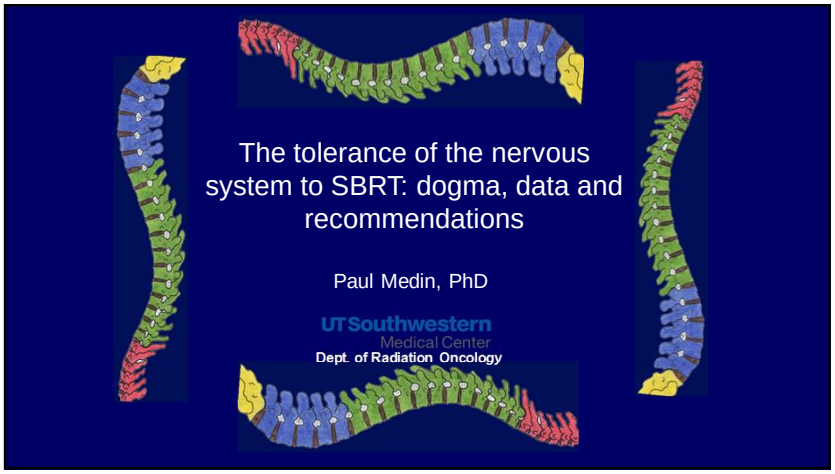


Disclosure

- Paul Medin teaches radiosurgery courses sponsored by BrainLAB
- Many animals (and humans) were harmed to make this presentation possible!

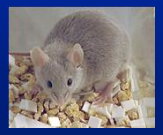
Dogma

- The spinal cord never forgets.
- Dose-volume constraints help us to prevent myelopathy in the spinal cord.
- The spinal cord exhibits regional sensitivity, *eg. cervical versus thoracic*.
- Peripheral nerves tolerate greater dose than the spinal cord.

Where does spinal cord toxicity data come from?

≈ 2%

≈ 80%



≈ 6%

≈ 6%

≈ 6%

Toxicity in humans following de novo SBRT

- 9 cases in the literature

First Author	Fractions	Maximum Cord Dose (Gy)	Latency (months)
Daly	1	17.8	5
Gibbs	1	8.5	2
Gibbs	1	10.0	5
Ryu	1	14.6	13
Sahgal	1	12.7	12
Sahgal	1	13.6	3
Sahgal	1	15.0	6
Gibbs	2	26.2	9
Gibbs	3	29.9	9

Used with permission from the forthcoming, Controversies in SRS, eds Sheehan and Gerszten, Thieme.

Sahgal, et al., IJROBP, 85(2):341-7, 2013
Daly, et al., IJROBP, 80(1):213-220, 2011
Gibbs, et al., Neurosurg, 64:A67-A72, 2009
Ryu, et al., Cancer, 109(3):628-36, 2007

Toxicity in humans following Retreatment with SBRT

- 6 cases in the literature

First Author	Prior Radiation, Maximum Cord Dose(Gy); fractions	Interval to Retreatment (months)	Second Course, Maximum Cord Dose(Gy); fractions	Latency to Deficit (months)
Gibbs	40; 22	80.8	19.2; 2	6
Gibbs	25.2*; 28	70	13.9; 2	4
Gwak	51.9*; 28	18	32.9; 3	8
Sahgal	12.3**; 1	11	21.2; 5	3
Sahgal	43.2; 15	12	14.7**; 1	3
Sahgal	30; 10	1.5	14.7; 1	15

*dose estimated by Sahgal
**dose reported to thecal sac

Sahgal, et al., IJROBP, 82(1):107-16, 2012
Sahgal, et al., IJROBP, 85(2):341-7, 2013
Gibbs, et. al., Neurosurg, 64:A67-A72, 2009
Gwak, et. al., Stereotact Funct Neurosurg, 83:233-243, 2005

Animal Studies of Retreatment

- Retreatment with Single-fraction SBRT 1 year after 3 Gy times 10.

Initial Dose	ED_{50} (Gy)
Zero	20.0
3 Gy times 10	19.7

Medin, et. al., IJROBP, 83(3): 1031-1037, 2012.

Both Dose-Response Curves are nearly identical!

Animal Studies of Retreatment

- Retreatment with Single-fraction SBRT after SBRT dose scheme

Initial Dose	**Re-Tx 8 weeks** ED50 (95% CI)	**Re-Tx 28 weeks** ED50 (95% CI)
9 Gy times 2	14.8 Gy (12.2-17.3)	16.2 Gy (15.8-16.7)
9 Gy times 3	9.8 Gy (8.4-11.2)	14.6 Gy (13.9-15.3)
10.25 Gy times 3	6.1 Gy (5.1-7.0)	12.2 Gy (11.6-12.8)

CS Wong, et. al., IJROBP, 37(1):171-179, 1997

Animal Studies of Retreatment

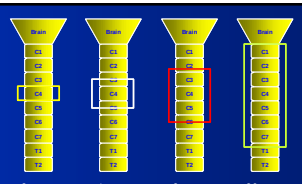
- Retreatment with Single-fraction radiosurgery 1 year after Single-fraction radiosurgery

Initial Dose	ED_{50} (Gy)
Zero	20.5
10 Gy	19.5

Knowles, Int J Radiat Biol Relat Stud Phys Chem Med, 1983.

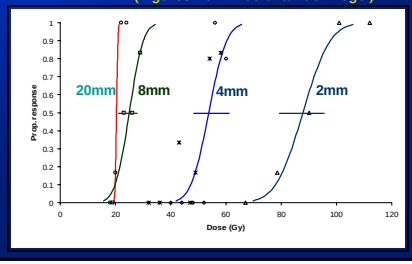
Volume Effect: Length

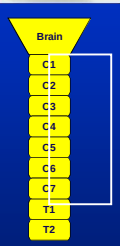
Single-dose irradiation.
Endpoint: paralysis.
Bijl, et. al., IJROBP, 2002.



(Figures from Albert van der Kogel)

Rat ED_{50}'s
- 20 mm: ED_{50} = 20.4 Gy
- 8 mm: ED_{50} = 24.9 Gy (22-29)
- 4 mm: ED_{50} = 53.7 Gy (49-62)
- 2 mm: ED_{50} = 87.8 Gy

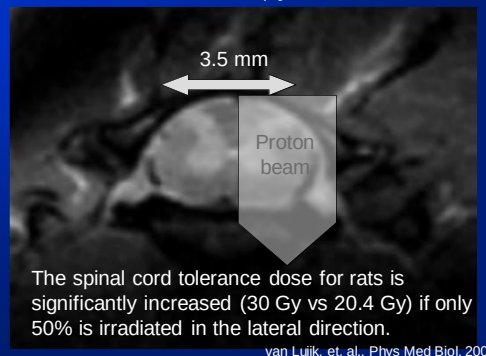




20 mm

Volume Effect: Width

Grazing Proton Beam:
50% isodose at midline of spinal cord



The spinal cord tolerance dose for rats is significantly increased (30 Gy vs 20.4 Gy) if only 50% is irradiated in the lateral direction.

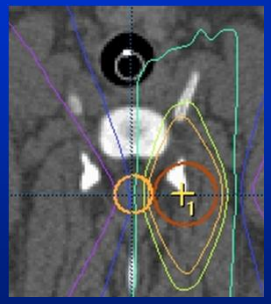
Figures from Albert van der Kogel

van Luijk, et. al., Phys Med Biol, 2001
Bijl, et. al., IJROBP, 2005

Grazing Distribution in a Pig

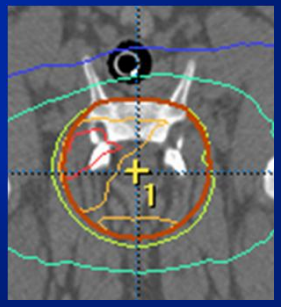
(Medin, et al., IJROBP 79:226-32, 2011) *(Medin, et al. Radiother Oncol 106:101-105, 2013)*

Non-uniform Distribution



ED_{50}=20.0 Gy

Uniform Distribution



ED_{50}=20.2 Gy

Dose-volume effect in humans?

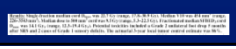
TOLERANCE OF THE SPINAL CORD TO STEREOTACTIC RADIOSURGERY: INSIGHTS FROM HEMANGIOBLASTOMAS

MEGAN E. DALY, M.D.,* CLARA Y. H. CHOI, M.D., PH.D.,† IRIS C. GIBBS, M.D.,* JOHN R. ADLER, JR., M.D.,† STEVEN D. CHANG, M.D.,† ROBERT E. LIEBERSON, M.D.,† AND SCOTT G. SOLTYS, M.D.*

- 17 patients
- Median single–fraction max cord dose = 22.7 Gy (range 17.8-30.9 Gy)

Extremely small volumes and short lengths!
Median V_{10} = 454 mm^3 (range 226-3543 mm^3)

Patient with potential Grade 2 toxicity had lowest cord dose of the series (17.8 Gy)



IJROBP, 80:213-20, 2011

Regional Sensitivity

Cervical vs Thoracic vs Lumbar

- *Regional variation in radiosensitivity has been suggested in the human spinal cord literature but never established by objective analysis.
- **All regions have been studied in rats with similar results.
- RTOG 0631 protocol is consistent with animal data in that prescribed dose is not dependent on vertebral level.

*Schultheiss TE, Stephens LC. Invited review: permanent radiation myelopathy. *Br J Radiol* 1992;65:737-753.
**Van der Kogel A. Late Effects of Radiation On The Spinal Cord. Vol PhD. Amsterdam: University of Amsterdam; 1979. p. 160.
**Scalliet P, et al. Repair kinetics as a determining factor for late tolerance of central nervous system to low dose rate irradiation. *Radiother and Oncol* 1989;14:345-353.
**Bijl HP, *et al*. Dose-volume effects in the rat cervical spinal cord after proton irradiation. *Int J Radiat Oncol Biol Phys* 2002;52:205-211.
**Hopewell JW, et al. The influence of field size on the late tolerance of the rat spinal cord to single doses of X rays. *Br J Radiol* 1987;60:1099-1108.
**Philippens ME, *et al*. Dose-volume effects in rat thoracolumbar spinal cord: the effects of nonuniform dose distribution. *Int J Radiat Oncol Biol Phys* 2007;69:204-213.
**van der Kogel AJ. Radiation tolerance of the rat spinal cord: time-dose relationships. *Radiology* 1977;122:505-509.

Spinal Cord Dose Recommendations, de novo SBRT

- Ryu, et al. 2007
  - partial-volume tolerance is at least 10 Gy to 10% of the spinal cord volume when the spinal cord volume is defined to extend 6 mm superior and inferior to the radiosurgery target.
- Gibbs, et al. 2009
  - caution when considering radiosurgery plans that expose more than 1.0 cm^3 of spinal cord to greater than 8 Gy dose equivalent.
- Sahgal, et al. 2010
  - dose threshold of 10 Gy to the thecal sac
- Sahgal, et al. 2013
  - Risk of RM 5% or less for max thecal sac dose
    - 12.4Gy in one fraction
    - 17.0 Gy in two fractions
    - 20.3 Gy in three fractions
    - 23.0 Gy in four fractions
    - 25.3 Gy in five fractions

Ryu, et al., Cancer, 109(3):628-36, 2007
Gibbs, et. al., Neurosurg, 64:A67-A72, 2009
Sahgal, et al., IJROBP, 77(2):548-553, 2010
Sahgal, et al., IJROBP, 85(2):341-7, 2013

•RTOG 0631—dose constraint table

Table 1: One Fraction Dose Constraints for Arms 1 and 2

Serial Tissue	Volume	Volume Max (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	<0.035 cc <0.35cc <1.2 cc (SBRT only)	14 Gy 10 Gy 7 Gy (SBRT only)	myelitis

Spinal Cord Dose Recommendations, Reirradiation

- Sahgal, et al. 2012
  - SBRT at least 5 months after conventional radiotherapy
  - Reirradiation thecal sac point max dose nBED = 20-25 $Gy_{2/2}$
  - Total point max nBED < 70 $Gy_{2/2}$
  - SBRT thecal sac point max dose nBED < 50% of total nBED

Sahgal, et al., IJROBP, 82(1):107-116, 2012

Conclusions: Spinal Cord Tolerance

- Spinal cord tolerance data from animals is abundant and consistent.
- Spinal cord tolerance data from humans is sparse and inconsistent.
- The field appears to have arrived at 14 Gy as an acceptable maximum spinal cord dose. By animal standards, 14 Gy is conservative and appears be safe for humans.
- I believe the tolerance of young, healthy humans is similar to animal tolerance but acknowledge that humans have many variables not present in animal studies, (advanced age, comorbidities, other therapies, etc).

What is the source of SBRT peripheral nerve tolerance data?

≈ 25

≈ 15

≈ 37

≈ 126

The dog data is actually from the intraoperative radiotherapy setting.

Clinical Neuropathy from Spine SBRT

Year	First Author	Cases	Neuropathy	Rx Dose (Gy)	Fx	Latency to Deficit (months)
2017	Stubblefield	14 (in 557 Tx's)	Pain and weakness Grade 1=14% Grade 2=64% Grade 3=21%	18-24 Gy	1	4-32 (median=10)

*No relationship between dose and injury detected

Stubblefield, et al. Neurosurg Focus. 42(3):E12, 2017

Clinical Neuropathy from lung SBRT

Year	First Author	Cases	Neuropathy	Dose(Gy)	Fractions	Latency to Deficit (months)
2014	Chang, JY	3	Grade 2-3 Brachialplexopathy	>35Gy	4	Not stated
2013	Prendergast, BM	1	Grade 3 Brachialplexopathy	Not Stated	Not Stated	> 3
2009	Kawase, T	1	Thumb Numbness (Brachial Plexus)	47 Gy (mean), 62.5 Gy (max)	5	2
2008	Forquer, JA	7	Grade 2-4 Brachialplexopathy	18-82 Gy (max), 30 Gy (med)	3-4	7 median (6-23)

Constraints for single-fraction SBRT

	Volume (mL)	Volume Max (Gy)	Endpoint(≥Grade 3)
Spinal Cord	<0.035 <0.35 < 1.2	14 10 7	Myelitis
Cauda equina	<0.035 <5	16 14	Neuritis
Sacral Plexus	<0.035 <5	18 14.4	Neuropathy
Brachial Plexus	<0.035 <3	17.5 14	Neuropathy

Single Fraction dose constraints. RTOG 0631 (Spinal Metastases)

	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint(≥Grade 3)
Spinal Cord	<0.35 < 1.2	10 7	14	Myelitis
Brachial Plexus	<3	14	17.5	Neuropathy

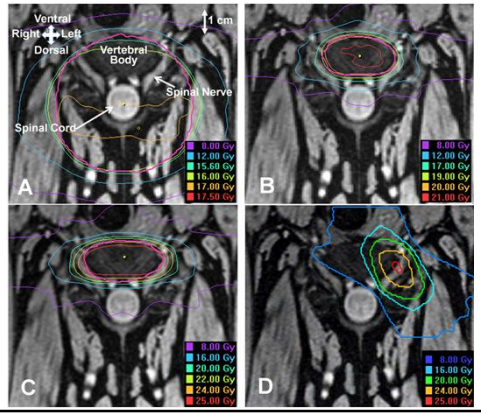
Single-Fraction Constraints, RTOG 0915 (Stage 1, NSCLC)

	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint(≥Grade 3)
Spinal Cord	<0.25 < 1.2	10 7	14	Myelitis
Cauda equina	<5	14	16	Neuritis
Sacral Plexus	<3	14.4	16	Neuropathy
Brachial Plexus	<3	14.4	16	Neuropathy

Single Fraction dose constraints. Timmerman. Seminar Radiat Oncol , 18(4):215-222, 2008

SBRT Animal data

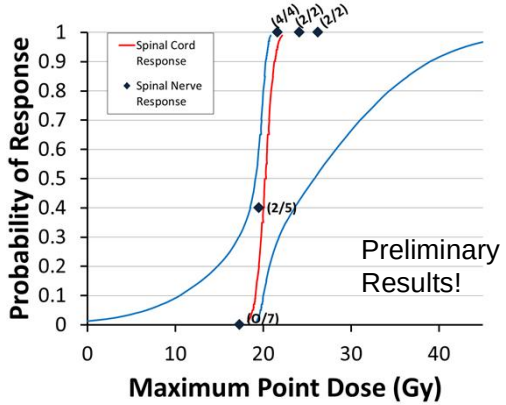
UT Southwestern



A= normal
B= normal
C= paralysis
D= paralysis

Medin, et al., Radiother Oncol, 109:107-111, 2013

Spinal nerve dose-response (15mm segment)



Conclusions: Peripheral Nerves

- Peripheral nerve tolerance is still poorly understood.
- Animal and human data is very limited.
- A study is in progress to evaluate spinal nerve tolerance using pigs.
- Human guidelines for sacral and brachial plexus indicate that these peripheral nerves have a greater tolerance than the spinal cord.
- Emerging data from a pig study suggests that spinal nerve tolerance is the same as the spinal cord tolerance.