Lessons from the Conception and Development of a Prospective National SRS Registry
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Conflicts of interest
I have served as an (uncompensated) beta tester for some aspects of the registry solution discussed in this presentation.
Some of the material in this presentation was provided by Brainlab.
I have no financial COI.

Objectives
To review the organization and governance of the NeuroPoint Alliance (NPA) Prospective SRS registry.
To discuss some of the features of the NPA SRS Registry that are relevant to longitudinal follow-up for brain metastases.
To discuss the successes and challenges of implementing the SRS registry at the University of Virginia.

How do we decide if a treatment is safe and effective?
One brain, multiple radiosurgeries

<table>
<thead>
<tr>
<th>Date</th>
<th># tumors</th>
<th>Vol 12Gy (cc)</th>
<th>Skull mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/2013</td>
<td>1</td>
<td>0.6</td>
<td>0.1 (0.2)</td>
</tr>
<tr>
<td>10/13</td>
<td>5</td>
<td>3.4</td>
<td>0.4 (0.7)</td>
</tr>
<tr>
<td>2/14</td>
<td>5</td>
<td>1.5</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>5/14</td>
<td>11</td>
<td>1.8</td>
<td>0.8 (1.0)</td>
</tr>
<tr>
<td>6/15</td>
<td>8</td>
<td>43.9</td>
<td>1.4 (2.0)</td>
</tr>
<tr>
<td>7/15</td>
<td>4</td>
<td>2.0</td>
<td>0.2 (0.5)</td>
</tr>
<tr>
<td>10/15</td>
<td>6</td>
<td>14.6</td>
<td>0.6 (0.9)</td>
</tr>
<tr>
<td>2/16</td>
<td>9</td>
<td>46.2</td>
<td>1.6 (2.3)</td>
</tr>
<tr>
<td>5/16</td>
<td>6</td>
<td>6.2</td>
<td>0.4 (0.9)</td>
</tr>
</tbody>
</table>

55 tumors, 9 SRS procedures, 3 years

9/2014 - WBRT (30 Gy in 10 fractions)

What is the traditional path for evidence for SRS?

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What does the NPA registry do?

What is a prospective registry?

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What are some successes and challenges?

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What might the future look like for registries?

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In 1987 – SRS as a concept was already ~35 years old

<table>
<thead>
<tr>
<th>Indication</th>
<th>Report date</th>
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</thead>
<tbody>
<tr>
<td>Gammathalamotomy</td>
<td>1964</td>
</tr>
<tr>
<td>Acoustic tumors</td>
<td>1971</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>1972</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>1971</td>
</tr>
<tr>
<td>Gammacapsulotomy</td>
<td>1979</td>
</tr>
<tr>
<td>Craniohypophyseal tumors</td>
<td>1979</td>
</tr>
<tr>
<td>Cushing's Disease</td>
<td>1980</td>
</tr>
</tbody>
</table>

SRS Evidence: First someone has an idea...

1987

In 7 patients w deep-seated, "radioreistant" metastases

- 20 Gy – 30 Gy, single-fraction SRS on a linac
- 100% symptomatic improvement
- Tumor volume reduction in 5 of 7 patients

No unwanted side effects (one patient hemiated due to untreated second metastasis)
....then observational studies.

1991

RADIO SURGERY FOR SOLITARY BRAIN METASTASES USING THE CORALINE GAMMA KNIFE: METHODS AND RESULTS IN 24 PATIENTS

Robert J. Coffey, MD, Jaclyn L. von Pawel, MD, Robert H. Sterman, MD, and J. Brian Clagan, MD

n=24 consecutive patients w solitary brain mets (mixed histology, some "radioresistant")

20 patients: SRS was a boost (16-20 Gy) after 30-40 Gy WBRT

Median KPS = 90 (range 50-90)

1994

Meanwhile...someone has pushed the envelope

n=33 patients, 52 brain metastases

15 patients had multiple metastases (up to 4)

7 patients had WBRT (prior, concurrent, or after)

4 MeV linac, 80 cm SSD, 4 non-coplanar arcs

Mean dose = 25 Gy to 80% isodose (range 16-35 Gy)

91% local control (mean FU 5.5 months)
Multicenter randomized trials tend to come later...

- 2004
  - Enrolled 333 patients from 1996-2001, 55 centers (about 4.5 years)
  - KPS > 70, 1-3 metastases
  - Randomized to WBRT+SRS (567) or WBRT (164)
  - WBRT (all patients): 37.5 Gy (2.5 Gy/fx)
  - SRS Group: Dose from RTOG 9005 (156 patients, 100 solitary brain mets) - pub 2000
  - Significantly better local control in the SRS+WBRT group, better survival for single mets only in the SRS+WBRT group

...but some practices have already pushed further

- 2006
  - 205 patients
  - (some with prior/concurrent WBRT)
  - Yes, SRS seems to be effective for 4 or more (4-18) metastases.

...and further.

- 2013
  - n=103 patients (46 with FU imaging, 2000-2010)
  - Mix of prior treatments (prior SRS, WBRT, etc.)
  - Yes, SRS seems to be effective for 5 or more metastases.

...and further.

- 2022
  - n=95 patients from 2015-2021
  - Yes, SRS seems to be effective in carefully selected patients with 5-15 mets.
RCTs or Observational Studies: Which is better?

Fool's gold, lost treasures, and the randomized clinical trial

Why not more RCTs?

Randomized Control Trials (RCTs) are the gold standard

Prospective
Randomization and blinding mitigates bias
Well-defined endpoints and data collection
Can control for unmeasured confounders

BUT....

Cost Avg $47,000 / patient in 2011)
{Lack of} Clinical equipoise / study ethics
Too many possible comparisons
Too few patients for some indications
Limited duration / lack of long-term follow-up

Quality of evidence remains low

Radiation therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

Quality of evidence remains low

Review to summarize the evidence for SRS+WBRT (by looking for RCTs)

Found 3 studies and 1 abstract for inclusion

Could only include 2 studies, 358 patients.

No difference in overall survival (OS) HR=0.82 (CI 0.65-1.02) – moderate quality evidence

WBRT+SRS had decreased local failure HR=0.27 (CI 0.14-0.52) – moderate quality evidence
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What are patient outcome registries?

Frameworks that make possible observational study designs.

Patients are observed as they present for care and collected data reflect what is needed for clinical practice.

Inclusion criteria are kept to a minimum to study a broad range of patients.

Can provide outcomes information on diverse populations under real-world conditions.

SRS/SBRT Registries

NPA SRS Registry Organization

Interested parties

Government

Academic Partners

Payers

Quality Improvement

Sites maintain access to their own data

Only anonymized and LDS data kept in repository at NPA

Firewall between corporate partners and data!
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Registry Patients and Events

NPA SRS Registry High Level Architecture

Registry key outcome variables
Quentry Data Processing

- Registry software captures DICOM-RT (imaging, treatment plans, contours)
- Auto-controuling of normal anatomy
- Automated lesion matching across studies
- Reduces variability and minimizes clinician effort
- Possibilities for dosimetric and radiomics analysis

Quentry Data Entry

- Web platform simplifies distribution of labor
- Limited number of data entry fields

Longitudinal Lesion Tracking

- Software assists in matching lesions across primary and follow-up scans
- UI allows user to quickly confirm/edit lesion matches to link through time
- Still requires discipline in naming conventions

Per-patient tracking

- Clinicians can view patient progress over time via web interface
Clinicians can view practice patterns and other clinical data across all of their patients and compare against the registry as a whole.

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Real world lessons

Getting people to do things is hard ...especially without funding!

Junk in= junk out (contouring, clinical data)

Efficiently dividing work among the team is critical!

Automation is important to limiting effort and standardizing data.

Developing standardized nomenclature helps data consistency

Internal discipline around things like naming conventions helps with longitudinal tracking

How is the registry doing?

Initial phase envisioned 30 pilot sites

By year 3: 27,000 patients accrued

Current phase has 10 centers, with more currently contracting

>4000 patients accrued

>4500 SRS events

>3500 follow-up events
What have we learned about brain metastases?

Factors associated with progression and mortality among patients undergoing stereotactic radiosurgery: Interrogated metastasis: results from a national real-world registry

J Neurosurg 131, 2019

J Neurosurg 134, 2021

J Neurosurg, 2022

JNO 152, 2021

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Leveraging AI and Big Data

Agreement with University Medical Center, Hamburg-Eppendorf

Advanced analysis and research using the registry image repository

Using registries as a platform for RCTs

Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) trial

Study investigating the efficacy of thrombus aspiration in a particular type of myocardial infarction (ST-segment elevation MI – STEMI)

Used the Swedish national angiography and angioplasty registry as a platform for the trial (SCAAR) – all PCI centers in Sweden, Iceland, and selected in Denmark

Patients were consented orally and reimbursed at time of referral. Written confirmation within 24 hours.
Trial was able to accrue patients quickly
Majority of PCI patients participated
Total incremental trial cost ~$300,000 (about $50 per patient)
Results generalizable because of diverse patient population

Questions: Data quality in registries? Is blinding possible?

M.Lauer et al., NEJM 369(17), 2013.

Using registries as a platform for RCTs

Conclusions

Prospective registries have the potential to create large standardized datastores of clinical information and relatively low cost
Can be used for observational studies, and potentially for registry-based RCTs
Allows investigation of indications that are rare or that don't warrant an RCT
Data collection effort and center recruitment remain a formidable problem
More work required to understand effects of data quality

Interested in participating?

Acknowledgements

Joel Fuchs (Registry Program Coordinator)