Advances in the Use of Gamma Knife in Brain Tumors

An Ochsner Health Perspective

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Disclosures

- Medical Director, Gamma Radiosurgery Center of New Orleans (2008 - 2023)

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Goals

- Provide a context to understand the role of radiosurgery as part of the CNS Tumor Strategy at Ochsner Health.
- Provide a history of radiosurgery
- Describe current plan for growth and success of radiosurgery program at Ochsner Health

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CNS Tumors

Scope of Problem

- Approximately 70,000 new cases of primary CNS tumors are diagnosed in the United States each year. Of these lesions, roughly 24,620 will be malignant.
- Although primary CNS tumors comprise only 1.4% of all cancers, they are among the most aggressive tumors and result in a combined mortality rate of about 60% .
- The five-year survival rate for primary malignant brain and central nervous system tumors is the sixth lowest among all types of cancers.
- Roughly 170,000 new cases of brain metastases are diagnosed each year. This is likely an underestimate of the actual incidence as the number of patients diagnosed with cancer is increasing.

CNS Tumor Program at Ochsner Health

Objectives

Objectives

- To improve the care of patients with CNS tumors.
  - Provide a multidisciplinary team approach to patients
    - Increase the number of patients seen at multidisciplinary clinics and presented at tumor board.
    - Provide general and comprehensive plans of care.
  - Provide both medical and psychosocial support for patients with CNS tumors.
  - Track patients to provide feedback regarding care and keep vital statistics of program.

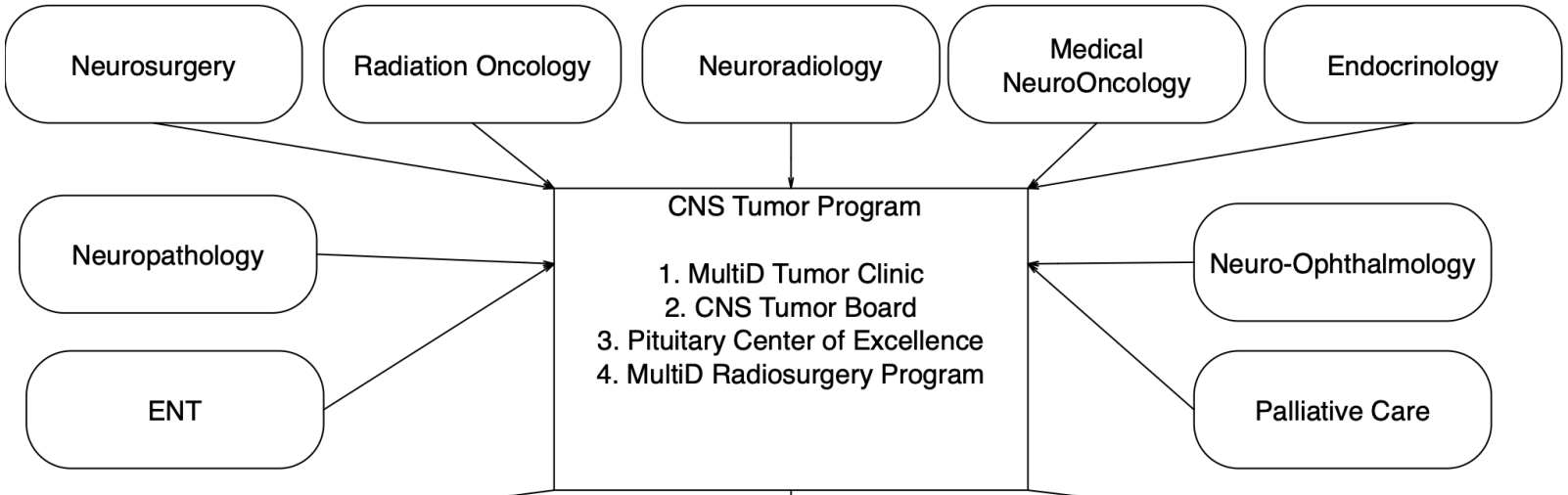
- To promote and support clinical research.
  - Development and support of clinical projects within the neurosciences.
  - Promote patient accrual into ongoing clinical trials.
  - Provide support with grant-writing and IRB process, to increase the number of clinical trials.

- To promote and support basic science research.
  - Encourage basic science collaboration with industry and other academic centers.
  - To encourage the collection of CNS tumors operated to the tissue bank.

Benefits

1. Provide infrastructure to attract more basic science and clinical studies.
2. Increase the number of patients with CNS tumors treated.
3. Provide community with better options for treatment of CNS tumors.
4. Improve efficiency and quality of care of patients and improve the satisfaction of care of patients with CNS tumors.

CNS Tumor Program at Ochsner Health



Innovations in Clinical Care

1. Minimally Invasive Intracranial Surgery Program

2. Anatomical, DTI and Functional mapping in Intracranial Surgery.

Active and Ongoing Clinical Trials

1. Safety and Tolerance of 4-Demethyl-4-cholesteryloxycarbonylpenclomedine (DM-CHOC-PEN) plus SRS or WBRT in Adult Subjects with Advanced Cancer Involving the CNS.

2. METIS trial: A multi-center, phase 3, pivotal, open-label study of radiosurgery with or without Tumor Treating Fields (TTFields) for 1-10 brain metastases from non-small cell lung cancer (NSCLC).

3. A study to assess the efficacy and safety of minimally invasive keyhole craniotomy and brachytherapy compared to radiosurgery for the treatment of brain metastases.

4. Safety and tolerance of 4-Demethyl-4-cholesteryloxycarbonylpenclomedine (DM-CHOCH-PEN) in adolescent and young adult (AYA) subjects with cancers.

Translational Studies

1. Central Nervous System (CNS) Molecular Characterization and Chemotherapeutic Susceptibility.

2. Efficacy of radiosurgery as part of a multimodal treatment protocol for central nervous system pathologies.

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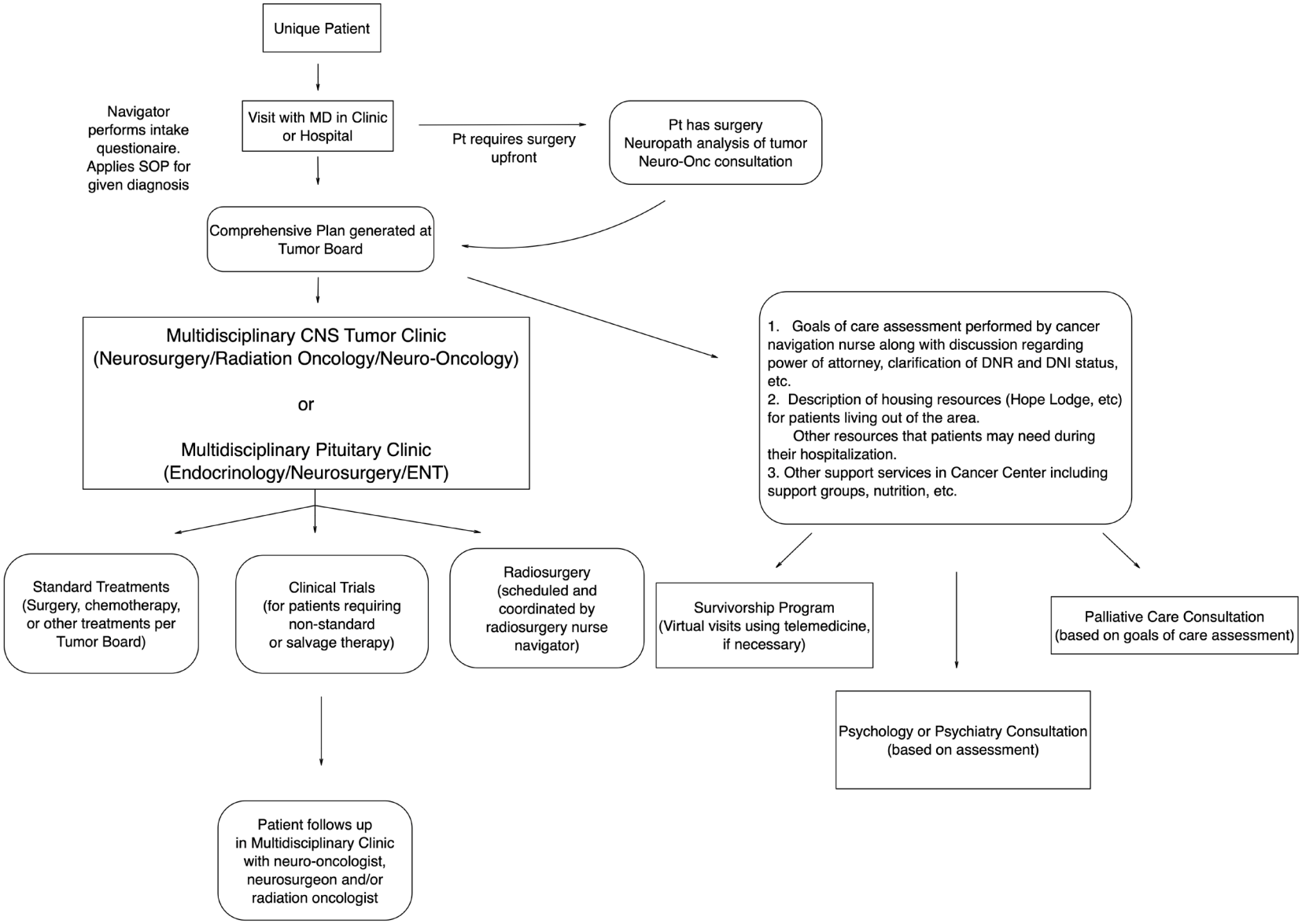
Patient Care at Ochsner Health



Clinical Trials

1. A protocol for the safety and tolerance of intravenous 4-Demethylcholesteryloxycarbonylpenclomedine (DM-CHOC-PEN) in patients with advanced cancer.
2. Efficacy of radiosurgery as part of a multimodal treatment protocol for central nervous system pathologies.
3. Central Nervous System (CNS) Molecular Characterization and Chemotherapeutic Susceptibility. This study allows for the collection of brain and spine tumors removed during surgery and evaluation of those tissues.
4. A Phase II Trial: Safety and Tolerance of Intravenous 4-Demethyl-4-cholesteryloxycarbonylpenclomedine (DM-CHOC-PEN) in Patients with Malignancies Involving the Central Nervous System.
5. A Single-Blinded, Randomized, Controlled Study to Evaluate the Safety and Effectiveness of EVICEL®Fibrin Sealant (Human) Compared to a Hydrogel Sealant as an Adjunct to Sutured Dural Repair.
6. A Phase 1/2 Study of SL-701, a Subcutaneously Injected Multivalent Glioma-Associated Antigen Vaccine, in Adult Patients with Recurrent Glioblastoma Multiforme.
7. METIS trial: A multi-center, phase 3, pivotal, open-label study of radiosurgery with or without Tumor Treating Fields (TTFields) for 1-10 brain metastases from non-small cell lung cancer (NSCLC).
8. A study to assess the efficacy and safety of minimally invasive keyhole craniotomy and brachytherapy compared to radiosurgery for the treatment of brain metastases.
9. Safety and tolerance of 4-Demethyl-4-cholesteryloxycarbonylpenclomedine (DM-CHOCH-PEN) in adolescent and young adult (AYA) subjects with cancers.
10. TRIDENT EF-32: A Pivotal Randomized, Open-Label Study of Optune® (TTFields, 200khz) Concomitant with Radiation Therapy and Temozolomide for the Treatment of Newly Diagnosed Glioblastoma

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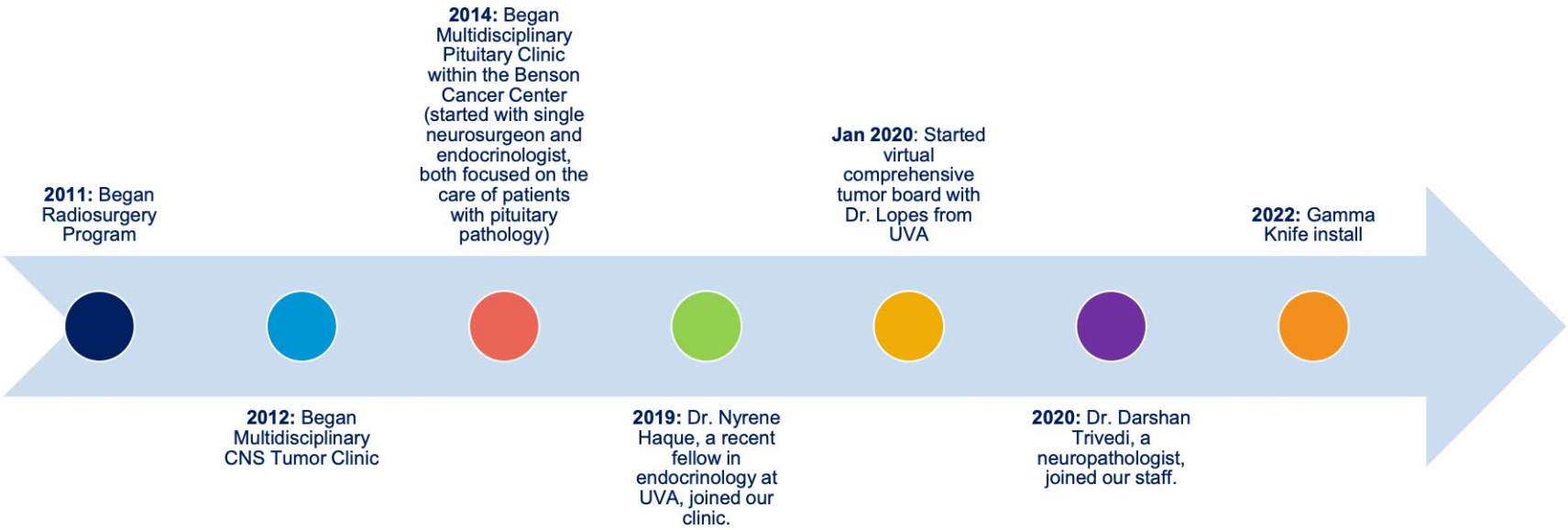
Our History



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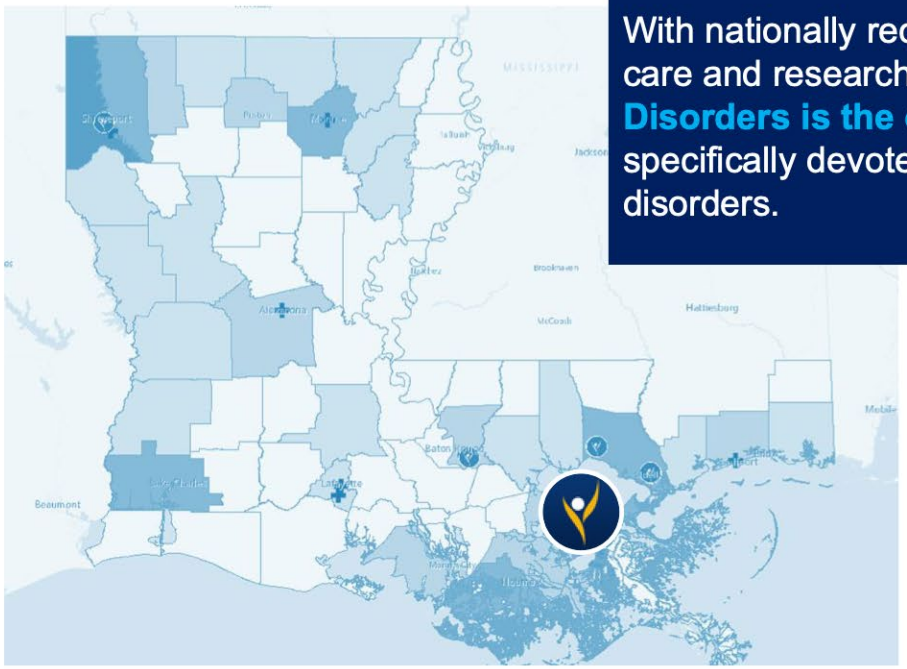
Multidisciplinary CNS Tumor Clinic

- CNS Tumor Clinic in the Benson Cancer Center was started in 2014.
- This clinic is a direct collaboration between Neurosurgery, Oncology, Radiation Oncology, and Endocrinology (Pituitary Program).
- Each provider will see patients who require multidisciplinary care within the same time block and if possible within the same space.
- We currently have dedicated space for our CNS Tumor clinics on the 3rd floor with two dedicated days for multidisciplinary clinics.

Multidisciplinary CNS Tumor Board

- In 2019, we started our first dedicated CNS Tumor Board within the Ochsner system.
- The goal of this tumor board is to provide a forum for the discussion of all elective CNS tumor patients and allow for multidisciplinary input into more comprehensive plans.
- Currently this meeting is held everyTuesdays at 0800. These meetings are held via Zoom.
- Required participants include Dr. Marcus Ware (Neurosurgery), Dr. Clayton Smith (Radiation Oncology), Dr. Caroline Goldin (Radiation Oncology) and Dr. Darshan Trivedi (Neuropathology).
- All CNS cancer providers across the system are encouraged and invited to join.

Pituitary Clinic Overview



With nationally recognized excellence in neurosurgical and neuroendocrine care and research, **Ochsner's Multidisciplinary Center for Pituitary Disorders is the only multidisciplinary center in the Gulf South** specifically devoted to the comprehensive care of patients with pituitary disorders.

- Patients seen from LA, MS, AL, FL, TX
  - In person and virtual options available
- Patient centered coordinated care
- Appropriate imaging and labs are typically obtained prior to visit
- Same day visits with multiple specialties and imaging if needed
- 263 unique patients seen in 2021 despite COVID-19 pandemic

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Services

Conditions treated:

- Nonfunctional pituitary adenoma/carcinoma
- Craniopharyngioma
- Rathke's Cleft Cyst
- Hyperprolactinemia/prolactinoma
- Acromegaly
- Cushing's Disease
- Hypopituitarism
- Pituitary Apoplexy
- Hypophysitis
- Infertility due to pituitary disorders
- Visual impairment from sellar lesions

Treatments:

- Transsphenoidal Endoscopic Surgery
- Craniotomy
- Gamma Knife Stereotactic Radiosurgery
- Fractionated Radiation
- Medical management including treatment of
  - functional adenomas
  - Pituitary hormone deficiencies

Pituitary Center of Excellence

Ochsner Health Neuroscience Institute

Goals of Care

- Early detection of pituitary abnormalities
- Establishing the correct diagnosis
- Determining the most suitable treatment
  - Observation, surgery, medication, radiotherapy, or combination
- If surgical - removing the pituitary mass but preserving the normal pituitary tissue and nearby structures
- Eliminate hormonal hypersecretion and its effects
- Monitoring for and prevention of lesion recurrence
- Recognizing and caring for the acute and delayed complications of the disease like hypopituitarism

Requires coordinated care often including medical therapy, surgery, and radiation therapy with long-term multidisciplinary follow-up

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Meet Our Multidisciplinary Team

Blair Barton, MD
Otolaryngology/
Rhinology

Rachel Calix, MD
Neuro-Ophthalmology

Nyrene Haque, MD
Endocrinology

Joseph Keen, DO
Neurosurgical Oncology

Andrew Lawton, MD
Neuro-Ophthalmology

Clayton Smith, MD
Radiation Oncology

Darshan Trivedi, MD
Neuropathology

Marcus Ware, MD
Neurosurgical Oncology

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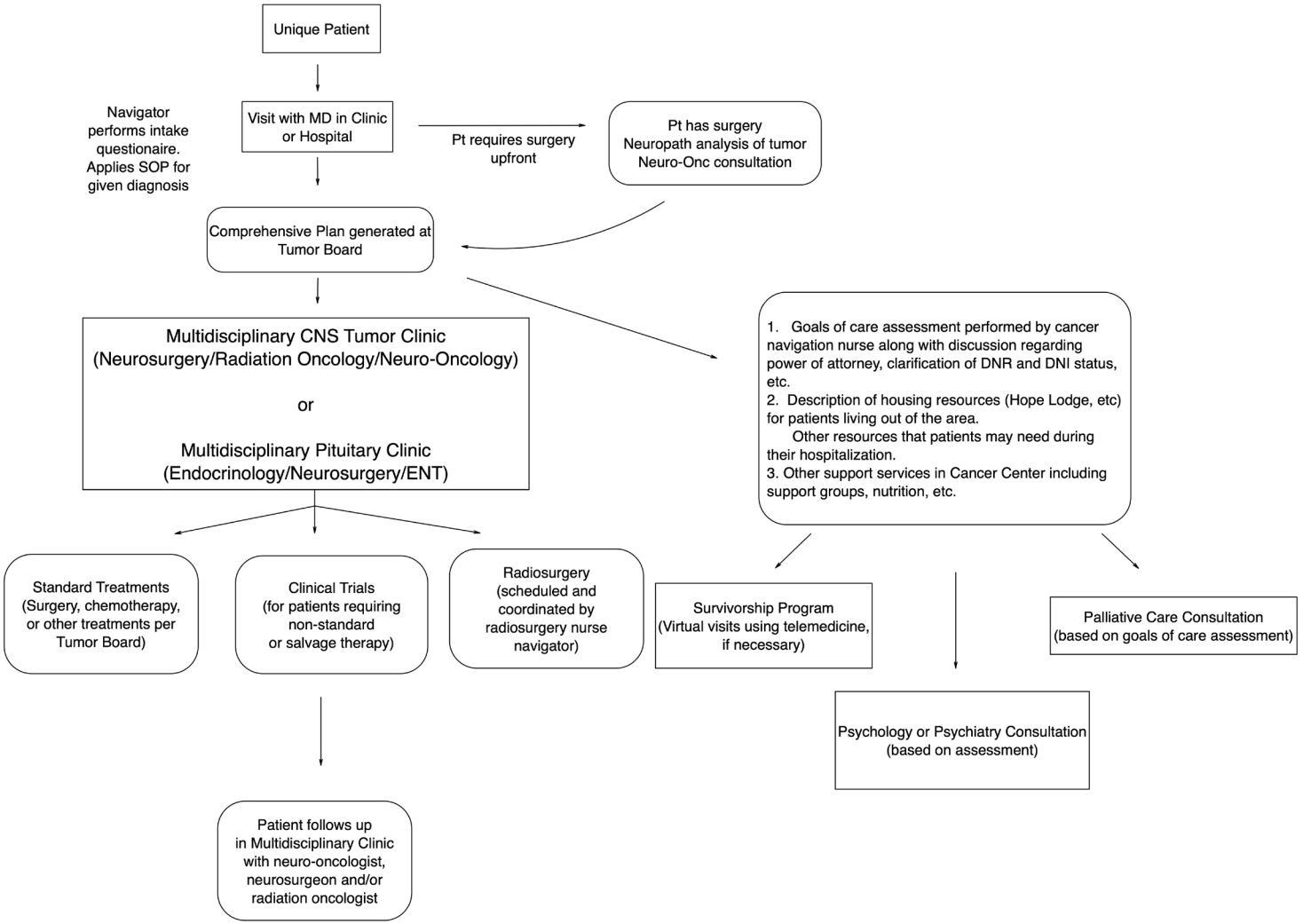
CNS Tumor Patient Care at Ochsner Health



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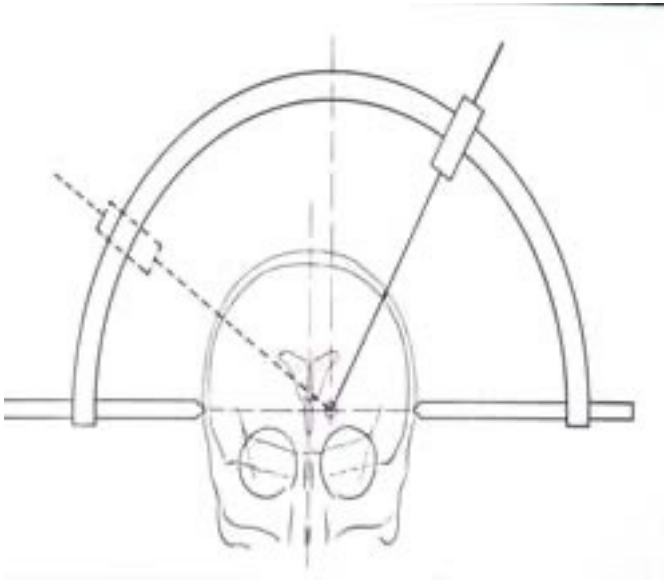
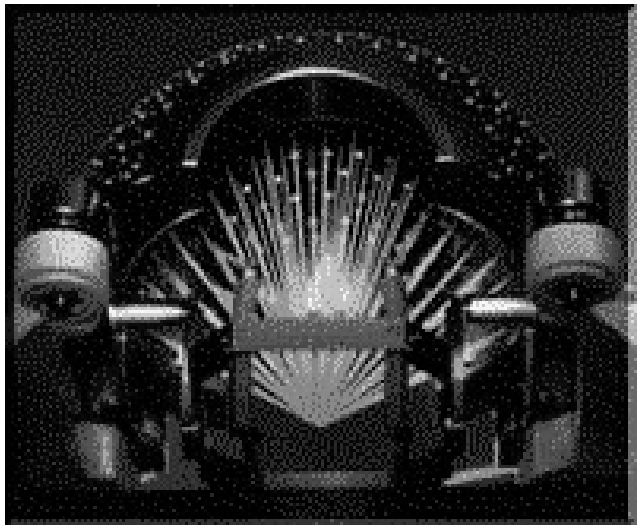
Radiosurgery Program

- Radiosurgery - A nonsurgical technique that delivers numerous narrow, precisely aimed, highly focused beams of ionizing radiation that converge at a specific point.
- Radiosurgery is a very important tool in the treatment of brain tumors. Because the radiation can be focus to small areas of tumor, normal structures such as the brain, and other vascular and neural structures around it, are relatively spared.
- Because of its low morbidity, radiosurgery allows patients who are not candidates for open surgery because of co-morbidities and/or life to be treated and have their disease controlled.





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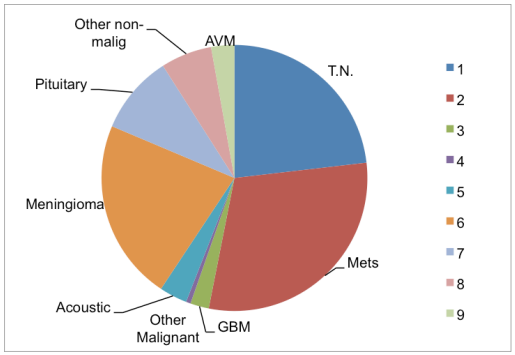
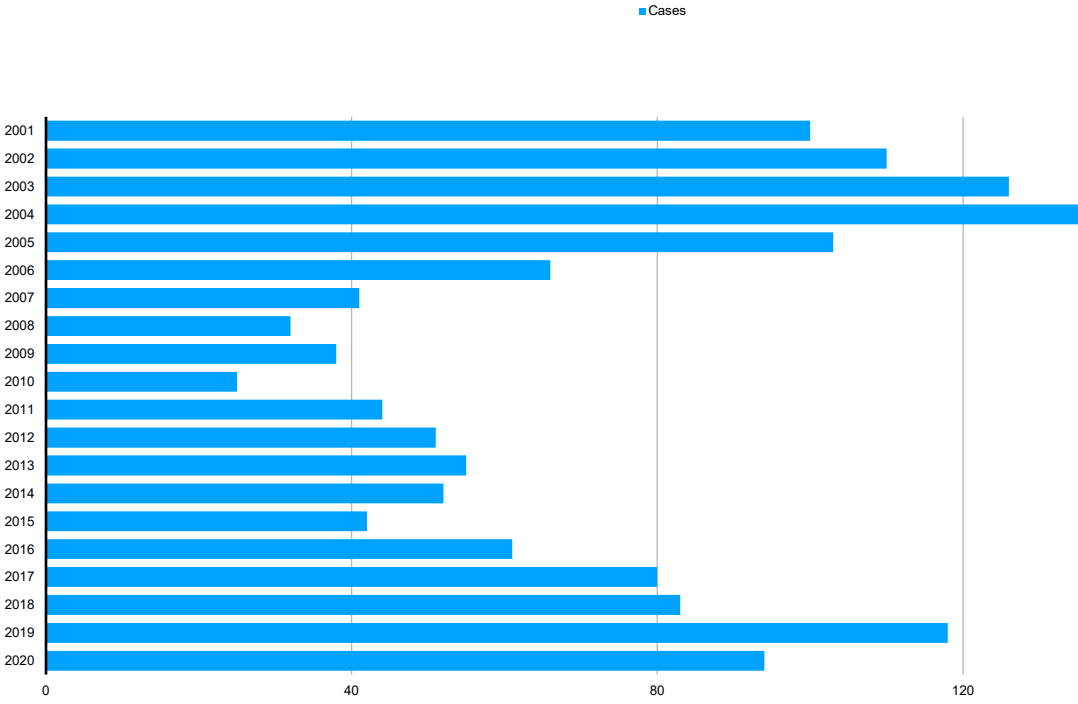
Radiosurgery Program

- Stereotactic Radiosurgery (SRS) is a treatment for tumors that uses well-collimated, multiple small beams of ionizing radiation to treat tumors, while reducing toxic exposure to surrounding brain tissues.
- In 2011, we began our radiosurgery program at OMC. In 2014, we also began treating patients with image-guided radiosurgery (IGRS) using Novalis® Radiosurgery and the TrueBeam™ STx systems. Though not ideal for the treatment of all tumors in all locations, this allowed us to increase our in-house capabilities.
- In 2015, we began using the Masep Infini at the Radiosurgery Center of New Orleans which allowed for better treatment of more complex lesions.
- With our programmatic growth, we have had a sharp increase in the number of radiosurgery cases performed.
- In the last quarter of 2020, we plan to open a Gamma Knife Center here at OMC. This unit will allow us to expand the radiosurgery practice and firmly anchor that practice at OMC.





Radiosurgery Program Components

- Human Capital
  - Neurosurgeon
  - Radiation Oncologist
  - Physicist
  - Nursing support
- Technology
  - Cobalt 60 based units
  - Linear accelerator based units

Historical Milestones in Stereotactic Radiosurgery

Gamma Knife

1987: Dade Lunsford
First GK unit in US

1985: Lars Leksell
Introduction of MRI to GK

1974: Lars Leksell
Introduction of CT to GK

1970: Steiner
First GK in a AVM

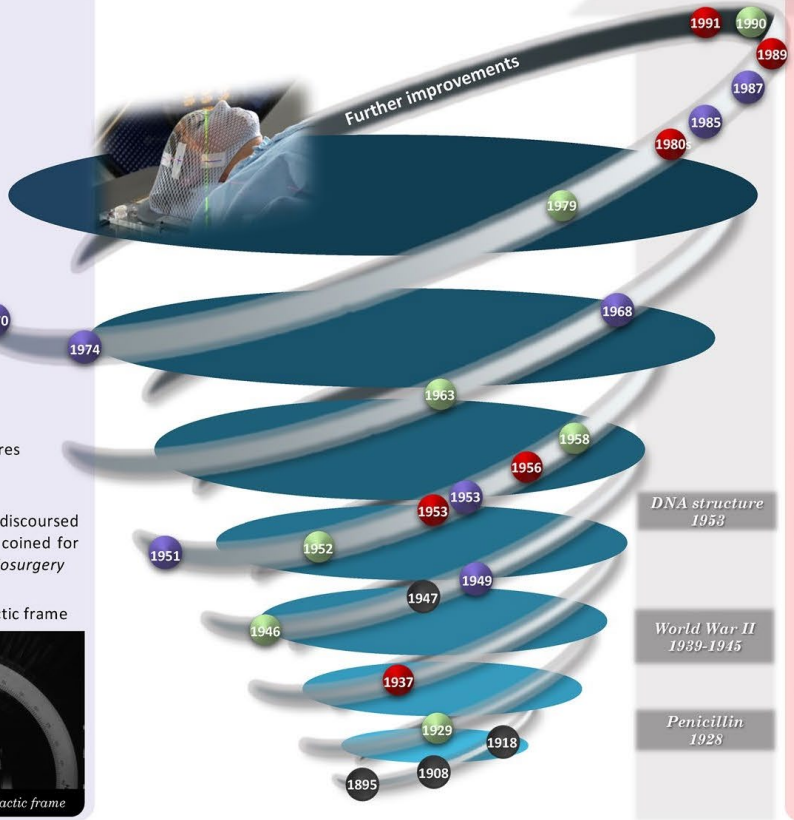
1968: Lars Leksell
First Gamma Knife (GK) procedures (using Co-60 as source of energy)

1953: Lars Leksell
First Stereotactic Radiosurgery procedures (using orthovoltage X-rays)

1951: Lars Leksell
Published his seminal paper where he discoursed about a novel procedure for which he coined for the first time the term *Stereotactic Radiosurgery*

1949: Lars Leksell
Designed a novel center of arc stereotactic frame

Lars Leksell and his target centered arc stereotactic frame



LINAC

1991: Adler
First CyberKnife unit

1989: Lutz & Winston
LINAC dosimetry

1980s: Colombo & Betti
First LINAC-based SRS procedure

1956: US
First LINAC-based Radiotherapy

1953: England
First LINAC-based Radiotherapy procedure

1939: Varian brothers
First klystron invention

Proton Therapy

1990: Loma Linda Medical Center
First hospital-based facility for Proton Therapy

1979: R. Kejllberg
Dose-effect curves concept

1963: R. Kejllberg
Bragg peak Proton Therapy for pituitary adenomas

1958: Lars Leksell
Upsala Cyclotron for first Proton Therapy

1952: Lawrence Berkeley Lab
First-in-human Cross-firing Proton Therapy

1946: Ernest Lawrence
184-inch Synchrocyclotron completion

1946: Robert Wilson
Proton therapy and Bragg peak concepts

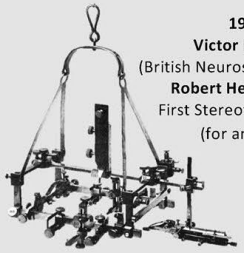
1929: Ernest Lawrence
First particle accelerator (60-inch cyclotron)

184-inch Synchrocyclotron: Developed as part of the Manhattan Project during World War II

Common Milestones

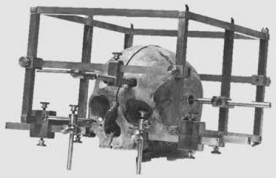
1895: Wilhelm Roentgen
X-rays Discovery

First X-rays were taken on Roentgen's wife hand

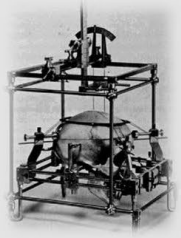


1908
Victor Horsley
(British Neurosurgery Father)
Robert Henry Clarke
First Stereotactic Frame
(for animals)

1918:Aubrey T. Mussen
First stereotactic frame adapted for humans



1947
Ernst A. Spiegel
(Neurologist) **&**
Henry T. Wycis
(Neurosurgeon)
Performed the first stereotactic neurosurgeries in humans at Temple University - Philadelphia



Health System

Henry Ruiz-Garcia

Current State of the Art: Elekta Icon

- High degree of accuracy using 192 beams
- Limited radiation exposure to healthy brain and other tissue
- Ultra-precise stereotactic radiosurgery with or without framing
- Allows for single or multiple fractions
- Ability to spread treatments over several days
- Ability to treat larger tumors and AVMs which were not well treated with other systems

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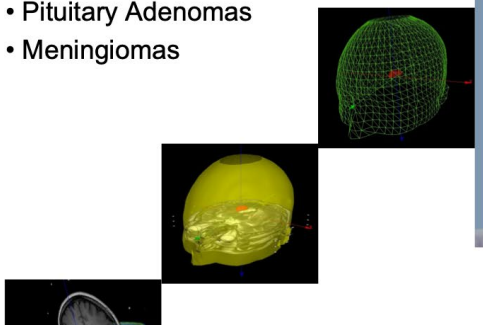
Gamma Knife Benefits

- The Gamma Knife's accuracy - within less than two-tenths of a millimeter - makes this the technology of choice to safely treat certain diseases of the brain, especially those in which nearby brain tissue is crucial for normal functioning of the patient.
- Procedures can be performed in a short time period with unmatched precision.
- More than 300,000 patients around the world have had Gamma Knife radiosurgery and its impressive results have truly revolutionized the treatment of brain disorders.

Radiosurgery Indications: A Brief Review (Intracranial Disease)

- Brain Metastases
- Other
  - Arteriovenous Malformations
  - Trigeminal Neuralgias
  - Vestibular Schwannomas
  - Pituitary Adenomas
  - Meningiomas



Radiosurgery for Metastases

- Brain metastases are the most common malignancy encountered in the central nervous system (CNS), with up to 30-40% of cancer patients developing brain metastases at some point during the course of their disease.
- In the more recent MD Anderson Cancer Center (MDACC) study, patients who underwent resection of brain metastasis were randomized to observation or SRS. SRS improved the 12-month rate of local control (72% vs. 45%) and median time to local recurrence (not reached vs. 7.6 months) but SRS neither reduced the rate of distant brain failure nor did it improve overall survival.
- SRS+/- surgery has become the standard of care for treatment of metastases.

Radiosurgery for AVMs

- In the 1970s, reports began to appear documenting the successful obliteration of arteriovenous malformations (AVMs) with radiosurgery.
- Intracranial arteriovenous malformations (AVMs) consist of an abnormal nidus of blood vessels that shunt blood directly from an artery to a vein and thereby bypass an intervening capillary bed.
- When an AVM is treated with radiosurgery, a pathologic process appears to be induced that is similar to the response-to-injury model of atherosclerosis. Radiation injury to the vascular endothelium is believed to induce the proliferation of smooth-muscle cells and the elaboration of extracellular collagen, which leads to progressive stenosis and obliteration of the AVM nidus thereby eliminating the risk of hemorrhage.
- The advantages of radiosurgery - compared to microsurgical and endovascular treatments - are that it is noninvasive, has minimal risk of acute complications, and is performed as an outpatient procedure requiring no recovery time for the patient. The primary disadvantage of radiosurgery is that cure is not immediate. While thrombosis of the lesion is achieved in the majority of cases, it commonly does not occur until two or three years after treatment.
- During the interval between radiosurgery treatment and AVM thrombosis, the risk of hemorrhage remains

Radiosurgery for Trigeminal Neuralgia

- Trigeminal neuralgia (TN) is a rare disorder of the fifth cranial nerve and is considered one of the most excruciatingly painful conditions that may be encountered in clinical daily practice.
- The first-line therapy is pharmacological (carbamazepine).
- Radiosurgery has been shown to be a very useful treatment.

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The Very Long-Term Outcome of Radiosurgery for Classical Trigeminal Neuralgia

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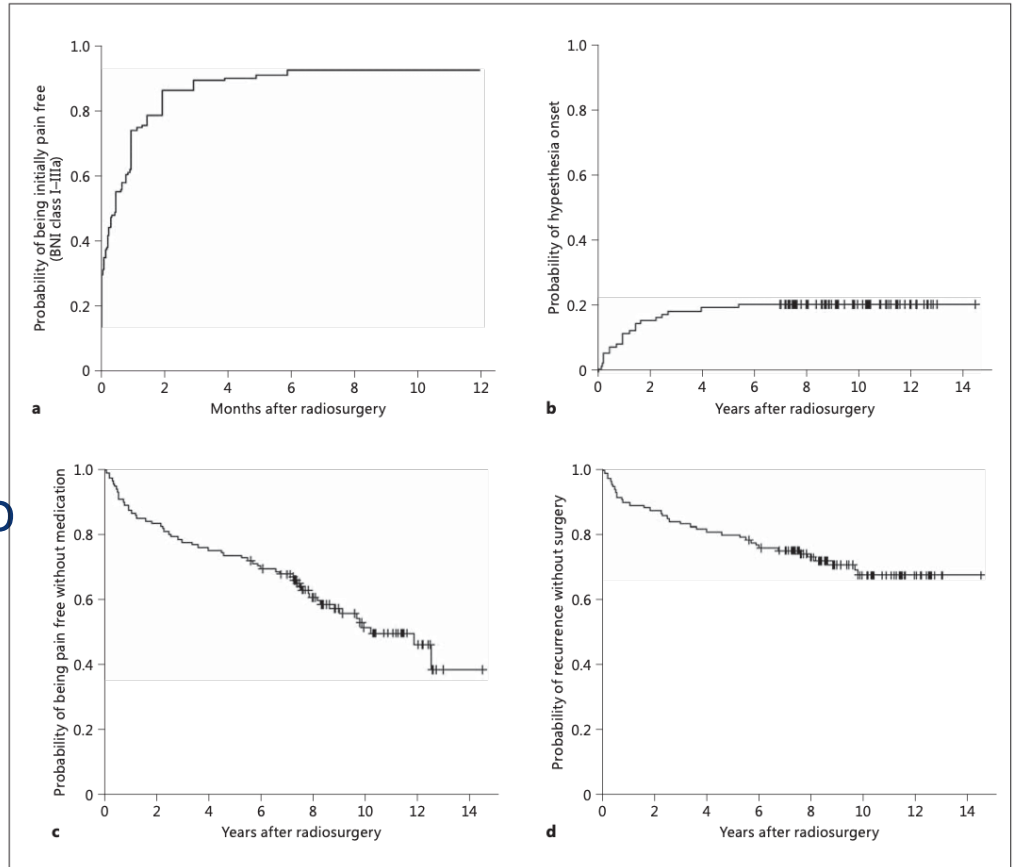

Radiosurgery for Pituitary Adenomas

- For the treatment of pituitary adenomas, transsphenoidal surgery is established as one of the most reliable treatment modalities.
- Stereotactic radiosurgery (SRS) is a choice of treatment for pituitary adenomas (PA), particularly for residual or recurrent disease.
- Radiosurgery for pituitary adenomas achieves 85–100% of tumor control rates were for 3–6 years, with only mild and transient neurological complications in most cases.

Radiosurgery for Vestibular Schwannomas

- Vestibular schwannoma (VS) or acoustic neuroma is a benign tumor which originates from the vestibulocochlear nerve division, precisely from the nerve Schwann cells.
- Treatments for VS include conservative, surgery and radiosurgery.
- GKRS is also considered to be a good treatment method for solitary VS's that are <30 mm in cisternal diameter.
- Above this size, ons should strongly consider surgical removal/debulking (especially symptomatic pts) or fractionated treatment.

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Radiosurgery for Meningiomas

- Meningiomas are the most common non-glial intracranial tumor in adults, accounting for 30% of all central nervous system tumors.
- The majority of these tumors are benign (WHO grade I), with a typical slow growth pattern.
- Surgical resection is the preferred treatment for accessible meningiomas as it results in immediate resolution of mass effect and allows for complete treatment of the tumor, including the affected bone. The long-term efficacy of surgical resection is largely dependent on the extent of resection achieved.
- Local control rates following SRS of benign meningiomas range from 86 to 100% at 5 years and 83–95% at 10 years.
- 5-year local control rates for radiosurgery are similar to historical control rates obtained with GTR. Reduction in tumor size was reported in 12–70% of patients with clinical improvement ranging from 8 to 66%.

Closing Remarks

- Radiosurgery is tool that is important in the treatment of brain tumors.
- Like any other tool it can provide great benefits with properly utilized.
- This tool is one that fits well in our current clinical programs.
- Despite the low risk of complications at the time of treatment, SRS is associated with a range of toxicities including radiation necrosis, peritumoral edema, hemiparesis, cranial nerve deficits, vascular occlusion, and delayed hydrocephalus.

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