ROLE OF GAMMA KNIFE IN BRAIN TUMORS

- History
- Equipment and its working
- Indications
- Results
- Complications

Historical background

- The **Gamma Knife** (stereotactic radiosurgery)

  in which narrow beams of highly focused and destructive dose of radiation is given in a single session using an external reference frame fixed to the head.

- Term introduced by Lars Leksell in 1951
  (Professor of Neurosurgery, Karolinska University)
- 1967 , 1st GKRS installed by Leksell & Larsson at Stockholm
  (For treatment of intractable pain managements & functional procedure using 179 CO -60 source)
- 1975 , 2nd generation GKRS used at Karolinska institute using round collimetors (4,8,14,18mm) for treatment of vascular malformation & tumors
- Focal distance from radiation source to target is 40.3 cms

- Four models are used –
- Model U : uses a hemispherical array – dose profile greater in superior / inferior extent
- model B/ C: uses circular array of radiation sources –dose profile greater in right/left
- New model C: contain an automatic positioning system
- latest version (perfexion):was first installed at Mayo Clinic in September 2007.

How does it work?

- Radiation does not remove the tumor or tissue abnormality.
- Radiation distorts DNA (ionizing induces mutations and other forms of DNA damage & cell cycle arrest).
- Radiation induce apoptosis to proliferating cells.
- The cell lose its ability to retain fluids.
  - For arteriovenous malformations, radiation induces the thickening and closing off the blood vessels.

Gamma Knife "Cure"

- Tumor loses its ability to grow
- Remains the same size
- Never grow again

Benign tumors take up to 2 years to disappear

Metastatic (Cancerous) tumors take only months to disappear

Radiosurgery Technique

- Three part of the procedure
  - 3 D Stereotactic localization
  - Dose planning- Most crucial
  - Radiation exposure

3-D Stereotactic Localization

- Aim – to place stereotactic frame such a way that lesion to be treated is located as close to 3-D frame centre as possible .
- Use imaging and 3-D mapping techniques to target tissue of interest
- Tomography Techniques:
  - PET (CT) and MRI
  - Good for tumor pathologies
- X-ray-based Techniques:
  - X-ray and Digital Subtracted Angiography
  - Good for vascular imaging

Treatment Planning

Gamma Plan 4.12 software used to plan GK treatment of a frontal lobe meningioma. Note abrupt fall off of radiation at tumor edge. The tumor volume is red and the yellow lines represent the 50% isodose curves.

Treatment Planning

- Image transferred & using Leksell Gamma Knife 3-D planning software, a treatment protocol is planned
- Surgeon, radiation oncologist and radiation physicist decide dose plans
  - different collimator sizes and added "shots“ required
- Tumors may not be exactly spherical
  - Require additional "shots"

- High dose delivered to tumor core
  Tumor tissue less oxygenated at center
- Normal surrounding parenchyma spared
- Dose most lethal when surrounding tissue receives a higher dose of radiation

Dose limiting factors

- Dose rate
- Volume of tumor-

  maximal tumor volume that could be radiated is around 25 cc
- Cranial nerves sensitivity
- Effect on surrounding vessels

  Usually not a limiting factor

  Endothelial damage in large vessels does not leads to thrombosis in most of the cases

Cranial nerve sensitivity

- Factors determining cranial nerve dysfunction
  - Nature of the nerve
    -Optic and Acoustic
  - Length of nerve irradiated
  - Volume of nerve roots exposed
  - Mechanical stretching of the nerve by tumor

Dose limits of cranial nerves

- Optic nerve- 8 Gy
- Cavernous sinus nerves- 30-40 Gy
- Trigeminal nerve- 10-25 Gy
- Facial nerve- 10-25 Gy
- Lower cranial nerves- 10-25 Gy

Tishler CA, loeffler JS et al :Tolerance of cranal nerve to radiosurgery :Int J Radiate Oncol Biol Phys, 1193

Advantage of GKRS

- Noninvasive method of treating inoperable lesions
- Eliminates the risk of open surgery

- patients experience little discomfort.
- Low immediate procedural morbidity
- Patients can immediately resume their previous activities

- Short hospitalization

- The lesion being treated receives a high dose of radiation with minimum risk to nearby tissue and structures

Disadvantage

- Delayed complication of radiation
- Use is limited to tumor located adjacent to critical neurovascular structure

Patient Selection

- Lesions characteristic
  - small -less than 3 cms in diameter
    - Larger not appropriate
      - require two or more "shots“
      - radiation dose to surrounding brain is more - damage tissue
      - Radiation Necrosis
  - Geometrically
    - Regular- spherical, ovoid or cylindrical is good
    - irregular shaped i.e. star or crescent shaped- not good candidates
      - Difficult to plan radiation dose volume

        or
      - it deliver lethal dose of radiation to the surrounding brain

Indications

- **Tumors**
  - Acoustic neuromas
  - Pituitary adenomas
  - Meningiomas
  - Skull-based tumors
    - Meningiomas of cavernous sinus
    - Chordomas and chondrosarcomas
  - Craniopharyngiomas
  - Metastases
  - Gliomas and other primary intra-axial tumors
  - Pineal tumors
  - Haemagioblastoma
  - Glomus tumors

Indications

- **Vascular abnormalities**:
  - Arteriovenous malformations
  - Cavernous malformations
- **Functional problems**:
  - Trigeminal neuralgia
  - Parkinson's disease (pallidotomy)
  - OCD
  - Radiosurgical thalamotomy
- **For epilepsy**
  - Cavernous malformation
  - Arteriovenous malformation
  - Hypothelamic hemartoma
  - -Mesial temporal epilepsy
- **Ocular tumors**
  - Uveal melamona
  - Orbital metastases
  - Optic nerve sheath meningioma

Vestibular schwannomas

- First GKRS by Leksell and steiner, in 1969
- Effect is either no further growth or slight diminution of tumor volume
- In past 25 years, results favoring GK as compared to microsurgery
- No reports of cancer being caused by radio surgery
- Tumor control rate : 93 - 98%
- Hearing preservation superior with Gamma knife as compared to micro neurosurgery.
- Rare loss of facial movement or sensation
- Most patients retain some hearing

Indications of radio surgery

- Small tumors with maximum intracisternal diameter : < 3 cm
- Residual / Recurrent tumor after microsurgery
- In elderly population
- High risk patients refuse microsurgery.
- In younger subset, hearing preservation is an important issue

Contraindication :

Tumor causing mass effect on brain stem with clinical deficit

Dose recommendations

- Marginal dose for small tumors -14 Gy

  medium tumors - 12 Gy

  large tumors -10 Gy
- Margin dose 11 to 15Gy at 50% isodose curve.

Comparison of Radiosurgical & Microsurgical Treatment for Acoustic Neuromas

Procedure	Cure/ Control	Death	Hearing Preservation	Facial Nerve Preservation
GK Radiosurgery	**90-96%**	0%	70%	100%
Microsurgery	98%	1.5%	7%	63%

Regis J,Delsanti C,Roche P-H,Thomassin J-M,Pellete W. Functional outcomes of radiosurgical treatment of vestibular schwannomas:
1000 successive cases and review of the literature.Neurochirurgie 2004:50(2-3):301-311

J. Neurosurg94(5):1091-1100,2002,Modern management of vestibular schwannomas

Results

- Earliest change includes loss of contrast or gadolinium enhancement, most marked in center of tumor
- Poorer response in NF-2-life long follow up required
- SRS – high rate of tumor control, higher hearing preservation , low morbidity
- Initial loss of contrast enhancement may be followed by period of increased volume and dense enhancement
- Decrease in tumor volume with increased length of follow up-up to 90 % at 10 years

Chopra R, Kondzoilka D,Niranjan A,Lunsford LD,Flickinger JC. Long term follow-up of acoustic schwannoma radiosurgery with marginal tumor doses of 12 to 14 Gy.Int J Radiat Oncol Biol phys 2007:68:845-851

Meningiomas

- Microsurgery is the initial treatment of choice
- First Meningioma radiated in 1975

- GKRS used as an alternative to post operative radiotherapy for residual meningiomas
- Advantages include unique accuracy and precision ; minimizing risk

Meningiomas

- Indications
  - primary treatment (for difficult to operate)
    - cavernous sinus / basal meningioma
    - petroclival tumors of the posterior fosse
    - Medical illness /advanced age
  - For residual meningiomas
  - Recurrent tumor after open surgery

  - Contraindicated
    - Tumor with symptomatic optic nerve or chiasmal compression
    - optic nerve sheath tumor with preserved vision
    - > 3 cms in diameter with mass effect

Meningiomas

- Mean dose to tumor margin :14 Gy
- Mean tumor volume: 7.4 ml
- mean 7.5 isocenter used
- Results
  - 94% tumor control rate
  - 10% edema risk
  - Subsequent surgery - 5.2 %,
  - Additional RT :2.9%
  - Morbidity –7.7%

Kondziolka,Niranjan A,long term result after radiosurgery for benign intra cranil tumors, Neurosurgery 2003, 53

Gliomas

- SRS recommended mainly for Pilocytic astrocytomas located in thalamus, hypothalamus, brain stem, optic tract etc.
- Low grade gliomas (grade 2) are usually diffusely infiltrating hence role of radiosurgery limited for residual lesion
- Low grade glioma in medial temporal lobe is usually well circumscribed and amendable to SRS
- Two groups where it can be used
  patients with low Karnofsky's score
  well localized small lesions

- **Primary Low Grade Gliomas**
  - 95% response rate.
  - 10-year follow-ups in most patients treated show no evidence of residual tumor

Kida Y,Kobayashi T,Mori Y,Gamma knife radiosurgery for low-grade astrocytomas:results of long term follow-up. J Neurosurg 2000:93

Glioblastomas and anaplastic astrocytoma (High grade)

- Cytoreduction followed by GK
- MR scan within 48 hours of surgery
- residual, enhancing tissue is boosted with GK followed by conventional radiation therapy
- recurrence treated with GK, if tumor nidus is small
- High grade gliomas are usually bulky tumors; SRS again has a limited role

- Controlled studies need to be completed to conclusively demonstrate the role of GKRS
- Recent studies indicate radiosurgery is useful in extending survival in patients with recurrent glioblastoma
- Median tumor progression free interval of 12 months

Hsieh PC et al, Adjuvant Gamma Knife stereotactic radioosurgery , treatment option for recurrent GBM, Neurosurgery 2005,57

Metastatic Brain Tumors

- Metastatic tumors are usually well circumscribed; hence amendable to GKRS
- GKRS used in two forms
  - As local boost in combination with WBRT
  - As exclusive primary therapy
- As a primary therapy can be used in patients with low Karnofsky's score where WBRT is not desirable
- Dose recommendations

  adjunctive therapy 15-20 Gy

  primary therapy 25-30 Gy

Metastatic Brain Tumors

- Surgical removal + radiation
  - benefits patients' quality of life and survival
  - must control primary tumor first
- Gamma Knife radiosurgery
  - As effective as open surgery combined with brain radiotherapy

J Neurosurgery / Volume 93 / Dec 2000

- Effective even for tumors relatively resistant to external beam radiation therapy
- In selected individuals, whole brain radiotherapy not necessary
- Some multiple brain metastases are also candidates for GK

J Neurosurgery / Volume 93 / Dec 2000

- Recurrent or new tumor deposits can be retreated by GK

Results

- Success rate up to 90% reported
- Increase in tumor volume in some cases can be due to radionecrosis
- Recurrence rate is 7-15% Vs 20% for craniotomy + WBRT; hence Gamma knife superior
- Best results are obtained in patients with Melanoma and Renal cell carcinoma
- Results are poor with Bronchogenic carcinoma
- Hence, SRS recommended as primary modality for metastasis except in very large tumors

Hasegawa ,et al,Brain metastasis treated with radiosurgery alone, an alternative to WBRT,Neurosurgery 2003,52

Pituitary Tumors

- Best managed by microsurgery
- Gamma Knife radiosurgery useful in
  - recurrent
  - residual tumors, especially in the cavernous sinus.
- Excellent preservation of cranial nerve and pituitary function.

Pituitary adenomas- Nonsecretory

- Goal :to stabilize or reduce adenoma volume
- SRS indicated:
  - failure of total resection / parasellar region
  - recurrence after surgery and radiotherapy
- Dose required is less as compared to functional tumors
- Edge dose to tumor ranges from 10-15 Gy
- Dose to optic apparatus should be kept below 8 Gy
- Excellent tumor control rate 93% (68 - 100 %)
- Relatively safe

  no neuro-opthalmological complications reported

  1 case of pan- hypopituitarism reported

Sheehan JP ,Kondziolka,Radiosurgery for residual/recurrent nonfunctioning pituitary adenoma ,J Neurosurgery 97,2002

GH producing tumors

- Complete surgical resection not possible in many cases because of frequent parasellar growth
- SRS indicated in these cases
- Also used as an initial modality by some and in recurrence after surgery
- Edge dose to tumor ranges from 10-25 Gy
- In 70% cases GH levels fall below 5 ng /ml

Pollock BE Radiosurgery of GH producing pituitary adenoma :factor associated with biochemical remission ,J Neurosurgery 2007 ,106

ACTH Producing tumors

- Microsurgery considered gold standard for microadenomas - excellent results
- SRS indicated - Recurrent cases
  - Inaccessible tumor
- dose to tumor margin 20 Gy.
- Normal 24 hour UFC:63% at 1 year
- Hypocortisolism/recurrent disease not correlated with radiation doses.
- Tumor volume decreased in 73% cases not significantly correlated with endocrine outcome

Sheehan JM.,Vance ML,Sheehan JP,et al Radiosurgery for cushing`s disease after failed transphenidal surgery. J.Neurosurg 93(5):738-42 2000

Prolactinoma

- GK - primary
  - unsuccessful surgery (residual)
  - failed medical treatments
- Mean dose to tumor margin 13-30 GY
- Endocrine cure rate 52 %
- Remission rate poor in pt receiving antisecretory medication at time of GK

Pan L,zhang N,Wang EM.Wang BJ,Gamma knife radiosurgery as a priary treatment for prolactinomas.J Neurosurgery 2000:93

Craniopharyngiomas –

- Complete surgical resection not possible

- Multimodality therapeutic approach
  -Surgery + post op radiotherapy
  -Stereotactic cyst aspiration& injection of radioactive Yttrium-90
  - GKRS + Stereotactic single dose radiation

Chiou SM,Lunsford LD,Niranjan A,et al:Steriotactic radiosurgery of residual or recurrent craniopharygioma, after surgery,with or without radiation therapy.Neurooncol 3:159-166,2001.

Role of GKRS craniopharyngioma

- GKRS used
  - Primary treatment
  - adjunctive treatment alone
  - combining with intralesional brachytherapy
  - Salvage treatment for recurrence.
- Optimum dose to achieve local control was 12 Gy.(10 – 20)
- Tumor control: 79%, complete response:19%, at 65 months mean follow-up.
- Results are better with squamous histology as compared to adamantinomatous type.

Kobayanshi et al. Japan Long-term results of Gamma Knife surgery for the treatment of craniopharyngioma in 98 cinsecutive cases.J Neurosurg 2005:103(6 suppl)

Glomas Jugulare

- Role of GKRS remains controversial
- Indication
  - Elderly patients with symptomatic tumor
  - Residual / recurrent tumor
  - Smaller tumors
- Contraindication
  - Young patient with large tumors causing significant mass effect
  - Patient with catecholamine secreting tumor
- Tumor growth control rate of 94%
- Mean dose of 16.4 Gy.
- Margin dose 16.4 – Maximum dose 30
- Mean follow-up 46 months.
- Tumor control rate : 94%

Complications

- Low morbidity-zero mortality.
- Hearing lose: 54%
- Lower cranial dysfunction is extremely rare
- Nausea,vomitting and dizziness/vestibular dysfunction
- Transient facial or glossopharyngeal neuropathies
- Neither target volume nor the radiation dose associated with the incidence of cranial neuropathies.
- Severe vertigo after radiosurgery

Hemangioblastomas

- Gold standard treatment – surgical resection of the solid components
- GKRS can be given to solid portion ,with max dose 28 - 60 Gy and peripheral dose 11 – 20 Gy
- Tumor size – Decrease in size - 70 %

  No change in size – 30 %

Niemela M young J et al ,Gamma knife radiosurgery in 11 Hemangioblastoma,in 7th international meeting fLeksell Gamma Knife Society,1995

Chordomas & chondrosarcomas

- Rare skull base tumors
- Both highly invasive locally
- Challenges to treat due to their invasiveness, proximity to vital structure
- Post op GKRS – modest reduction in tumor size and long term survival

Muthukumar N,Kondzoilka D,Lundsford LD,et al: Stereotactic radiosurgery for chrdoma and chondrosarcoma: Further experiences. Int J Radiat Oncol Biol Phys 41:387-392,1998.

Pediatric Tumors

- Technical issue
- Indication:
  - Pilocytic astrocytomas / low grade glioma
  - High grade glioma
  - Medulloblastomas
  - Ependymomas
  - Craniopharyngioma
  - Pituitary Adenomas
  - Pineal region tumors
  - Gangliogliomas
  - Choroid plexus papillomas
  - Neurocytomas

GKRS After Care

- No initial effects of radiosurgery
- Few patients have experienced seizures
  - almost always with established seizure disorder
  - adjust anticonvulsant prior to treatment
- Local pain in the scalp
  - simple, oral pain medication

Side Effects of GKRS

- -Brain edema
  cells lose ability to retain fluid,
  swelling within the adjacent brain
  Rx -oral steroids/ self-limiting

- Psychological side effects:
  loss of memory, decreased cognitive abilities

- Cranial nerve dysfunction
  - double vision /visual loss
  - facial numbness, weakness
  - hearing loss
  - Rare with modern gamma ray doses

Side Effects

- **Radiation Necrosis**
  - radiosurgery turns a live tumor into a dead tumor
  - large tumors are not good candidates ??
    - risk of radiation necrosis increases with size
    - dead tissue cleared from brain by an inflammatory reaction
    - bigger the mass of dead tissue = greater the inflammation
      - high doses of steroids
      - 6 and 18 months after procedure
      - Sometimes open surgery to remove dead tissue

Follow up

- MR/CT imaging
  - every 3 months to every year
  - assure control of tumor
- Arteriovenous malformations-MR angiograms
- Follow-up protocols vary from center to center

Neurol India. 2008 Jan-Mar;56(1):57-61.

Gamma knife radiosurgery for glomus jugulare tumors: therapeutic advantages of minimalism in the skull base.

1601 patients who underwent GKS from 1997 to 2006, 24 patients with GJ underwent 25 procedures.

J Neurooncol. 2010 Jun;98(2):265-70. Epub 2010 Apr 20.
***Tumor control and hearing preservation after Gamma Knife radiosurgery for vestibular schwannomas in neurofibromatosis type* 2.**

Tumor control and hearing preservation after *Gamma Knife* radiosurgery for management of *acoustic* neuromas
Journal of Neurosurgery - 1999/05/01