Lessons from the Conception and Development of a Prospective National SRS Registry

David Schlesinger, Ph.D.

Departments of Radiation Oncology and Neurological Surgery
University of Virginia

Department of Radiation Oncology

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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.

2

Objectives

To discuss the historical limitations of clinical evidence generation for SRS.

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.

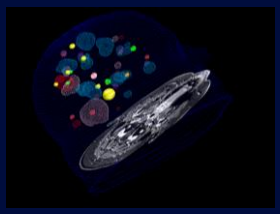
To discuss the successes and challenges of implementing the SRS registry at the University of Virginia.

3

How do we decide if a treatment is safe and effective?

4

One brain, multiple radiosurgeries



Date	# tumors	Vol 12Gy (cc)	Skull mean(SD) dose (Gy)
7/2013	1	0.6	0.1 (0.3)
10/13	5	3.4	0.4 (0.8)
2/14	5	15.9	0.9 (1.7)
5/14	11	5.1	0.6 (0.9)
6/15	8	43.8	1.4 (2.3)
7/15	4	2.0	0.2 (0.5)
10/15	6	14.6	0.6 (1.4)
2/16	9	46.2	1.6 (2.3)
5/16	6	6.2	0.4 (0.9)

55 tumors, 9 SRS procedures, 3 years

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

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What is the traditional path for evidence for SRS?

What is a prospective registry?

What does the NPA registry do?

What are some successes and challenges?

What might the future look like for registries?

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

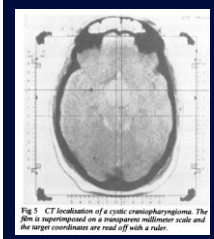

Fig 5 CT localisation of a cystic craniopharyngioma. The film is superimposed on a transparent millimeter scale and the target coordinates are read off with a ruler.

Indication	Report date
Gammathalamotomy	1968
Acoustic tumors	1971
Arteriovenous malformation	1972
Trigeminal neuralgia	1971
Gammacapsulotomy	1979
Craniopharyngioma	1979
Cushing's Disease	1980

L. Leksell, Neurol. Neursurg and Psych 46, 1983.

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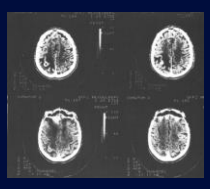
SRS Evidence: First someone has an idea…

1987

STEREOTACTIC PERCUTANEOUS SINGLE DOSE IRRADIATION OF BRAIN METASTASES WITH A LINEAR ACCELERATOR

VOLKER STURM, M.D.,* BERND KOBER, M.D.,† KARL-HEINZ HÖVER, PH.D.,‡ WOLFGANG SCHLEGEL, PH.D.,‡ ROBERT BOESECKE, PH.D.‡ OTTO PASTYR, ENG.,‡ GÜNTHER H. HARTMANN, PH.D., SIGRID SCHABBERT, M.D.,* KARL ZUM WINKEL, M.D.,† STEFAN KUNZE, M.D.* AND WALTER J. LORENZ, PH.D.‡



n=7 patients w deep-seated, "radioresistant" 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 herniated due to untreated second metastasis)

V. Sturm, et al., IJROBP 13(2),1987

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Table 1.

Case no.	Age [y] and sex	Histology of primary tumour	Localization, diameter [cm] of metastasis	Irradiation dosis [Gy]	Time of follow-up [months]	Clinical symptoms	CT-changes (tumour, edema)	Alive/dead, cause of death
1	49 m	Hypernephroma, lung metastases	Diencephalon 2	20	9%	Complete disappearance for 9 months	disappearance of metastasis, reduction of edema	Dead, generalized metastazation
2	60 f	Hypernephroma 2	Cerebellum, 4th ventricle 2	24	9	Marked improvement	Marked reduction	Alive
3	64 m	Hypernephroma, lung metastases	Motor region 1	20	3	Complete disappearance	Complete disappearance of edema (only native scans performable, tumor not visible)	Alive, worsening because of generalized metastazation after 2½ months
4	74 m	Fibrosarcoma (pre-sternal) Lung metastases	Cerebellum 3	22	3	Marked improvement	Unchanged	Dead, second cerebellar metastases
5	57 m	Adeno-carcinoma (lung) contralateral lung metastases	Central-retrocentral 2, 2	30	3½	Marked improvement	Subtotal disappearance of edema, decrease of contrast enhancement of metastasis	Dead, generalized metastazation
6	60 f	Papillar thyroid carcinoma, lung metastases	Central 3	20	5	Complete disappearance	Marked reduction	Dead, generalized metastazation
7		Hypernephroma	Frontal lobe 2	25	3	Moderate improvement	Slight reduction	Alive, after 3 months occurrence of other brain metastases

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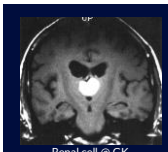
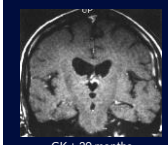


Renal cell @ GK



GK + 20 months

....then observational studies.

1991

RADIOSURGERY FOR SOLITARY BRAIN METASTASES USING THE COBALT-60 GAMMA UNIT: METHODS AND RESULTS IN 24 PATIENTS

ROBERT J. COFFEY, M.D.,[1] JOHN C. FLICKINGER, M.D.,[2,4] DAVID J. BISSONETTE, PA-C[2] AND L. DADE LUNSFORD, M.D.[2,3,4]

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)

Table 5. Results of radiosurgery for brain metastases (n = 24)

Tumor size*				Neurologic status			Deaths	
Absent	Decreased	Stable	Increased	Improved	Stable	Worse	Systemic disease	New brain metastasis
3	8	6	1	6	8	1†	8	2

* On imaging studies (CT, MRI) or post mortem examination.
† Temporarily worsened hemiparesis in single patient who required open operation.

R.J.Coffey et al., IJROBP 20, 1991

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Table 3. Univariate analysis of potential prognostic factors affecting local tumor control

Variable	p value	Favorable group
Pathology	0.0003	Melanoma and renal cell carcinoma
Combined XRT/GK*	0.0040	Combined XRT and GK
Initial/recurrent†	0.1049	Initial GK
Tumor diameter	0.4319	Diameter ≤ 2 cm
Minimum tumor dose	0.5157	Dose ≥ 18 Gy
Isodose	0.5407	Isodose ≥ 50%
Maximum dose	0.5970	Dose ≤ 35 Gy

* Combined fractionated radiotherapy (XRT) with gamma knife radiosurgery (GK) vs. GK alone.
† Tumors initially managed with radiosurgery vs. tumors that recurred after XRT.

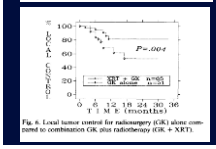

Fig. 6. Local tumor control for radiosurgery (GK) alone compared to combination GK plus radiotherapy (GK + XRT).

...then observational studies...

Multi-institutional!

1994

A MULTI-INSTITUTIONAL EXPERIENCE WITH STEREOTACTIC RADIOSURGERY FOR SOLITARY BRAIN METASTASIS

JOHN C. FLICKINGER, M.D.,[1] DOUGLAS KONDZIOLKA, M.D.,[1] L. DADE LUNSFORD, M.D.,[1] ROBERT J. COFFEY, M.D.,[2] MICHAEL L. GOODMAN, M.D.,[3] EDWARD G. SHAW, M.D.,[3] W. ROBERT HUDGINS, M.D.,[4] RICHARD WEINER, M.D.,[4] GRIFFITH R. HARSH, IV, M.D.,[5] PENNY K. SNEED, M.D.[3] AND DAVID A. LARSON, M.D., PH.D.[3]

n=116 consecutive patients w solitary brain at 5 institutions

n=45 failed prior WBRT, 71 no prior radiation

Mean SRS dose 17.5 Gy (range 8-30)

65 combined with WBRT (mean 33.8 Gy)

2 year actuarial control rate = 67%

J.C. Flickinger et al., IJROBP 28(4), 1994

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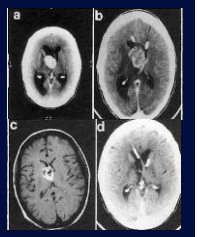
Meanwhile...someone has pushed the envelope

1992

Stereotactic radiosurgical treatment of brain metastases

JOHN R. ADLER, M.D., RICHARD S. COX, PH.D., IRVING KAPLAN, M.D., AND DAVID P. MARTIN, M.D.

Departments of Neurosurgery and Radiation Therapy, Stanford University Medical Center, Stanford, California



n=33 patients, 52 brain metastases

13 patients had multiple metastases (up to 4)

27 patients had WBRT (prior, concomitant, 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)

J. Adler et al.,J. Neurosurg 76, 1992

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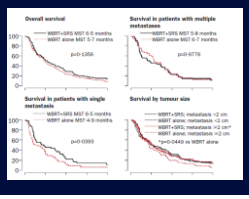
Multicenter randomized trials tend to come later…

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

David W Andrews, Charles B Scott, Paul W Sperduto, Adam E Flanders, Laurie E Gaspar, Michael C Schell, Maria Werner-Wasik, William Demas, Jackie Ryu, Jean-Paul Bahary, Luis Souhami, Warren Rotman, Minesh P Mehta, Walter J Curran Jr

2004

Enrolled 333 patients from 1996-2001, 55 centers (about 4.5 years)



KPS > 70, 1-3 metastases

Randomized to WBRT+SRS(!67) 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

D. W. Andrews et al., Lancet 363, 20

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…but some practices have already pushed further

STEREOTACTIC RADIOSURGERY FOR FOUR OR MORE INTRACRANIAL METASTASES

Ajay K. Bhatnagar, M.D.,* John C. Flickinger, M.D.,*† Douglas Kondziolka, M.D., M.Sc., F.R.C.S.(C),*† and L. Dade Lunsford, M.D.*†

2006

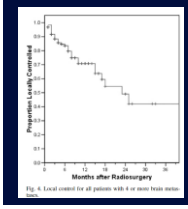

Fig. 4. Local control for all patients with 4 or more brain metas

Table 3. Multivariate analysis of factors associated with local control

Variable	*p* value
Total treatment volume	0.002
Age	0.320
Recursive partioning analysis class	0.376
Marginal dose	0.830
Number of intracranial metastases	0.091
Gender	0.326
Visceral metastases vs. nonvisceral metastases	0.310
Breast cancer vs. other histologic subtypes	0.631
Non–small-cell lung carcinoma vs. other histologic subtypes	0.671
Melanoma vs. other histologic subtypes	0.639

205 patients (some with prior/concurrent WBRT)

Yes, SRS seems to be effective for 4 or more (4-18) metastases.

A. Bhatnagar et al., IJROBP 64, 2006

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….and further.

Survival and Intracranial Control of Patients With 5 or More Brain Metastases Treated With Gamma Knife Stereotactic Radiosurgery

Ann C. Raldow, BS, Veronica L. Chiang, MD,† Jonathan P. Knisely, MD, FRCPC,‡ and James B. Yu, MD**

2013

n=103 patients (46 with FU imaging), 2000-2010

Mix of prior treatments (prior SRS, WBRT, etc.)

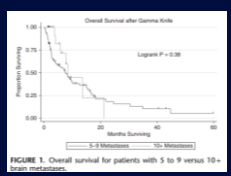

FIGURE 1. Overall survival for patients with 5 to 9 versus 10+ brain metastases.

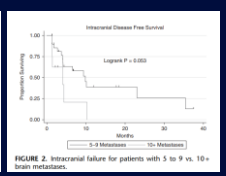

FIGURE 2. Intracranial failure for patients with 5 to 9 vs. 10+ brain metastases.

Yes, SRS seems to be effective for 5 or more metastases.

A.C. Raldow, et al., Am J Clin Oncol 36, 2013

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….and further.

Radiosurgery for Five to Fifteen Brain Metastases: A Single Centre Experience and a Review of the Literature

Susanne J. Rogers', Nicoletta Lomax, Sara Alonso, Tessa Lazeroms and Oliver Riesterer

2022

n=35 patients from 2015-2021

Yes, SRS seems to be effective in carefully selected patients with 5-15 mets

S.J. Rogers et al., Front Oncol, May 10, 2022

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RCTs or Observational Studies: Which is better?

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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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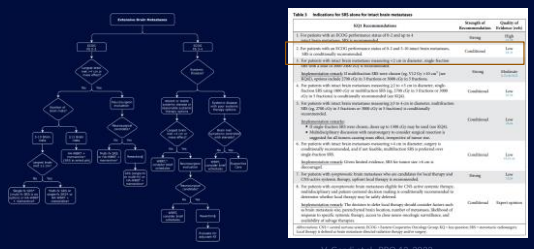
Quality of evidence remains low

Radiation therapy for Brain Metastases: An ASTRO Clinical Practice Guideline



V. Gondi et al., PRO 12, 2022.

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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

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What is the traditional path for evidence for SRS?

What is a prospective registry?

What does the NPA registry do?

What are some successes and challenges?

What might the future look like for registries?

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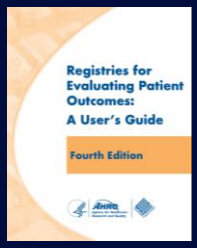
What are patient outcome registries?



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.

AHRQ Agency for Healthcare Research and Quality

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SRS/SBRT Registries

STEREOTACTIC RADIOSURGERY

NEUROPOINT ALLIANCE

NVQI-QOD

ASR

RAD-PD ADVANCING USE

QOD TUMOR

RSSearch Patient Registry

the Radiosurgery Society

NYU Langone Health

ASTRO TARGETING CANCER CARE

(POSSIBLY)

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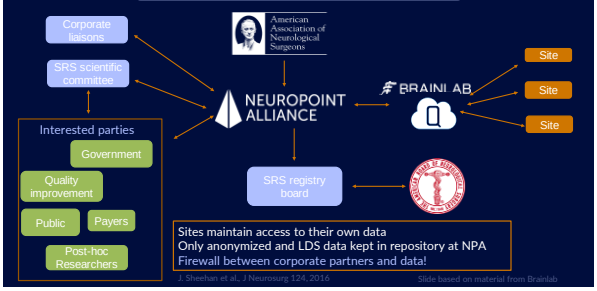
NPA SRS Registry Organization



J. Sheehan et al., J Neurosurg 124, 2016

Slide based on material from Brainlab

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What is the traditional path for evidence for SRS?

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Registry Patients and Events

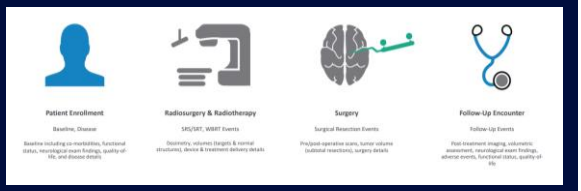

Image courtesy of Brainlab

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Registry key outcome variables

Category	Parameters
Disease	Disease classification, initial diagnosis date, primary/systemic disease controlled, genetic alteration
Lesions	Location, volume (cm^3, RECIST, Macdonald), disappearance, recurrence, hemorrhage, radiation necrosis
Dosimetry	Fractionation and dose to targets, OARs & Whole Brain
Quality of Life	Patient-reported EQ-5D-3L, EQ-VAS
Adverse Events	NCI CTCAE
Neurological Exam	Physician-reported observations
Functional Status	Karnofsky Performance Status (KPS)
Survival	Date, Cause(s) of Mortality

Image courtesy of Brainlab

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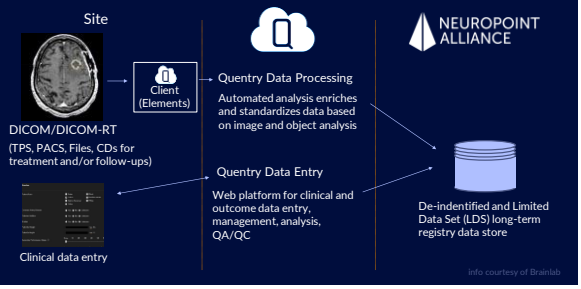
NPA SRS Registry High Level Architecture



info courtesy of Brainlab

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Quentry Data Processing

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

image courtesy of UVA

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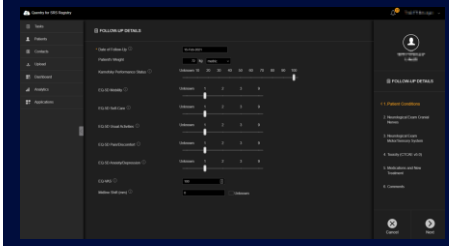
Quentry Data Entry



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

image courtesy of UVA

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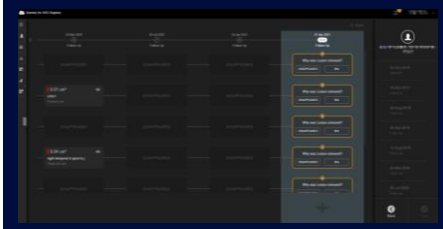
Longitudinal Lesion Tracking



- 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!

image courtesy of UVA

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Per-patient tracking

- Clinicians can view patient progress over time via web interface

image courtesy of Brainlab

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Practice management data

Clinicians can view practice patterns and other clinical data across all of their patients and compare against the registry as a whole.

image courtesy of Brainlab

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- What is the traditional path for evidence for SRS?
- What is a prospective registry?
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- **What are some successes and challenges?**
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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

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How is the registry doing?

Map of current registry sites

https://www.neuropoint.org/registries/stereotactic-radiosurgery-registry/src-current-sites/, accessed 7/11/2022

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

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What have we learned about brain metastases?

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

Mohammed Ali Alvi, MBBS, MS,[1,2] Anthony L. Asher, MD,[1] Giorgos D. Michalopoulos, MD,[1,2] Inga S. Grills, MD,[3] Ronald E. Warnick, MD,[4] James McInerney, MD,[4] Veronica L. Chiang, MD,[1] Albert Attia, MD,[1] Robert Timmerman, MD,[5] Eric Chang, MD,[5] Brian D. Kavanagh, MD,[5] David W. Andrews, MD,[1] Kevin Walter, MD,[1] Mohamad Bydon, MD,[1,2] and Jason P. Sheehan, MD, PhD[1]

J Neurosurg, 2022

Quality of life outcomes for brain metastasis patients treated with stereotactic radiosurgery: pre-procedural predictive factors from a prospective national registry

Jason P. Sheehan, MD, PhD,[1] Inga Grills, MD,[2] Veronica L. Chiang, MD,[1] Huamei Dong, PhD,[2] Arthur Berg, PhD,[2] Ronald E. Warnick, MD,[1] Douglas Kondziolka, MD, MS,[1] and Brian Kavanagh, MD, MPH[3]

J Neurosurg 131, 2019

Local failure after stereotactic radiosurgery (SRS) for intracranial metastasis: analysis from a cooperative, prospective national registry

Anthony L. Asher[1] · Mohammed Ali Alvi[2] · Mohamad Bydon[2] · Nader Pouratian[3] · Ronald E. Warnick[4] · James McInerney[4] · Inga S. Grills[5] · Jason Sheehan[1]

JNO 152, 2021

Quality-of-life trajectories after stereotactic radiosurgery for brain metastases

Adomas Bunevicius, MD, PhD,[1] Karen Lavezzo, RN, BSN,[1] Leah Shabo, BS,[1] Jesse McClure, PharmD, PhD,[1] and Jason P. Sheehan, MD, PhD[1]

J Neurosurg 134, 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

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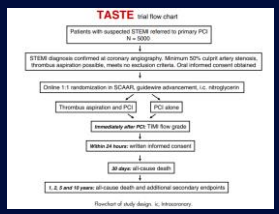
Using registries as a platform for RCTs

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



Flowchart of study design. i.c. Intracoronary.

Study investigating the efficacy of thrombus activation 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 randomized at time of referral. Written confirmation within 24 hours.

O. Fröbert et al., Am Hearth J 160(6), 2010.

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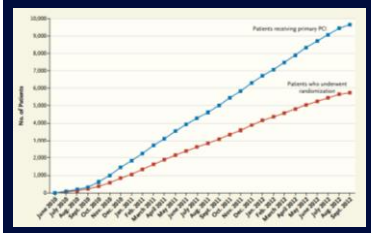
Using registries as a platform for RCTs



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.

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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 problems

More work required to understand effects of data quality

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Interested in participating?

https://www.neuropoint.org/registries/stereotactic-radiosurgery-registry/

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