<0.01$). Also, the patients treated with surgery remained functionally independent longer (median, 38 weeks versus 8 weeks in the radiation group; $P<0.005$).

In order to measure a patient's quality of life, most clinicians will make an evaluation using the Karnofsky

Performance Score (KPS) (Karnofsky 1945). The KPS ranges from 100% to 0% (Table 1).

X-rays were discovered by Roentgen in 1895. Since then, radiotherapy has played an integral role in the treatment of cancer. Radiotherapy has become the standard post-operative procedure for patients with malignant astrocytomas and metastases. Recently, radiosurgery (Linear Accelerator and Gamma Knife) has been introduced into the United States, and many hospitals have been using this procedure to treat a myriad of lesions. This paper is being written to explore the role of radiosurgery in the treatment of malignant brain tumors. Also, the biological and physical principles that underlie radiosurgery will be discussed. Furthermore, this paper will review many of the radiosurgical studies that have been performed in the treatment of malignant brain tumors. Finally, an experiment will be proposed to study the effects of growth factors on the total obliteration time course of a rat model for arteriovenous malformations.

Table 1

From: Karnofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. In MacLeod CM ed. Evaluation of Chemotherapeutic Agents, Columbia University Press, New York, 191-205, 1945.

Karnofsky Performance Score

Percentage	Comments
100%	Normal, no complaints, no evidence of disease.
90%	Able to carry on normal activity, minor signs or symptoms of disease.
80%	Normal activity with effort, some signs or symptoms of disease.
70%	Cares for self. Unable to carry on normal activity or to do active work.
60%	Requires occasional assistance, but is able to care for most needs.
50%	Requires considerable assistance and frequent medical care.
40%	Disabled, requires special care.
30%	Severely disabled, hospitalization is indicated, although death is not imminent.
20%	Hospitalization necessary, very sick.
10%	Moribund.
0%	Dead.

Radiobiology

The goal of radiation therapy is the sterilization or loss of reproductive integrity of malignant cells (Weichselbaum 1993). The primary cellular event that results from radiotherapy is DNA damage which can be classified as: double-strand breaks, single-strand breaks, cross-linking of DNA to DNA or to other molecules, or base damage. Repair may be undertaken in some tumor cells by enzymatic systems such as nucleases and ligases (Schiffer 1993). Unrepaired or misrepaired double strand breaks are believed to be the critical component involved in producing proliferative cell death. Proliferative cell death will eventually result in necrosis and degeneration of target tissues of radiotherapy (Larsson 1992).

Gamma rays and X-rays are classified as low linear energy transfer radiations which yield relatively low doses of energy along their path (0.3-2.0 keV/micrometer). When photons interact with water, they produce free radicals (OH· and H·) which damage DNA by extracting hydrogen ions. This is termed indirect DNA damage. Under hypoxic conditions, reducing agents such as sulfahydryl compounds may repair the damage. Direct killing of cells generally involves radiation doses in excess of 100 Gy and has been termed interphase death (Schiffer 1993). Interphase death is characterized by the lysis and destruction of the cell at approximately one to

four hours after irradiation. Interphase death does not require the cell to pass through mitosis. The most likely targets include cellular or nuclear membranes. It has been hypothesized that damage to mitochondrial membranes could have an adverse effect on energy production. Also, a breakdown of the lysosomal membranes would cause internal lysis of the cell. The targets for direct damage are primarily nondividing cells such as neurons (Kilmer 1994).

Within the cell cycle, cells in mitosis (M phase) or those in late G_2 phase are radiosensitive. Cells which are in the late S phase are radioresistant (Hall 1991). Tumor cells by their very nature undergo a high rate of mitosis. All tumor cells are thought to contain a population of hypoxic cells (up to 15%). Hypoxic cells are not present in normal brain tissue. They are more radioresistant than oxygenated cells. In order to produce the same radiobiological effect, hypoxic cells must be subjected to a radiation dose three times larger than that required by oxygenated cells. This has been termed the oxygen enhancement ratio (Schiffer 1993).

When a cell is irradiated by either X-rays or gamma rays, some portion of cells do not undergo lethal damage. These cells have endured sublethal damage which can be repaired usually within an hour. However as the radiation dosage is increased, the proportion of cells which are lethally damaged increases. Therefore, the proportion of cells which are able to undergo repair decreases (Schiffer

1993).

The reactions of the brain to irradiation can be placed into three categories. An acute reaction may occur during the course or a few days after irradiation. This reaction manifests itself through uncharacteristic headache and signs of increased intracranial pressure such as nausea and vomiting. The symptoms are generally reversible within hours. The early-delayed reaction occurs within a few weeks or months after radiotherapy. This reaction is characterized by lethargy and somnolence. The effects are temporary in nature, and they may be reversible within a few weeks without treatment. Late reactions generally manifest themselves within months or years after irradiation. The results are usually irreversible, progressive, and they eventually lead to death. Late reactions result in vascular damage, necrosis, and perifocal edema (Sauer 1987).

When the brain is irradiated with high doses (14-70 Gy), the first cell populations to be eradicated are those with the highest rate of mitosis. Within normal brain tissue, endothelial and oligodendroglial cells are the most sensitive to the effects of irradiation (Larsson 1992). Oligodendroglial cells are involved in early delayed radiation damage. Endothelial cells are identified with late delayed radiation injury (Rosander et al., 1991).

The term radioresistant describes a tumor cell that is able to repair damage or produce self replacement at a rate equal to the surrounding normal brain tissue. High-grade

astrocytoma cells are considered to be very radioresistant (Sauer 1987). One of the objectives of radiosurgery is to overcome the radioresistance of certain malignant brain tumors. Radiosurgery enables the delivery of high doses of radiation (gamma rays or X-rays) to a stereotactically demarcated target without exposing the surrounding normal brain tissue to toxic doses of radiation (Alexander and Loeffler 1992).

Interstitial Brachytherapy

Interstitial brachytherapy is an invasive procedure which allows for the stereotactic delivery of tumoricidal doses by radioactive sources which are implanted directly into the tumor. In the United States, the procedure was first used to treat malignant gliomas at the University of California San Francisco in 1977. Radioactive sources that have been used include: gold-198, iridium-192, and iodine-125. Two advantages of interstitial brachytherapy include: a sharp dosage drop off as the distance from the tumor increases, and the favorable radiation biology of a low dose rate of irradiation (approximately 0.4 to 0.6 Gy per hour) (McDermott et al., 1991). Interstitial brachytherapy trials have been conducted in the initial management of patients with glioblastoma (Loeffler et al., 1990b). Also, this treatment modality has been used to treat patients with recurrent malignant gliomas (Leibel et al., 1989).

Generally speaking, proliferating cells are most sensitive to radiation at the G_2 and M phases of the cell cycle. During the continuous low dose irradiation emitted in brachytherapy, cells in the resistant phases of the cell cycle may proceed to the sensitive phases. This phenomenon of redistribution allows for a more effective killing of tumor cells. It has been hypothesized that the total dose

per cell cycle is an important factor in halting mitosis. In vivo and in vitro studies have shown that most cell systems require between 7.2 and 9.9 Gy per cycle to inhibit mitosis. Since most brachytherapy protocols use a dose rate of between 0.4 and 0.6 Gy per hour, and malignant gliomas have cell cycle times anywhere between 24 and 120 hours, the delivered dosage will usually be above the critical value for inhibiting cell mitosis (McDermott et al., 1991).

The most popular isotope in North America is iodine-125. The isotope is absorbed onto resin balls and surrounded by a 0.05 mm thick titanium capsule that is approximately 4 mm in length and 0.8 mm in diameter. This conformation is what makes up the so called "seeds". There are two forms of the ^{125}I seeds: high activity (10-50 mCi) seeds which are used for cerebral metastases and malignant gliomas, and low activity (0.5 mCi) which are used for the permanent implantation of skull base neoplasms. A Curie (Ci) is a unit by which activity is measured. One Curie is equal to 3.7×10^{10} disintegrations per second. The iodine-125 isotope decays by electron capture with the subsequent emission of gamma rays, x-rays, and electrons. The electrons and the x-rays are absorbed by the titanium capsule. The gamma rays that are emitted have an energy of between 27 and 35 keV (McDermott et al., 1991).

What is Radiosurgery?

In 1951, Lars Leksell innovated stereotactic radiotherapy of the brain (Leksell 1951). The technique utilized a stereotactic apparatus that he developed in 1949 (Leksell 1949) and a collimated 200 kilovolt x-ray tube. This apparatus allowed the beams to enter the brain throughout the convexity of the skull and converge upon the targeted structure (Leksell 1951).

Presently, the term radiosurgery is used to describe a noninvasive procedure using a single fraction of radiation that can usually be performed on an outpatient basis. The purpose of radiosurgery is to deliver a high dose of radiation to an intracerebral target without the exposure of adjacent normal tissue to clinically significant doses of radiation. Most of the cerebral neoplasms that have been treated with radiosurgery are recurrent or inoperable. A tumor is considered to be inoperable if it is deeply localized, or if the patient's condition (example, respiratory or cardiac disease) preclude craniotomy (Larson 1990). The two most widely used devices for radiosurgery are the gamma knife and the linear accelerator. The gamma knife uses gamma radiation emitted by the beta decay of cobalt-60. The linear accelerator produces x-rays by microwave power (Bova 1990). Both devices have been used to treat benign and malignant brain tumors such as: meningiomas, metastases,

anaplastic astrocytomas, and glioblastoma multifome. The majority of the treatments have been for vascular malformations such as arteriovenous malformations and angiographically occult vascular malformations (Larson 1990). Arteriovenous malformations (AVM) are fistulous communications between cerebral arteries and veins (Okazaki 1989). Additional information concerning AVM may be found on page 68.

The general protocol involved with treatment with either the gamma knife or linear accelerator is similar. A stereotactic frame is attached to a patient's head using four pins placed circumfrentially 1" above the supraorbital line. The regions where the pins are placed are injected with 10 cc of local anesthetic (lidocaine-1% and epinephrine-0.5%). If an arteriovenous malformation is being treated, biplane angiography of the main vessels supplying the lesion is conducted. This is followed by an enhanced CT scan, performed with a CT localizing frame attached to the head ring. A series of 1.5 mm transverse CT slices are taken through the lesion. For brain tumors, an enhanced CT and or an MRI is taken (Shields et al., 1993). Prior to the development of computed tomography in the 1970s and magnetic resonance imaging in the 1980s, radiosurgical procedures were dependent upon the localization of tumors via angiography or skull roentgenography (Lunsford and Kondziolka 1993).

After the imaging tests have been conducted, a team consisting of neurosurgeons, radiation oncologists,

neuroradiologists, and medical physicists generates a treatment plan. The treatment plan is devised using computer software and the data obtained from the imaging tests. The volume of the lesion or brain tumor and its stereotactic coordinates are determined. The neurosurgeon and the radiation oncologist determine the radiation dose. Isodose distributions and the characteristics of the treatment arcs are determined by the treatment planning system (Shields et al., 1993).

LINAC Radiosurgery

During the 1950s, linear accelerators (LINAC) were developed simultaneously in the United States and in the United Kingdom. Linear accelerators accelerate electrons to near the speed of light. Microwaves with frequencies in the 3-GHz range are used to accelerate the electrons which takes place on a wave guide. The electrons are injected onto the microwaves at an energy of between 30 to 50 kilovolts, which is roughly 30% of the speed of light. The wave guide concentrates the electrons onto a portion of the wave where they can be most efficiently accelerated. The maximum energy of this acceleration is dependent upon the design of the linear accelerator. Energies ranging from 4 MV (99.5% of the speed of light) to 25 MV (99.97% of the speed of light) are commonly used. The electrons are then focused onto a heavy metal target. The electrons lose energy as they come into contact with the heavy metal target. The majority of the energy is lost as heat, but there is an element of radiative loss. The radiative loss of the electron's energy is a result of an interaction between the high velocity electrons and the large nuclei of the heavy metal target. This interaction produces a deflection of the electron and a subsequent change in its acceleration. The result of this radiative loss is the emission of x-rays or photons. The x-rays are focused by primary and secondary collimators (Bova

1990).

Linear accelerators are the most commonly used devices in conventional radiotherapy. A linear accelerator consists of a gantry which houses the photon producing appratus and a couch which is used to position the patient. During the treatment process, the gantry rotates around the patient delivering the prescribed dose of radiation. Since they have been in use for decades, linear accelerators are designed and produced to meet very stringent standards (Friedman et al., 1992).

In February of 1986, doctors at the Brigham and Women's Hospital in Boston treated the first radiosurgery patient with a modified 6 MeV linear accelerator (Alexander and Leoffler 1992). The very first patient treated was a 31 year old woman with a left motor strip AVM (Alexander, personal communication). Lutz and Winston (1988) developed various modifications to the Boston linear accelerator that enabled its use in treating small, precisely located lesions (0.5 to 8 cc) within the brain. They developed a collimation system (Figure 1) that enabled the collimators to be placed closer to the isocenter (approximately 23 cm) than the conventional linear accelerator (70 cm). The conventional collimator system was inadequate for radiosurgery because small movements of the radiation source would result in magnified movements of the beam at the isocenter. The newly devised collimator system was designed to accept one collimator insert ranging from 2.5 mm to 30 mm in 2.5 mm increments

(Figure 2). This would enable a very precise enclosure of the target within the isodose lines. During treatment, the patient's body is supported by the couch while the head is supported by the Brown Roberts Wells (BRW) floor stand via the BRW head ring (Figure 3). The stand is mounted to the plate of the couch floor bearing. This system enables rapid, accurate, rigid, and reproducible setups. The stand has a mechanism which enables the patient's head to be moved to the desired cartesian coordinates (antero-posterior, lateral, and vertical). The development of the Gill Thomas Cossman relocatable head holder (Figure 4) allows fractionated stereotactic radiosurgery to be performed. During the different fractions, the accuracy of the head hold position can be checked using a depth helmet and a depth probe with a millimeter scale (Figure 5). The BRW system can be used in conjunction with a BRW localizer frame to precisely identify the target via CT. Localization of an arteriovenous malformation is via angiography using a specially designed localizer box and the BRW localizer system. The imaging procedures allow for the precise stereotactic localization of the intracerebral target.

A very important result of the linear accelerator modifications developed by Lutz and Winston (1988) is the capability to verify the alignment of the setup. A steel ball is used to represent the intracranial target at the exact isocenter. The steel ball is localized in the precise cartesian coordinates as the patient's lesion (Figure 6).

The verification procedure exposes film to the linac x-rays at a combination of at least eight possible gantry and turntable positions. If the steel ball is centered within the acceptable limits of all eight exposures, it can be concluded that setup is correct and properly aligned (Figure 7). The verification procedure can detect such errors as: a misalignment of the collimator insert or the BRW stand, or an incorrect setting of the cartesian coordinates. Basically, this verification procedure checks all aspects of the treatment except localization of the lesion via computerized tomography or angiography (Lutz and Winston 1988).

Lutz and Winston (1988) also calculated the accuracy of the imaging sources and the precision of the linear accelerator beam. They found that localization via CT resulted in an error of 1.3 ± 0.7 mm. Angiography produced a smaller margin of error of 0.2 ± 0.2 mm. The linear accelerator produced an isocenter localization error of 0.48 ± 0.16 mm.

Other linear accelerator centers have made changes that decreased the isocenter localization error produced by the LINAC. At the University of Florida, Friedman et al. (1992) designed a system that produced a localization error comparable to any existing radiosurgical system. During treatment, the prescribed treatment arc is produced by rotating the gantry from a vertical to a horizontal position.

Due to the weight of the gantry, this movement causes a sagging of the gantry resulting in a misalignment of the

collimator. This misalignment will result in a photon beam that is focused below the isocenter. Also, error is introduced into the treatment plan when the patient is repositioned between arcs. To solve these problems, they devised a system of high-precision bearings. The bearing system for the gantry and the patient rotational device were mechanically coupled to ensure that both rotational axes coincided. Also, another bearing system was devised for the collimator that effectively separated it from the gantry and avoided any transfer of torque between the gantry and the collimator. The three bearing systems produce an isocenter accuracy of 0.2 ± 0.1 mm (Friedman et al., 1992). This is approximately 1% of the average beam diameter used in linear accelerator radiosurgery (Bova 1990).

The treatment planning phase is the most critical aspect of radiosurgery. The treatment team consists of neurosurgeons, radiation oncologists, radiation physicists, and neuroradiologists. There are many objectives which must be met during the planning phase. One of the most important decisions to be made is what dosage should be used. This determination is generally made by the neurosurgeon and the radiation oncologist (Podgorsak 1992). The radiation oncologist may rely upon past experience or published clinical trials to determine the dosage. When prescribing a dosage, factors such as the target's shape and volume, the collimator size, and dose inhomogeneity are considered. Also, the risk of brain necrosis is an important factor when

determining radiation dosage.

Dose inhomogeneity plays a crucial role in the resulting complications of radiosurgery. The total dose inhomogeneity (TDI) is defined as the difference between the maximal tumor dose and the minimal tumor dose (Nedzi et al., 1991). Dose inhomogeneity may result from treating larger or irregularly-shaped targets. The collimators used in both linear accelerator and gamma knife radiosurgery produce a spherical dosage distribution. Some lesions may not conform to a spherical shape; therefore, multiple isocenters can be used to more fully circumscribe the target. In LINAC radiosurgery, multiple isocenters are created by moving the convergence of radiation beams a predetermined distance between treatments. This will cause an overlapping of radiation fields. Certain regions of the treatment volume will receive more than two to three times the dose of the single isocenter (Nedzi et al., 1991). Inhomogeneity may seem to be an insignificant factor if the tumor volume contained only tumor cells, but some tumors and treatment designs include normal tissue within the target volume. Nedzi et al. (1991) treated 64 recurrent or inoperable intracranial tumors in 60 patients (40 primary, 24 metastatic) with a 6 MeV linear accelerator. They determined that tumor dose inhomogeneity was the most significant factor related to complications due to toxicity. Other variables that were highly correlated with tumor dose inhomogeneity included: maximum tumor dose, number of isocenters, maximum normal tissue dose, and tumor volume. They determined that a

low risk of complications existed for lesions with volumes less than 10 cc treated with a single isocenter with a maximum dose of 25 Gy and a minimum tumor dose inhomogeneity of less than 10 Gy.

During LINAC radiosurgery, the tumor is surrounded by a beam of x-rays whose diameter is determined by the size of the circular collimator. Collimator sizes range from 5 to 40 mm in diameter (Friedman et al., 1992). The photon beams all intersect at the target from a number of noncoplanar arcs. This causes the tumor to be surrounded in three-dimensions by the photon beam, usually in the shape of a sphere (Podgorsak 1992). The geometric center of the tumor is the usual isocenter, i.e. the point where 100% of the prescribed dose is concentrated. Moving away from the geometric center of the tumor toward the outlying normal tissue, there is a decrease in the radiation dose. The concentrations of radiation throughout the tumor and normal tissue is represented by isodose lines. During the planning procedure, there is a superposition of isodose distributions on the CT, MRI, or angiographic images which have been transfered to a computer via magnetic tape (Figure 8). This enables the team to view in three dimensions the path of the photon beam (Podgorsak 1992). The arcs are defined in terms of arc-start angle, arc-end angle, and couch angle. Each arc may contribute an arbitrary fraction of the total dose to the target. If they find that the beam is going through any critical or dose sensitive structures such as the optic

nerves and chiasm, eyes, area postrema, or the brain stem, they must modify the arcs (Alexander and Loeffler 1992).

The presence of a sharp dose fall-off immediately outside of the target is another objective that must be met. This enables only the target to receive biologically significant doses of radiation while the outlying normal brain tissue is spared from high doses of radiation (Podgorsak 1990).

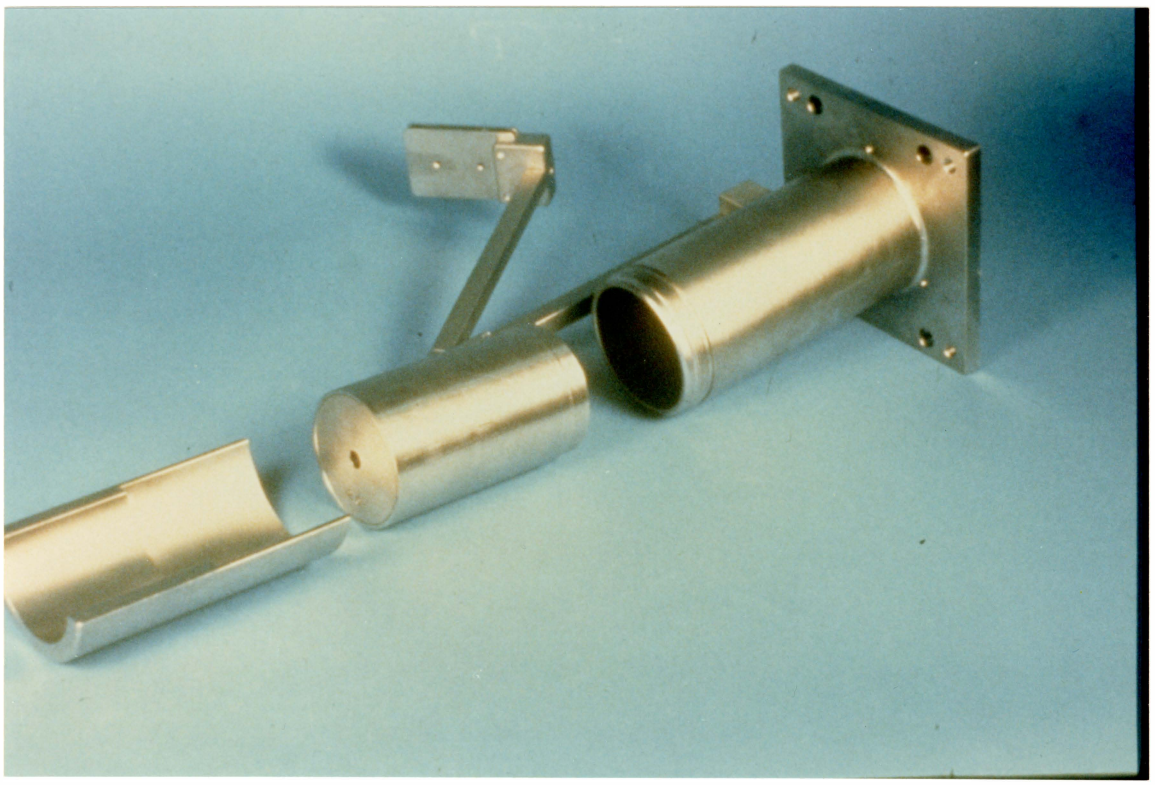

Figure 1: Linear Accelerator Collimation System (Courtesy of Radionics Inc., Burlington, Massachusetts).

Figure 2: Collimator Inserts (Courtesy of Radionics Inc., Burlington, Massachusetts).

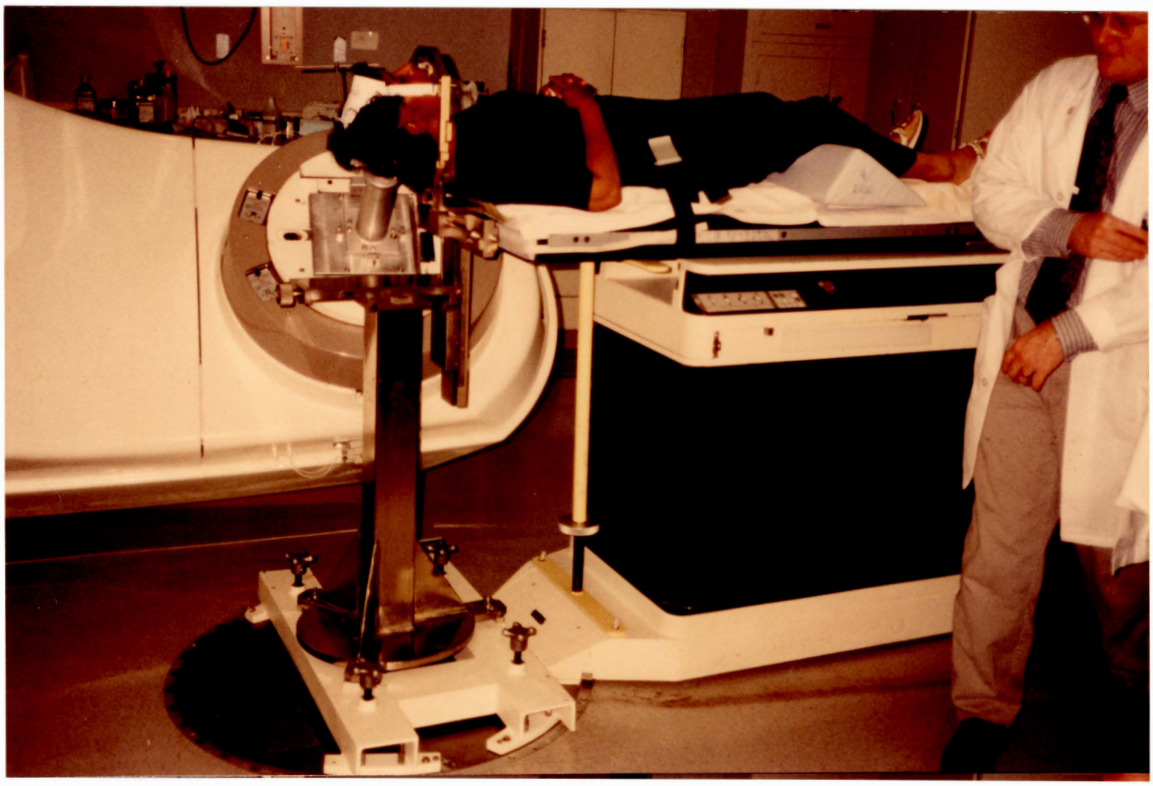

Figure 3: Brown Roberts Wells Floor Stand and Head Ring.

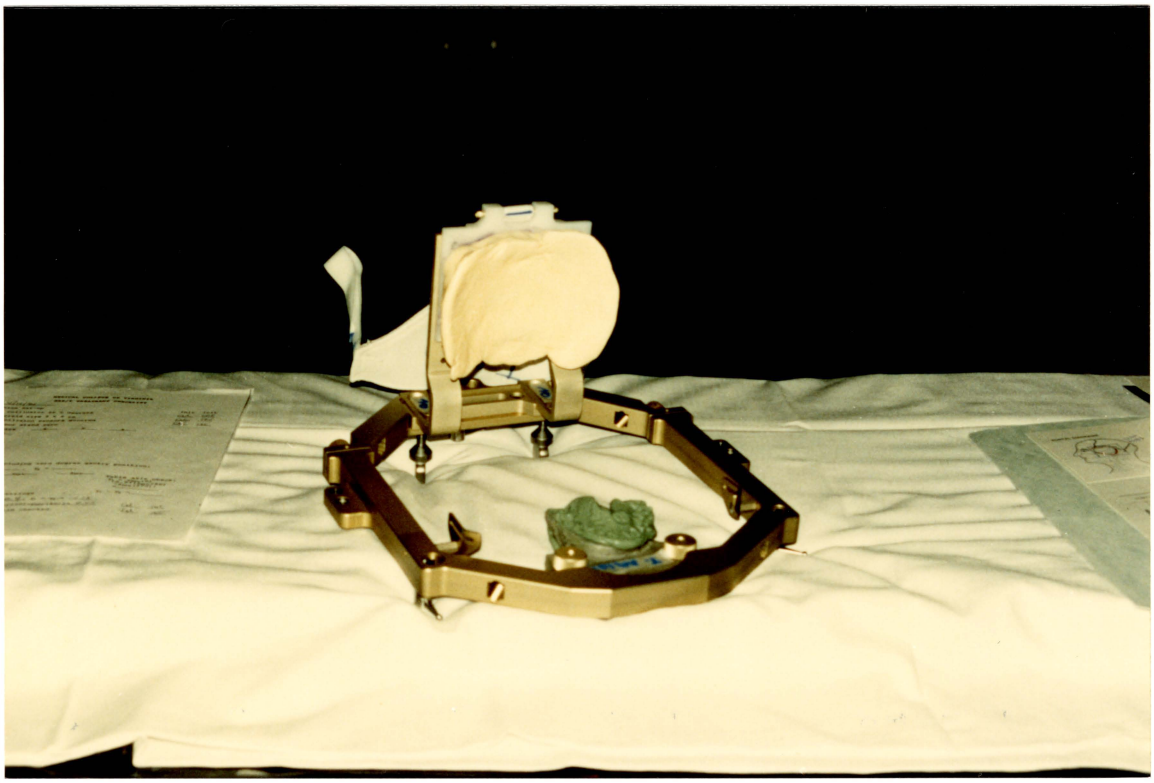

Figure 4: Gill Thomas Cosman Relocatable Head Holder.

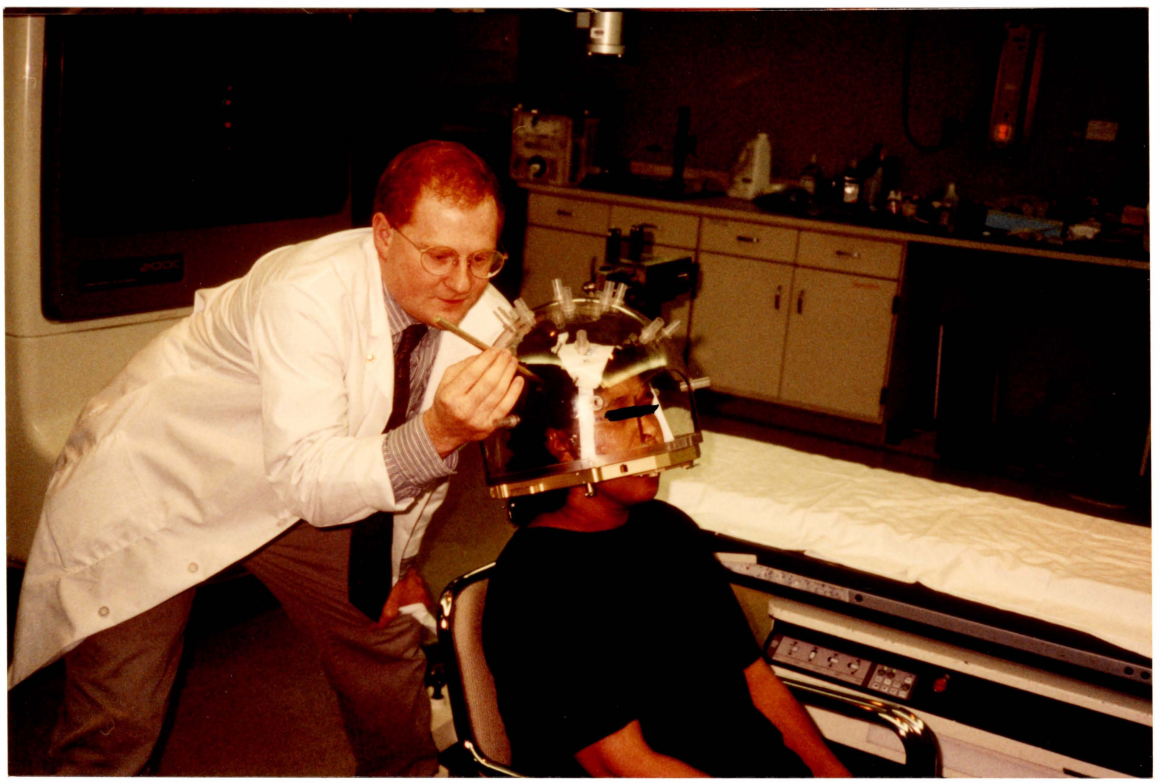

Figure 5: Accuracy of the Head Holder placement being checked via a Depth Helmet and a Depth Probe.

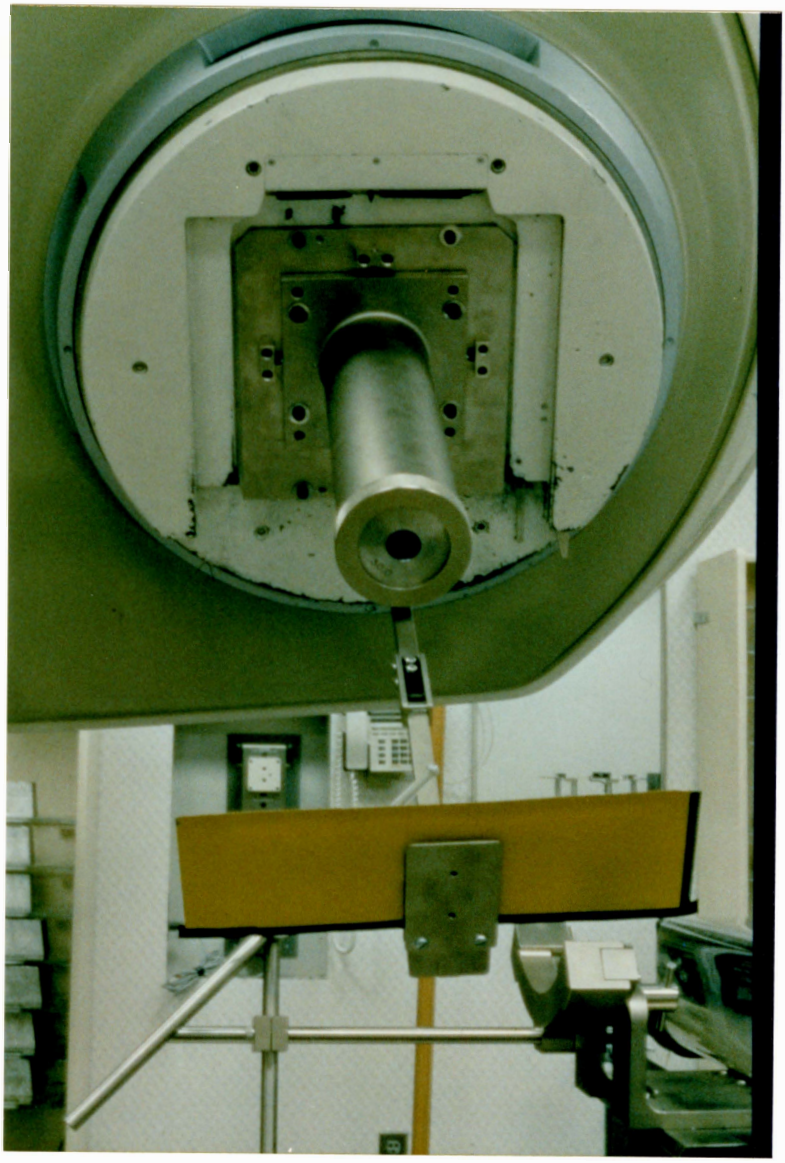

Figure 6: LINAC Verification Procedure (Courtesy of Radionics Inc., Burlington, Massachusetts).

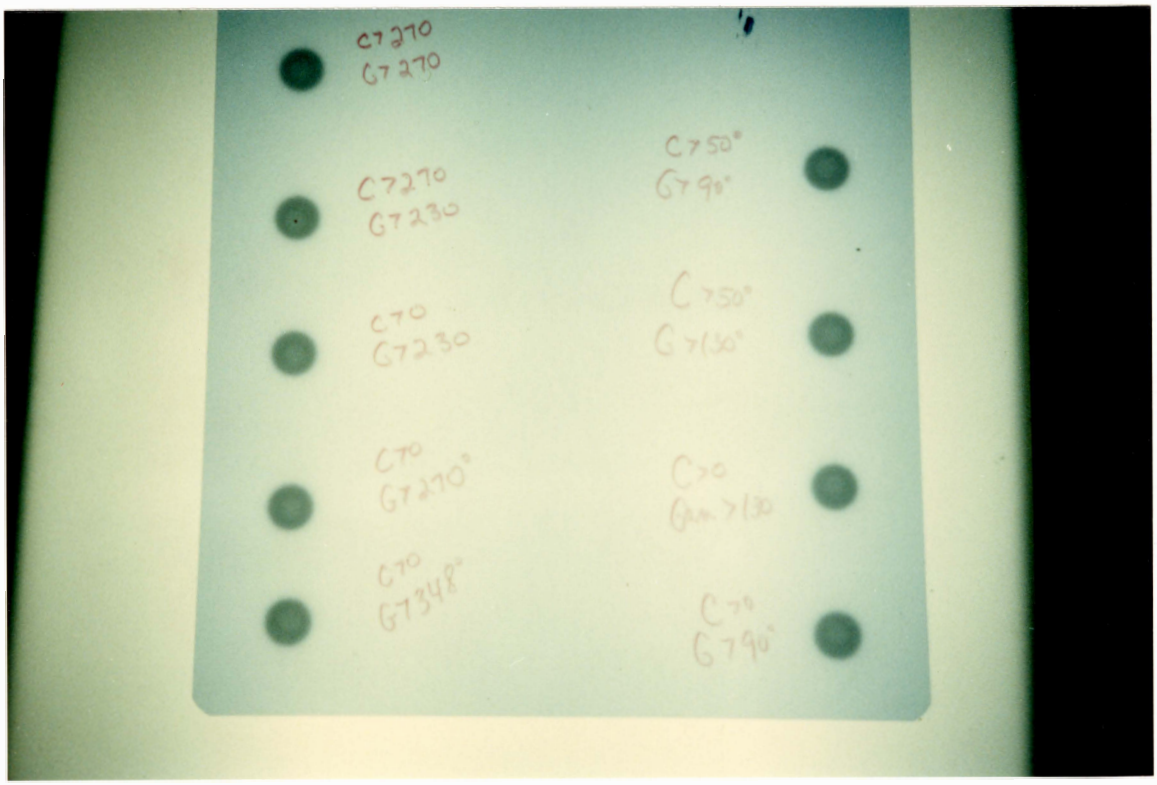

Figure 7: X-ray film of 9 arcs taken during the LINAC Verification Procedure.

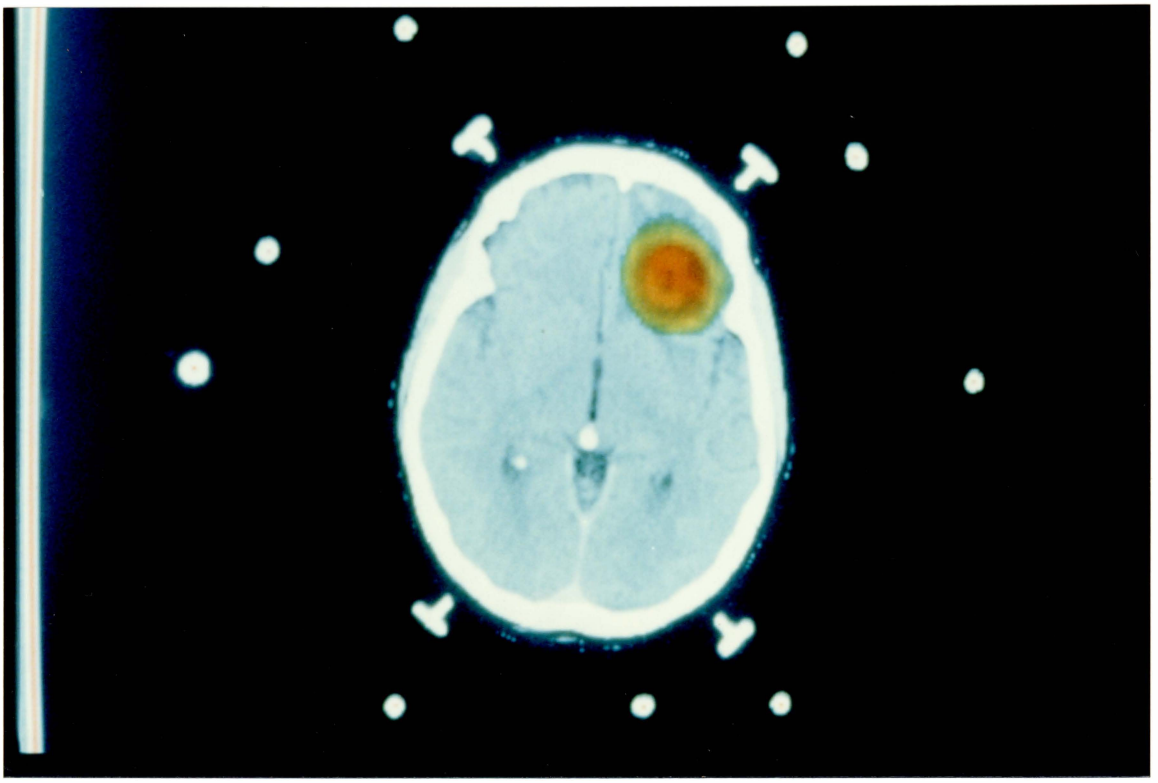

Figure 8: Isodose Distributions. Yellow-red color represents the 80% isodose line. Green represents the 50% isodose line (Courtesy of Radionics Inc., Burlington, Massachusetts).

Theoretical Physics of the Interaction Between Tissue and Photons

As the photon beam penetrates tissue, there is a rapid rise in dosage from a relatively low value at the surface of the skin toward a maximum dosage reached at a depth termed the d_{max}. The d_{max} represents the depth at which the maximum dosage is reached. The region between the surface and d_{max} is termed the dose buildup region. Beyond the depth of maximum dosage, there is an exponential decrease in the dosage. The tissue build-up region depends upon the source. X-rays in the orthovoltage range do not have a tissue buildup region; their maximal dosage occurs at the surface. X-rays with sources of 6 MV and 10 MV have build-up regions of 1.5 cm and 2.5 cm respectively. Gamma rays produced by the beta decay of ^{60}Co have a dose build-up region of 0.5 cm. Photons in the megavoltage range, therefore, exhibit a skin sparing effect (Podgorsak 1992).

The dominant interaction that occurs between the photon and the tissue medium is the Compton interaction (Khan 1994). The photon interacts with the free electrons in the absorbing medium. The photon collides with an outer loosely bound orbital electron. This scatters the incident photon and imparts a kinetic energy upon the electron. These high energy Compton electrons are scattered toward the forward

direction, which imparts a skin sparing effect (Weichselbaum et al., 1993). There is a point in depth where the electrons created near the surface approach the end of their range. At the same point, the decrease in the number of photons will result in a decrease in newly created high-energy electrons. The depth where the electron density will reach its maximum is known at the d_{max} or maximum dose. All other points within the medium will have a lower electron density and therefore a lower dose, called the fall-off region (Bova 1990).

"Boost" versus Single Dose Radiosurgery

Recently, there has been some debate regarding the method by which the prescribed radiation dosage should be delivered to malignant brain tumors. Using radiobiological theory, Hall and Brenner (1993) believe that the delivery of radiation in a single dose to a malignant brain tumor will result in a suboptimal therapeutic ratio. However, they believe that treatment of benign lesions such as arteriovenous malformations is optimal under single fraction radiation dose treatment. Their reasoning is based upon two different radiobiological principles. Malignant tumors of all sizes contain some portion of hypoxic cells. Hypoxic cells are resistant to killing by either X-rays or gamma rays. A single fraction of radiation will kill a larger fraction of the metabolically active (radiosensitive) than the hypoxic cells. After irradiation, a large portion of the tumor is hypoxic. Given a short period of time there will be a re-establishment of the original proportions of oxygenated and hypoxic cells. This allows many of the previously hypoxic cells, which have become metabolically active, to be killed by a second and subsequent fractions of radiation. Although many human tumors have been eradicated with radiotherapy doses of 60 Gy given in 30 fractions, it is not known whether or not human tumors rexoygenate (Hall 1994). Tissues have been classified into two different categories:

late responding and early responding. Arteriovenous malformations and normal brain tissue are said to be late responding tissues. The effects of radiation are manifest weeks to months after the radiation treatment. Malignant tumors are classified as early responding tissues in that they are affected within hours or a few days of the radiation treatment. Due to the differing dose-response relationships of early and late responding tissues, a fractionated treatment schedule will produce a greater sparing effect on late responding normal tissues than would a single dose of radiation. A fractionated treatment will result in less damage to normal brain tissue and a greater degree of malignant tumor cell death than single dose treatment. Since arteriovenous malformations and normal brain tissue are both late responding tissues, there will be no gain in preferential killing of the lesion and sparing of normal tissue via fractionated therapy (Hall and Brenner 1993). One of the advantages of single dose radiosurgery is its ability to kill radioresistant tumors such as metastases from renal cell sarcomas and melanomas. This is because radiosurgery uses a higher single dose of radiation than fractionated radiotherapy. Hall and Brenner (1993) proposed a system using a noninvasive relocatable stereotactic head frame and a treatment plan consisting of five or six fractions. They believe that keeping the number of fractions low will not cause a significant decrease in radioresistant tumor death. This protocol incorporates the advantages of fractionated

radiotherapy with a high tumor dose (Hall and Brenner 1993).

Larson et al. (1993) believe that despite the two radiobiological principles cited by Hall and Brenner (1993) there is little to be gained by fractionating treatments for most small intracranial targets. Larson et al. (1993) developed a graphical model comparing the fractionated dose at 2 Gy per fraction that is required to produce the same radiobiologic effect for a given radiosurgical dose. The graph included late and early responding tissues. Their reasoning is based upon the differing composition of malignant tumors (early responding tissue). Malignant tumors can be embedded within late responding normal tissue as is the case with low grade astrocytomas. The term embedded means that the target contains malignant tumor tissue and normal brain tissue. Also, malignant tumors can be surrounded by late responding normal tissue which would include GBM and metastases. Within low grade astrocytomas, reside normal glial cells, neuronal cell bodies, axons, microglia, and blood vessels. With a single treatment dose of 30-40 Gy, the malignant tissue experiences a radiobiologic effect of 50-100 Gy of fractionated radiotherapy. The normal tissue within the target experiences the radiobiologic effect of 100-200 Gy of fractionated radiotherapy (Larson et al., 1993). Although Pozza et al. (1989) reported a favorable therapeutic ratio in the treatment of low grade astrocytomas with radiosurgery, few, if any low grade astrocytomas are being treated with radiosurgery in North America (Larson et

al., 1993). GBM and metastases fall into the category of early responding tissue surrounded by late responding normal tissue. There is little if any normal brain tissue within the target. During radiosurgery, the target receives 20-40 Gy which is radiobiologically equivalent to 50-100 Gy of fractionated radiotherapy. The normal brain tissue in the areas immediately surrounding the target receive 5-10 Gy during radiosurgery which is radiobiologically equivalent to 10-30 Gy of fractionated therapy. In general, malignant tumors that are treated with radiosurgery are exposed to a high dose of radiation. The surrounding normal tissue receives a significantly lower dose of radiation.

Different LINAC Radiosurgical Techniques

Currently, there are three methods of linear accelerator radiosurgery in use; the techniques vary with regard to their dose gradient drop-offs. The degree of radiation dose drop off is an important consideration in evaluating a radiosurgical system. Dose regions below 20% are not considered to be significant (Podgorsak et al., 1989). One of the goals of radiosurgery is the deposition of a high dose of radiation to the target while subjecting adjacent normal tissue to biologically insignificant doses of radiation. Podgorsak et al.(1989) calculated the dose drop-offs for various systems based upon a spherical target with a 1 cm diameter. Please see Table 2 for a comparison of the dose fall-offs.

Single plane rotation (Houdek 1985) is almost identical to the rotational techniques used in standard rotational radiotherapy. Single plane rotation differs in that the dose is given in a single session, a stereotactic frame is used for treatment, the radiation field is smaller, and the patient is immobilized during therapy. During treatment, the gantry rotates around the patient in a 360° arc (Podgorsak 1992). The dose fall-offs that occur in the plane perpendicular to the plane of rotation are very steep. From the 90% isodose line to the 50%, 20%, and 10% isodose lines the distances are 2.0 mm, 2.5 mm, and 3.0 mm respectively.

However, the dose fall-offs in the plane of rotation are very shallow. This is because there is an infinite number of parallel opposed beams. During the 360° rotation, the entry pathway for one beam coincides with the exit of another beam. From the 90% isodose line to the 50%, 20%, and 10% isodose lines the distances are 3.5 mm, 14.4 mm, and 32.0 mm respectively (Podgorsak et al., 1989).

Varying numbers of multiple noncoplanar converging arcs are in use at many different linear accelerator facilities. This technique involves a different treatment couch position for each arc which allows the dose to be spread out over as large a volume as possible. The arc angles are usually smaller than 180° to avoid parallel opposed beams. Lutz and Winston (1988) used a system of 4 converging noncoplanar arcs. One arc (couch angle = 0°) is in the transverse plane from ø = 50° to ø = 310°. Three 100° arcs were produced with couch angles of 90°, +45°, and -45°. The steepest dose fall-offs from the 90% isodose line to the 50%, 20%, and 10% isodose lines were 2.1 mm, 4.0 mm, and 7.6 mm respectively. The shallowest dose fall-offs from the 90% isodose line to the 50%, 20%, and 10% isodose lines were 2.9 mm, 8.0 mm, and 19.3 mm respectively (Podgorsak et al., 1989). Hartmann et al. (1985) used a system of up to 11 noncoplanar converging arcs for their treatment protocol. Depending upon the position of the treatment couch, the arc angles were from 20° to 160° or 200° to 340°. The steepest dose fall-offs from

the 90% isodose line to the 50%, 20%, and 10% isodose lines were 2.3 mm, 4.6 mm, and 7.3 mm, respectively. The shallowest dose fall-offs from the 90% isodose line to the 50%, 20%, and 10% isodose lines were 2.6 mm, 6.9 mm, and 11.4 mm (Podgorsak et al., 1989).

Podgorsak et al. (1988) developed a system of linear accelerator radiosurgery termed dynamic radiosurgery. Dynamic radiosurgery incorporates continuous and simultaneous rotation of the gantry and the treatment couch throughout the treatment procedure. The gantry rotates 300° from 30° to 330°, and the treatment couch rotates 150°, from 75° to -75°. The mechanics of dynamic radiosurgery enable the entry points of all beams to lie in the upper hemisphere while the beam exit points reside in the lower hemisphere. This ensures that there are never parallel opposed beams produced which would degrade the steep dose fall-off outside of the target. The steepest dose fall-off for this technique from the 90% isodose line to the 50%, 20%, and 10% isodose lines was 2.0 mm, 3.8 mm, and 5.0 mm, respectively, which is quite similar to the gamma unit value of 2.0 mm, 3.5 mm and 5.0 mm, respectively. The shallowest dose fall-off for dynamic radiosurgery from the 90% isodose line to the 50%, 20%, and 10% isodose lines was 2.5 mm, 7.7 mm, and 18.0 mm respectively. Respective gamma unit values were 4.0 mm, 12.0 mm, and 22.0 mm (Podgorsak et al., 1989).

Fall-Off Distances from the 90% Isodose Line (Table 2)

Radiosurgical Technique	Isodose Line 50%	20%	10%
Single Plane:			
Steepest	2.0 mm	2.5 mm	3.0 mm
Shallowest	3.5 mm	14.4 mm	32.0 mm
4 Noncoplanar Arcs:			
Steepest	2.1 mm	4.0 mm	7.6 mm
Shallowest	2.9 mm	8.0 mm	19.3 mm
11 Noncoplanar Arcs:			
Steepest	2.3 mm	4.6 mm	7.3 mm
Shallowest	2.6 mm	6.9 mm	11.4 mm
Dynamic:			
Steepest	2.0 mm	3.8 mm	5.0 mm
Shallowest	2.5 mm	7.7 mm	18.0 mm
Gamma Knife:			
Steepest	2.0 mm	3.5 mm	5.0 mm
Shallowest	4.0 mm	12.0 mm	22.0 mm

Malignant Gliomas

Anaplastic astrocytomas (WHO Grade III) and GBM (WHO Grade IV) are malignant tumors with varying degrees of hypercellularity and changes in blood vessels. Their cells divide rapidly, and they are characterized by their infiltrating nature (Schiffer 1993). Tumors cells have been verified histopathologically at several centimeters away from a lesion defined by imaging techniques (Alexander and Loeffler 1992). However, a patient's death is usually attributable to the inability to locally control the tumor (Wallner 1989). Regardless of subsequent therapy, the median survival for patients who have undergone an excision of a GBM is twelve months. Patients with AA have a median survival rate of 27 months (Chang et al., 1983).

Studies have been conducted to determine the efficacy of radiosurgery as a boost to conventional radiotherapy for AA and GBM. Loeffler et al. (1992) used LINAC radiosurgery after the patients had undergone surgical resection or biopsy and fractionated external beam radiotherapy. They treated 37 patients, 23 who were diagnosed with GBM and 14 who had an AA. Participants of the study were selected upon the basis of strict criteria: 1) a minimum Karnofsky performance score of 70%, 2) a radiographically well-defined tumor; and 3) a lesion no larger than 4 cm in greatest diameter after surgery. Twenty patients underwent a surgical resection

procedure, and 17 patients underwent biopsy. All of the patients were subjected to conventional radiotherapy beginning 2 weeks after surgery. Each patient received a total of 5940 cGy given in 33 fractions. Approximately 2 to 4 weeks after radiotherapy, radiosurgery was performed. The median tumor volume was 4.8 cc which included a 2-4 mm margin. The median follow-up period for the study was 19 months. Almost all of the patients had to undergo corticosteroid therapy at some point after radiosurgery due to symptoms resulting from peritumoral edema. Fourteen of the 30 patients who were followed for over one year still required corticosteroids on an intermittent basis. Patients who were diagnosed with GBM had a median survival of 26 months. At the time of publishing, the median survival for patients with AA had not been reached. As of June 1994, the addition of 35 AA patients treated by the radiosurgical protocol has not allowed for the median survival to be reached (Loeffler, personal communication). Among the 23 GBM patients, 16 were alive and 15 were disease free. The 7 deaths could be attributed to failures at the margins of the treatment volume and local progression of the tumor within the treatment volume. Among the patients diagnosed with AA, 2 died. One death was attributed to bulbar amyotrophic lateral sclerosis while the other was due to a seizure in a patient who had refused anticonvulsant medication. Eleven of the surviving patients with AA were followed for one year, and they all remained free of disease progression. The

authors concluded that the use of LINAC radiosurgery as a boost treatment for GBM and AA compared favorably with other therapies.

Treatment of Brain Metastases with LINAC Radiosurgery

Although surgical resection followed by radiation therapy is the method of treatment for solitary cerebral metastases, approximately 60%-80% of patients are not suitable for surgery. The criteria that must be met for a patient to undergo surgery include: solitary and surgically accessible metastases, limited systemic disease, and good Karnofsky performance status. Radiosurgery may be an option for patients who have single or multiple cerebral metastases that are recurrent, persistent, radioresistant, or are inaccessible by surgery. Most cerebral metastases are amenable to radiosurgery because they are usually spherical, well circumscribed, and have radiographically distinct enhancing margins. Also, microscopic infiltration of surrounding normal brain tissue is infrequent (Engenhart et al., 1993).

Sturm et al. (1987) studied the effects of LINAC radiosurgery on radioresistant and deeply localized cerebral metastases in seven patients. Single doses of 20-30 Gy were given at the 80% isodose line. During the follow-up period of greater than three months, all of the patients presented an arrest in the growth of the tumor and in four cases, there was a shrinkage in the tumor mass. In all of the patients who

had edema, there was reduction of the edema which could be directly attributed to the irradiation. There were no recurrences in the growth of the irradiated tumors and there were no reported side effects. All patients, showed clinical and radiological improvement within the first few days following irradiation. At the time of publication, most of the patients (four) died due to a generalization of the metastases or the occurrence of other brain metastases.

Loeffler et al. (1990) reported the results of a clinical investigation on the treatment of recurrent brain metastases with LINAC radiosurgery. Their 18 patients had a Karnofsky performance score greater than or equal to 70 and no evidence of systemic disease. Also, the patients must have failed prior radiotherapy and surgery. The volumes of the treated lesions were less than 27 cc. The median dose of prior whole-brain radiotherapy was 36 Gy with a mean interval between radiotherapy and radiosurgery of 10 months. Of the 21 lesions that were treated, there was either a decrease in size or a stabilization of their contrast-enhancing volume. Also, the majority of the patients showed an improved neurological condition and were able to be discontinued from steroid therapy. Lethargy, headache, nausea, and vomiting which are considered to be clinical symptoms of increased intracranial pressure, were eliminated or decreased within 6 weeks of radiosurgery. Surprisingly, despite previous exposure to radiotherapy there were no signs of symptomatic radionecrosis in any of the patients.

The clinical investigations of Loeffler et al. (1990) and Strum et al. (1987) had relatively short follow-up periods. Engenhart et al.(1993) conducted a long-term follow-up of 57 patients with inoperable brain metastases who were treated with LINAC radiosurgery. The mean follow-up was 8.6 months (range, 1-56 months). Complete remission was found in 20%, partial remission in 35%, stable disease in 40%, and relapse in 5% of the cases. Of the 22 patients who had metastases located only within the brain, 5 remained alive for greater than two years.

Low Grade Astrocytomas

Treatment of primary low grade astrocytomas with radiosurgery is not recommended because normal and malignant glial cells reside within the target volume (Larson et al., 1993). Larson et al. (1993) devised a model to predict the effects of a single dose of radiation on the early responding tumor cells and the late responding normal tissue within the target volume. They determined that a dose of 30-40 Gy produced a radiobiologic effect of 50-100 Gy of fractionated radiotherapy on the tumor cells and a 100-200 Gy radiobiologic effect on the normal tissue within the target. According to Larson's model, radiosurgery for low grade astrocytomas will cause a greater radiobiologic effect on the normal tissue within the target than on the tumor cells. Their model suggests that normal tissue in addition to tumor cells are killed as a result of radiosurgery for low grade astrocytomas.

Using LINAC radiosurgery, Pozza et al. (1989) treated 14 patients with inoperable low grade (WHO I or II) astrocytomas. All of the tumors were spherical in shape, no larger than 30 mm in diameter, and had clear-cut margins. A dosage of between 16-50 Gy was given via multiple noncoplanar arcs during 1 or 2 fractions separated by 8 days. The patients were followed for a period of 11-48 months. Ten of the 14 patients showed significant improvements in their

functional status. One patient who had a pre-radiosurgery Karnofsky score of 50% was scored at 100% at a follow up time of 48 months. In three patients, there was no improvement or only a slight improvement in their clinical conditions. One patient died 38 months after treatment. The two patients who received two 25 Gy fractions were the only subjects who displayed signs of acute toxicity which were manifest as headaches. They were treated with 4 mg of dexamethasone 3 times per day, and the symptoms subsided after 7 to 21 days. Three patients showed worsening of motor disturbances or increases in intracranial pressure from months 3 to 6 after treatment. These symptoms were attributed to a marked increase in the swelling of the tumor of up to 95% and were observed in 8 out of the 14 patients. Swelling occurred at a median time of 4.5 months after treatment. The swelling subsided from 12 to 24 months after treatment.

Although Pozza's clinical trial for low grade astrocytoma using LINAC radiosurgery demonstrated impressive results, there have been no other published trials for the radiosurgical treatment of low grade astrocytomas. More clinical trials should be conducted to determine the accuracy of the radiobiologic model developed by Larson et al. (1993).

Gamma Knife

The first stereotactic gamma unit was installed in 1968 at the Karolinska Institute in Stockholm. The unit was created through the combined efforts and extensive research of Lars Leksell, Borje Larsson, and Kurt Liden. Their prototype was designed to produce slit-like radiation lesions for the purpose of functional radiosurgery. Neurological symptoms that were treated included: involuntary movement disorders, behavioral disorders, and the relief of intractable pain. A second gamma knife was developed and in use at the Karolinska Institute in 1975. It contained 179 ^{60}Co sources. This unit was designed to produce spherical lesions in order to treat arteriovenous malformations (AVM) and brain tumors (Leksell 1983). In the 1980s, the third and fourth gamma units were installed in Buenos Aires, Argentina and Sheffield, England respectively. Each of these contained 201 ^{60}Co sources (Figure 9) (Wu et al., 1990). The fifth gamma knife was installed at the University of Pittsburgh Medical Center in 1987 (Lunsford et al., 1989). There are now approximately 42 gamma units in operation worldwide. As of January 1993, over 9,000 patients have been treated with gamma knife worldwide. Approximately half were treated for vascular malformations, and the other half for brain tumors. Functional radiosurgery with gamma knife represented roughly four percent of the procedures (Lunsford 1992).

Unlike the LINAC, which can be used for conventional radiotherapy to all body regions, the gamma knife is a unit dedicated to radiosurgery for the brain. The gamma knife must be housed within its own suite. At the University of Pittsburgh, the suite is located in the basement of the hospital and consists of: a patient preparation area used for the application of the stereotactic guiding device, a treatment room, an image evaluation area, a control area, and a computer physics site (Lunsford et al., 1989).

The gamma knife consists of a permanent 18,000 kg cast iron shield which surrounds a central body consisting of 201 ^{60}Co sources arranged in a hemispheric array. ^{60}Co has a half-life of 5.3 years. At the time the sources are loaded, each had an average activity of 30 Ci (Lunsford et al., 1989). Each of the 201 ^{60}Co sources consists of 20 pellets 1 mm in diameter that are stacked atop one another. The pellets are doubly encapsulated in a stainless steel capsule. The gamma knife also consists of four interchangeable collimator helmets with diameters of 4 mm, 8 mm, 14 mm, and 18mm. Other components include: a patient treatment table, a control console, a hydraulic system, and a treatment-planning computer system. Each of the 201 beams are directed through a beam channel which includes a tungsten alloy precollimator and a lead collimator. Depending upon the size of the lesion, one of the four different sized collimator helmets is used in the final collimation. The collimator helmets possess 201 channels which are perfectly aligned with the

central body. All of the 201 beams converge upon a single point at the center of the radiation unit (Figure 10). The distance from the collimator channel to the single point is 40.3 cm and is termed the focal distance. Any of the collimators may be plugged in order to prevent irradiation of the lenses or other critical structures near the target. Within each helmet, there are a pair of trunions which serve to affix the Leksell stereotactic frame. The central beam of the 201 sources is at a fixed angle of 55° to the horizontal plane. The sources are evenly distributed in an arc of ±48° along the treatment table and ±80° across the treatment table from the central beam (Wu 1992).

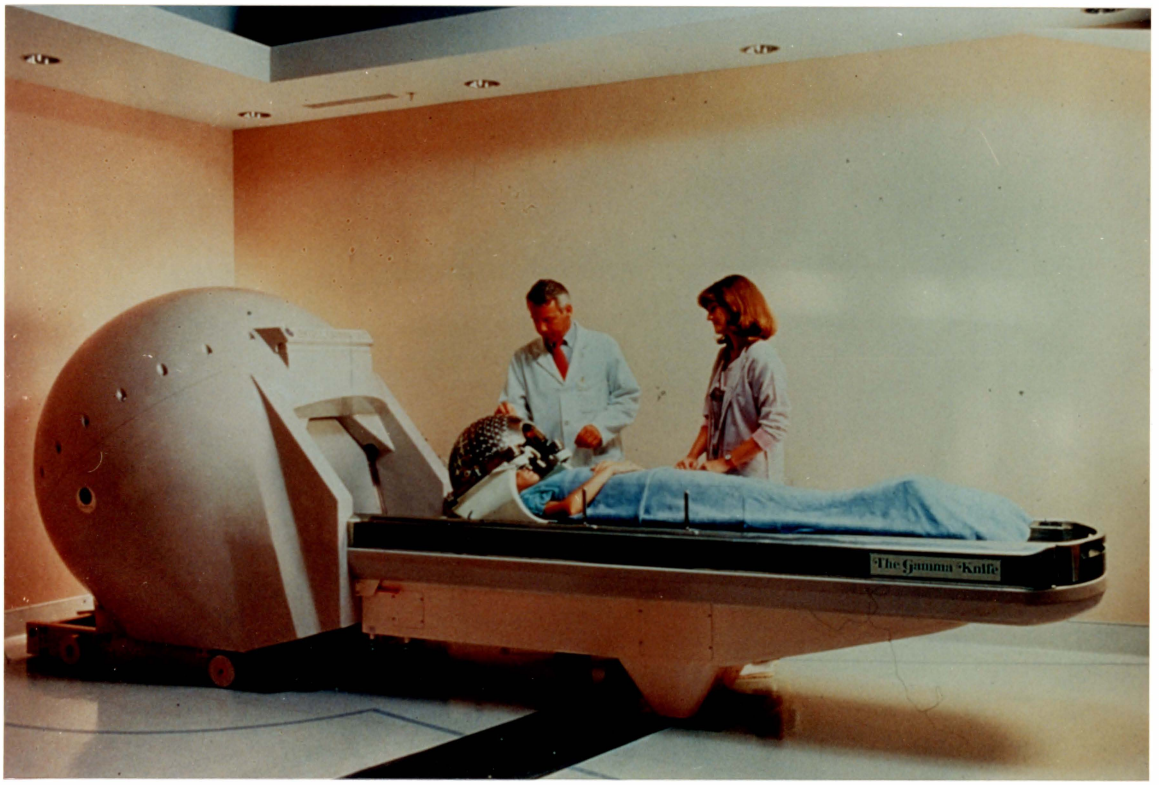

Figure 9: Gamma Knife (Courtesy of Elekta Radiosurgery Atlanta, Georgia).

Figure 10: Collimator Helmet and the convergence of 201 beams upon the focal point (Courtesy of Elekta Radiosurgery Atlanta, Georgia).

Gamma Knife Radiosurgery Procedure

Patients undergo the application of the Leksell Model G stereotactic head frame under local anesthesia. For children and teenage patients, frame placement and radiosurgery are done under general anesthesia (Coffey and Lunsford 1990). Next, the intracranial target is visualized. For arteriovenous malformations (AVM), biplane angiography is used. High resolution CT or MRI is used to visualize tumors. From these images, the precise rectilinear (x, y, and z) stereotactic coordinates of the target are determined (Lunsford and Kondziolka 1992). In order to account for the contours of the patient's skull, a special plastic helmet is used. The helmet is attached to the stereotactic frame and measurements are taken from the center of the frame to the surface of the skull at 24 preselected points. The gamma angle, which is defined as the angle of the patient's head with respect to the stereotactic frame, is also determined (Wu 1992). Multiple isocenters may be used to irradiate lesions that are too large to be circumscribed by one isocenter, or whose irregular shape necessitates the use of more than one isocenter. Dose selection is undertaken by the neurosurgeon and the radiation oncologist. They select dosage with respect to prior therapy, location and size of the target, and tumor pathology. In gamma knife radiosurgery, an 18 mm collimator is the largest one

available for use. Targets exist whose diameters are larger than 18 mm which may necessitate the use of multiple isocenters (Lunsford and Kondziolka 1992).

Using the estimated stereotactic coordinates, the collimator size, and the gamma angle, the treatment planning system will calculate the isodose distributions for all three axes. After the coordinates of the target have been determined, the patient and the stereotactic frame are affixed to the trunions of the collimator helmet. A flashlight is directed through the collimators to determine through which collimator radiation might reach the lenses of the eyes. Those collimators will be plugged. The plugging patterns and the dose prescription are entered into the treatment planning computer system which calculates the time for each isocenter required to deliver the prescribed dose to the lesion (Wu 1992). The gamma knife software system allows for the viewing of all of the 201 beams as they pass through the cranial vault and converge upon the focal point (Figure 11). The goal of the treatment planning session is to fully enclose the lesion margin within the 50% isodose line or greater. This will enable the maintenance of a steep dose fall-off beyond the target margin. The treatment planning may take from 20 minutes to several hours. The entire radiosurgery process from the application to the removal of the stereotactic frame may take from 2 to 5 hours (Lunsford and Kondziolka 1992).

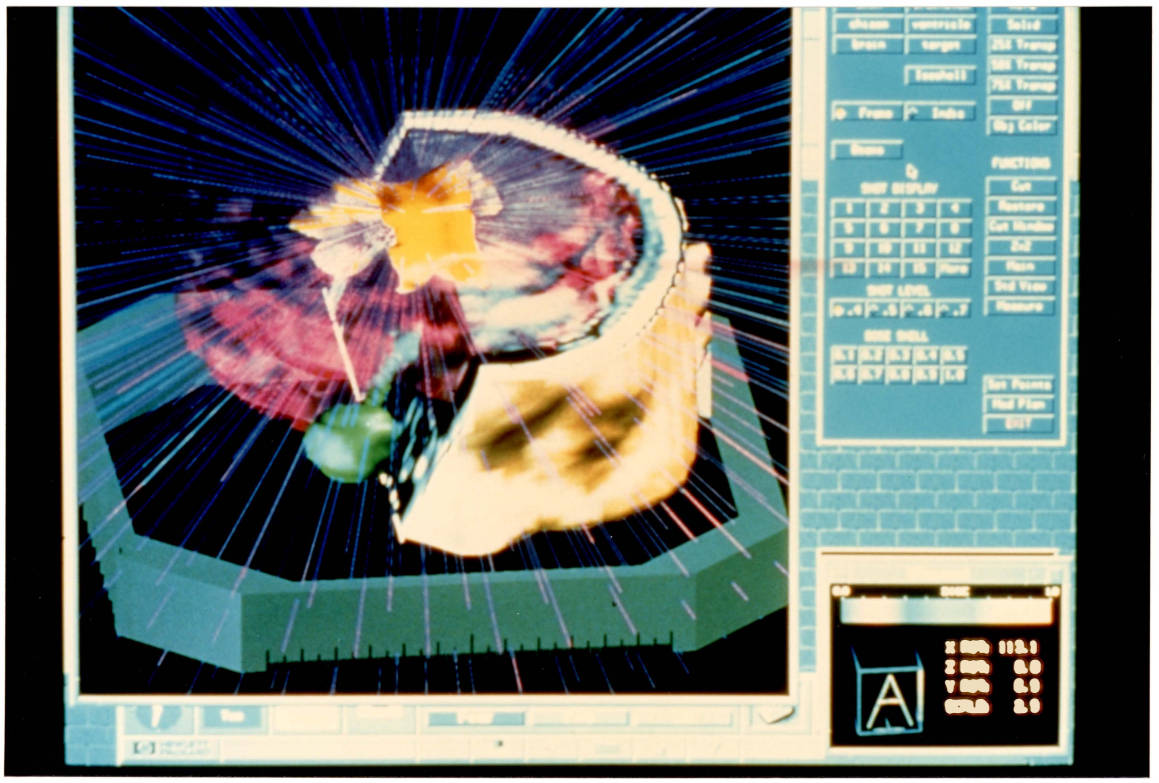

Figure 11: Gamma Knife System Software (Courtesy of Elekta Radiosurgery Atlanta, Georgia).

Initial Experience at the University of Pittsburgh

The gamma knife facility at the University of Pittsburgh treated the first patient in North America on August 14, 1987. Over the next 16 months they treated 207 patients (113 had arteriovenous malformations, 78 had extra-axial skull base neoplasms, 9 had glial neoplasms, and 7 had metastatic tumors). In order to be considered for radiosurgery, the patients had to fulfill one or more of the following criteria: 1) the patient had an AVM or intracranial tumor that was considered unresectable; 2) the patient was elderly or had a significant medical condition that posed excessive surgical risks; 3) although the patient had undergone surgical or endovascular embolization techniques, recurrent or residual tumor or AVM remained; 4) the patient refused the recommendation of direct surgical removal and requested radiosurgery instead. During this initial gamma knife radiosurgery experience, there was no surgical mortality. Approximately half of the patients required antiemetics to alleviate nausea and/or vomiting and mild analgesics to control postoperative headaches. One patient with a subcortical AVM and a known seizure disorder, had 2 grand mal seizures 8 hours after radiosurgical treatment. The seizures ceased after therapeutic anticonvulsant levels were

established (Lunsford et al., 1989).

Glioblastoma Multiforme and Anaplastic Astrocytoma

From August, 1987 to July, 1990, the University of Pittsburgh Gamma Knife Center treated 40 patients, nine with a GBM (mean Karnofsky performance score = 77) and four with an AA. Six of the GBM lesions had volumes between 1-10 cc and 3 were greater than 10 cc. Three of the AA tumors had a volume of between 1-10 cc and the fourth was larger than 10 cc. Three of the patients with GBM and 3 of the patients with AA were diagnosed via biopsy. The other patients had been diagnosed having undergone previous craniotomy. Radiosurgery was performed as a "boost" to fractionated external beam irradiation which had consisted of a total of between 55 to 60 Gy administered in 30 to 35 fractions (1.72-1.83 Gy/fraction). All of the tumors except one GBM were completely enclosed within the 50% or greater isodose lines. The mean dose to the tumor margins was 16.1 Gy and the mean central tumor dose was 29.7 Gy. Of the 13 patients treated, follow-up imaging studies were available in 6 patients with GBM and 4 patients with AA. Three AA and 4 GBM had stabilized or decreased in size for as long as 18 months after radiosurgery. However, 2 GBM and 1 AA continued to grow. Three patients with GBM died between 3 and 39 weeks after radiosurgery. No patient with AA died during the

follow-up of up to 24 months, but radiographic and clinical evidence of tumor progression developed in one patient. "Boost" radiosurgery was used in addition to fractionated external beam radiotherapy to achieve local tumor control in 75% of the AA and 67% of the GBM within the image defined treatment volume. However some patients with GBM died or underwent clinical progression due to the infiltration of neoplastic cells (Coffey et al., 1992).

From January 1990 to August 1992, 18 patients with 20 malignancies (glioblastoma multiforme or anaplastic astrocytoma) were treated at the Mayo Clinic. All of the tumors were diagnosed via biopsy or craniotomy and surgical resection. The patients had a mean Karnofsky performance score of 83%. All patients received conventional fractionated radiotherapy before or after radiosurgical treatment (10 days after treatment for newly diagnosed tumors). Half of the tumors were located in lobar regions and the rest were located in the basal ganglia, thalamus, or brainstem. The dose prescribed to the tumor margins was determined by a protocol based upon tumor volume. Of the 14 tumors that were followed-up with postoperative imaging, eight decreased in size. Six tumors increased in size, and in some instances this occurred after initial tumor shrinkage. Six of the patients remained neurologically stable, one patient's condition worsened, and seven patients' neurological conditions deteriorated, and they died. All of the patients' deaths were attributed to growth of the treated

lesion. The mean survival time was 10 months after radiosurgery (Coffey 1993).

Cerebral Metastases

Twenty-six patients with twenty-six cerebral metastatic tumors were treated with the gamma knife at the Karolinska Institute from 1975 to March of 1988. In most of the cases, the gamma knife radiosurgery was the only treatment. The median treatment volume was 4.4 cc, the median average dose was 53 Gy and the median minimum tumor dose was 31 Gy. In all but one of the tumors, there was "striking" shrinkage of the tumors beginning 2-4 months after treatment. Two metastases from melanomas and three from adenocarcinomas disappeared completely between two months and one year after treatment. Four of these five tumors had volumes of 1 cc or less, the other had a pretreatment volume of 5 cc. Nineteen tumors that ranged in volume from 2-13 cc decreased by 75% over a 3-6 month follow-up period. The patient that did not respond to treatment had a metastasis in the brain stem from an ovarian carcinoma. She received only a dose of 13 Gy as the minimum dose to the tumor (Kihlström 1991).

Arteriovenous Malformations

Arteriovenous malformations (AVM) are fistulous communications between cerebral arteries and veins. The lack of an intervening capillary network results in an increased rate of blood flow (Okazaki 1989). The core of the AVM is the nidus which is responsible for the arteriovenous shunting. The nidus is interposed between feeding arteries and terminal veins. Arteries that feed the AVM include: branches of the anterior, middle, and posterior cerebral arteries, their perforating branches, and the choroidal arteries. The main venous drainage is via a single large vein. The draining vein is usually situated at the center of the lesion, and they empty into one of the venous sinuses (Yasargil 1987). The feeding arteries and the draining veins are usually enlarged. The nidus is composed of a tangled mass of structurally abnormal blood vessels. The internal elastic lamina may be interrupted. Within a vessel, the muscular media may vary greatly in thickness. Thinning of the media may lead to the formation of an aneurysm (Russell and Rubenstein 1989). The vessels of the nidus have also been characterized as "arterialized" veins consisting of a thickened intima and muscularis but lacking elastic tissue. Also, the vessels have been characterized as having either a "closed" or a fenestrated endothelial layer (Yasargil 1987). Typically, an AVM lies within the subarachnoid space and

extends through the gray matter in the shape of the cone. The apex of the cone points towards the ventricles (Okazaki 1989).

Radiosurgery is performed in order to cause a total obliteration of the AVM secondary to the occlusion of the nidus. The precise mechanism of obliteration has not yet been found. Pathological evidence has shown that endothelial proliferation may be the most important factor in causing occlusion. Radiation has been shown to cause obliteration in small vessels due to endothelial cell swelling. Post-irradiation changes in vessels can be characterized as having an early or late time course. Early changes, occurring weeks after irradiation, have been shown to include endothelial cell swelling, degeneration, and necrosis. Subsequent thrombosis of the vessel walls has also been observed. Weeks to months after irradiation, late changes are manifest by the proliferation of endothelial cells and subendothelial connective tissue with subsequent narrowing and occlusion of vessels (Bunge et al., 1992). Also, it has been noted that the arterial vessels of AVM incur obliteration more frequently than normal arterial vasculature within the treatment field. An AVM that has not undergone complete obliteration has approximately a 2-3% per year probability of undergoing spontaneous bleeding. The time course for complete obliteration of an AVM can range from 8 months to 27 months (Levy et al., 1992). The rate of total obliteration at two years after radiosurgery was shown to be approximately

86%. During the time after radiosurgery but before total obliteration, the patient is still at risk for hemorrhage (Steiner 1985).

Experimental Design

Hypothesis

The addition of Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblast Growth Factor (bFGF) after the irradiation of a microsurgically created arteriovenous shunt, in laboratory rats, will result in a faster time course for vascular obliteration than irradiation alone.

Background

Vascular Endothelial Growth Factor (VEGF) is a heparin binding 45 KDa cationic protein that is specifically mitogenic for vascular endothelial cells in vitro. VEGF was identified in the conditioned media of bovine pituitary follicular cells (Ferrara and Henzel 1989). VEGF has a signal sequence; therefore the protein is secreted (Leung et al., 1989). Conditioned media from a human glioblastoma cell line enhanced the proliferation of bovine capillary endothelial cells (BCE) in vitro. The number of BCE recovered from cultures treated with the conditioned media of the glioblastoma cell line was over three times greater than those cultured in 10% calf serum. The major activity in the conditioned medium was found to be VEGF (Goto et al., 1993).

In rats, binding sites for VEGF have been demonstrated in sections of kidney, brain, pancreas, and heart. The binding site distribution reflects the vascularization of the organ. The VEGF binding sites have been associated with the vascular endothelial cells of fenestrated and nonfenestrated capillaries and the endothelium of large vessels. Binding of VEGF has been associated with quiescent and proliferating endothelial cells. This may support the hypothesis that VEGF plays a role in the maintenance and induction of endothelial cells. Also, a high density of binding sites has been demonstrated in the endothelial lining of the heart valves which are constantly subjected to the shear forces of blood flow under high pressure. VEGF could therefore play a role in the continual repair and maintenance of endothelial cells (Jakeman et al., 1992). However, it is not known whether the VEGF expressed in normal tissues is stored intracellularly or is secreted continuously (Senger et al., 1993).

Basic Fibroblast Growth Factor (bFGF) is an 18-25 kDa protein whose in vitro vascular targets include: endothelial cells, smooth muscle cells, and fibroblasts. This growth factor is a potent mitogen for the endothelial cells of small and large vessels. Like VEGF, bFGF has a strong affinity for the glycosaminoglycan heparin. However, bFGF does not have a signal sequence; therefore, the protein is not secreted (D'Amore 1992). Due to its lack of a signal sequence, it has been hypothesized that bFGF is released in response to cell injury. Damage to the vascular endothelial cells could

prompt the release of bFGF (D'Amore 1990).

VEGF and bFGF have been shown to synergistically increase the rate of vascular endothelial cell proliferation in vitro (Goto et al 1993). Endothelial cell swelling, necrosis, and lysis does not appear until weeks after irradiation. This may imply that bFGF is not released from the endothelial cell cytoplasm until weeks after irradiation. The addition of bFGF and VEGF at some point after irradiation may shorten the time course of vascular occlusion due to intimal thickening. Decreasing the time course for vascular occlusion following irradiation could decrease the time necessary for the complete obliteration of the AVM following radiosurgery.

Experimental Design

The time course of a microscopically discernable response of vascular endothelial cells to irradiation should be determined. This would allow for a characterization of time dependent endothelial cell changes such as: swelling, necrosis, lysis, and proliferation. The addition of growth factors to vascular endothelial cells at a time when they have demonstrated phenotypic change and/or endothelial proliferation may cause an increase in proliferative activity. Also, the growth factors may induce the proliferation of quiescent endothelial cells lying within the

irradiation field.

In order to simulate an AVM in vivo, a 1-1.5 mm diameter arteriovenous shunt is microsurgically created between the abdominal aorta and the vena cava of 24 laboratory rats as described by Altschuler et al. (1992) and Mickle et al. (1981). A small radiopaque metal clip is left at the site of the fistula to enable radiosurgical targeting. The fistula is allowed to mature for several weeks. The rats are divided into six groups (1A, 1B, 2A, 2B, 3A, 3B, n=4). Those rats in the A groups will not be irradiated. Using an animal modification of the Leksell Model G stereotactic frame and a 4 mm collimator, the rats in the B groups will be subjected to a maximal dose 40 Gy (Altshculer et al., 1992). After irradiation or sham, the rats will be sacrificed according to the following time schedule: 1A and 1B (3 weeks), 2A and 2B (6 months), 3A and 3B (18 months) (Table 3). At one hour and nine hours before sacrifice, the rats will be injected with tritiated thymidine as described by Linder et al. (1990). The rats will be sacrificed with an overdose of pentobarbitol and perfused with 4% paraformaldahyde in phosphate buffer (0.1M, pH 7.3) at physiologic flow for 4 minutes as described by Linder et al. (1990). Next, the abdominal aorta and inferior vena cava will undergo Hautchen Preparation (Lupinetti et al., 1993). These en face preparations will allow the determination of the percentage of endothelial cells that are in the S-phase via autoradiographic techniques described by Linder et al. (1990). Also, portions of the

arteriovenous shunt, the abdominal aorta, and the inferior vena cava will be embedded, sectioned, and stained with hematoxylin and eosin. Their histopathology will be studied under bright field microscopy in order to determine the presence of endothelial cell: swelling, necrosis, lysis and thrombus formation. The sections of the arteriovenous shunt will also be prepared for autoradiographic analysis. If a phenotypic change is discovered at any of the three time points, additional experiments should be conducted in order to pinpoint the time course of post-irradiation changes.

After determining the time course of post-irradiation phenotypic changes and/or endothelial cell proliferation, a separate experiment will be conducted to study the effects of growth factors on post-irradiation endothelial cells. A 1-1.5 mm diameter arteriovenous shunt is microsurgically created between the abdominal aorta and the vena cava of 36 laboratory rats as described by Altschuler et al. (1992) and Mickle et al. (1981). A small radiopaque metal clip is left at the site of the fistula to enable radiosurgical targeting. The fistula is allowed to mature for several weeks. The rats are divided into four groups (1 - 4, n=9). Animals in group 1 will not be irradiated and will be infused with 4 ml of saline. Members of group 2 will not be irradiated, and they will be infused with 2 ml of VEGF and 2 ml of bFGF. Group 3 rats will receive 40 Gy via gamma knife radiosurgery, and they will be infused with 4 ml of saline. Rats in group 4 will also be subjected to 40 Gy and infused with 2 ml of VEGF

and 2 ml of bFGF. The groups will be further subdivided into A, B, and C groupings. This designation corresponds to the time of sacrifice after infusion. Rats that make up the A, B, or C group will be sacrificed at 3 weeks, 6 months, and 18 months respectively (Table 4). The infusion of growth factor or saline is started at the post-irradiation time when there was a high endothelial cell tritiated thymidine index and microscopically observed phenotypic change.

The concentration of the growth factors that are to be administered are 19.2 mg of VEGF diluted in 2 ml of saline and 1.2 mg of bFGF diluted in 2 ml of saline. The infusion is to take place over an 8 hour time period via a catheter placed in the abdominal aorta. Initially, 0.5 ml of the VEGF and 0.5 ml of the bFGF solution or 1 ml of saline are to be administered in a bolus (Linder et al., 1990). The time period of infusion and the concentration of the bFGF were derived from an experiment conducted by Linder et al. (1990). Linder et al. (1990) studied the effects of 0.06 mg/ml of human bFGF on the proliferation rat common carotid artery endothelial cells which had been subjected to mechanical denudation. There was no reason given for the choice of the bFGF concentration. Twenty-five percent of the growth factor was given as an initial bolus and the rest was infused over 8 hours. Endothelial cells that received the bFGF infusion had a tritiated thymidine index of 38% versus 2% for those endothelial cells given saline. The proposal to administer a bFGF concentration of 0.6 mg/ml is being made in hopes of

increasing the replication index and therefore the quantity of endothelial cells in the arteriovenous shunt. Goto et al. (1993) found that VEGF and bFGF act synergistically to increase endothelial cell proliferation in vitro. They cited a VEGF:bFGF concentration ratio of 16:1. This ratio corresponds to the concentration of growth factors in the proposed experiment.

After the groups have been sacrificed, the abdominal aorta, vena cava, and the arteriovenous shunt will embedded, sectioned, and stained with hematoxylin and eosin. The tissue sections will be subjected to planimetry measurements of the areas of wall layers and lumens using a computerized planimetry system as described by Gillette et al. (1989). Measurements of the areas of the: intima, media, adventitia, and lumen will be made. Any thrombi present can be measured and expressed as a percentage of the lumen it is occupying. Also, the extent of thrombi covering the intimal surface can be measured by dividing the length of the thrombus covering the intima by the total length of the intima (Gillette et al., 1989). Statistical analysis will be used in order to determine the significance of any increases in vessel wall thickness or decreases in luminal area.

Time Course of Sacrifice (Table 3)

	Time		
	3 weeks	6 months	18 months
Dose			
0 Gy (Control)	1A (n=4)	2A (n=4)	3A (n=4)
40 Gy	1B (n=4)	2B (n=4)	3B (n=4)

Experimental Conditions and Schedule of Sacrifice (Table 4)

	Time		
	3 weeks	6 months	18 months
Conditions			
0 Gy & 4 ml saline	1A (n=3)	1B (n=3)	1C (n=3)
0 Gy & 2 ml VEGF+ 2 ml bFGF	2A (n=3)	2B (n=3)	2C (n=3)
40 Gy & 4 ml saline	3A (n=3)	3B (n=3)	3C (n=3)
40 Gy & 2 ml VEGF+ 2 ml bFGF	4A (n=3)	4B (n=3)	4C (n=3)

Conclusion

Radiosurgery using the Linear Accelerator or the Gamma Knife has proven to be an effective treatment modality for malignant brain tumors. In comparison to other treatments, radiosurgery can be performed on an outpatient basis and is noninvasive (Table 5). Due to the functional properties of radiosurgical devices, they are ideal for patients who are unable to undergo surgical removal of their brain tumors. The sharp dose drop-off beyond the tumor margin allows for high dosage tumor irradiation while sparing normal brain tissue. Many procedures that involve radiosurgery use it as a "boost" therapy in conjunction with surgical resection and whole brain irradiation. "Boost" therapy enhances the standard treatment procedure for malignant brain tumors.

Unfortunately, radiosurgery is not always able to halt the progression of malignant brain tumors. Patients with metastatic brain tumors usually succumb to systemic disease. Patients who have gliomas generally die due to the inability of local tumor control. However, the use of radiosurgery can contribute to increasing a patient's quality of life. Often, treatment is followed by a decrease in corticosteroid administration and an improvement in a patient's neurological status. The future directions of radiosurgery could include the development and implementation of a randomized studies to

determine a dose-volume protocol for gliomas and the different forms of metastases. Also, an investigation should be undertaken to determine whether the use of high (50 Gy or more) radiosurgical doses as the only treatment for gliomas and cerebral metastases would prove to be a more effective use than "boost" therapy.

Summary of Treatment Modalities for Malignant Brain Tumors (Table 5)

	Modality			
	Whole Brain	Brachytherapy	Gamma Knife	LINAC
Aspects				
Invasive	No	Yes	No	No
Total Radiation	30-60Gy	50-150Gy	16.1-71Gy	9-50Gy
Total Treatment Time	2-5 weeks	72 hrs - permanent	2-5 hrs	2-3 hrs
Tumor Dimensions	N/A	less than 6cm in greatest dimension	0.3-13cc	0.5-27cc

List of References

List of References

Alexander E, Loeffler JS: Radiosurgery using a modified linear accelerator. Neurosurgery Clinics of North America 3:167-190, 1992.

Altschuler E, Lunsford LD, Kondziolka D, Wu A, Maintz AH, Scalbassi R, Martinez AJ, Flickinger JC: Radiobiologic models for radiosurgery. Neurosurgery Clinics of North America 3:61-77, 1992.

Berk HW, Agarwal SK: Physical aspects of radiosurgery with the gamma knife. In Steiner L ed. Radiosurgery: Baseline and Trends, Raven Press, Ltd., New York, 49-62, 1992.

Boring CC, Squires TS, Tong T, Montgomery S: Cancer Statistics 1994. CA: A cancer journal for clinicians 44:7-8, 1994.

Bova FJ: Radiation physics. Neurosurgery Clinics of North America 1:909-931, 1990.

Bunge HJ, Chinela AB, Guevara JA, Antico JC, Lemme-Plaghos LA, Steiner: Radiosurgery in infratentorial arteriovenous malformations. In Steiner L ed. Radiosurgery: Baseline and Trends, Raven Press, Ltd., New York, 179-188, 1992.

Chang CH, Horton J, Schoenfeld D, et al: Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in a multidisciplinary management of malignant gliomas: A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. Cancer 52:997-1007, 1983.

Coffey RJ, Lunsford LD, Flickinger JC: The role of radiosurgery in the treatment of malignant brain tumors. Neurosurgery Clinics of North America 3:231-244, 1992.

Coffey RJ, Lunsford LD: Stereotactic radiosurgery using the 201 cobalt-60 source gamma knife. Neurosurgery Clinics of North America 4:933-955, 1990.

Coffey RJ, Flickinger JC, Lunsford LD, Bissonette DJ: Solitary brain metastasis: Radiosurgery in lieu of microsurgery in 32 patients. Acta Neurochirugica, Suppl. 52:90-92, 1991.

Coffey RJ: Boost gamma knife radiosurgery in the treatment of primary glial tumors. Stereotactic and Functional Neurosurgery 61(suppl 1):59-64, 1993.

Coffey RJ, Lunsford LD,, Flickinger JC: The role of radiosurgery in the treatment of malignant brain tumors. Neurosurgery Clinics of North America 3:231-244, 1992.

Colombo F, Benedetti A, Pozza F, Avanzo R, Marchetti C, Zanardo A: External stereotactic irradiation by linear accelerator. Neurosurgery 16:154-160, 1985.

D'Amore P: Modes of FGF release in vivo and in vitro. Cancer and Metastasis Reviews 9:227-238, 1990.

D'Amore P: Mechanisms of endothelial growth control. American Journal of Cell Molecular Biology 6:1-8, 1992.

Engenhart R, Kimmig BN, Hover KH, Wowra B, Romahn J, Lornez WJ, van Kaick G, Wannenmacher M: Long-Term follow-up for brain metastases treated by percutaneous stereotactic single high-dose irradiation. Cancer 71:1353-1361, 1993.

Ferrara N, Henzel WJ: Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. Biochemical and Biophysical Research Communications 161:851-858, 1989.

Flickinger JC: The integrated logistic formula and prediction of complications from radiosurgery. International Journal of Radiation Oncology Biology Physics 17:879-885, 1989.

Friedman WA, Bova FJ, Spiegelmann R: Linear accelerator radiosurgery at the University of Florida. Neurosurgery Clinics of North America 3:141-166, 1992.

Gillette et al: Response of aorta and branch arteries to experimental intraoperative irradiation. International Journal of Radiation Oncology Biology Physics 17:1247-1255, 1989.

Goto F et al: Synergistic effects of vascular endothelial growth factor and basic fibroblast growth factor on the proliferation and cord formation of bovine capillary endothelial cells within collagen gels. Laboratory Investigation 69:508-517, 1993.

Hall EJ: Factors that modify radiobiological response. In Lunsford LD ed. Stereotactic Radiosurgery Update, Elsevier Science Publishing Co., New York, 11-28, 1991.

Hall EJ: Radiobiology for the Radiologist, J.B. Lippincott Company, Philadelphia, 133-150, 1994.

Hall EJ, Brenner DJ: The radiobiology of radiosurgery: rationale for different treatment regimes for AVMs and malignancies. International Journal of Radiation Oncology Biology Physics 25:381-385, 1993.

Hartmann GH, Schlegel W, Sturm V, Kober B, Pastyr O, Lorenz WJ: Cerebral radiation surgery using moving field irradiation at a linear accelerator facility. International Journal of Radiation Oncology Biology Physics 11:1185-1192, 1985.

Houdek PV, Fayos JV, Van Buren JM, Ginsberg MS: Stereotaxic radiotherapy technique for small intracranial lesions. Medical Physics 12:469-472, 1985.

Jakeman LB et al: Binding sites for vascular endothelial growth factor are localized on endothelial cells in adult rat tissues. Journal of Clinical Investigation 89:244-253, 1992.

Jellinger K: Pathology of human intracranial neoplasia. In Jellinger K ed. Therapy of Malignant Brain Tumors, Springer-Verlag Wien, New York, 1-34, 1987.

Karnofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. In MacLeod CM ed. Evaluation of Chemotherapeutic Agents, Columbia University Press, New York, 191-205, 1945.

Khan FM: The Physics of Radiation Therapy, Williams and Wilkins, Baltimore 1994.

Kihlström L, Karlsson B, Lindquist Ch, Norén G, Rähn T: Gamma knife surgery for cerebral metastasis. Acta Neurochirugica Suppl. 52:87-89, 1991.

Kilmer BF: Radiotherapy of brain tumors: basic principles. In Morantz RA ed. Brain Tumors: A Comprehensive Text, Marcel Dekker, Inc., New York, 613-642, 1994.

Kjellberg RN, Hanamura T, Davis KR, et al: Bragg-peak proton-beam therapy for arteriovenous malformations of the brain. New England Journal of Medicine 309:269-274, 1983.

Kleihues P, Burger PC, Scheithauer BW: World Health Organization: Histological Typing of Tumours of the Central Nervous System, Springer-Verlag, Berlin 1993.

Larson DA, Flickinger JC, Loeffler JS: The radiobiology of radiosurgery. International Journal of Radiation Oncology Biology Physics 25:557-561, 1993.

Larson DA: Introduction to radiosurgery. Clinical Neurosurgery: Proceedings of the Congress of Neurological Surgeons, Williams and Wilkins, Los Angeles 391-404, 1990.

Larsson B: Radiobiological fundamentals in radiosurgery. In Steiner L ed. Radiosurgery: Baseline and Trends, Raven Press Ltd., New York, 3-14, 1992.

Laws RL, Thapar K: Brain Tumors. CA a Cancer Journal for Clinicians. 43:263-271, 1993.

Lee SH, Rao K, Zimmerman RA: Cranial MRI and CT, McGraw-Hill, Inc., New York, 1992.

Leibel SA, Gutin PH, Wara WM, Silver PS, Larson DA, Edwards MS, Lamb SA, Ham B, Weaver KA, Barnett C, Philips Tl: Survival and quality of lie after interstitial implantation of removable high-activity iodine-125 sources for the treatment of patients with recurrent malignant gliomas. International Journal of Radiation Oncology Biology Physics 17:1129-1139, 1989.

Leksell L: The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102:316-319, 1951.

Leksell L: A stereotaxic apparatus for intracerebral surgery. Acta Chir Scand 99:229-233, 1949.

Leksell L: Stereotactic radiosurgery. Journal of Neurology, Neurosurgery, and Psychiatry 46:797-803, 1983.Leung DW et al: Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 246:1306-1309, 1989.

Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Steinberg GK, Marks MP, DeLaPaz RL, Chuang FY: Clinical-radiological evaluation of sequelae of stereotactic radiosurgery for intracranial arteriovenous malformations. In Steiner L ed. Radiosurgery: Baseline and Trends, Raven Press, Ltd., New York, 209-219, 1992.

Linder V, Majack RA, Reidy MA: Basic fibroblast growth factor stimulates regrowth and proliferation in denuded arteries. Journal of Clinical Investigation 85:2004-2008, 1990.

Loeffler JS, Alexander E, Shea WM, Wen PY, Fine HA, Kooy KM, Black P: Radiosurgery as part of the initial management of patients with malignant gliomas. Journal of Clinical Oncology 9:1379-1385, 1992.

Loeffler JS, Alexander E, Wen PY, et al: Results of stereotactic brachytherapy used in the initial management of patients with glioblastoma. Journal of the National Cancer Institute 82:1918-1921, 1990b.

Loeffler JS, Kooy HM, Wen PY, Fine HA, Cheng CW, Mannarino EG, Tsai JS, Alexander E: The treatment of recurrent brain metastases with stereotactic radiosurgery. Journal of Clinical Oncology 8:576-582, 1990.

Loeffler JS, Alexander E, Wen PY, Fine HA, Kooy HM, Black PM: Radiosurgery for brain metastases: Five year experience at the Brigham and Women's Hospital. In Lunsford LD ed. Stereotactic Radiosurgery Update, Elsevier Science Publishing Co., New York, 383-392, 1991.

Lunsford LD, Flickinger JC, Lindner G, Maitz A: Stereotactic radiosurgery of the brain using the first United States cobalt-60 source gamma knife. Neurosurgery 24:151-158, 1989.

Lunsford LD, Flickinger JC, Coffey RJ: Stereotactic gamma knife radiosurgery: Initial North American experience in 207 patients. Arch Neurol 47:169-175, 1990.

Lunsford LD, Kondziolka D: Gamma knife radiosurgery for brain tumors. In: Thomas DGT ed. Stereotactic and Image Directed Surgery of Brain Tumors, Churchill Livingstone, 169-192, 1992.

Lupinetti FM, Tsai TT, Kneebone JM: Endothelial cell replication in an in vivo model of aortic allografts. Annals of Thoracic Surgery 56:237-241, 1993.

Lutz W, Winston KR, Maleki N: A system for stereotactic radiosurgery with a linear accelerator. International Journal of Radiation Oncology Biology Physics 14:373-381, 1988.

Mahadevan V, Hart IR: Metastasis and Angiogenesis. Acta Oncologica 29:97-103, 1990.

Maor MH, Frias AE, Oswald MJ: Palliative radiotherapy for brain metastases in renal carcinoma. Cancer 62:1912-1917, 1988.

McDermott MW, Gutin PH, Larson DA, Sneed PK: Interstitial brachytherapy. Neurosurgery Clinics of North America 4:801-824, 1990.

Mickle JP, Meneges IT, Day AL, et al: Experimental aortacaval fistulae in rats. Microsurgery 2:283-288, 1981.

Mornex F, Nayel H, Taillandier L: Radiation therapy for malignant astrocytomas in adults. International Journal of Radiation Oncology Biology Physics. 27:181-191, 1993.

Nedzi LA, Kooy H, Alexander E, Gelman RS, Leoffler JS: Variables associated with the development of complications from radiosurgery of intracranial tumors. International Journal of Radiation Oncology Biology Physics 21:591-599, 1991.

Okazaki H: Fundamentals of Neuropathology, Ed. 2. Igaku-Shoin, Tokyo, 76-82, 1989.

Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Marutama T, Kryscio RJ, Markesbery WR, Macdonald JS, Young B: A randomized trial of surgery in the treatment of single metastases to the brain. New England Journal of Medicine 322:494-500, 1990.

Pickren JW, Lopez G, Tzukada, et al: Brain metastases. An autopsy study. Cancer Treatment Symposium 2:295-313, 1983.

Podgorsak EB: Physics for radiosurgery with linear accelerators. Neurosurgery Clinics of North America 3:9-34, 1992.

Podgorsak EB, Pike GB, Olivier A, Pla M, Souhami L: Radiosurgery with high energy photon beams: A comparison among techniques. International Journal of Radiation Oncology Biology Physics 16:857-865, 1989.

Podgorsak EB, Olivier A, Pla M, Lefebvre PY, Hazel J: Dynamic stereotactic radiosurgery. International Journal of Radiation Oncology Biology Physics 14:115-126, 1988.

Pozza F, Colombo F, Chierego G, Avanzo RC, Marchetti C, Benedetti A, Caseentini L, Danieli D: Low-grade astrocytomas: Treatment with unconventionally fractionated external beam stereotactic radiation therapy. Radiology 171:565-569, 1989.

Prados MD, Wilson CB: Neoplasms of the central nervous system. In: Holland JF ed. Cancer Medicine, Ed. 3, Lea and Febiger, Philadelphia, 1080-1119, 1993.

Radhakrishnan K, Bohnen NI, Kurland LT: Epidemiology of brain tumors. In: Morantz RA ed. Brain Tumors: A Comprehensive Text, Ed. 1, Marcel Dekker Inc., New York, 1-14, 1994.

Rosander K, Fabrikant JI, Frankel KA, Cerda H, Phillips MH, Fabrikant IB, Levy RB: DNA damage in mammalian brain cells following charged particle irradiation: Implications for late radiation injury following stereotactic radiosurgery. In Lunsford LD ed. Stereotactic Radiosurgery Update, Elsevier Science Publishing Co., New York, 295-306, 1991.

Russell DS, Rubinstein LJ: Pathology of Tumors of the Nervous System, Williams and Wilkins, Baltimore, 1989.

Senger DR et al: Vascular permeability factor (VPF,VEGF) in tumor biology. Cancer and Metastasis Reviews 12:303-324, 1993.

Salcman M, Scholtz H, Kaplan RS, Kulik S: Long-term survival in patients with malignant astrocytoma. Neurosurgery 34:213-220, 1994.

Sauer R: Radiation therapy of brain tumors. In Jellinger K ed. Therapy of Malignant Brain Tumors, Springer-Verlag Wien, New York, 195-276, 1987.

Saunders WM, Winston KR, Siddon RL, et al: Radiosurgery for arteriovenous malformations of the brain using standard linear accelerator: Rationale and technique. International Journal of Radiation Oncology Biology Physics 15:441-447, 1988.

Schiffer D: Brain Tumors. Pathology and its Biological Correlates, Springer-Verlag, Berlin 1993.

Sheline G: Radiotherapy for high grade gliomas. International Journal of Radiation Oncology Biology Physics 18:793-803, 1990.

Shields CB, Guan YT, Almond PR, Garretson HD, Lindberg RD: Radioneurosurgery using the LINAC scalpel: Technique, indications, and literature review. Kentucky Medical Association Journal 91:276-283, 1993.

Steiner L: Radiosurgery for cerebral arteriovenous malformations. In Fein JM ed. Cerebrovascular Surgery, Springer Verlag, New York, 1161-1214, 1985.

Sturm V, Bernd K, Höver KH, Schlegel W, Boesecke R, Pastyr O, Hartmann GH, Schabbert S, zum Winkel K, Kunze S, Lorenz W: Stereotactic percutaneous single dose irradiation of brain metastases with a linear accelerator. International Journal of Radiation, Oncology, Biology, Physics 13:279-282, 1987.

Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolem JH, Hoekstra FH, Tans JT, Lambbij N, Metsaars JA, Wattendorff AR, Brand R, Hermans J: Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery?: Annals of Neurology 33:583-590, 1993.

Wallner KE, Galichich JH, Krol G et al: Patterns of failure following the treatment for glioblastoma multiforme and anaplastic astrocytoma. International Journal of Radiation Oncology Biology Physics 16:1405-1409, 1989.

Weichselbaum RR, Hallahan DE, Chen G: Biological and physical basis to radiation oncology. In: Holland JF ed. Cancer Medicine, Ed. 3, Lea and Febiger, Philadelphia, 539-566, 1993.

Woodruff WW: Fundamentals of Neuroimaging, W.B. Sauders Company, Philadelphia, 1993.

Wollin M, Kuruvilla A, Kagan AR, et al: Critique of venous malformations using a standard linear accelerator [letter]. International Journal of Radiation Oncology Biology Physics 18:1535-1536, 1990.

Wright DC, Delaney TF, Buckner JC: Treatment of metastatic cancer. In DeVita Jr VT ed. Cancer: Principles and Practice of Oncology, J.B. Lippincott Co., Philadelphia, 2170-2186, 1993.

Wu A: Physics and Dosimetry of the gamma knife. Neurosurgery Clinics of North America 3:35-50, 1992.

Wu A, Lindner G, Maitz AH, Kalend AM, Lunsford LD, Flickinger JC, Bloomer WD: Physics of gamma knife approach on convergent beams in stereotactic radiosurgery. International Journal of Radiation Oncology Biology Physics 18:941-949, 1990.

Yasargil MG: Microneurosurgery, Volume IIIA. Georg Thieme Verlag, Stuttgart, 1987.

Zeman W, Curtiss HJ, Baker CP: Histopathologic effect of high energy particle microbeams on the visual cortex of the mouse brain. Radiation Research 15:496-514, 1961.

Zülch KJ: Brain Tumors. Their Biology and Pathology, Ed. 3. Springer-Verlag, Berlin 1986.

Vita