Reirradiation Dose-Time Recovery Factors

aka: Reirradiation from Coast to Coast in 10 Years

AAPM SCC Midwinter Workshop Jan 30, 2026
Hollywood, Ca

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Wellstar

RADIOBIOLOGICAL CONSIDERATIONS
FOR RE-IRRADIATION
WITH HIGH DOSE PER FRACTION

AKA: BED FOR DUMMIES

NEAAPM MAY 29, 2015

AKA: BED FOR GENIUSES WHO JUST NEED AN EFFICIENT WAY TO IMPLEMENT IT CLINICALLY

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THE CHARLES A.
AND BETTY BOTT
CANCER CENTER
AT HOLY REDEEMER


THE CHARLES A.
AND BETTY BOTT
CANCER CENTER
AT HOLY REDEEMER

Conflict of Interest Disclosure

Dr. Grimm designed and holds intellectual property rights to the

DVH Evaluator software tool

(www.DiversiLabs.com) which is an FDA-cleared product in commercial use, and which has been used for this analysis

Funding from Accuray, NovoCure, PTW
Free dinners from Zap whenever I can!

FDA 510k Number K092928 Rx Only US Patents 9,019,307 & 9,192,782
www.DiversiLabs.com service@DiversiLabs.com
Soli Deo Gloria

Disclaimer

- Reirradiation is beyond the scope of the AAPM SBRT Working Group (WGSBRT), High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC)
- For Reirradiation, informed consent must be extremely thorough because the risks are much more uncertain. I cannot give any clinical advice, and I accept no responsibility or liability.

Part 1: Spinal Cord Recovery Model

Virtual Intermission:

Questions/Comments?

Part 2: Carotid Artery Recovery Model

Radiation has a dose response

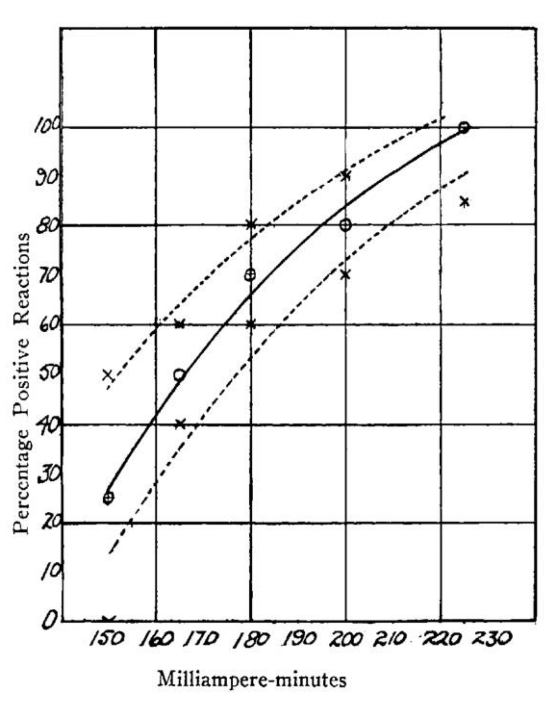
Organs might recover over time

- Edith Quimby
- 1928, RSNA
- Erythema dose

- The first electronic computer wasn't invented until a decade or so later!

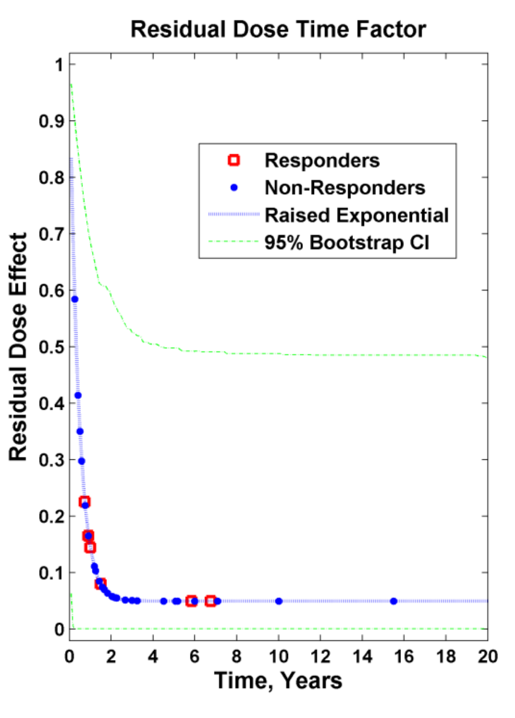
How it Started:

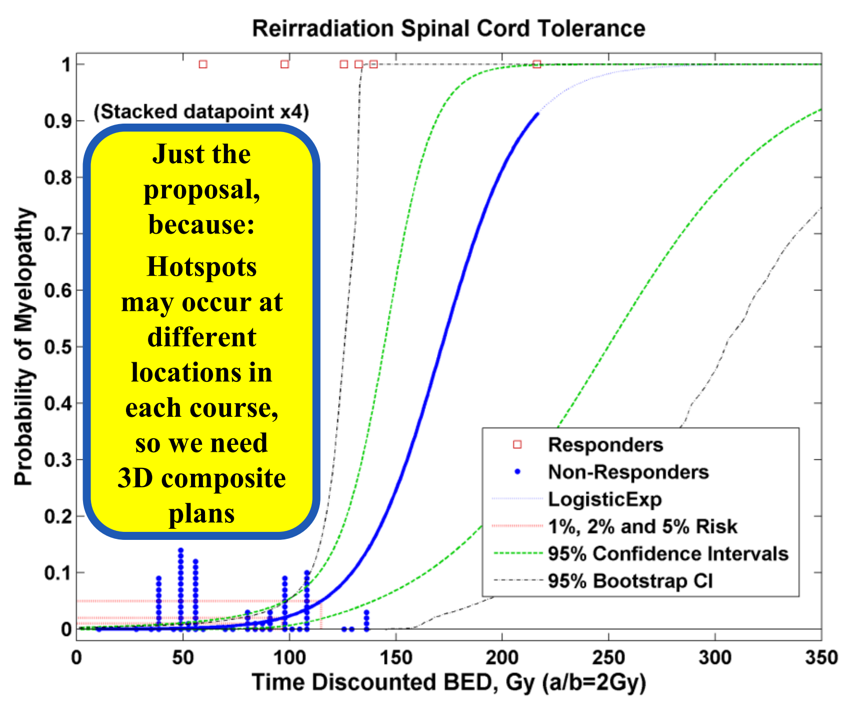
Quimby 1928, graph paper



How it's Going:

Spinal Cord Recovery Model, 2026





For 80% risk level, only need about a dozen cases…

For 1% risk level, need about 1000!

Simplest Case: 2Gy/day extra

- Example: Prior cord dose was 45Gy in 25fx, New lung treatment nearby
- If you can keep the new cord dose to 10Gy in 5fx,
  - Composite dose ≤ 55Gy in 30fx, EQD2 is only 52.7Gy
  - QUANTEC estimated risk for 54Gy is <1%
  - QUANTEC estimated risk for 61Gy is <10%
  - (IJROBP 2010 Mar 1;76(3 Suppl):S42-9)
- We do need to treat the tumor, so this is not always possible, but it is the safest approach when it is feasible

EQD2: Equivalent Dose in 2Gy fractions, using Linear Quadratic (LQ) with α/β=2Gy
QUANTEC: Quantitative Analysis of Normal Tissue Effects in the Clinic
IJROBP: International Journal of Radiation Oncology • Biology • Physics

Next Simplest, 2Gy/day to some small volume, Dx=2Gy/day

- If only 0.1cc of the critical structure exceeds 2Gy/day that sounds nice
- If only 1cc of the critical structure exceeds 2Gy/day …

- Watch out, it's a slippery slope!

- Best practice: Don't ignore Dmax on the reirradiation cases;
  instead use the Dx as an additional safety factor, not as the only factor

- In general: How much of the critical structure is
  exceeding 2Gy/day in the reirradiation plan?

Dr. Steven Goetsch,
Thank you for the invitation!!!

- "But I thought he Retired!"

- Doesn't Retired just mean
  - now you run the world!
  - If he can bring CK and GK and Klystron and All the Others together, isn't that World Peace!

50 Years of Reirradiation Data

- Denekamp J, Fowler JF, Kragt K, Parnell CJ, Field SB. Recovery and repopulation in **mouse skin** after irradiation with cyclotron neutrons as compared with 250-Kv x-rays or 15-Mev electrons. Radiat Res. 1966 Sep;29(1):71-84.
- Wong CS, Hao Y. Long-term recovery kinetics of radiation damage in **rat spinal cord**. Int J Radiat Oncol Biol Phys. 1997 Jan 1;37(1):171-9.
- Lebesque JV, Hart AA, Stewart FA. Reirradiation at long time intervals in **mouse kidney**: a comparison between experimental results and the predictions of the F-type tissue model. Int J Radiat Biol Relat Stud Phys Chem Med. 1988 Mar;53(3):417-28.
- Terry NH, Tucker SL, Travis EL. Residual radiation damage in **murine lung** assessed by pneumonitis. Int J Radiat Oncol Biol Phys. 1988 May;14(5):929-38.
- Stewart FA, Luts A, Lebesque JV. The lack of long-term recovery and reirradiation tolerance in the **mouse kidney**. Int J Radiat Biol. 1989 Oct;56(4):449-62.
- Stewart FA, Oussoren Y, Luts A. Long-term recovery and reirradiation tolerance of **mouse bladder**. Int J Radiat Oncol Biol Phys. 1990 Jun;18(6):1399-406.
- Robbins ME, Bywaters T, Rezvani M, Golding SJ, Hopewell JW. Residual radiation-induced damage to the **kidney of the pig** as assayed by retreatment. Int J Radiat Biol. 1991 Dec;60(6):917-28.
- Ruifrok AC, Kleiboer BJ, van der Kogel AJ. Fractionation sensitivity of the **rat cervical spinal cord** during radiation retreatment. Radiother Oncol. 1992 Dec;25(4):295-300.
- Wong CS, Poon JK, Hill RP. Re-irradiation tolerance in the **rat spinal cord**: influence of level of initial damage. Radiother Oncol. 1993 Feb;26(2):132-8.
- Ang KK, Pr … chultheiss TE, Peters LJ. The tolerance of **primate spinal cord** to re-irradiation. Int J Radiat Oncol Biol Phys. 1993 …
- Lavey RS, … Chon Y, McBride WH. The extent, time course, and fraction size dependence of **mouse spinal cord** recovery fr… Phys. 1994 Oct 15;30(3):609-17.
- Wondergem … EG. Reirradiation tolerance of the **rat heart**. Int J Radiat Oncol Biol Phys. 1996 Nov 1;36(4):811-9.
- Landuyt W… ogel A, van der Schueren E. Kinetics of repair in the **spinal cord of the rat**. Radiother Oncol. 1997 Oct;45(1):5…
- Medin PM, Foster RD, van der Kogel AJ, Sayre JW, McBride WH, Solberg TD. **Spinal cord** tolerance to reirradiation with single-fraction radiosurgery: a **swine** model. Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):1031-7.

If we worked in a zoo we'd be done already!

: -)

Universal Equation for Reirradiation

All they wanted to know
is just a universal equation
for any reirradiation from head to toe…

Spinal Cord Recovery: Paul Medin's Swine Model

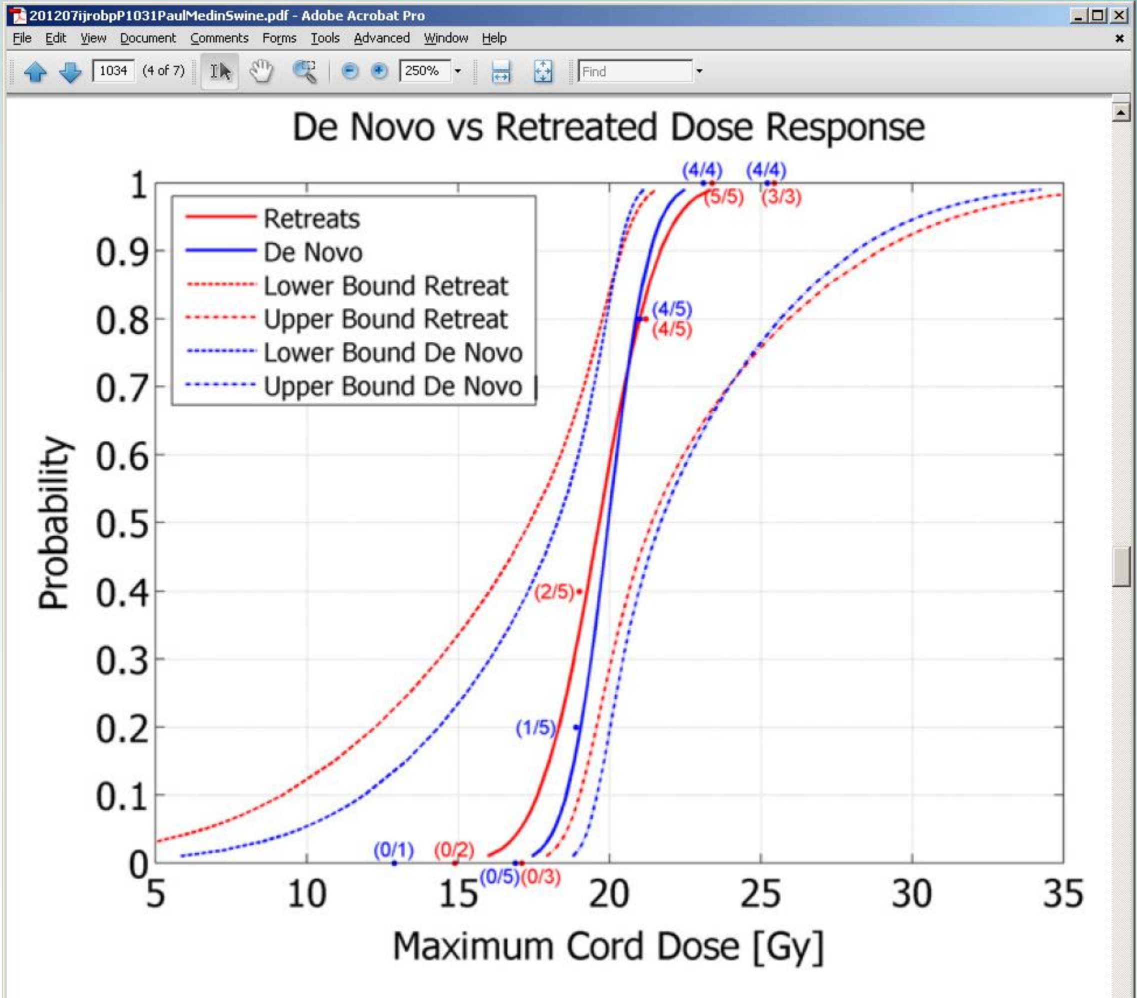


Fig. 3. Dose-response curves with 95% confidence limits for de novo radiosurgery versus retreatment are shown.

- 23 pigs, 6 dose groups
- 30Gy in 10fx, 1 yr prior
- Single fx reirradiation
- 14.9Gy – 25.4Gy new Dmax

- Endpoint: motor neurologic deficit as determined by a change in gait during a 1-year follow-up period

Medin PM, Foster RD, van der Kogel AJ, Sayre JW, McBride WH, Solberg TD. Spinal cord tolerance to reirradiation with single-fraction radiosurgery: a swine model. Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):1031-7.

Question!

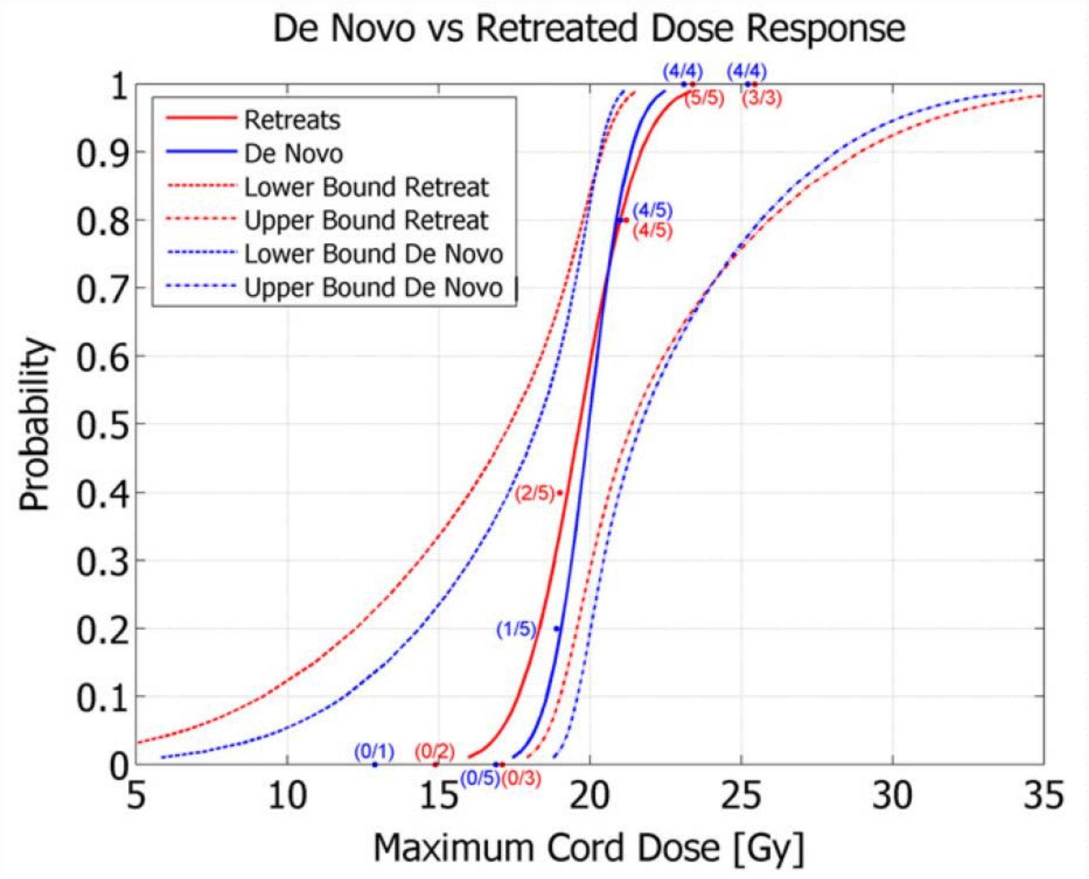
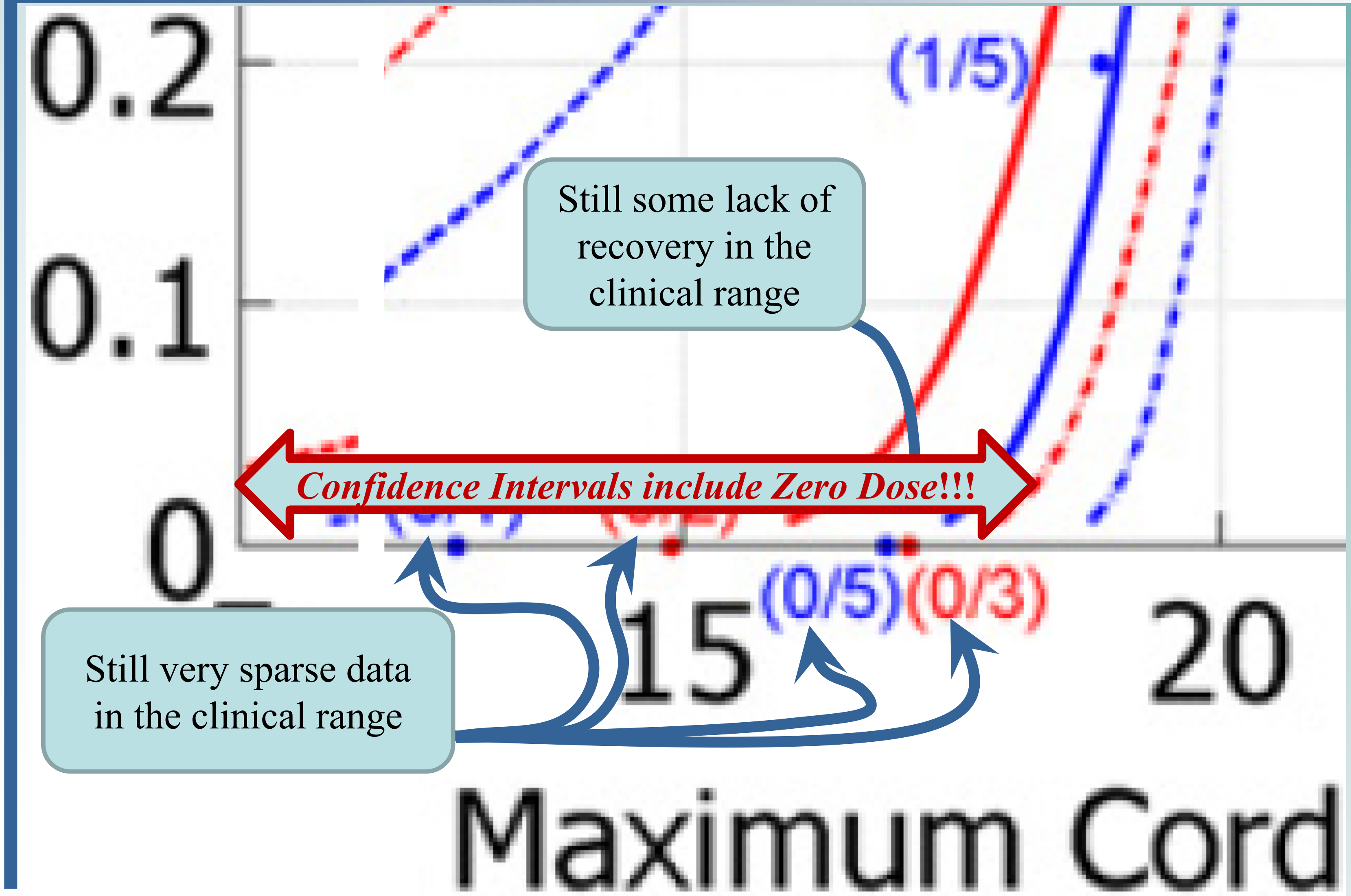


Fig. 3. Dose-response curves with 95% confidence limits for de novo radiosurgery versus retreatment are shown.

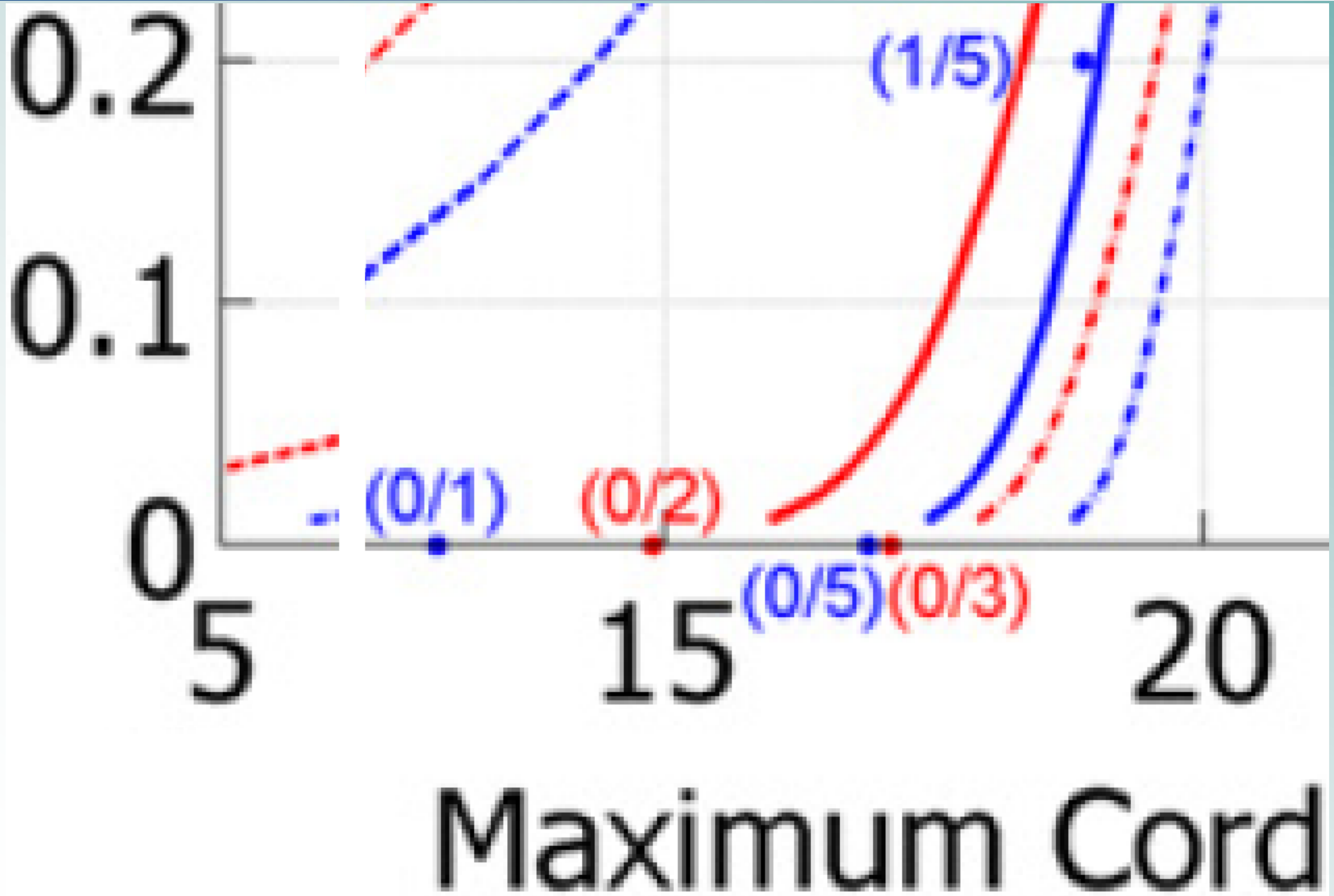
- What is the simple equation for recovery?

But what about in the clinical range?



- Still some lack of recovery in the clinical range
- Still very sparse data in the clinical range
- Not feasible to use 1000 swine to study this
- People are not swine
  - Usually…
- Need to save and analyze our clinical data!!

Question!



- Now what do you say the simple equation is for recovery?
- Dr. Medin's swine model is a landmark foundation, but we still need clinical data to finish the work!

Fitted monkey data and worked clinical examples

The change in r with time t in years, fitted to the data of Ang *et al.* [4] is fitted by the exponential function $r = 2.8 + \text{Exp}[1.66\,(t - 1)]$ (using the least squares method)

This is fairly recent work – someone needs to keep going with this…

$$BED_2 = \left[100^{r+1}\left(1 - \frac{BED_1}{100}\right)\right]^{\frac{1}{r+1}}$$

where BED_1 is the percentage of the tolerance BED value given in the first treatment

Retreatment BED = tolerance BED × $BED_2/100$

Clinical Oncology 26 (2014) 407–418

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

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Overview

Retreatment of Central Nervous System Tumours

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† Gloucestershire Hospitals NHS Foundation Trust, Cheltenham General Hospital, Cheltenham, UK
‡ EORTC Headquarters, Brussels, Belgium

- Marvelous and important work but needs validation with clinical data

Jones B, Grant W. Retreatment of central nervous system tumours. Clin Oncol (R Coll Radiol). 2014 Jul;26(7):407-18.

Primate Spinal Cord data has also been used for Aorta

ELSEVIER

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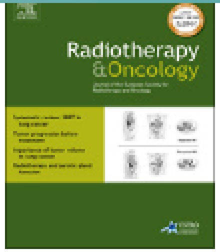


Re-irradiation of thoracic tumors

Aortic dose constraints when reirradiating thoracic tumors

Jaden D. Evans [a,c], Daniel R. Gomez [a,*], Arya Amini [a], Neal Rebueno [a], Pamela K. Allen [a], Mary K. Martel [b], Justin M. Rineer [d], Kie Kian Ang [a], Sarah McAvoy [a], James D. Cox [a], Ritsuko Komaki [a], James W. Welsh [a]

[a] *Department of Radiation Oncology;* [b] *Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, United States;* [c] *Texas Tech University Health Sciences Center School of Medicine, Lubbock;* [d] *Department of Radiation Oncology, Orlando Health MD Anderson Cancer Center, United States*

- “To our knowledge, the kinetics of repair of the aorta has not been sufficiently studied to accurately predict the extent to which it recovers after irradiation. Because of the lack of published studies in this area, we estimated recovery kinetics based on those of the spinal cord”

We could already know the answer to all these questions, if

- **Data pooling**

A lot more patients have been treated than animal studies!!

Deasy JO, Bentzen SM, Jackson A, Ten Haken RK, Yorke ED, Constine LS, Sharma A, Marks LB. Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S151-4.

We need data pooling

Deasy JO, Bentzen SM, Jackson A, Ten Haken RK, Yorke ED, Constine LS, Sharma A, Marks LB.

Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture.

Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S151-4.

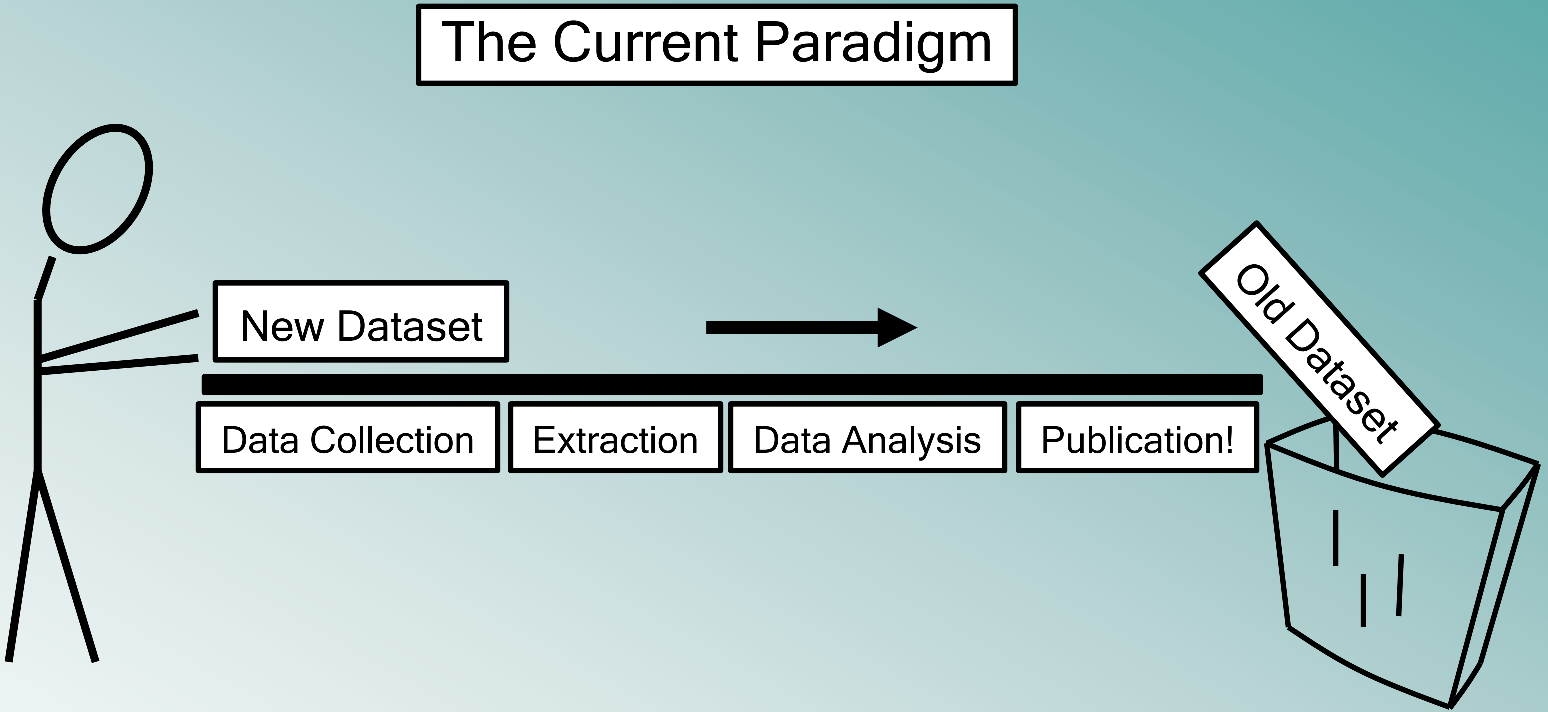


Fig. 2. "The current (data-loss) paradigm." Data are effectively lost to the wider scientific community after publication. Capturing key datasets in query-able data repositories would accelerate the discovery of causative factors and increase the accuracy of parameter estimates.

The Current Paradigm

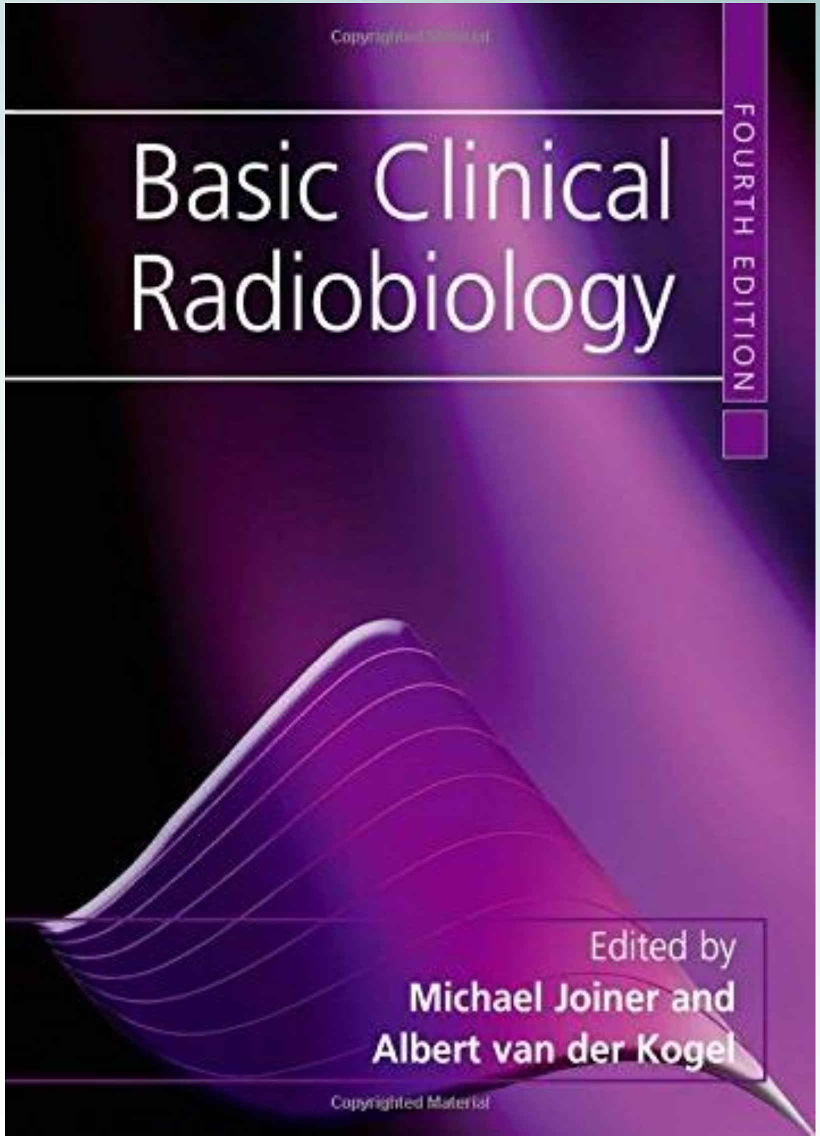
The ‘‘trash can,’’ of course, is typically a set of computer tapes or disks that simply gather dust. In many cases storage media have deteriorated over time or the device for reading these may no longer be available.

Several Formulae have been proposed but clinical validation is sparse

- Jones B, Hopewell JW. Alternative models for estimating the radiotherapy retreatment dose for the spinal cord. Int J Radiat Biol. 2014 Sep;90(9):731-41.
- Jones B, Grant W. Retreatment of central nervous system tumours. Clin Oncol (R Coll Radiol). 2014 Jul;26(7):407-18.
- Ma L, Kirby N, Korol R, Larson DA, Sahgal A. Assessing small-volume spinal cord dose for repeat spinal stereotactic body radiotherapy treatments. Phys Med Biol. 2012 Dec 7;57(23):7843-51.
- Huang Z, Mayr NA, Lo SS, Wang JZ, Jia G, Yuh WT, Johnke R. A generalized linear-quadratic model incorporating reciprocal time pattern of radiation damage repair. Med Phys. 2012 Jan;39(1):224-30.
- Lee AW, Foo W, Law SC, Peters LJ, Poon YF, Chappell R, Sze WM, Tung SY, Lau WH, Ho JH. Total biological effect on late reactive tissues following reirradiation for recurrent nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2000 Mar 1;46(4):865-72.
- Wong CS, Hao Y. Long-term recovery kinetics of radiation damage in rat spinal cord. Int J Radiat Oncol Biol Phys. 1997 Jan 1;37(1):171-9.
- Wondergem J, van Ravels FJ, Reijnart IW, Strootman EG. Reirradiation tolerance of the rat heart. Int J Radiat Oncol Biol Phys. 1996 Nov 1;36(4):811-9.
- Terry NH, Tucker SL, Travis EL. Residual radiation damage in murine lung assessed by pneumonitis. Int J Radiat Oncol Biol Phys. 1988 May;14(5):929-38.

All of these and several others have equations to account for reirradiation, and one of them might ultimately become the standard, but for now I don't see any of them with an overwhelming amount of clinical evidence…

Textbook Solution:



- Chapter 19, Retreatment tolerance to normal tissue

- Early Tissue Reactions
  - Epidermis
  - Oral & oesophageal mucosa
  - Bone marrow
  - Urinary bladder

- Late Effects
  - Skin
  - Lung
  - Kidney
  - Urinary bladder
  - Spinal cord

- Very important descriptions, but not very quantitative for ReTx

Ideal Solution:

- Some target areas will be solved quantitatively via prospective cooperative trials:
  - Spine reirradiation
  - H&N reirradiation

- These are among the most common reirradiation sites and several institutions have much expertise in these and cooperative trials are underway

- For the rest, it is likely to be case-by-case situations for at least the next 5-10 years, and we need to save our data and collaborate to accumulate sufficient data

Pragmatic Solution:
Time-Discounted Prior BED

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 5, pp. 1369–1375, 2009

0360-3016/09/$–see front matter

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doi:10.1016/j.ijrobp.2008.06.1949

CLINICAL INVESTIGATION **Spine**

STEREOTACTIC BODY RADIOTHERAPY FOR LESIONS OF THE SPINE AND PARASPINAL REGIONS

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Departments of *Radiation Oncology and †Surgery, Duke University Medical Center, Durham, NC

Purpose: To describe our experience and clinical strategy for stereotactic body radiotherapy (SBRT) of spinal lesions.
Methods and Materials: Thirty-two patients with 33 spinal lesions underwent computed tomography–based simulation while free breathing. Gross/clinical target volumes included involved portions of the vertebral body and paravertebral/epidural tumor. Planning target volume (PTV) expansion was 6 mm axially and 3 mm radially; the cord was excluded from the PTV. Biologic equivalent dose was calculated using the linear quadratic model with $\alpha/\beta = 3$ Gy. Treatment was linear accelerator based with on-board imaging; dose was adjusted to maintain cord dose within tolerance. Survival, local control, pain, and neurologic status were monitored.
Results: Twenty-one patients are alive at 1 year (median survival, 14 months). Median follow-up is 6 months for all patients (7 months for survivors). Mean previous radiotherapy dose to 22 patients was 35 Gy, and median interval was 17 months. Renal (31%), breast, and lung (19% each) were the most common histologic sites. Three SBRT fractions (range, one to four fractions) of 7 Gy (range, 5–16 Gy) were delivered. Median cord and target biologic equivalent doses were 70 Gy_3 and 34.3 Gy_{10}, respectively. Thirteen patients reported complete and 17 patients reported partial pain relief at 1 month. There were four failures (mean, 5.8 months) with magnetic resonance imaging evidence of in-field progression. No dosimetric parameters predictive of failure were identified. No treatment-related toxicity was seen.
Conclusions: Spinal SBRT is effective in the palliative/re-treatment setting. Volume expansion must ensure optimal PTV coverage while avoiding spinal cord toxicity. The long-term safety of spinal SBRT and the applicability of the linear-quadratic model in this setting remain to be determined, particularly the time-adjusted impact of prior radiotherapy. © 2009 Elsevier Inc.

Pragmatic Solution:
Time-Discounted Prior BED

In cases of re-treatment, we limited the SBRT dose based on the following guidelines:

1. Assume cord tolerance of 50 Gy in 2 Gy/fraction (BED = 83.3 Gy_3), a dose shown to result in a risk of transverse myelitis less than 0.2% (15, 16).
2. Calculate the time-discounted prior BED (BED_{prior}) to the cord by assuming dose recovery of 25%, 33%, and 50% at 6 months, 1 year, and 2 years, respectively (13, 16–18). This is a purposefully more conservative estimate of dose recovery than that predicted from animal models, particularly given that those studies were based on full-thickness conventional reirradiation of the cord, whereas for SBRT, only partial thickness of the cord is exposed to the highest doses (discussed later).
3. Set the maximum tolerable cord dose as the maximum dose to 99% of the contoured cord volume over the region of treatment as 83.3 $Gy_3 - BED_{prior}$.

For previously untreated cord, we limit single-fraction dose to 99% of the cord volume in the region of treatment to 12 Gy or less (9).

- Straightforward implementation
- Don’t just use the equation
  - Read the full paper
  - Look up the references
  - Think about what it means
  - Watch out for caveats!
- At least this is very usable clinically
- Save the data for analysis!

“…assuming dose recovery of 25%, 33%, and 50% at 6 months, 1 year, and 2 years…”

Comparing the Past and Future

- This style is for NEAAPM presentation 10 years ago, virtually unchanged slides

- This style is for SCC AAPM presentation 10 years later

"The future ain't what it used to be"
"It's deja vu all over again"
- Yogi Berra

Protocol Solution:
Brainstem ReTx Tolerance Example

- Clinical case:
  - Whole brain RT one year ago, 30Gy in 10fx
  - New brain met near the brainstem
  - What is acceptable brainstem tolerance?
  - 18Gy in 1fx prescription is planned

Protocol Solution: RTOG 90-05 allowed prior WBRT within 3-month interval

- "To be eligible, patients ≥18 years old must have received partial or whole brain fractionated external beam radiotherapy ≥ 3 months prior to study entry for either a primary brain tumor or brain metastases."
- The prescriptions in a single fraction were 24Gy, 18Gy, or 15Gy, depending on whether the tumor was less than 2cm diameter or greater than 3cm diameter.

- Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Farnan N. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000 May 1;47(2):291-8.

RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-08

A PHASE III TRIAL COMPARING WHOLE BRAIN IRRADIATION WITH VERSUS WITHOUT STEREOTACTIC RADIOSURGERY BOOST FOR PATIENTS WITH ONE TO THREE UNRESECTED BRAIN METASTASES

Amazing!
. . . so what are the
ReTx dose constraints . . .

SCHEMA

REGISTER:

STRATIFY

<u>Number of Metastases</u>
1. Single
2. 2-3 *(discontinued 6/14/99)*

<u>Extent of Extracranial Disease</u>
1. None
2. Present

RANDOMIZE

<u>Arm 1</u>: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/ week followed by radiosurgery to all *(1-3)* metastase*(i)s*

<u>Arm 2</u>: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/ week

"No metastases to brain stem, midbrain, pons, or medulla or within 10 mm of the optic apparatus (optic nerves and chiasm)."

<u>Arm 1</u>: All patients will receive whole brain radiation therapy delivered to 37.5 Gy in 15 daily fractions of 2.5 Gy followed by stereotactic radiosurgery *(SRS)* to all *(1-3)* known metastase*(i)*s. SRS dose will be tumor size dependent *(See Section 6.2.2)* and will be prescribed to the isodose surface *(≥ 50% to ≤ 90% of the maximum dose [maximum = 100%])* which encompasses the margin of the tumor.

<u>Arm 2</u>: All patients will receive whole brain radiation therapy delivered to 37.5 Gy in 15 daily fractions of 2.5 Gy.

- RTOG 95-08 randomized the 90-05 prescription scheme plus WBRT against WBRT alone.
- So all cases in RTOG 95-08 had WBRT, whether they had 24/18/15 Gy of radiosurgery or not

Enough patients have been reirradiated clinically that we could have had an answer for this by now…

Deasy JO, Bentzen SM, Jackson A, Ten Haken RK, Yorke ED, Constine LS, Sharma A, Marks LB.

Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture.

Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S151-4.

- If you treat patients, you have data
  - We need to analyze the outcomes to optimize the treatments!

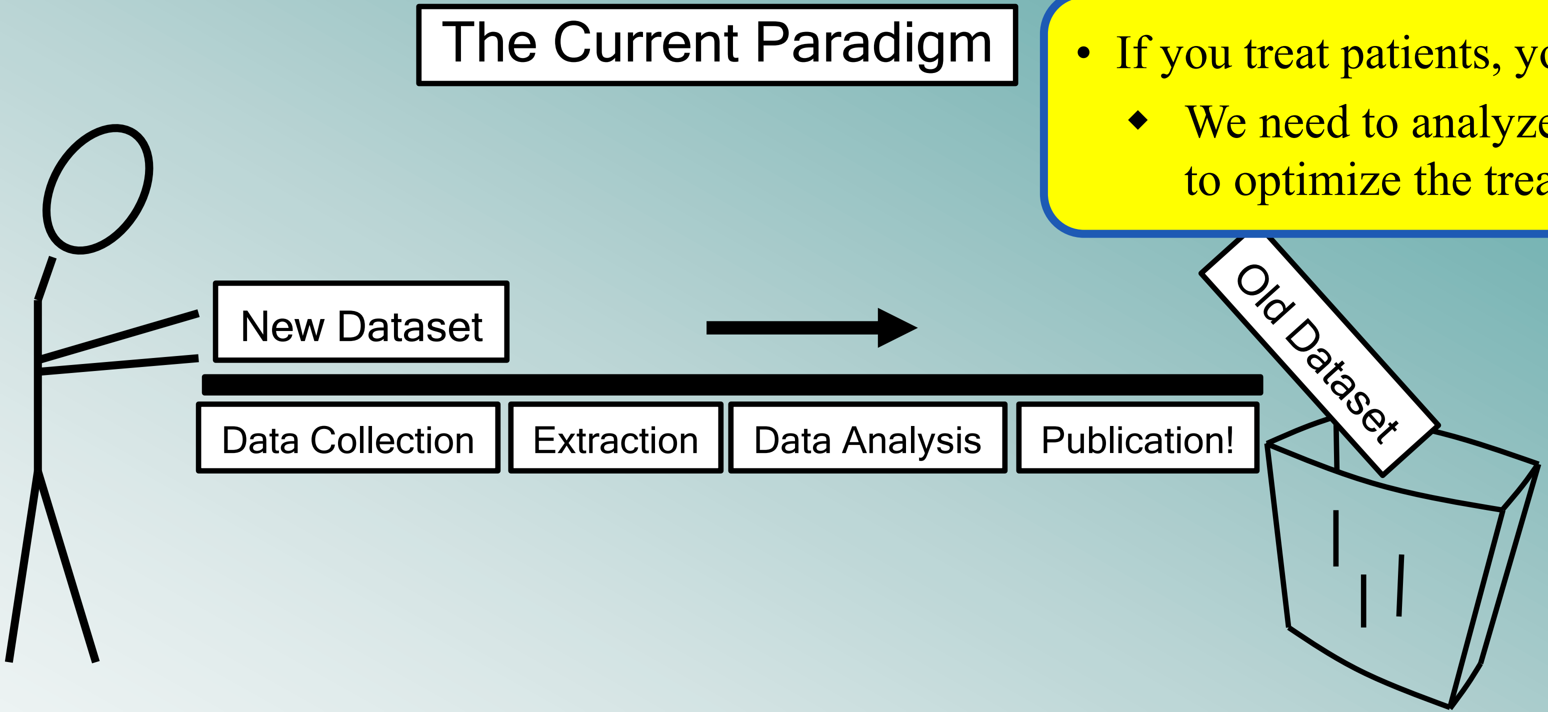

Fig. 2. "The current (data-loss) paradigm." Data are effectively lost to the wider scientific community after publication. Capturing key datasets in query-able data repositories would accelerate the discovery of causative factors and increase the accuracy of parameter estimates.

OK, Actual Reality:

- Progress towards the ideal solution for
  - Spinal Cord
  - Head and Neck

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 107–116, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.08.021

CLINICAL INVESTIGATION **Central Nervous System Tumor**

REIRRADIATION HUMAN SPINAL CORD TOLERANCE FOR STEREOTACTIC BODY RADIOTHERAPY

Arjun Sahgal, M.D.,* Lijun Ma, Ph.D.,† Vivian Weinberg, Ph.D.,‡ Iris C. Gibbs, M.D.,§ Sam Chao, M.D.,¶ Ung-Kyu Chang, M.D.,‖ Maria Werner-Wasik, M.D.,** Liliyanna Angelov, M.D.,¶ Eric L. Chang, M.D.,†† Moon-Jun Sohn, M.D.,‡‡ Scott G. Soltys, M.D.,§ Daniel Létourneau, Ph.D.,§§ Sam Ryu, M.D.,¶¶ Peter C. Gerszten, M.D.,‖‖ Jack Fowler, Ph.D.,*** C. Shun Wong,††† and David A. Larson.†

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Spinal Cord: Many Experts from Many Leading Institutions, and Actual Clinical Data

Table 3. Thecal sac dosimetric SBRT data for the RM group

Patient/tumor	SBRT dose to thecal sac P_{max} (Gy)/fx	Thecal sac nBED to P_{max} ($Gy_{2/2}$)	Thecal sac nBED to 0.1 cc ($Gy_{2/2}$)	Thecal sac nBED to 1.0 cc ($Gy_{2/2}$)	Thecal Sac nBED to 2.0 cc ($Gy_{2/2}$)
A	20.3/2	61.4	54.6	42.3	33.5
B	20.9/2	65.1	52.0	35.2	24.7
C	12.3/1	44.1	37.8	19.3	11.6
D	32.6/3	104.9	95.6	82.6	70.5
E	14.7/1	61.7	41.4	16.8	10.8

Abbreviations: fx = fraction; nBED = normalized biologically effective doses; RM = radiation myelopathy; SBRT = stereotactic body radiotherapy.

- The article has detailed description of the symptoms and circumstances of each case
- Compared to 14 control cases.
- Tables 1 and 2 of the manuscript show the patient and tumor characteristics of the two groups
- Contours are thecal sac instead of spinal cord, **thecal sac dose ≥ spinal cord dose**

Reasonable Reirradiation Thecal Sac Dose Tolerance

Table 6. Reasonable reirradiation SBRT doses to the thecal sac P_{max} following common initial conventional radiotherapy regimens

Conventional Radiotherapy (nBED)	1 fraction: SBRT dose to thecal sac P_{max}	2 fractions: SBRT dose to thecal sac P_{max}	3 fractions: SBRT dose to thecal sac P_{max}	4 fractions: SBRT dose to thecal sac P_{max}	5 fractions: SBRT dose to thecal sac P_{max}
0*	10 Gy	14.5 Gy	17.5 Gy	20 Gy	22 Gy
20 Gy in 5 fractions (30 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
30 Gy in 10 fractions (37.5 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
37.5 Gy in 15 fractions (42 $Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
40 Gy in 20 fractions (40 $Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
45 Gy in 25 fractions (43 $Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fractions (50 $Gy_{2/2}$)	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy

Abbreviations: N/A = not applicable; nBED = normalized biologically effective doses; SBRT = stereotactic body radiotherapy.

* These dose limits are based on our prior publication for spinal cord tolerance in patients treated with SBRT and no prior history of radiation (7).

- **“the minimum time interval to retreatment SBRT should be at least 5 months”**

It became HyTEC Spinal Cord Table 4!

HyTEC Organ-Specific Paper: Spinal Cord

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy

Arjun Sahgal, MD,* Joe H. Chang, MBChB, PhD,* Lijun Ma, PhD,[†] Lawrence B. Marks, MD,[‡] Michael T. Milano, MD, PhD,[§] Paul Medin, PhD,[||] Andrzej Niemierko, PhD,[¶] Scott G. Soltys, MD,[#] Wolfgang A. Tomé, PhD,** C. Shun Wong, MD,* Ellen Yorke, PhD,[††] Jimm Grimm, PhD,[‡‡] and Andrew Jackson, PhD[††]

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Table 4 Maximal spinal cord doses for reirradiation associated with a low risk of RM according to Sahgal et al 2012[43]

Prior RT		Recommended spinal cord* D_{max} in 1-5 fractions (Gy)				
Dose, Gy/fractions	$EQD2_2$, Gy	1 fraction	2 fractions	3 fractions	4 fractions	5 fractions
20/5	30	9	12.2	14.5	16.2	18
30/10	37.5	9	12.2	14.5	16.2	18
40/20	40	N/A	12.2	14.5	16.2	18
45/25	43	N/A	12.2	14.5	16.2	18
50/25	50	N/A	11	12.5	14	15.5

Abbreviations: D_{max} = maximum dose; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); RT = radiation therapy.
* The thecal sac was used as a surrogate structure for the spinal cord in this study.[43]

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Abbreviations: D_{max} = maximum dose; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); RT = radiation therapy.
* The thecal sac was used as a surrogate structure for the spinal cord in this study.[43]

Example B → 30/10

Example A → 50/25

In a few moments I'll show you a clinical example scaled to Example A…
…for Example B, please read the upcoming paper!

Let's model those 5 cases and all the data we could find

Reference	Spinal Cord Dmax 1 (BED2, Gy)	Time Interval crs1 to crs2, 3 (Months)	Spinal Cord Dmax 2, 3 (BED2, Gy)	Follow-up (Months)	Myelopathy	Non-Sacrum Cord+Cauda NumCases	Notes
Gwak 2005	95.76	54	85.9	32		1	
Gwak 2005	75	120	120.9	24		1	
Gerszten 2006	75	3	40	4		1	
Parikh 2009	75	6	77.34	26		1	
Choi 2010	80	19	49.5	7		7	
Choi 2010	80	19	84.99	7		10	
Choi 2010	80	19	82.9	7		5	
Choi 2010	80	19	76.1	7		3	
Choi 2010	80	19	73.1	7		12	
Damast 2011	75	25	33.6	12.1		35	
Nikolajek 2011	85.6	15	40	14.5		53	
Nikolajek 2011	85.6	8.8	40	14.5	1	1	
Sahgal 2012	60	5	20.14	9		1	
Sahgal 2012	103	61	3.71	26		1	

BED_2 = Biological Effective Dose, with Linear Quadratic model, α/β=2 Gy

Let’s model those 5 cases and all the data we could find, cont’d

Reference	Spinal Cord Dmax 1 (BED2, Gy)	Time Interval crs1 to crs2, 3 (Months)	Spinal Cord Dmax 2, 3 (BED2, Gy)	Follow-up (Months)	Myelopathy	Non-Sacrum Cord+Cauda NumCases	Notes
Sahgal 2012	100	11	56.85	8		1	
Sahgal 2012	76	81	123.32	55	1	1	Case A, Gibbs 2007, Choi 2010
Sahgal 2012	37	70	130.1	29	1	1	Case B, Gibbs 2007
Sahgal 2012	66	11	87.95	17	1	1	Case C
Sahgal 2012	100	18	209.73	11	1	1	Case D, Gwak 2005
Sahgal 2012	105	12	122.75	3	1	1	Case E
Chang 2012	74.36	24.5	92.4	17.3		37	
Wang 2014	80	9	117.2	9.4		12	
Thibault 2015	66.8	14.3	47	6.8		24	
Thibault 2015	75	12.9, 14.3	39.4, 49	6.8		17	
Zschaeck 2017	90	18, 8	127.6, 70.8	12		1	
Zschaeck 2017	96	61, 11	107, 45.6	12		1	
Ehret 2021	79.2	17.2	103.2	22.2		38	
Bentahila 2023	69.4	101, 85	5.78, 7.88	8		1	

A total of 282 Evaluable Treatments,

each with at least one course of SBRT

BED_2 = Biological Effective Dose, with Linear Quadratic model, α/β=2 Gy

Proposal!

- **QUANTEC:** Quantitative Analysis of Normal Tissue Effects in the Clinic

- **HyTEC:** High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic

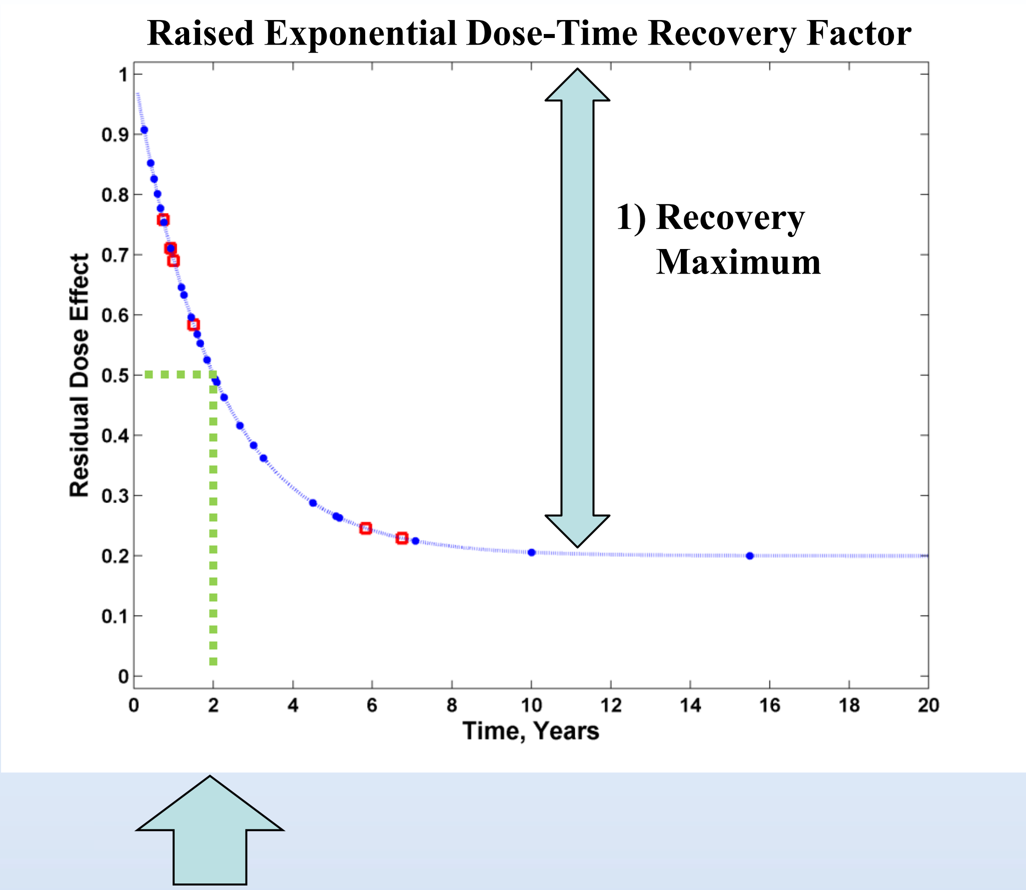
We propose:

- **ReTEC:** Reirradiation Treatment Effects in the Clinic

That was general concept,

this is specific example:

For Reirradiation, fit 2 parameters using Maximum Likelihood: 1) Recovery Maximum, and 2) Recovery Halftime



2) Recovery Halftime

1) RecoveryMaximum is asymptotically the maximum recovery achieved at the longest time intervals between treatments

2) RecoveryHalftime is the time required for 50% recovery to be achieved

Maximum Likelihood parameter fitting is used to optimize 1) RecoveryMaximum and 2) RecoveryHalftime from clinical outcomes data

Clinical Example from HyTEC Spinal Cord NTCP paper

134 Sahgal et al. International Journal of Radiation Oncology • Biology • Physics

Table 4 Maximal spinal cord doses for reirradiation associated with a low risk of RM according to Sahgal et al 2012[43]

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50/25	50	N/A	11	12.5	14	15.5

Abbreviations: D_{max} = maximum dose; $EQD2_2$ = equivalent dose in 2 Gy fractions (α/β = 2 Gy); RT = radiation therapy.
* The thecal sac was used as a surrogate structure for the spinal cord in this study.[43]

Example A

Sahgal 2021 IJROBP May 1;110(1):124-136

Prior Dose: 50Gy/25fx

BED = 100Gy

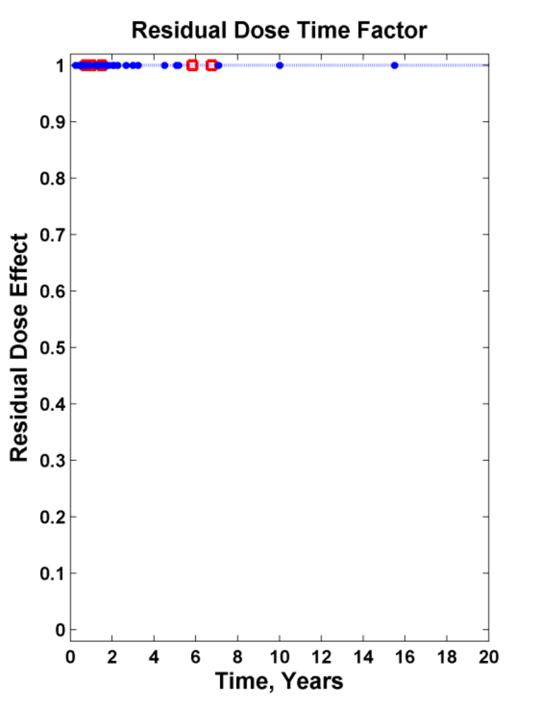
1 Year Interval

SBRT Spinal Cord Dmax: 15.5Gy/5fx

BED = 40Gy

Linear Quadratic (LQ) Model
α/β=2Gy

Scenario 1: No Recovery

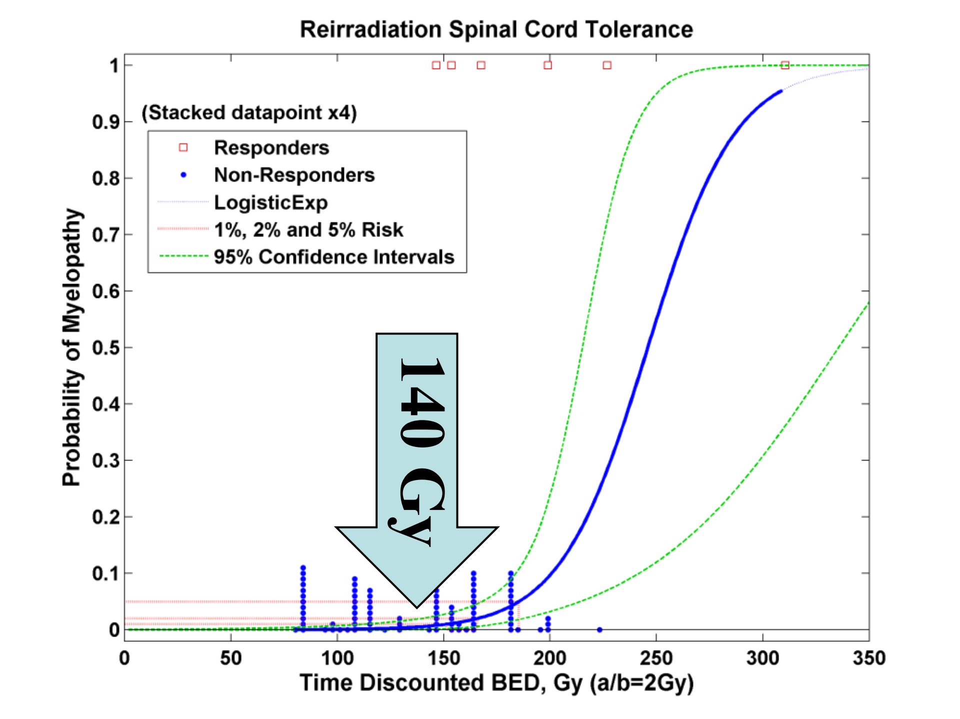


1 Year Interval

No Recovery BED
100Gy*100%

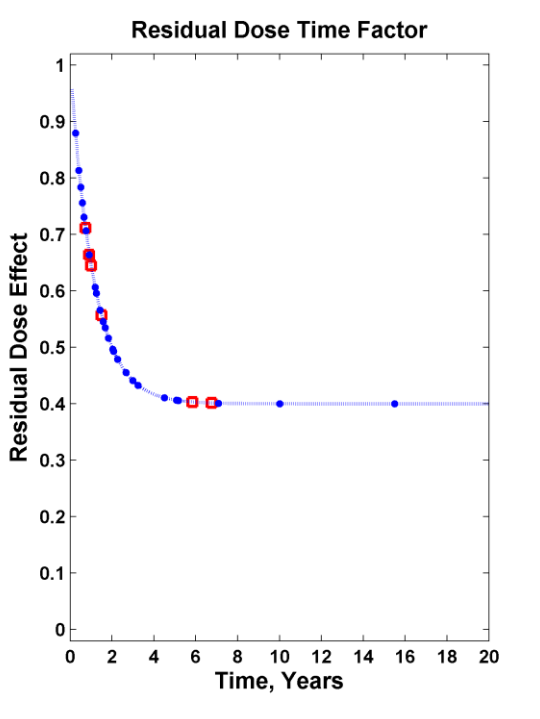
BED 100Gy
+
BED 40Gy
=
140Gy

< 1% risk



Warning: Time Discounted BED is calculated differently in each model, can't just mix and match them

Scenario 2: Fit to Nelson 2009 assumption



"…assuming dose recovery of 25%, 33%, and 50% at 6 months, 1 year, and 2 years…"

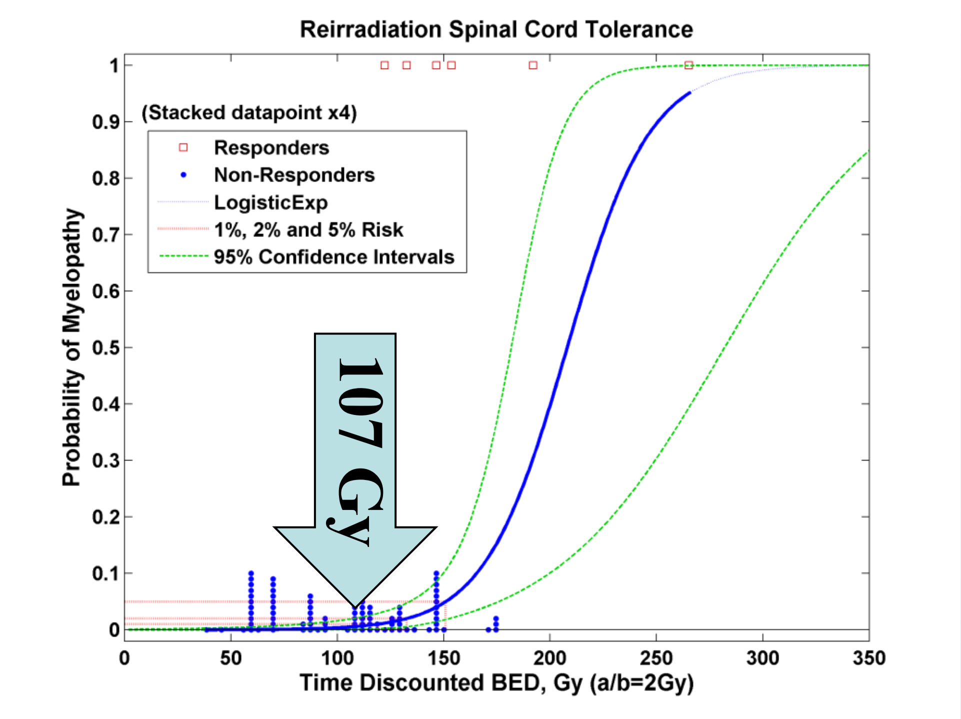
Nelson 2009 IJROBP Apr 1;73(5):1369-75

1 Year Interval

Recovered BED
100Gy*67%

BED 67Gy
+
BED 40Gy
=
107Gy

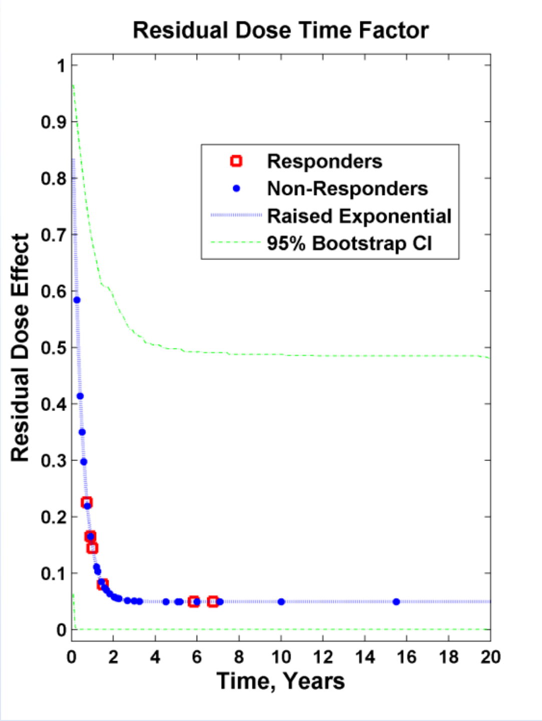
< 1% risk



Warning: Time Discounted BED is calculated differently in each model, can't just mix and match them

Values when fitted to Nelson 2009 assumption
Recovery Halftime: 2 years
Recovery Maximum: 60%

Scenario 3: Maximum Likelihood fitted values

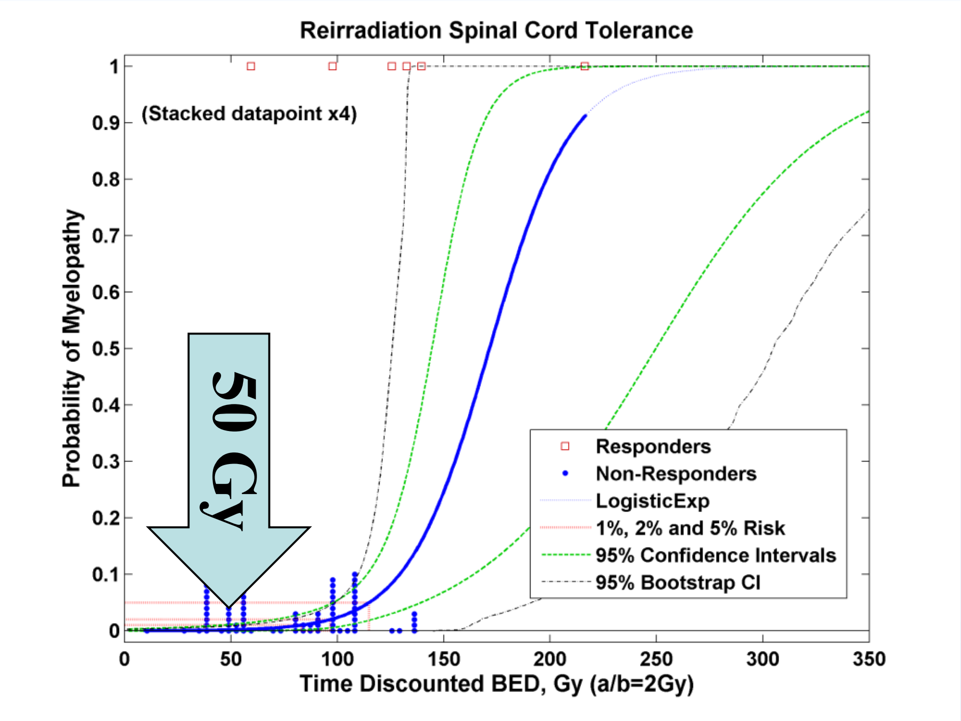


1 Year Interval

Recovered BED
100Gy*10%

BED 10Gy
+
BED 40Gy
=
50Gy

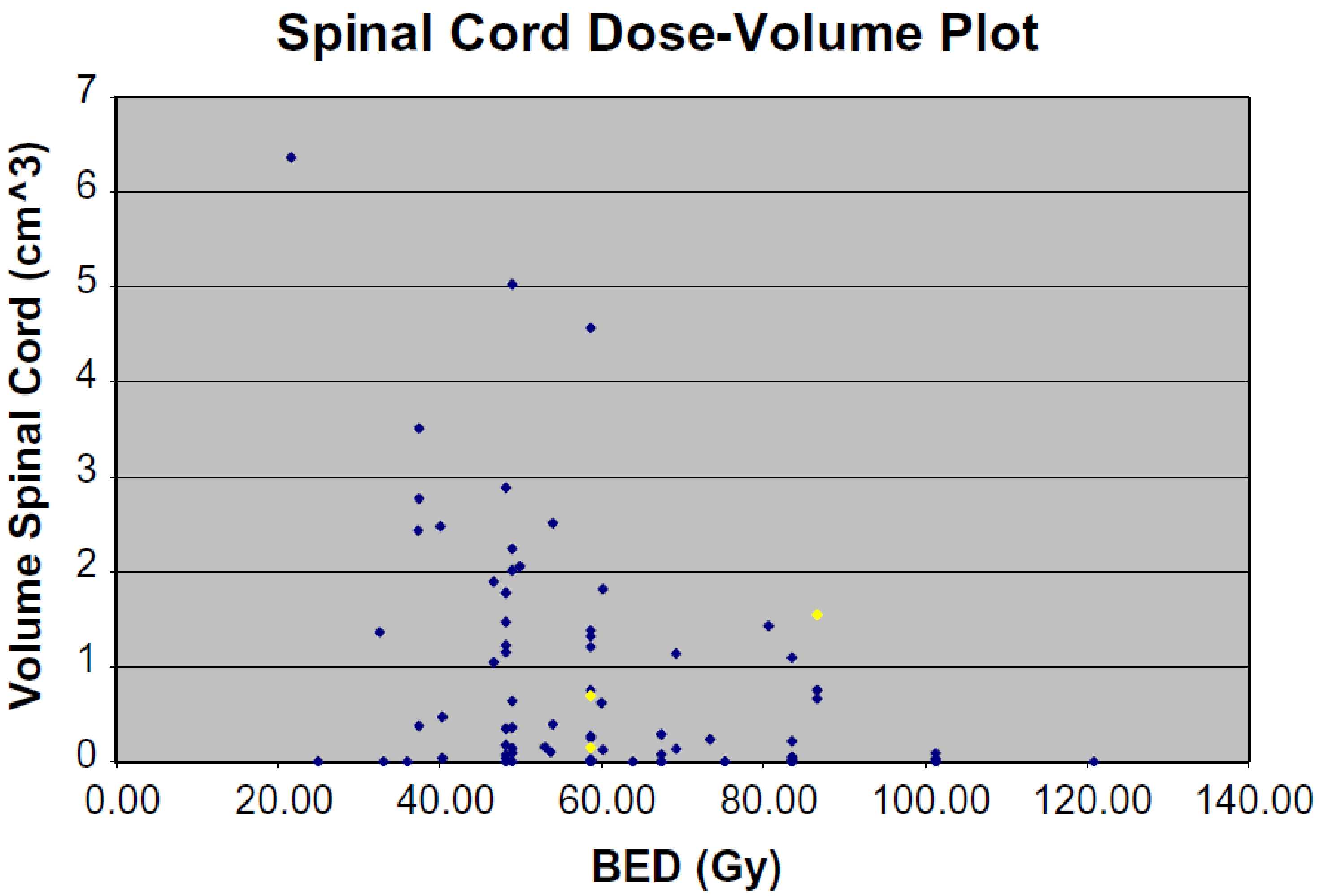
< 1% risk



Warning: Time Discounted BED is calculated differently in each model, can't just mix and match them

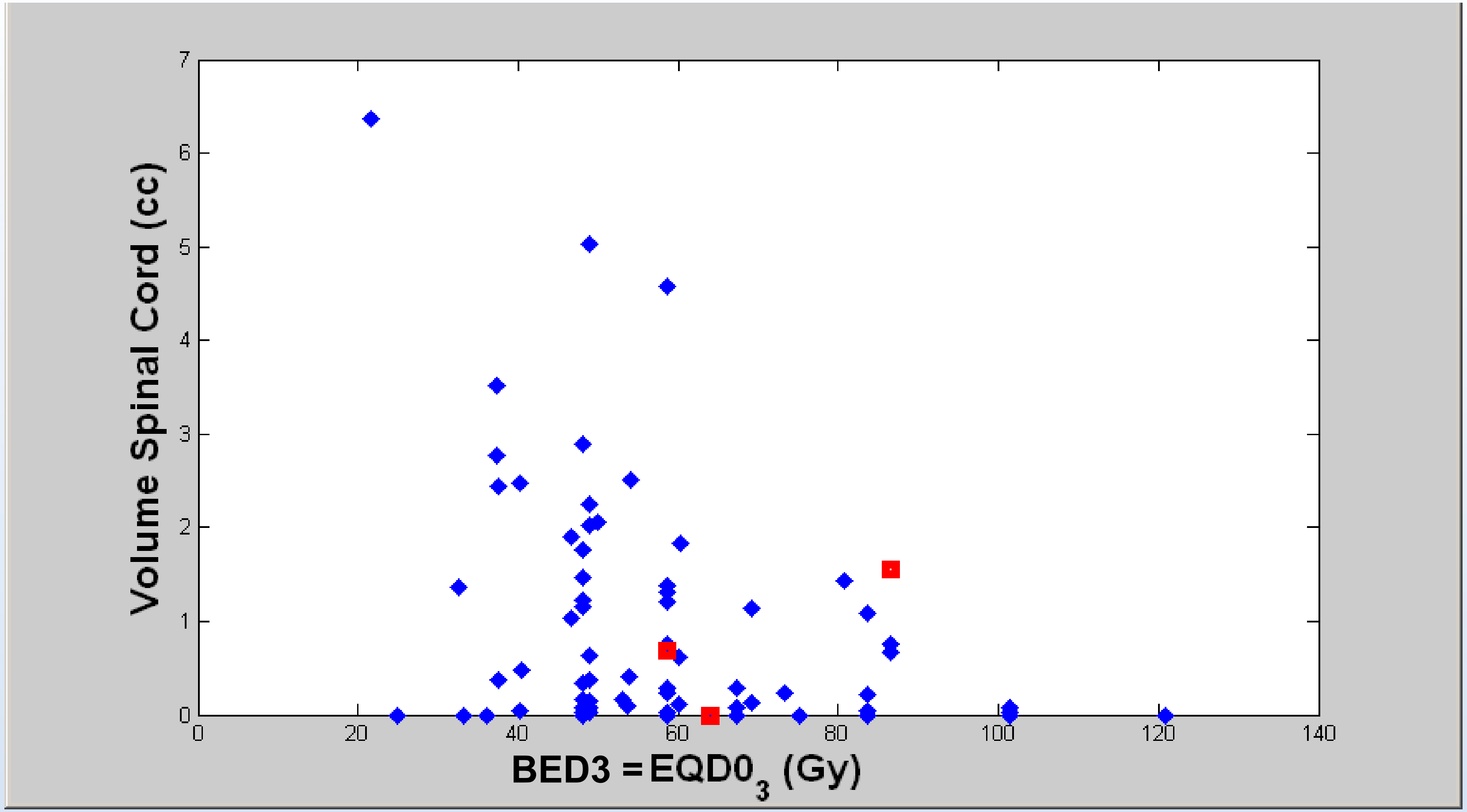
<u>Maximum Likelihood Values</u>
Recovery Halftime: <6 months
Recovery Maximum: 95%

Quest for Data!!!
Fig. 2 of Gibbs 2007 (Green Journal)

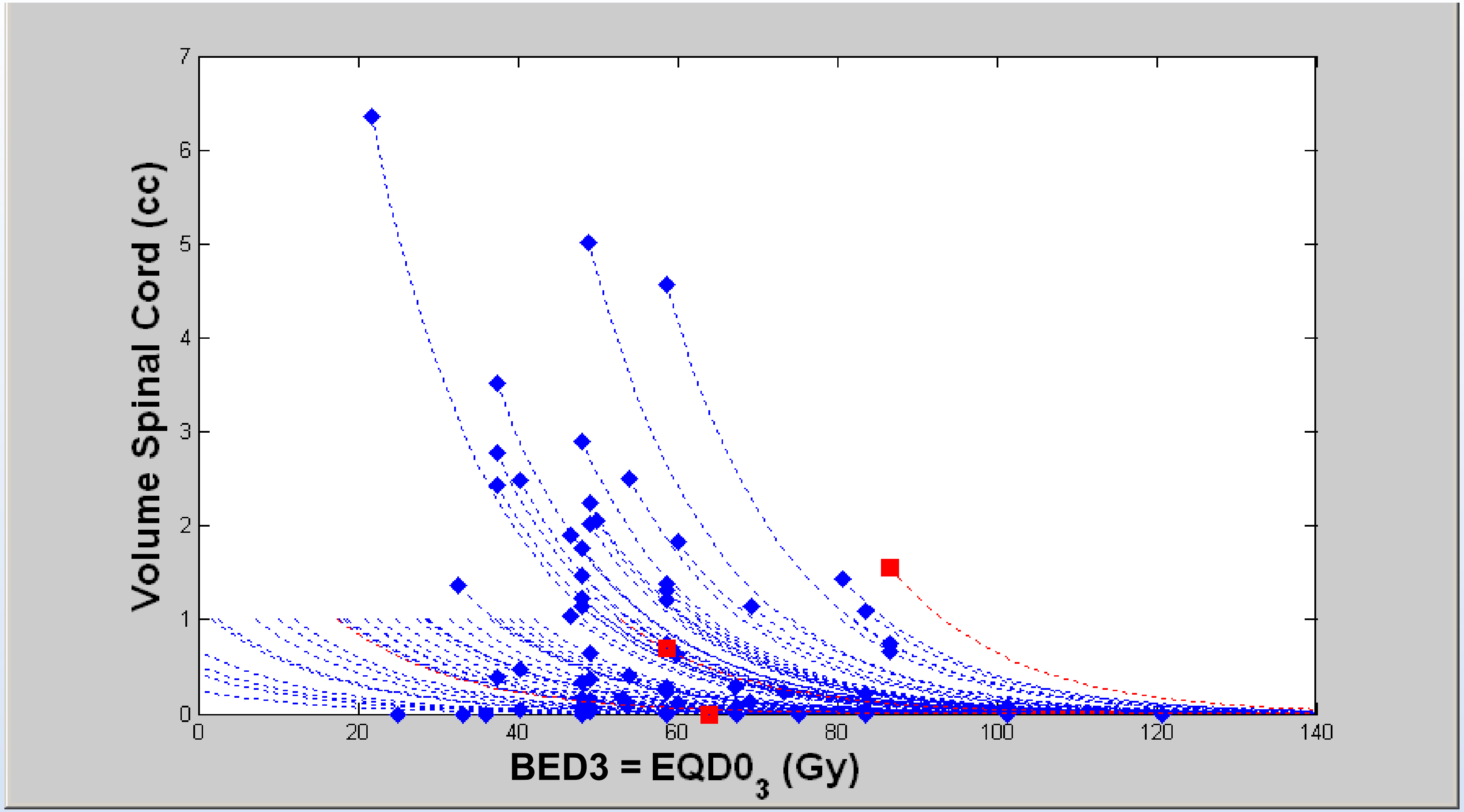


Gibbs IC, Kamnerdsupaphon P, Ryu MR, Dodd R, Kiernan M, Chang SD, Adler JR Jr.
Image-guided robotic radiosurgery for spinal metastases. Radiother. Oncol. 2007;82:185–190

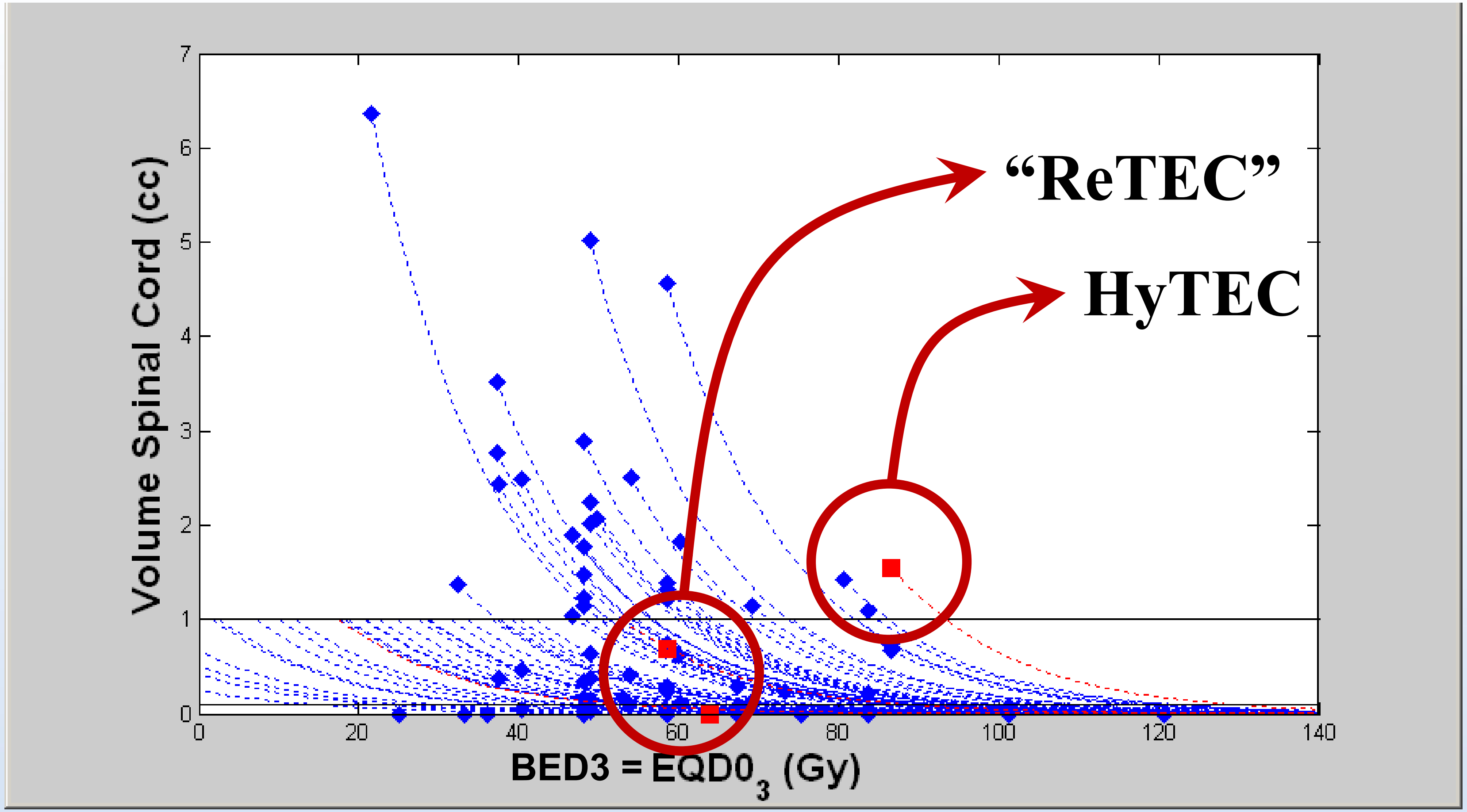
Quest for Data!!!
Digitized in DVH Evaluator



Quest for Data!!!
Approximated DVHs



Quest for Data!!!
Dose-Descriptors Extracted: D_{1cc}, $D_{0.1cc}$, D_{max}



Exact D_{1cc} and $D_{0.1cc}$ for the three myelopathy cases are known and used
Exact D_{max} for all cases are known and used

Part 1: Spinal Cord Recovery Model

Virtual Intermission:

Questions/Comments?

Part 2: Carotid Artery Recovery Model

Head and Neck Reirradiation:
Leading Experts, and Actual Clinical Data

ORIGINAL ARTICLE

Fractionated Stereotactic Body Radiation Therapy in the Treatment of Previously-Irradiated Recurrent Head and Neck Carcinoma

Updated Report of the University of Pittsburgh Experience

Jean-Claude Rwigema, BS, Dwight E. Heron, MD, FACRO,* Robert L. Ferris, MD, PhD,† Michael Gibson, MD,‡ Annette Quinn, RN, MSN,* Yong Yang, PhD,* Cihat Ozhasoglu, PhD,* and Steven Burton, MD**

H&N Reirradiation Limits

5fx H&N ReTx Limits	
Structure	**Dmax Limit, Gy**
Brain	20
Brainstem	9
Carotid Artery	20
Chiasm	10
Esophagus	< 20
Larynx	< 20
Lens of the Eye	6
Optic Nerves	10
Retina	10
Spinal Cord	12

- "As most of these normal tissues are not considered to be arranged 'in series' from a radiobiological standpoint, small portions were allowed to reach the maximum tolerance dose" – Rwigema 2010
- It is best to also limit the amount of critical structure that exceeds 2-3Gy/fx to as small a volume as possible
- Save the data for analysis!

Rwigema JC, Heron DE, Ferris RL, Gibson M, Quinn A, Yang Y, Ozhasoglu C, Burton S. Fractionated stereotactic body radiation therapy in the treatment of previously-irradiated recurrent head and neck carcinoma: updated report of the University of Pittsburgh experience. Am J Clin Oncol. 2010 Jun;33(3):286-93.

- **Ribs had not been recognized as an organ at risk**
- Pettersson 2009
- 13 fractures were found in 7 patients (of 81 ribs)
- “You mean you give such a high dose it can break people’s bones?!?”

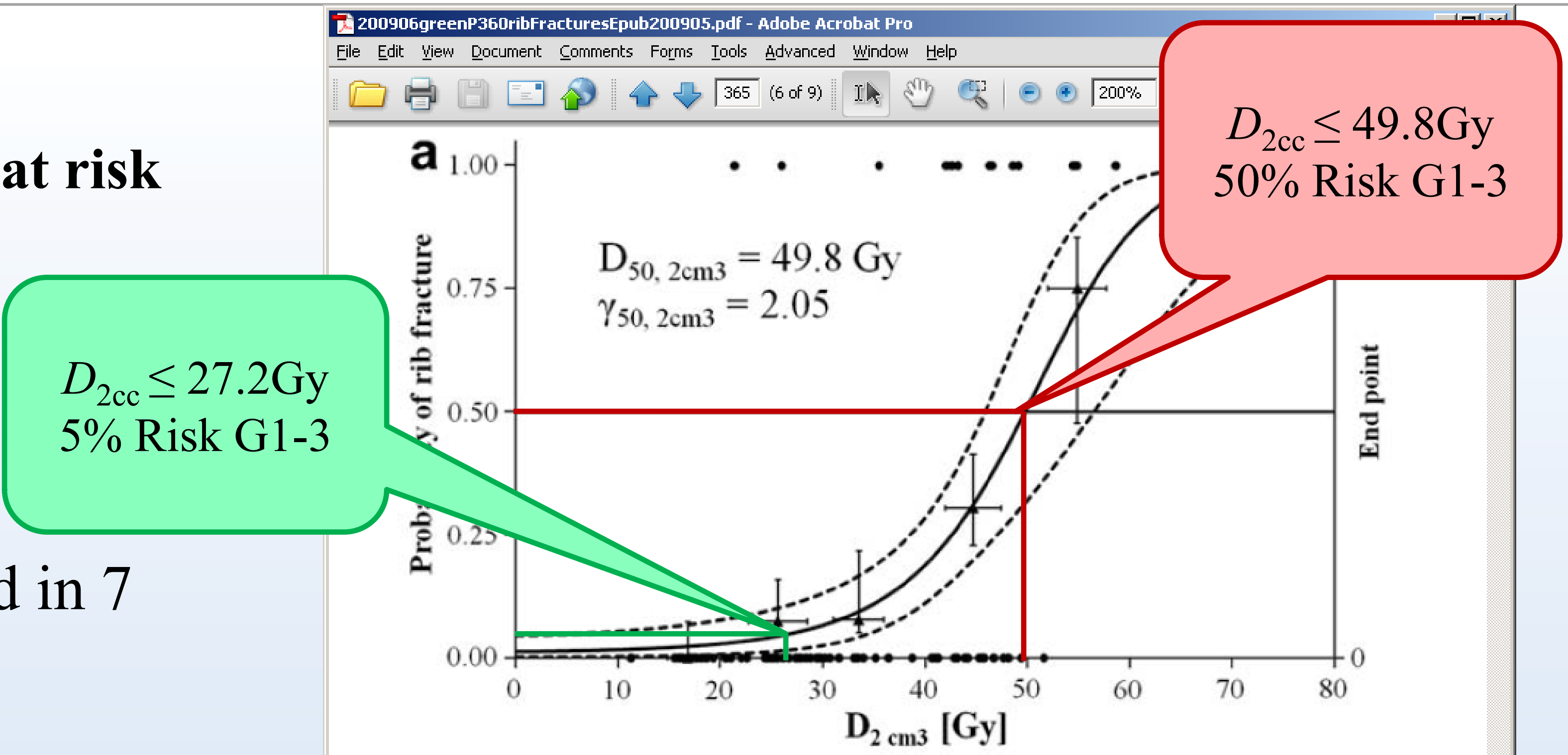


Fig. 5. Resulting logistic dose–response or volume–response curves for each descriptor model. Each diagram (a)–(e) shows the following: the value of the descriptor along the *x*-axis and the end point of 0 or 1 on the right-hand side *y*-axis (circles), the dose– or volume–response curve (solid curve) fitted to those points and the 68% confidence interval (dashed curves) calculated as described in Methods. The descriptor values have been arbitrarily binned into four or five bins for ease of viewing (triangles); the horizontal bars show ±1 standard deviation of the mean and the vertical error bars show the 68% confidence interval for the observed probability calculated with binomial statistics.

- **Carotid Artery had not been recognized as an organ at risk**

- Cengiz 2011

- 8 carotid blowout syndrome (CBOS) were found among 46 patients (17.3%)

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 104–109, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.04.027

CLINICAL INVESTIGATION **Head and Neck**

SALVAGE REIRRADIATON WITH STEREOTACTIC BODY RADIOTHERAPY FOR LOCALLY RECURRENT HEAD-AND-NECK TUMORS

Mustafa Cengiz, M.D.,* Gökhan Özyiğit, M.D.,* Gözde Yazici, M.D.,* Ali Doğan, M.S.,* Ferah Yildiz, M.D.,* Faruk Zorlu, M.D.,* Murat Gürkaynak, M.D.,* Ibrahim H. Gullu, M.D.,† Sefik Hosal, M.D.,‡ and Fadil Akyol, M.D.*

Departments of *Radiation Oncology, †Medical Oncology, and ‡Ear, Nose, and Throat Surgery, Hacettepe University, Faculty of Medicine, Ankara, Turkey

Purpose: In this study, we present our results of reirradiation of locally recurrent head-and-neck cancer with image-guided, fractionated, frameless stereotactic body radiotherapy technique.
Methods and Materials: From July 2007 to February 2009, 46 patients were treated using the CyberKnife (Accuray, Sunnyvale, CA) at the Department of Radiation Oncology, Hacettepe University, Ankara, Turkey. All patients had recurrent, unresectable, and previously irradiated head-and-neck cancer. The most prominent site was the nasopharynx (32.6%), and the most common histopathology was epidermoid carcinoma. The planning target volume was defined as the gross tumor volume identified on magnetic resonance imaging and computed tomography. There were 22 female and 24 male patients. Median age was 53 years (range, 19–87 years). The median tumor dose with stereotactic body radiotherapy was 30 Gy (range, 18–35 Gy) in a median of five (range, one to five) fractions.
Results: Of 37 patients whose response to therapy was evaluated, 10 patients (27%) had complete tumor regression, 11 (29.8%) had partial response, and 10 (27%) had stable disease. Ultimate local disease control was achieved in 31 patients (83.8%). The overall survival was 11.93 months in median (ranged, 11.4 – 17.4 months), and the median progression free survival was 10.5 months. One-year progression-free survival and overall survival were 41% and 46%, respectively. Grade II or greater long-term complications were observed in 6 (13.3%) patients. On follow-up, 8 (17.3%) patients had carotid blow-out syndrome, and 7 (15.2%) patients died of bleeding from carotid arteries. We discovered that this fatal syndrome occurred only in patients with tumor surrounding carotid arteries and carotid arteries receiving all prescribed dose.
Conclusions: Stereotactic body radiotherapy is an appealing treatment option for patients with recurrent head-and-neck cancer previously treated with radiation to high doses. Good local control with considerable 1-year survival is achieved with a relatively high rate of morbidity and related mortality. © 2011 Elsevier Inc.

Quest for Data!!!

- **Carotid Artery had not been recognized as an organ at risk**

- We reached out to the authors, worked through IRBs, accessed the data, and published dose response models

Fitting NTCP models to SBRT dose and carotid blowout syndrome data

Panayiotis Mavroidis[a]
Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC, USA

Jimm Grimm
Department of Radiation Oncology, Johns Hopkins University, Baltimore, MA, USA

Mustafa Cengiz
Department of Radiation Oncology, Hacettepe University, Faculty of Medicine Sihhiye, Ankara, Turkey

Shiva Das
Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC, USA

Xianming Tan
UNC Lineberger Comprehensive Cancer Center University of North Carolina Hospitals, Chapel Hill, NC, USA

Gozde Yazici and Gokhan Ozyigit
Department of Radiation Oncology, Hacettepe University, Faculty of Medicine Sihhiye, Ankara, Turkey

(Received 31 August 2017; revised 1 June 2018; accepted for publication 27 July 2018; published 31 August 2018)

4754 Med. Phys. 45 (10), October 2018 0094-2405/2018/45(10)/4754/9 **4754**

It became part of the HyTEC Carotid Artery NTCP paper
Modeled Reirradiation Dose Only, ****not Composite****

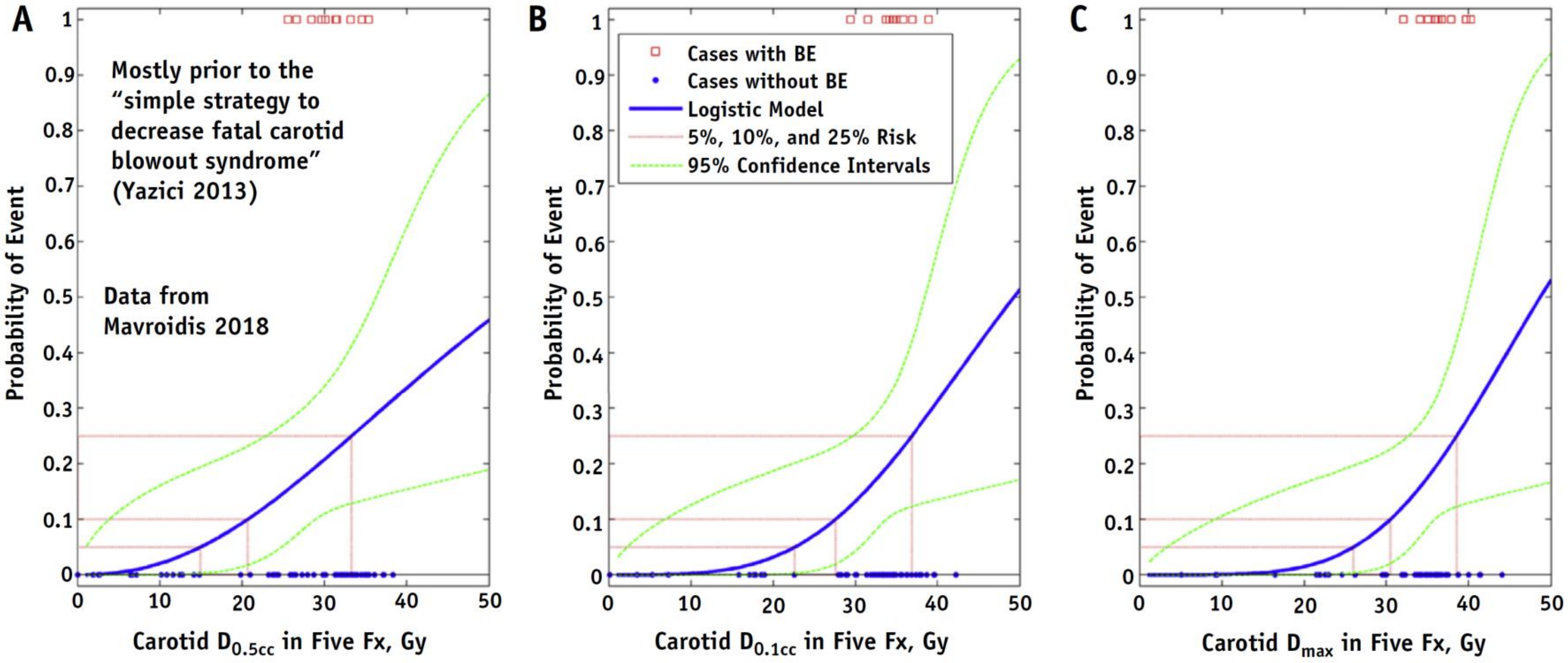


Fig. 3. Logistic dose-response model for the data from Mavroidis et al,[32] which was a recalculation of the data from Yacizi et al,[11] and were from patients treated largely before the risk-reduction strategies summarized in "Factors Potentially Affecting Reported Outcomes." These complications are designated as BE because some of the patients had persistent or recurrent disease that may have been the cause instead of radiation effects. A model was generated separately for each of 3 dose volume histogram cutpoints: (A) $D_{0.5cc}$, (B) $D_{0.1cc}$, and (C) D_{max}. None of the data in Figures 2 to 4 include the prior conventional radiation dose.

Jour. of Radiosurgery and SBRT, Vol. 6, pp. 83-89
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Quest for Data!!!

"You mean you give such a high dose it can break people's bones?!? and hurt other organs?"

CLINICAL INVESTIGATION

And her Dad said, hey while you're at UPMC, you could get some data…

Dose-response modeling the risk of carotid bleeding events after stereotactic body radiation therapy for previously irradiated head and neck cancer

Diane C. Ling, MD[1], John A. Vargo, MD[1], Brian J. Gebhardt, MD[1], Rachel J. Grimm[2], David A. Clump, MD, PhD[1], Robert L. Ferris, MD, PhD[3], James P. Ohr, DO[4] and Dwight E. Heron, MD, MBA, FACRO, FACR[1]

[1]Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[2]University of Pittsburgh, Pittsburgh, PA, USA
[3]Department of Otolaryngology, UPMC Hillman Cancer Center, Pittsburgh, PA, USA
[4]Department of Medical Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, USA

Head and Neck Reirradiation dose tolerance model: Carotid Artery

QUANTEC / HyTEC Section 5:
Factors Potentially Affecting Reported Outcomes

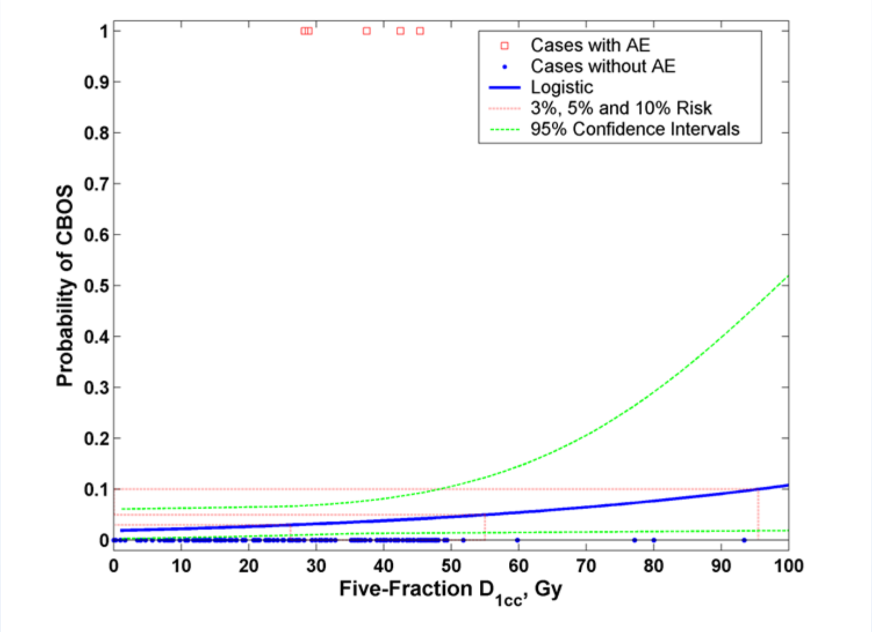
A. Factors primarily related to dose, volume, and fractionation schedules

- 1. Contour and constrain carotid arteries and other major vessels
- 2. Review DVHs for Carotid artery/Major vessel in original, SBRT, and composite plans
- 3. Use every-other-day fractionation
- 4. At least 6-month interval between prior course of irradiation is preferable per RTOG 3507
- 5. Degree circumferential involvement of carotid/major vessel by tumor
- 6. Greater degrees of dose heterogeneity: (e.g. "dose painting" or selective boosting of tumor subvolumes has potential to increase local control, but increases the need for targeting accuracy to prevent complications, because the delivered higher dose must be kept away from the carotid artery/major vessels)
- 7. Targeting accuracy is of paramount importance; a simple consideration of a typical radiation beam penumbra shows that a targeting difference of 1.5mm at the beam edge can increase Dmax dose of a critical structure by about 50%, and indeed, an adaptive replanning study for 5-fraction SBRT found up to 50% higher carotid artery Dmax dose than planned

B. Other primarily non-dosimetric factors

- 8. The presence of skin invasion by the recurrent cancer, especially in post-operative patients
- 9. Tumor site involving the lymph nodes versus mucosa
- 10. The presence of necrosis or infection prior to SBRT
- 11. Concurrent chemotherapy and other systemic agents have potential to increase toxicity
- 12. Surgical manipulation prior to, or following, radiation
- 13. Tumor response – even "stable disease" as observed on diagnostic imaging can cause complications if the initial location was already invading the critical structure

UPMC data had much lower risk of complications – what did they do differently?



Diane Ling … Rachel Grimm, et al. 2019

86 Journal of Radiosurgery and SBRT Vol. 6 2019

but these got sliced and diced away by the HyTEC authors…

Can you see any difference?

QUANTEC / HyTEC Section 5:
Factors Potentially Affecting Reported Outcomes

A. Factors primarily related to dose, volume, and fractionation schedules

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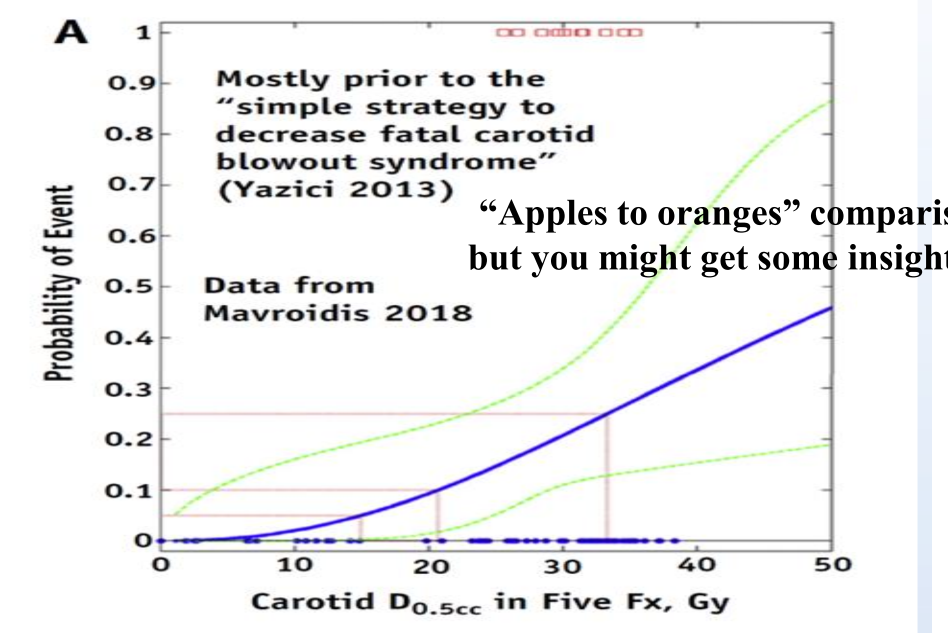
UPMC data had much lower risk of complications – what did they do differently?



“Apples to oranges” comparison but you might get some insights…

Diane Ling … Rachel Grimm, et al. 2019

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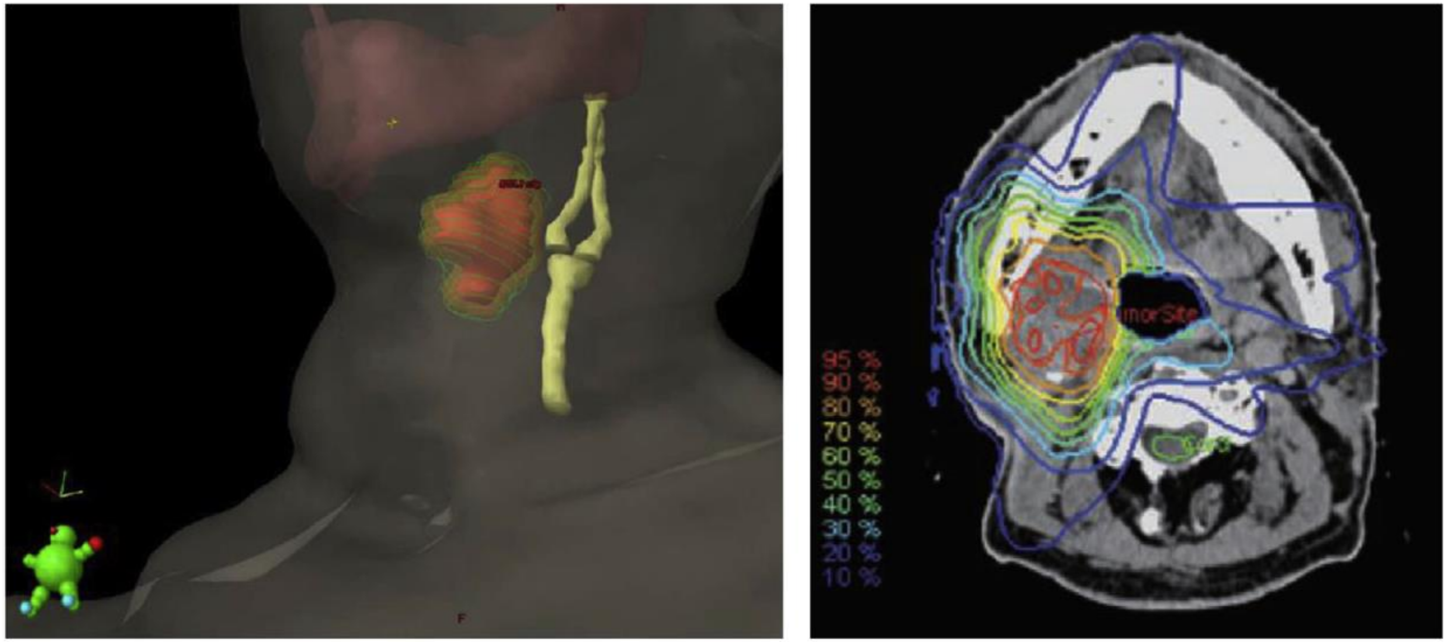
but these got sliced and diced away by the HyTEC authors…

HyTEC summarized the most important factors, but the rest might have some relevance too…

Factors Potentially Affecting Reported Outcomes:

a picture is worth 1000 words and maybe more

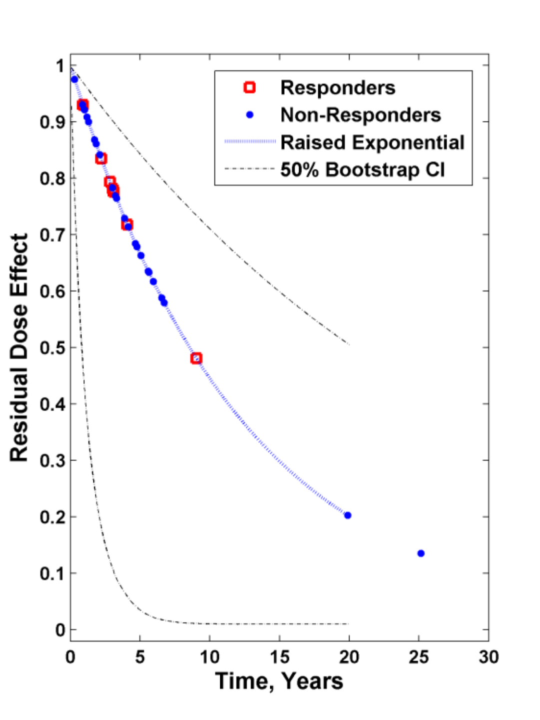


(A) (B)

Fig. 1. Example showing which head and neck geometries may or may not be feasible for stereotactic body radiation therapy (SBRT) reirradiation. In example (A) there was a geometric separation between tumor (in red) and the carotid (in yellow) enabling SBRT with relatively favorable carotid doses. In contrast, example (B) is from Kodani et al[10] in which the carotid is intimately associated with the tumor and as a result the entire cross-section of the carotid is in the SBRT high-dose region, which may require extra consideration of risk-reduction strategies, as in "Factors Potentially Affecting Reported Outcomes." (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.12.037.)

Cengiz/Mavroidis Turkish data with ≥180-degree involvement

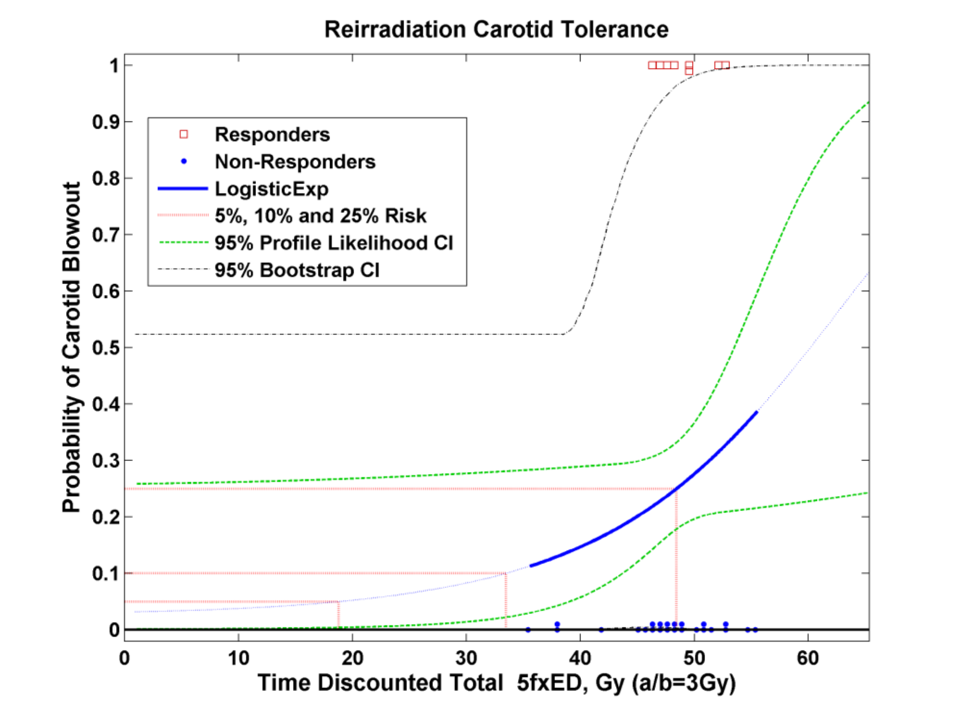
32 patients, 8 CBOS → 50% recovery in >100 months



Note:

The “180-degree involvement” is measured on the *Reirradiation* course.

It seems that reirradiation of large volumes might require more recovery time

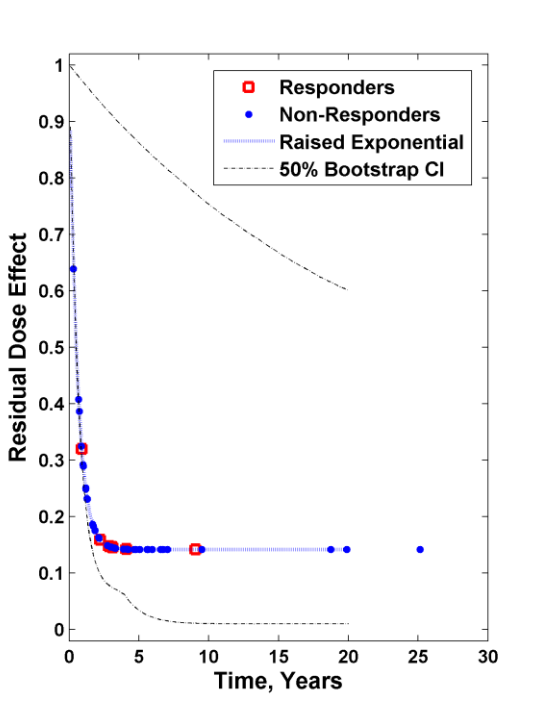


Warning: Time Discounted BED is calculated differently in each model, can’t just mix and match them

Cengiz 2011 IJROBP Sep 1;81(1):104-9, Epub 2010 Aug

Cengiz/Mavroidis Turkish data with all patients

46 patients, 8 CBOS → 50% recovery in <6 months



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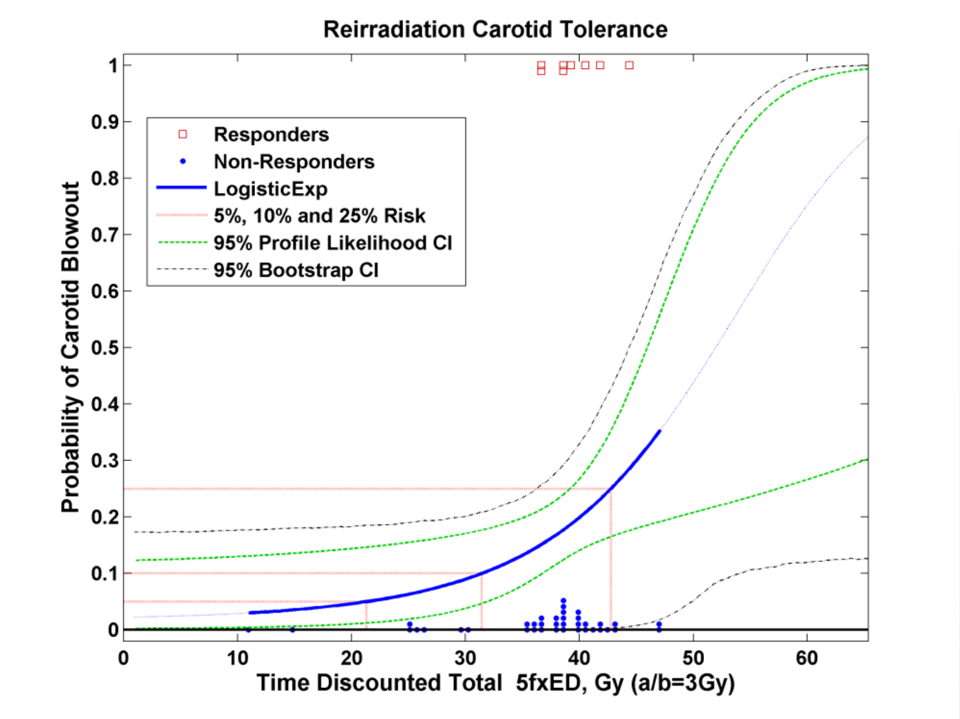
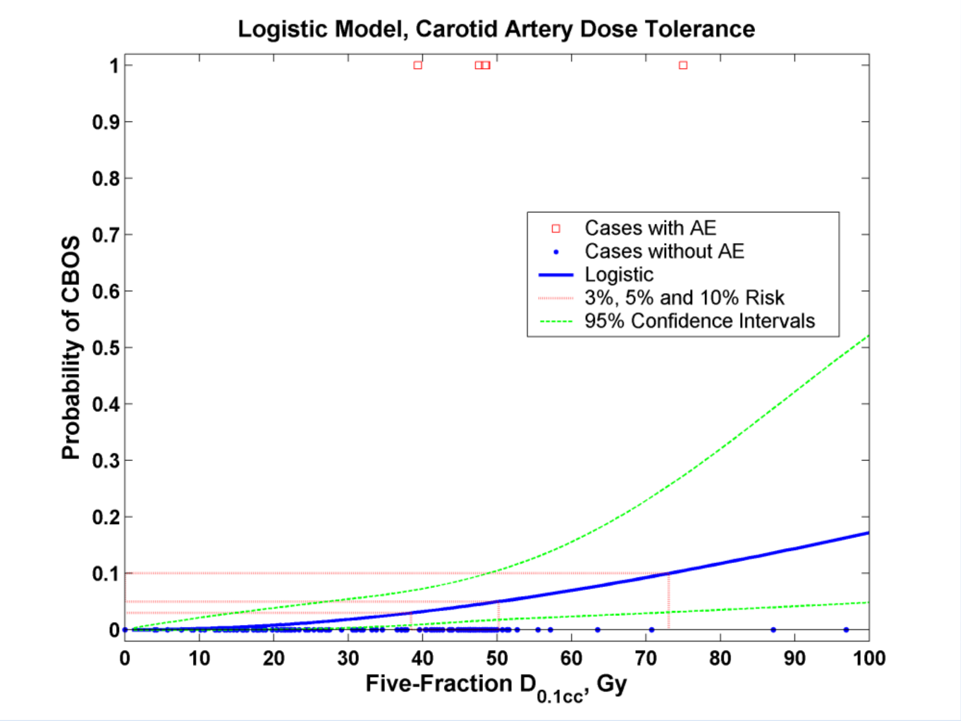


Warning: Time Discounted BED is calculated differently in each model, can't just mix and match them

Cengiz 2011 IJROBP Sep 1;81(1):104-9, Epub 2010 Aug

Ling et al 2019 UPMC D0.1cc, without recovery factor (direct sum)

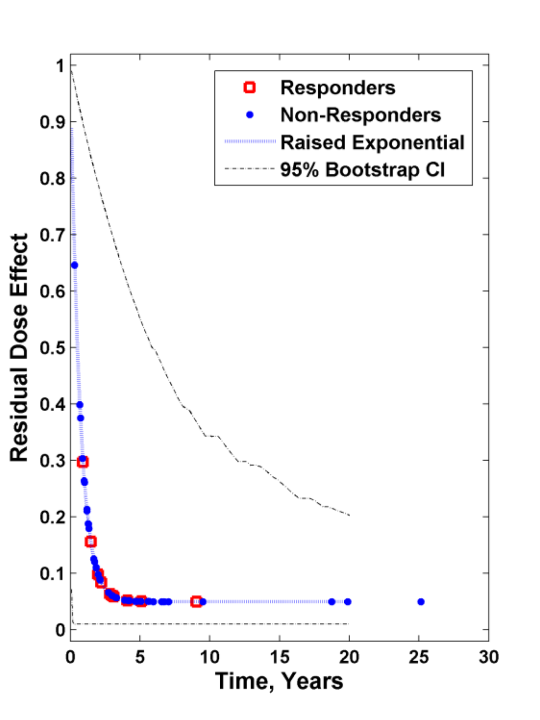
75 patients, 4 bleeding events, initial analysis using “Scenario 1: No Recovery”

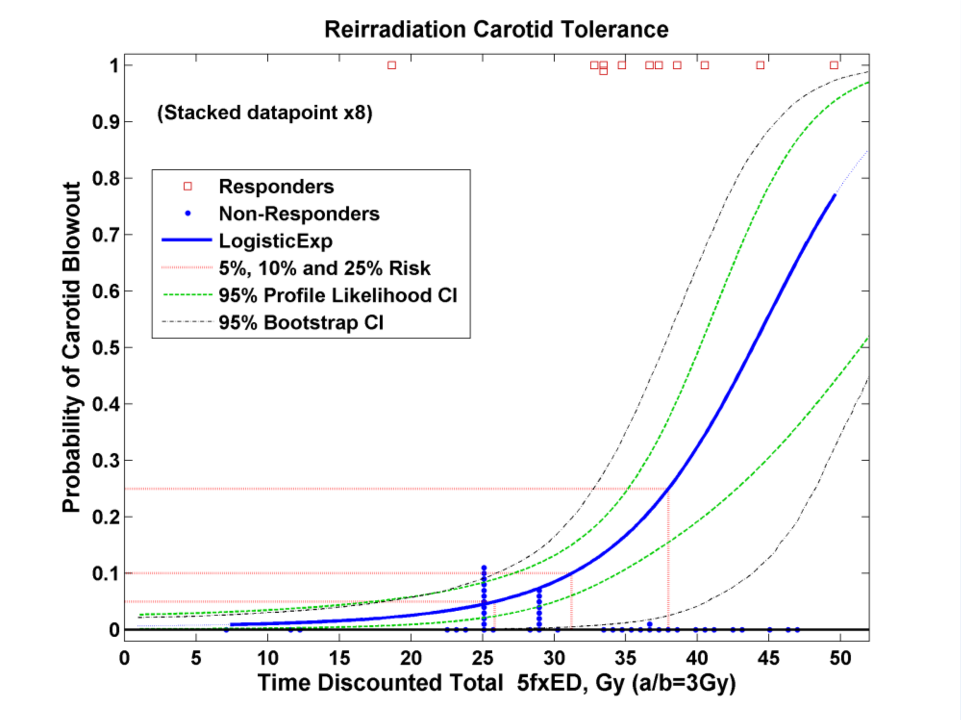


Warning: Time Discounted BED is calculated differently in each model, can’t just mix and match them

Initial pooled model, from all datasets in the HyTEC Carotid paper

207 patients, 13 bleeding events, pooled from 4 studies, 50% recovery in <6 months





Warning: Time Discounted BED is calculated differently in each model, can't just mix and match them

But what about Time?

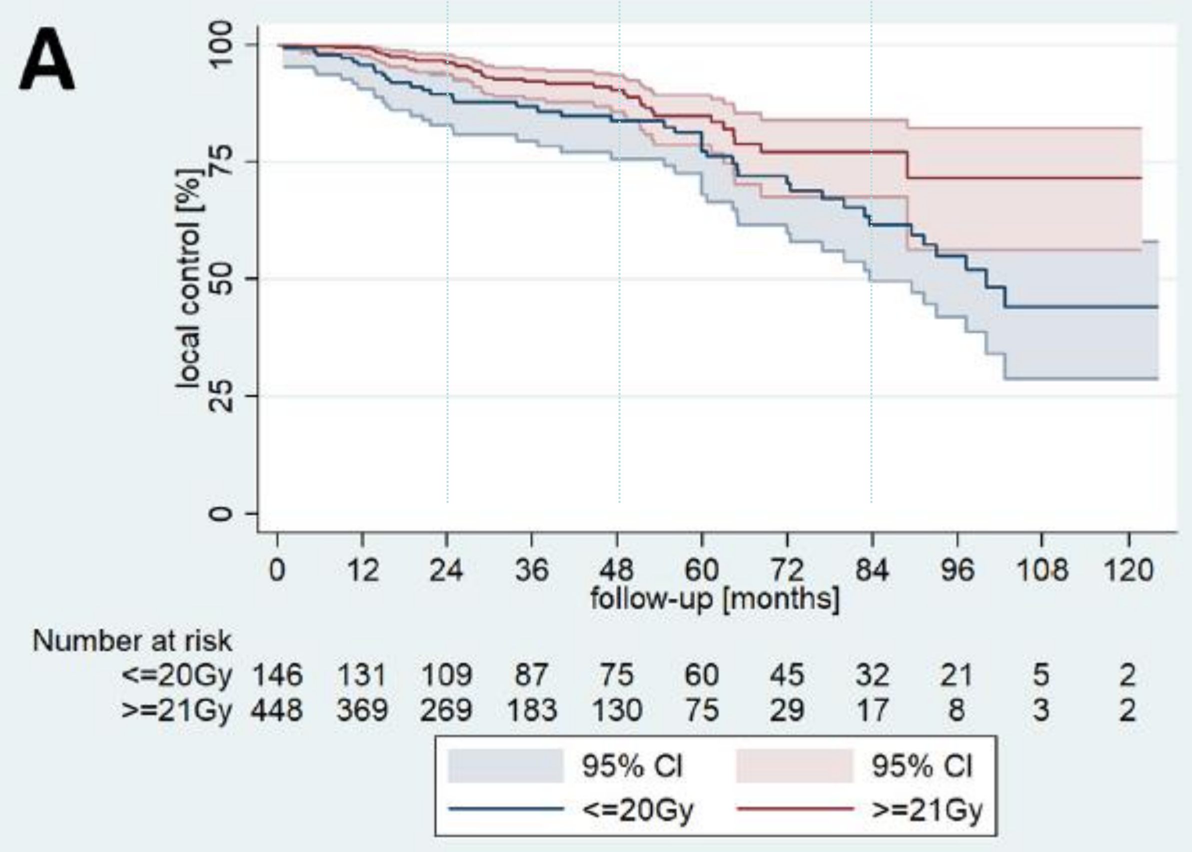
AMERICAN JOURNAL OF OPHTHALMOLOGY

Robotic CyberKnife Radiosurgery for the Treatment of Choroidal and Ciliary Body Melanoma

Raffael Liegl • Valerie Schmelter • Christoph Fuerweger • Felix Ehret • Siegfried Priglinger • Alexander Muacevic • Paul Foerster • Show less

- 594 consecutive patients CyberKnife Centre Munich
- Choroidal and ciliary body melanomas from 2005 to 2019
- Up to 10-year follow-up

- Prescribed doses and patient distribution per group were:
  - 17-19 Gy, 24 patients;
  - 20 Gy, 122 patients;
  - 21 Gy, 442 patients;
  - 22 Gy, 6 patients



INTERNATIONAL JOURNAL OF
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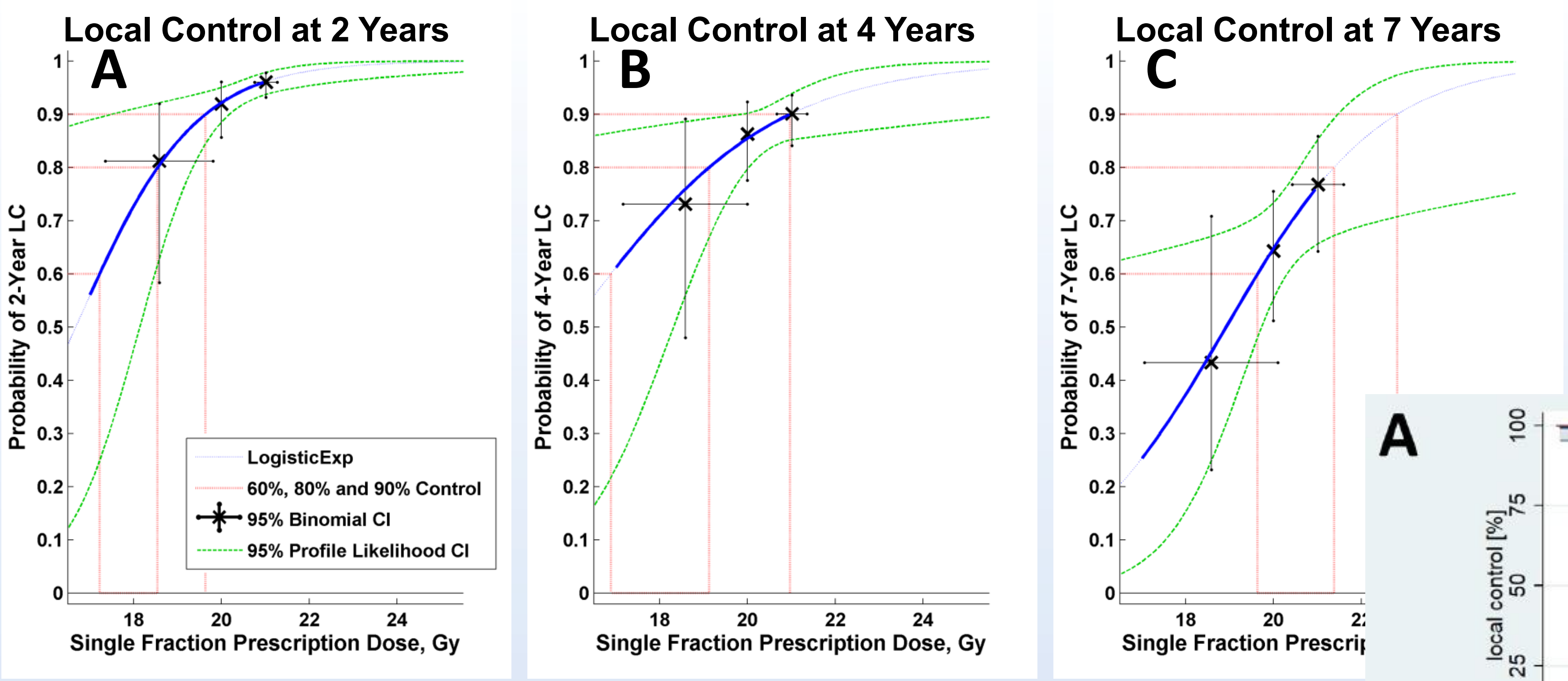
ASTRO

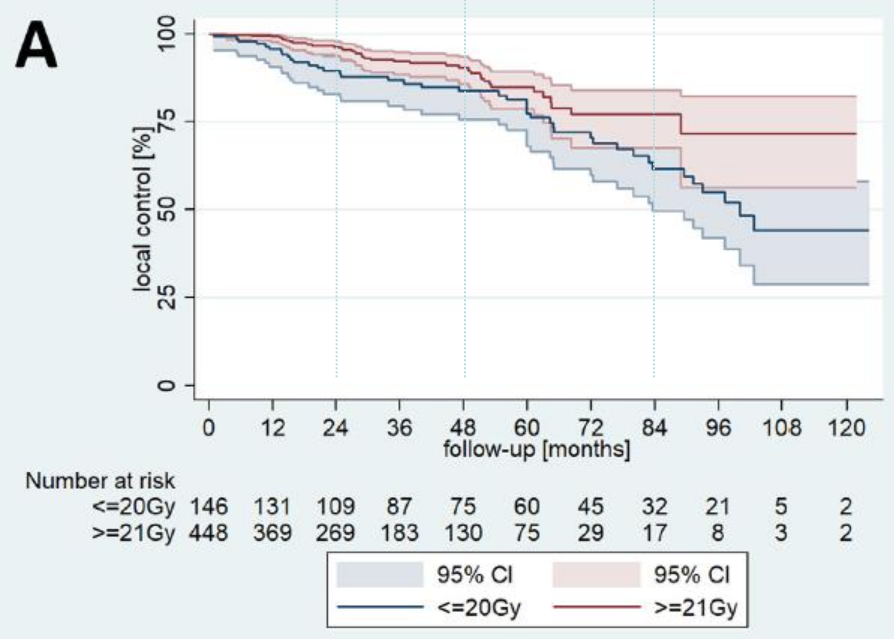
Tumor Control Probability and Time-Dose Response Modeling for Stereotactic Radiosurgery of Uveal Melanoma

Felix Ehret, MD • Christoph Fürweger, PhD • Raffael Liegl, MD • Valerie Schmelter, MD • Siegfried Priglinger, MD • Gopal Subedi, MSc • David Grimm • Paul Foerster, MD • Alexander Muacevic, MD • Jimm Grimm, PhD • Show less

Open Access • Published: June 03, 2024 • DOI: https://doi.org/10.1016/j.ijrobp.2024.05.025



Multivariable Cox regression highlighted a significant correlation between prescription dose and LC (p = 0.018)



- 20 Gy achieved over 90% LC at 2 years, while 22 Gy surpassed 95%.
- But 21 Gy was necessary for 4-year LC of 90%, and
- At 7 years, 20 Gy would have dropped to almost 60% LC

What about time:
DoseTimeKM modeling

Conclusion

- Spine reirradiation and H&N reirradiation can resolve these issues systematically through cooperative trials
- Most other reirradiation sites are likely to be case-by-case situations for at least the next 5-10 years, and we need to save our data and collaborate to accumulate sufficient data

- This is not the end
  - It is just the beginning!!

•If you treat patients, you have data
  - We need to analyze the outcomes to optimize the treatments!