Buschke on Radiation Oncology

“...includes a fundamental knowledge in gross and microscopic pathology, of diagnostic technics for cancer in all its locations (including the less complicated endoscopic procedures), judgments as to the indications for and knowledge of the pharmacology and technic of chemotherapeutic agents (nitrogen mustard, urethane, antifolics), plus a comprehensive understanding of physics, clinical indications for, and technics of x-ray, radium, and isotope therapy, and the psychological management of the cancer patients.”

Letter to a referring physician, 1952

The Fifth “R” in Radiation Oncology

Why fractionation?

Normal cells
  - Repair of sub-lethal damage
  - Repopulation

Tumor cells
  - Reoxygenation increases radiosensitivity
  - Reassortment into radiosensitive phases
Factors affecting dose fractionation
- Repair of sub-lethal damage
- Reassortment of cells within cell cycle
- Repopulation
- Reoxygenation
- Radiosensitization?

Factors affecting dose fractionation
- Repair of sub-lethal damage
- Reassortment of cells within cell cycle
- Repopulation
- Reoxygenation
- Radioresistance?

Factors affecting dose fractionation
- Repair of sub-lethal damage
- Reassortment of cells within cell cycle
- Repopulation
- Reoxygenation
- Reimbursement?

Factors affecting dose fractionation
- Repair of sub-lethal damage
- Reassortment of cells within cell cycle
- Repopulation
- Reoxygenation
- Radiosurgery?
Factors affecting dose fractionation
- Repair of sub-lethal damage
- Reassortment of cells within cell cycle
- Repopulation
- Reoxygenation
- Radiosurgery
  Changed how we think about fractionation for targets throughout the body

Nomenclature
SRS refers to CNS sites, 1-5 fx
SBRT refers to non-CNS sites, 1-5 fx
This terminology is accepted by
- AMA Specialty Society Relative Value Scale (RVS) Update Committee (RUC)
- Centers for Medicare and Medicaid Services (CMS)
- Most commercial payers

Historical Role of Fractionation

Buschke on Radiotoxicity
“…Coutard taught us that the incidence of radiation sickness is related to the incompetence of the radiation therapist.”
Letter to a referring physician, 1952
Buschke on Fractionation

Symposium on Protraction and Fractionation
45th Meeting of American Radium Society
San Francisco, 1963

“…the prolongation of over-all treatment time is one of the most important factors for increasing the differential between effect on tumor and the effect on the vasculo-connective tissue. The awareness of this situation and its increasingly common utilization, it seems to me, are probably the greatest progress radiation therapy has made during the last decade”

Symposium Chair Franz Buschke

Fractionated Radiotherapy for Pituitary Adenoma

• “Satisfactory outcomes” with radiotherapy (70%) are more frequent than with surgery (40-60%) for chromophobic and eosinophilic adenomas

• Recommended target dose of 4000 r with parallel opposed fields
  – 800 KV x-rays, pituitary dose is 55% of skin dose
  – 200 KV x-rays, pituitary dose is 46% of skin dose

Franz Buschke
West J Surg 1950

Stereotactic radiotherapy, UCSF, 1940’s
Localized Radiolesions

- During the 1950’s-1960’s, numerous investigators produced localized CNS radio-lesions in animals
- Locations: cerebral cortex, medulla oblongata, thalamus, hypothalamus, internal capsule, hypophysis, spinal cord
- Radiation sources: implanted radon seeds, implanted isotopes (Au^{198}, Co^{60}), betatron X-rays, protons, deuterons
Internist John Lawrence

Lawrence’s Pituitary Dose Escalation

<table>
<thead>
<tr>
<th></th>
<th>Total dose (rads)</th>
<th>Elapsed Time (days)</th>
<th>Dose per session (rads)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Pts</td>
<td>14,000</td>
<td>63</td>
<td>650</td>
</tr>
<tr>
<td>Later Pts</td>
<td>30,000</td>
<td>14</td>
<td>5000</td>
</tr>
</tbody>
</table>

Fig. 3: Relationship between dose and time of onset of changes resembling hypopituitarism.
Exophthalmos 2 years after He ions 10,000 rads

Pituitary Ablation

“...we have achieved our purpose: the destruction of a deep-seated organ without damage to the intervening tissues...it is possible to remove the pituitary by proton irradiation...in the future it is going to be necessary to deliver only 24,000 rads to these patients.”

Neurosurgeon Lars Leksell

“The stereotactic technique enables the accurate insertion of a needle electrode into any given structure of the brain… It would therefore be feasible to replace the needle by narrow beams of radiant energy directed at the target in the brain and thereby produce a local destruction of the tissue…”

“…by careful selection of doses and dose distributions, well-circumscribed lesions of appropriate size and shape can be produced…a suitable dose for the production of a discrete lesion is 20 krad…” Leksell, 1960

3 x 7 mm lesion one month after 200 Gy to internal capsule
Proton radiosurgery

First Gamma Knife, Stockholm (1968)

**First Gamma Knife Procedures**

<table>
<thead>
<tr>
<th>Date</th>
<th>Indication</th>
<th>Max Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/67</td>
<td>Craniopharyngioma</td>
<td>20</td>
</tr>
<tr>
<td>1/68</td>
<td>Pituitary adenoma</td>
<td>28</td>
</tr>
<tr>
<td>2/68</td>
<td>Intractable cancer pain</td>
<td>150*</td>
</tr>
<tr>
<td>2/68</td>
<td>Intractable cancer pain</td>
<td>150*</td>
</tr>
<tr>
<td>3/68</td>
<td>Intractable cancer pain</td>
<td>150*</td>
</tr>
<tr>
<td>4/68</td>
<td>Intractable cancer pain</td>
<td>150*</td>
</tr>
<tr>
<td>5/68</td>
<td>Craniopharyngioma</td>
<td>50</td>
</tr>
<tr>
<td>5/68</td>
<td>Intractable cancer pain</td>
<td>200*</td>
</tr>
<tr>
<td>6/68</td>
<td>Intractable cancer pain</td>
<td>200*</td>
</tr>
</tbody>
</table>

*ablative dose

Control Schwann cells  Schwann cells s/p 30 Gy
Vestibular Schwannoma, Pneumoencephalography (1971)

Pituitary Adenoma Dose Plan (1968)

Neurosurgeon Ray Kjellberg  Single fraction proton radiosurgery, Boston, 1961
Dose to Produce Brain Necrosis

Radiosurgery Development

1951 Leksell Sweden X-rays
1954 Lawrence US Protons, He ions
1961 Leksell Sweden Protons
1961 Kjellberg US Protons
1968 Leksell Sweden Gamma Knife
1975 Barcia-Salorio Spain Co$^{60}$
1983 Betti Argentina Linac
1984 Heifitz US Linac
1984 Colombo Italy Linac
1984 Winston US Linac
1985 Hartmann Germany Linac
1987 Olivier Canada Linac
1988 Larson US Linac
1988 Friedman US Linac

Many Neurosurgeons Did Not Accept Radiosurgery

“...we saw but few, if any, appreciating glances from the neurosurgical community in the world...not even in Sweden...our work was far from recognized as a step forward by influential microsurgeons...the provocative principle of not removing a tumor but inactivating or obliterating it primarily with the aim of minimizing the risk for the patient was even awfully insulting”

Erik-Olaf Backlund, MD, PhD
Linkoping, Sweden
Many Radiation Oncologists Did Not Accept Radiosurgery

- Lack of reliable tolerance dose information
- Lack of familiarity with initial indications (movement disorders, AVM, vestibular Schwannoma)
- Lack of accurate and reproducible stereotactic targeting and immobilization
- Lack of accurate imaging for targeting
- Lack of computerized dose planning
- Successful treatments do not require necrosis
- Violates fractionation principles (4 R’s)

Buschke On Radiosurgery

Leksell’s surgical approach to fractionation uses “…massive single-dose therapy, based on the assumption that radiation therapy is effective in the treatment of cancer through its caustic effects - a slough in lieu of excision.”


Winston-Lutz Linac Radiosurgery

Fig. 10: Head schematic showing the three coordinate axes and the four arcs of the typical treatment.
Winston-Lutz Linac Radiosurgery

“…for small volumes, normal tissue risks will be small… I’d like to treat recurrent medulloblastoma with radiosurgery”

J. Robert Cassady, MD, 1984

ASTRO October 1984

Stereotactic radiation surgery in the brain using a 6 MV linear accelerator

Lutz, Winston, Malaki, Cassady, Svensson, Zervas

- “…capable of delivering very high, single fraction, photon radiation doses (100-150 Gy) to small, precisely located, volumes (0.5-2 cm$^3$) within the brain…stimulated by the work of Leksell…”

- Positional accuracy ±1.5 mm

- For AN, AVM, meningioma, pituitary tumors, or low dose GBM boost
Development of Radiosurgery in North America

<table>
<thead>
<tr>
<th>Start</th>
<th>City</th>
<th>First Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/86</td>
<td>Boston</td>
<td>AVM</td>
</tr>
<tr>
<td>12/86</td>
<td>Montreal</td>
<td>AVM</td>
</tr>
<tr>
<td>8/87</td>
<td>Pittsburgh</td>
<td>Acoustic neuroma</td>
</tr>
<tr>
<td>3/88</td>
<td>San Francisco</td>
<td>AVM</td>
</tr>
<tr>
<td>5/88</td>
<td>Gainesville</td>
<td>AVM</td>
</tr>
<tr>
<td>11/88</td>
<td>Wisconsin</td>
<td>Met hemangiopericytoma</td>
</tr>
<tr>
<td>2/89</td>
<td>St. Louis</td>
<td>Recurrent glioblastoma</td>
</tr>
<tr>
<td>3/89</td>
<td>Stanford</td>
<td>Brain metastasis</td>
</tr>
<tr>
<td>3/89</td>
<td>Salt Lake</td>
<td>AVM</td>
</tr>
</tbody>
</table>
Stereotactic radiotherapy, UCSF, 1988-91

UCSF 1988

39 yo RH male, H/A, Sz, slurred speech, SAH x2, 3.5 cm AVM, dominant hemisphere
Radiosurgery 1800 cGy @ 80%, 2 isocenters, Winston-Lutz apparatus

Radiosurgery Publications

Technical

Clinical

3/88 Radiosurgery
3/89 1 year
3/91 3 years
Neurosurgeons

RS believers
• 4R’s unimportant radonc hocus-pocus
• Focal ablation desirable
• Radiosurgery a branch of neurosurgery
RS skeptics
• Very limited role for RS
• Surgery far preferable to RS

Radiation Oncologists

RS believers
• 4R’s apply to a volume containing nl and abnl cells, all getting same dose (unlike most radiosurgery targets)
• RS a branch of radiation oncology
RS skeptics
• 4R’s of overriding importance

BED versus Number of Fractions

\( \alpha/\beta = 3 \)

Constant BED for increasing fx number (equivalent to 20 Gy in 1 fraction)
Radiosurgery Skeptic

“Anything you can treat with N fractions, I can treat better with N+1 fractions.”

Jim Schwade, 1991

“Had Coutard and Baclesse not pioneered fractionation, radiotherapy probably would have fallen into oblivion due to the morbidities of single shot treatment. Indeed, much of the first half of this century was spent learning that doses large enough to sterilize a mass of tumor cells (10 logs) cannot be predictably given safely. Instead, fractionation evolved which permitted us to exploit repopulation, redistribution, reoxygenation, and repair.”

Eli Glatstein, 1997

Four factors affecting dose fractionation
- Repair
- Repopulation
- Reoxygenation
- Reassortment

Conventional Radiotherapy
Four factors affecting dose fractionation

- Repair
- Repopulation
- Reoxygenation
- Reassortment

Example
Glioblastoma

Radiosurgery

There is Level I-III evidence that the use of radiosurgery boost does not confer benefit in terms of overall survival, local brain control, or quality of life…

IJROBP 2005

SRS Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Med surv (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM</td>
<td></td>
</tr>
<tr>
<td>Boost</td>
<td>SRS</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Brachy</td>
</tr>
<tr>
<td></td>
<td>14-21</td>
</tr>
<tr>
<td></td>
<td>10-23</td>
</tr>
<tr>
<td></td>
<td>8-10</td>
</tr>
<tr>
<td></td>
<td>9-12</td>
</tr>
</tbody>
</table>

Four factors affecting dose fractionation

- Repair
- Repopulation
- Reoxygenation
- Reassortment

Example
AVM
Acoustic Schwan Meningioma
Pituitary adenoma

Radiosurgery
### SRS Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose (Gy)</th>
<th>Local control (%)</th>
<th>Actuarial time (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVM</td>
<td>18-24</td>
<td>75-92%</td>
<td>2-5</td>
</tr>
<tr>
<td>Meningioma</td>
<td>13-16</td>
<td>93-96%</td>
<td>5</td>
</tr>
<tr>
<td>Acoustic Neuroma</td>
<td>12-13</td>
<td>90-98%</td>
<td>5-10</td>
</tr>
</tbody>
</table>

### SRS Outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose (Gy)</th>
<th>Local control (%)</th>
<th>Actuarial time (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenoma</td>
<td>Non-funct</td>
<td>16-20</td>
<td>2-5</td>
</tr>
<tr>
<td></td>
<td>Acromegaly*</td>
<td>20-35</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Cushing’s*</td>
<td>16-20</td>
<td>1-10</td>
</tr>
</tbody>
</table>

*Biochemical control 50%

### Four factors affecting dose fractionation

- Repair
- Repopulation
- Reoxygenation
- Reassortment

**Example**

**Metastasis**

### Radiosurgery for Mets (1990’s)

<table>
<thead>
<tr>
<th>Author</th>
<th>Mets</th>
<th>Pts</th>
<th>Mets/pt</th>
<th>LC</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auchter</td>
<td>122</td>
<td>122</td>
<td>1.0</td>
<td>86%</td>
<td>0%</td>
</tr>
<tr>
<td>Engenhart</td>
<td>102</td>
<td>69</td>
<td>1.5</td>
<td>95%</td>
<td>3%</td>
</tr>
<tr>
<td>Flickinger</td>
<td>229</td>
<td>157</td>
<td>1.5</td>
<td>89%</td>
<td>1%</td>
</tr>
<tr>
<td>Gerosa</td>
<td>343</td>
<td>225</td>
<td>1.5</td>
<td>88%</td>
<td>2%</td>
</tr>
<tr>
<td>Kim</td>
<td>115</td>
<td>77</td>
<td>1.5</td>
<td>85%</td>
<td>4%</td>
</tr>
<tr>
<td>Moriarty</td>
<td>643</td>
<td>353</td>
<td>1.8</td>
<td>88%</td>
<td>3-6%</td>
</tr>
<tr>
<td>Cho</td>
<td>136</td>
<td>73</td>
<td>1.9</td>
<td>80%</td>
<td>3-8%</td>
</tr>
<tr>
<td>Shu</td>
<td>248</td>
<td>116</td>
<td>2.1</td>
<td>76%</td>
<td>3%</td>
</tr>
<tr>
<td>Schoegg</td>
<td>266</td>
<td>97</td>
<td>2.7</td>
<td>98%</td>
<td>1%</td>
</tr>
</tbody>
</table>
“The maximum tolerated doses of single fraction radiosurgery were defined for this population of patients as 24 Gy, 18 Gy, and 15 Gy for tumors \( \leq 20 \) mm, 21-30 mm, and 31-40 mm in maximum diameter.”

### Brain Mets Treatment Strategies

<table>
<thead>
<tr>
<th>KPS</th>
<th>( \geq 70 )</th>
<th>&lt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-cranial disease</td>
<td>Controlled</td>
<td>Progressive</td>
</tr>
<tr>
<td>Number of brain mets</td>
<td>1</td>
<td>2-3</td>
</tr>
<tr>
<td>Conventional recommendation</td>
<td>RS±WBRT</td>
<td>WBRT±RS</td>
</tr>
</tbody>
</table>

RS not appropriate for large tumor volumes, massive edema, impending herniation, small cell lung ca, etc

### SRS Outcomes

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Local control</th>
<th>Actuarial time (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 Brain mets</td>
<td>16-20</td>
<td>80-95%</td>
</tr>
</tbody>
</table>

### WBRT Controversy

- WBRT may cause NCF decline because of toxicity
- RS without WBRT may result in NCF decline because of new mets
Phase III Data Support Various Treatment Preferences

**WBRT+RS** is preferable to **WBRT** alone
- Better local control
- Increased survival for some subsets of pts
- Improved KPS

**WBRT+RS** is preferable to **RS** alone
- Better local control
- Fewer new brain mets

**RS** alone is preferable to **WBRT+RS**
- Less chance of NCF decline
- Fewer total days undergoing brain irradiation
- No need for chemotherapy delay

Hippocampus receives <20% of prescription dose

---

**Brain Mets Treatment Strategies**

<table>
<thead>
<tr>
<th>KPS</th>
<th>≥70</th>
<th>&lt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-cranial disease Control</td>
<td>Progressive</td>
<td></td>
</tr>
<tr>
<td>Number of brain mets 1 2-3 &gt;3 1 &gt;1</td>
<td>1 2-3 &gt;3 1 &gt;1</td>
<td></td>
</tr>
<tr>
<td>Conventional recommendation</td>
<td>RS±WBRT</td>
<td>WBRT±RS</td>
</tr>
<tr>
<td>RS alternative</td>
<td>RS</td>
<td>RS</td>
</tr>
</tbody>
</table>

RS not appropriate for large tumor volumes, massive edema, impending herniation, small cell lung ca, etc
Birth of SBRT

• In the early 1990’s Karolinska physicist Ingmar Lax and radiation/medical oncologist Henric Blomgren developed stereotactic body radiosurgery
• Treated liver, lung, peritoneal malignancies
• Mean target volume 80 cc, 1-4 fractions, ~30 Gy prescribed at 50% IDL
• Local control 80%
• 50% of tumors deceased or disappeared

Stereotactic Body Radiosurgery

Pancreatic cancer (700 cGy x 3)

Pre-Treatment

9 mo. Post-Treatment

Blomgren and Lax, Karolinska Hospital
preliminary report
Extracranial Stereotactic Radioablation*
Results of a Phase I Study in Medically Inoperable Stage I Non-small Cell Lung Cancer

Robert Timmerman, MD; Lech Papiez, PhD; Ronald McGarry, MD; Laura Lakis, RT; Colleen DeRivieres, MS; Stephanie Froot, MS; and Mark Williams, MD

Stereotactic Body Radiosurgery
Stage I NSCLC Phase II Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>Dose</th>
<th>Med f/u</th>
<th>3-yr LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fakiris 2009</td>
<td>70</td>
<td>T1: 20 Gy x3</td>
<td>50 mo</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2: 22 Gy x3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baumann 2009</td>
<td>57</td>
<td>15 Gy x3</td>
<td>35 mo</td>
<td>92%</td>
</tr>
<tr>
<td>Ricardi 2010</td>
<td>62</td>
<td>15 Gy x3</td>
<td>28 mo</td>
<td>88%</td>
</tr>
<tr>
<td>Timmerman 2010</td>
<td>55</td>
<td>18 Gy x3</td>
<td>34 mo</td>
<td>98%</td>
</tr>
</tbody>
</table>

*Figure 3. CXRs of a patient with a stage T2 tumor located behind the left ventricle that was treated with a dose of 1,500 cGy per fraction three fractions before treatment (left) and at 6 weeks after treatment (right).
Surgical fixation for spinal radiosurgery
Hamilton and Lulu, 1995

Prescription
- 2400 cGy in 2 fx
- Thecal sac max 1420 cGy in 2 fx
- Spinal cord max 1020 cGy in 2 fx

Stereotactic Body Radiosurgery

**Spinal Tumors**

<table>
<thead>
<tr>
<th>Target</th>
<th>Fracts</th>
<th>Local control</th>
<th>Pain response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine mets</td>
<td>1-5</td>
<td>85-95%</td>
<td>50-95%</td>
</tr>
<tr>
<td>Benign intradural tumor</td>
<td>1-5</td>
<td>85-100%</td>
<td>50-75%</td>
</tr>
</tbody>
</table>

How Common is SRS/SBRT?

- ~ 2,000 U.S. radiation oncology facilities
- ~ 1,000,000 treatment courses/year
- ~ 5% of treatment courses are SRS/SBRT
- ~ 900 linac purchases are being planned, 500 of which will have SRS and/or SBRT capability
Estimated Market Penetration

- SBRT
- SRS
- IMRT

Estimated U.S. Yearly SRS Procedures

- 70-80% single fraction
- 50% GK, 50% linac

Estimated SRS Courses By Indication (2010)
UCSF SRS and SBRT Treatment Courses

Published Radiosurgery Errors

- ~400 radiosurgery accidents occurred during 2004-2010 in the US, France, Spain
- Reported errors: over-dosage (miscalibration), wrong side of brain treated, incorrect collimator setting, etc
- Reported sequella: at least one death, numerous cranial neuropathies, some pts in vegetative state
- Numerous publications address SRS/SBRT safety (ASTRO, AAPM, CAPCA, ACR, WHO, ICRP, BIR)

The New York Times

Recent Headlines

- A Pinpoint Beam Strays Invisibly, Harming Instead of Healing
- The Mark of an Overdose
- As Technology Surges, Radiation Safeguards Lag
- Radiation Safety Falls Behind
- New Risks for Medical Radiation
- Radiation Offers New Cures, and Ways to Do Harm

Buschke on Machinery

“There is an exaggerated emphasis on the importance of the machine available without appreciation of the fact that the prognosis is determined in decreasing order of importance by the biology of the disease, the competence and skill of the therapist, and, least significantly, by the apparatus…”

Am J Surg 1961
UCSF’S Historical SBRT/SRS Role

- Published over 100 papers
- Trained over 100 residents and fellows
- Trained over 100 radiation oncologists, neurosurgeons, and physicists
- Held radiosurgery leadership positions in numerous professional societies
- Hosted numerous national and international radiosurgery conferences

Research and Controversy

- Brain mets - WBRT vs SRS vs both?
- Brain mets - how many is too many for SRS?
- Movement disorders - role of SRS lesioning
- Ocular melanoma - linac vs GK vs protons?
- Spine mets - SBRT vs AP-PA?
- Emerging role of SBRT: NSCLC, Prostate Ca, H&N Ca, Periaortic nodes, Hepatoma, Mets
- Apparatus - my apparatus is better than yours
- Etc, etc, etc
Summary

- SBRT/SRS therapeutic ratios are favorable for well-defined, small targets at all body sites
- Radiosurgery has changed how we think about fractionation

Buschke on Coutard

“We have often been asked what is the secret of the results of our great teacher, Coutard, whose accomplishments...have so far never been surpassed... The secret was not the much quoted ‘Coutard technic’ - it was rather his clinical approach with the radiotherapist acting as a physician and not as a technician.”

Letter to a referring physician, 1952

Buschke on Philosophy

- “Mustard is for hotdogs.”
- “The day begins at 8 and never ends.”
- “I am perfectly willing to let you make your own mistakes.”
- “Statistics are like a bikini - what they reveal is interesting, but what they hide is essential.”
- “Primum non nocere.”