Gamma Knife and its applications

Steven Seung, M.D., Ph.D., FACR
Medical Director
The Gamma Knife Center of Oregon
The Oregon Clinic, Radiation Oncologist
Topics for Today

- Brief history of radiation therapy
- Gamma Knife development
  - How it works
- Present Indications for Gamma Knife
  - Focus on brain metastases
Brief history of radiation therapy
Discoverers of Radioactivity

Interior of drafty and leaky shed at the School of Physics where radium was discovered.  

Antoine-Henri Becquerel (1852-1908).  
Marie Curie (1867-1934).  
Pierre Curie (1859-1906).
Roentgen Discovers X-rays 1895
First X-ray

Mrs. Roentgen’s hand
Ooohh!
Aaahh!
Early Safety Apparel
X-ray Tx of Skin Ca
First to Treat Cancer
Moses' first and last day as a lifeguard.
Radium Tx of Hemangioma
Cobalt Unit 1950’s

Kingsbury Center for Cancer Care / Cobalt Therapy
Dr. Henry Kaplan with the first linear accelerator

Stanford accelerator with young boy to be treated for retinoblastoma
From modest beginnings...
To modern marvels
Gamma Knife development
How it works
“The delivery of a single, high dose of radiation to a small and critically located intracranial volume through the intact skull.” - Lars Leksell, M.D. Ph.D., 1951
Gamma Knife Radiosurgery:

- Conceived by Dr. Lars Leksell as a means of precise destruction of intracranial targets with ionizing beams of radiation in a single treatment
- Create functional lesions via liquefaction necrosis of treatment volume in physiologic nuclei or nerve tracts
Gamma Knife Radiosurgery:

Past History

- Initially developed with orthovoltage radiation
- First Cobalt 60 design used in 1969
- Initially treated patients with functional disorders and inoperable arteriovenous malformations (AVMs)
- Benign tumors also occasionally treated
RADIOSURGERY
Early Attempts
Lesion Produced Through a Gammathalamotomy for Intractable Pain

Image courtesy of L. Leksell, M.D., Ph.D., Karolinska Hospital
The First Gamma Knife® - 1969
Early Attempts

Existing technologies lacked:

- Precision
- Reliability
- Accessibility
- Ease of use
The Gamma Knife

- Dedicated neurosurgical tool for performing surgery
- Non invasive, “bloodless surgery”
- Uses highly focused Cobalt$^{60}$ sources
- Allows high doses to target with rapid dose fall-off to protect adjacent critical structures
The Gamma Knife

- Procedure performed with local anesthesia for placement of the head frame
- Highly accurate volumetric MRI obtained for treatment planning
- Treatment planning derived quickly
Gamma Knife Radiosurgery
Gamma Knife Surgery

The delivery of a single, high dose of irradiation to a small and critically located intracranial volume through the intact skull.

201 beams intersecting in one focal point.
“Say ... now I’m starting to feel kinda warm!”
Collimator system 8-16-8-16-8-16-8-16
Outstanding dosimetry

- Dose performance
  - Patented collimator design provides almost unlimited ability for sculpturing the dose distribution
  - Optimized design guarantees full backwards compatibility to existing Gamma Knife surgery protocols and methods

- Shot features enabled
  - Classic
  - Composite
  - Dynamic shaping
Composite shot
Dynamic shaping
The Gamma Knife

- Treatment delivered over 20-60 minutes
- Patients usually go home the day of treatment
- Patients can resume normal activities the next day
The Time Factor

Symptom → Diagnosis

Gamma Knife Surgery

Open Surgery → 2-4 days ICU → 10-16 days hospitalization → 4-6 weeks convalescence
Topics for Today

- Historical perspective
- Present Indications for Gamma Knife
  - Focus on brain metastases
Gamma Knife Radiosurgery:

- Malignant Brain Tumors
  - Metastatic disease
  - Gliomas
  - Extra-axial intracranial tumors (chordomas, craniopharyngiomas, chondrosarcomas)

- Benign Brain Tumors
  - Acoustic neuromas
  - Other Schwanomas (trigeminal, jugular)
  - Meningiomas
Gamma Knife Radiosurgery:

- Pituitary Adenomas
  - Non secreting
  - Secreting
    - Acromegaly
    - Cushing’s Disease
    - Prolactinomas
Gamma Knife Radiosurgery:

- Vascular Malformations
  - AVMs
  - Cavernous Malformations
- Functional Neurosurgery
  - Trigeminal neuralgia (including Cluster HA)
- Movement disorders
Brain metastases

Figure A
Female, 66 years old. Colon cancer - left hand paralysis PRE Gamma Knife

Figure B
6 weeks POST Gamma Knife - Paralysis resolved
Dose plan for melanoma-metastases

Yellow line: 22 Gy
Green line: 3 Gy
Melanoma

Before and 3 months after GKS
Brain Metastases

- Develops in 10-30% of cancer patients
- In adults, it is the most common intracranial tumor
- Usually occurs in limited numbers*
  - 39% solitary
  - 54% two or less
  - 72% four or less

Brain metastases

- Most common sources in adults
  - Lung 50%
  - Breast 10-20%
  - Unknown primary 10-15%
  - Melanoma 10%
  - Colon 5%
Brain Mets – Autopsy Data

- 2,375 autopsied cancer pts at MSKCC between 1970-1975
- 24% of autopsied pts had brain mets
  - Solitary – 47%
    - Cerebrum – 81%
    - Cerebellum – 19%
  - Multiple – 53%

Posner et al.
Brain Mets – Autopsy Data

- Incidence of brain mets by primary tumor type and solitary vs multiple
  - Lung Cancer
    - 34% autopsied pts had brain mets
    - 41% solitary, 59% multiple
  - Breast Cancer
    - 30% autopsied pts had brain mets
    - 58% solitary, 42% multiple
  - Melanoma
    - 72% autopsied pts had brain mets
    - 38% solitary, 62% multiple
Based on these data (~half of patients with brain mets have multiple lesions), WBRT became the standard of care for the treatment of brain mets.
Whole brain irradiation
Prognostic Factors

RPA Classes

As defined by RTOG randomized trials: No clinical or radiographic evidence of progression of extracranial disease in the month prior to randomization. (Patients who present with symptoms of brain metastases at the time of initial diagnosis are eligible and do not need to demonstrate one month of stable scans.)
### Prognosis of Patients With Brain Metastases by Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) Score

<table>
<thead>
<tr>
<th>Lung Cancer</th>
<th>GPA Scoring Criteria</th>
<th>Total Score</th>
<th>Median Survival Time in Months (95% CI)</th>
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<tbody>
<tr>
<td>Prognostic Factor</td>
<td>0 0.5 1.0</td>
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<td>Age, years</td>
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<tr>
<td>KPS</td>
<td>&lt; 70 70–80 90–100</td>
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<tr>
<td>ECM</td>
<td>+ n/a –</td>
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<tr>
<td>No. of BM</td>
<td>&gt; 3 2–3 1</td>
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<td>Total Score =</td>
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<th>Melanoma</th>
<th>GPA Scoring Criteria</th>
<th>Total Score</th>
<th>Median Survival Time in Months (95% CI)</th>
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<td>Prognostic Factor</td>
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<tr>
<td>KPS</td>
<td>&lt; 70 70–80 90–100</td>
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<tr>
<td>No. of BM</td>
<td>&gt; 3 2–3 1</td>
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<td>Total Score =</td>
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</tr>
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<td>KPS</td>
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<tr>
<td>Subtype</td>
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<th>Renal Cell Carcinoma</th>
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<th>Median Survival Time in Months (95% CI)</th>
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<td>Prognostic Factor</td>
<td>0 1.0 2.0</td>
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<tr>
<td>KPS</td>
<td>&lt; 70 70–80 90–100</td>
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<tr>
<td>No. of BM</td>
<td>&gt; 3 2–3 1</td>
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<th>GI Cancers</th>
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<th>Median Survival Time in Months (95% CI)</th>
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<tr>
<td>KPS</td>
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<tr>
<td>Total Score =</td>
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</table>

Fig 1. Prognosis of patients with brain metastases (BM) by Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) score. Breast cancer subtypes are as follows: basal: triple negative; luminal A (LumA): estrogen receptor (ER)/progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER2) negative; luminal B (LumB): triple positive; HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases; KPS, Karnofsky performance score; n/a, not applicable; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer. Data adapted.
Whole Brain RT Necessary?
Brain Mets – Autopsy Data

The “Cup Half Empty” Viewpoint

- 1: 40%
- 2: 15%
- 3: 10%
- >=4: 35%

2/3 of patients have 1, 2 or 3 brain mets.
12 patients cured of brain mets after WBRT using 25-29 Gy at 3-6 Gy/fx

Initial response: all NED by CT, sx resolved

Late response: onset of progressive dementia at 5-36 mo. (median 14 mo) with disabling ataxia, urinary incontinence, cortical atrophy, hypodense white matter, ventricular dilatation.
Long-term Effect of WBRT
WBRT Toxicity – Radiation Induced Dementia
Phase III Trial
SRS +/- WBRT for
Pts Newly Diagnosed with
1 - 3 Brain Metastases

Eric L. Chang, M.D.
Associate Professor
Department of Radiation Oncology

ASTRO Plenary Session
September 22, 2008
Monday 2:05 - 2:55 PM
Introduction/Objective:

Whether immediate WBRT is indicated after SRS for pts with 1-3 newly diagnosed brain metastases is controversial and the subject of intense debate.

FOR WBRT: highlight importance of disease control

AGAINST WBRT: underscore its potential toxicity

Objective: To test the hypothesis that pts randomized to initial SRS + WBRT would have inferior neurocognitive function compared to pts randomized to initial SRS alone.
Primary endpoint

Primary endpoint - cognitive decline in learning and memory

**Hopkins Verbal Learning Test (HVLT)** used to measure decline in learning and memory by detecting a >5 point drop 4 months from baseline

HVLT is a widely used standardized psychometric instrument with demonstrated sensitivity to neurotoxic effects of cancer treatment
Randomized Clinical Trial Schema

- RPA class I vs. II
- 1 or 2 vs. 3 Brain Mets
- Melanoma / Renal cell carcinoma vs. Other

SRS + WBRT

SRS alone
Radiation Therapy

SRS to 1-3 brain metastases was given first
Prescription based on RTOG 90-05 guidelines

<table>
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<tr>
<th>Lesion diameter</th>
<th>&lt;2cm</th>
<th>&gt;2 to &lt;3cm</th>
<th>&gt;3cm</th>
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<tbody>
<tr>
<td>SRS dose</td>
<td>20-24Gy</td>
<td>18 Gy</td>
<td>15 Gy</td>
</tr>
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</table>

For pts randomized to WBRT, it was given within 3 wks after SRS:

WBRT 30 Gy in 12 fxs at 2.5 Gy QD

• 2.5 Gy fraction size used to minimize toxicity
Follow-up schedule

Comprised clinic visit, brain MRI, and formal neurocognitive evaluation

<table>
<thead>
<tr>
<th>First 18 mos</th>
<th>1mo 2mos 4mos 6mos 9mos 12mos 15 mos 18mos</th>
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<td>After 18 mos</td>
<td>Every 6 months</td>
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### Neurocognitive Decline by HVLT

<table>
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<tr>
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<th>Mean Probability of NCF Decline</th>
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<tr>
<td>SRS</td>
<td>23%</td>
</tr>
<tr>
<td>SRS+WBRT</td>
<td>49%</td>
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</table>

96% conf
Actuarial Freedom from Local Tumor Progression

Number at risk

<table>
<thead>
<tr>
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<th>SRS</th>
<th>SRS+WBRT</th>
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<td>66</td>
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<td>72</td>
<td>1</td>
<td>0</td>
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<td>78</td>
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<td>0</td>
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<tr>
<td>84</td>
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</table>
Distant Brain Tumor Recurrence

Number at risk

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<tr>
<th>Months</th>
<th>SRS</th>
<th>SRS + WBRT</th>
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<tbody>
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<td>28</td>
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<tr>
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<td>12</td>
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Overall Survival

Number at risk

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Log Rank p=0.003
# Lifetime salvage therapies

<table>
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<th>Salvage therapy for brain metastasis</th>
<th>SRS  ((N=30))</th>
<th>SRS+WBRT ((N=28))</th>
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<td>Craniotomy</td>
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<tr>
<td>WBRT</td>
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<td>SRS</td>
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<tr>
<td>Chemo</td>
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<td>1</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>27</strong></td>
<td><strong>3</strong></td>
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Conclusion

• Pts randomized to SRS+WBRT had twice the risk of cognitive decline in learning and memory compared to SRS pts (49% versus 23%)

• Despite significantly higher DBC in SRS+WBRT arm (73%), learning and memory was better for pts randomized to SRS (DBC 45%)

• These data suggest that decline in learning and memory is primarily due to WBRT toxicity rather than brain tumor relapse
Conclusion

• Based on level I evidence presented today, SRS alone coupled with close clinical monitoring could be considered the new standard of care for pts newly diagnosed with 1 - 3 brain metastases
GKCO Consensus?

• Solitary brain met with KPS > 70, RPA class I/II
  • Surgery if big, mass effect, or need tissue
    • WBRT post surgery is the standard of care
    • Observation appropriate for GTR if patient refuses WBRT
    • SRS to resection cavity appropriate if patient refuses WBRT
  • SRS is standard of care for solitary brain met without acute need for surgical intervention
  • WBRT is an alternative with consideration of SRS boost if the tumor is large
• Multiple brain mets with KPS >70, RPA class I/II
  • Pick your endpoint
    • Limited survival → WBRT alone
    • Local control and QOL → SRS alone or SRS +/- WBRT for salvage vs. WBRT+SRS
GKCO Consensus?

- KPS <70, RPA class III
  - WBRT alone (SRS salvage if PS improves)
  - Nothing ?
Arteriovenous Malformation

Pre

2 Years Post

Images courtesy of L. D. Lunsford, M.D., University of Pittsburgh
AVM

Patient presented is a 9 year old female with a 4.8 cc AVM. The patient was treated using the Gamma Knife using 21 Gy to the 50% isodose. The 25% and 50% isodose lines are shown.

Day of Tx  Day of Tx  8.5 month followup
Acoustic Neuroma

Pre 24 Months Post

Images courtesy of J. Peragut, M.D., Ph.D., C.H.U. La Timone, Marseille, France
Acoustic Neuroma

Acoustic neuroma treated with 12 Gy to the tumor margin, 24 Gy maximum dose. The follow up image is the same patient 12 months later.
Meningioma

Images courtesy of G. Pendl, M.D., University of Graz, Austria
Malignant Tumor

25 year old male, 2.5 x 1.7 x 1.5 cm enhancing lesion of the left thalamic region. Biopsy identified a germinoma. Patient was treated with 8 isocenters using the Gamma Knife in 1992, and is disease free as of March 1, 2000.

Figure A
Gamma Knife radiosurgery plan used to deliver 14 Gy to the conformally shaped 40% isodose encompassing the enhancing left thalamic germinoma.

Figure B
Follow-up MRI at 2 years status post Gamma Knife radiosurgery showing no evidence of residual tumor.
Trigeminal Neuralgia Dose Plan

Images courtesy of D. Kondziolka, M.D., University of Pittsburgh
Do we need Gamma Knife?
Applications

- Malignant tumors
  - Mestastases
  - Recurrent gliomas
  - others
- Benign tumors
  - Acoustic neuromas
  - Meningiomas
  - others
- Functional
  - Trigeminal neuralgia
  - Essential tremors
The Gamma Knife Center of Oregon

- Panel of neurosurgeons and radiation oncologists from Providence, Legacy, Compass Oncology and OHSU
- Nurses: Cindy Ryan, RN, Valerie Perkins, RN
- Physicists: Joanna Haper, MS
More Doctors Smoke CAMELS than any other cigarette!

According to repeated nationwide surveys,

Doctors in every branch of medicine were asked, “What cigarette do you smoke?” The brand named most was Camel.

You’ll enjoy Camels for the same reasons so many doctors enjoy them. Camels have cool, sweet satisfaction, pack after pack, and a flavor unmarred by any other cigarette.

Try Camels for 30 days and see how well Camels please your taste. How well they suit your smoking tastes. You’ll see how enjoyable a cigarette can be!

THE DOCTORS’ CHOICE IS AMERICA’S CHOICE!

For 30 days, test Camels in your “T-Zone” (T for Throat, T for Taste).

www.StrangeCosmos.com