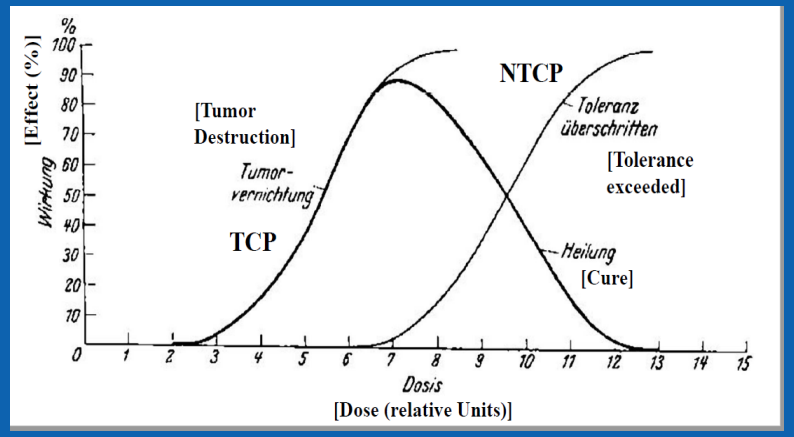
HyTEC- The Project and the Product

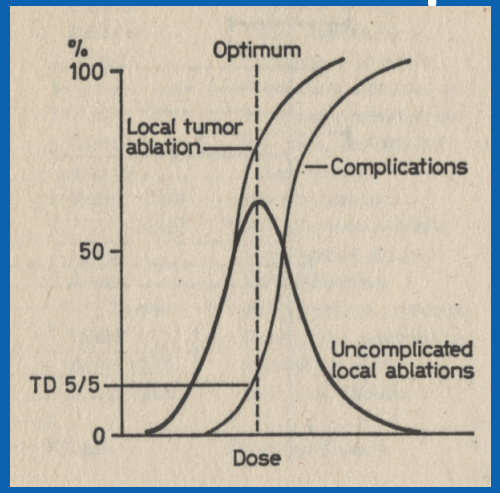
Ellen Yorke

Memorial Sloan Kettering Cancer Center

History: Quest for Optimal Uncomplicated Tumor Control



Holthusen H. Strahlentherapie. 1936;57:254–269.



Rubin P, Bakemeir RF. Clinical Oncology for medical students and physicians: a multidisciplinary approach, 4th ed. American Cancer Society 1974

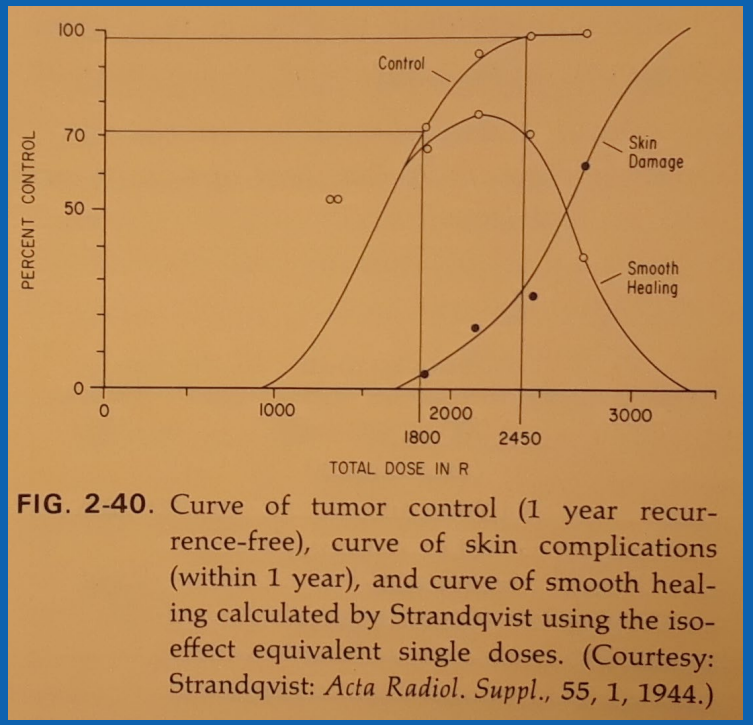
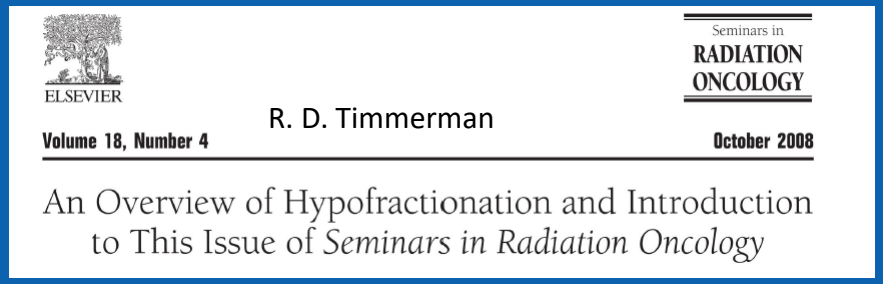


FIG. 2-40. Curve of tumor control (1 year recurrence-free), curve of skin complications (within 1 year), and curve of smooth healing calculated by Strandqvist using the iso-effect equivalent single doses. (Courtesy: Strandqvist: *Acta Radiol. Suppl.*, 55, 1, 1944.)

Strandqvist 1944
in Gilbert Fletcher's textbook, 1973 Edition


ELSEVIER

Seminars in RADIATION ONCOLOGY

Volume 18, Number 4 October 2008

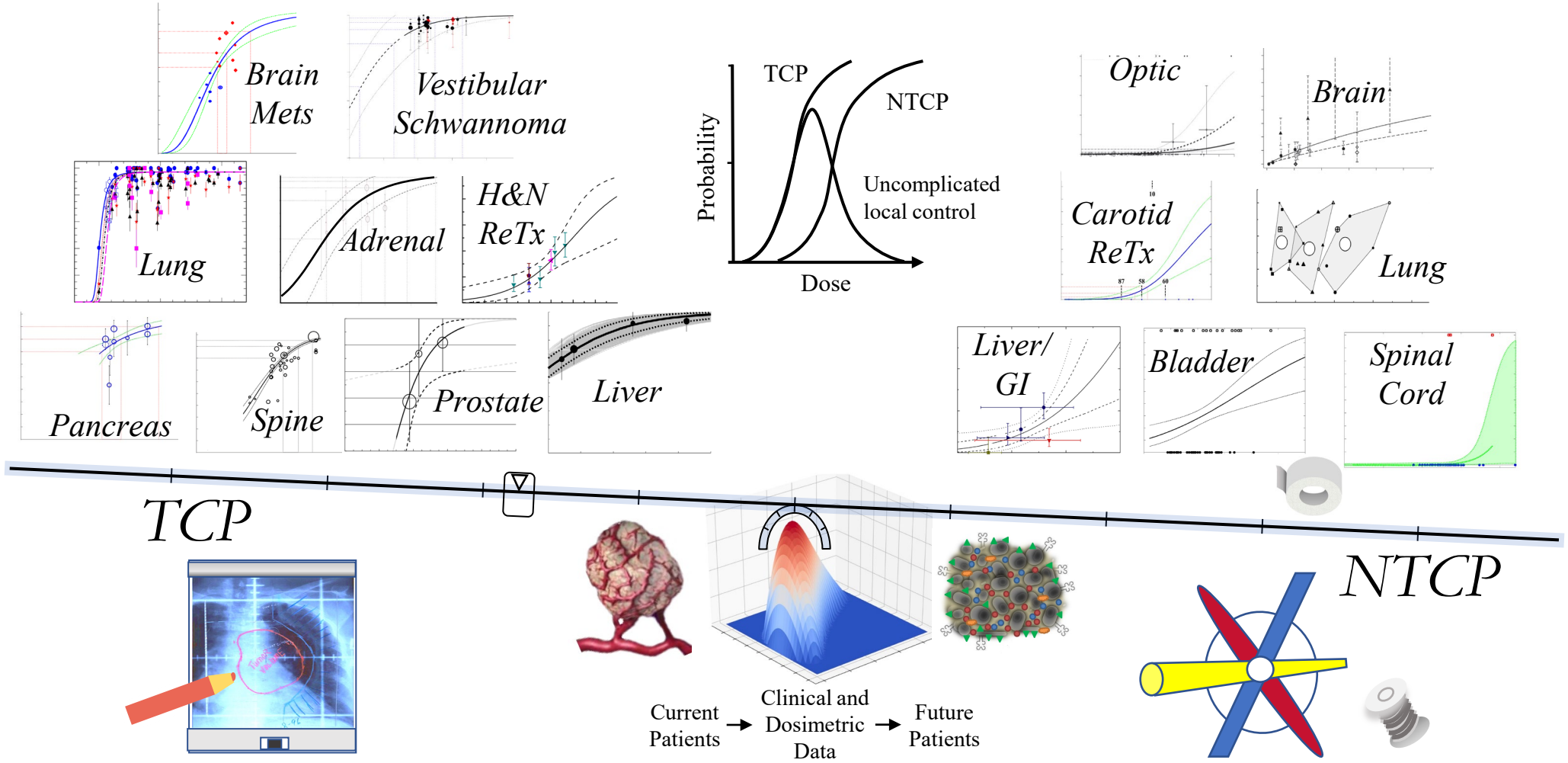
R. D. Timmerman

An Overview of Hypofractionation and Introduction to This Issue of *Seminars in Radiation Oncology*

- Early 1900's: Hypofractionation-convenience, technical simplicity
- 1920's-30's and on: observed complications lead to 'conventional fractionation' for curative treatments
- 1950's Leksell- Gamma Knife
- Yet most new technology develops with conventional fractionation

Leksell L: The stereotaxic method and radiosurgery of the brain. Acta Chirurg Scand 102:316-319, 1951

HyTEC: 'Hy' Dose per Fraction, Hypofractionated Treatment Effects in the Clinic



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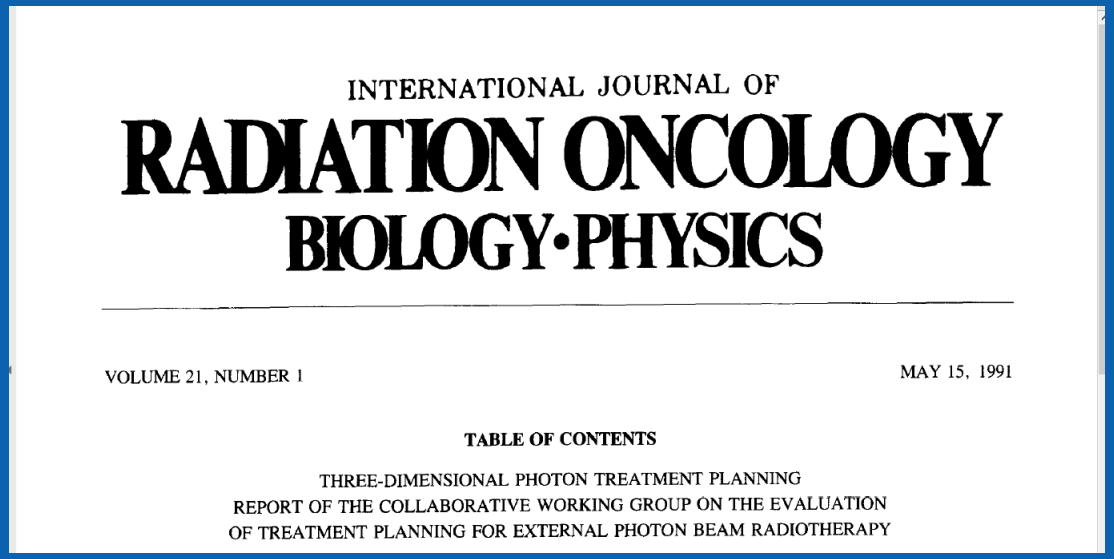
AAPM Working Group on SBRT (WGSBRT), Biological Effects Subcommittee (BESC)



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BIOLOGY·PHYSICS

VOLUME 21, NUMBER 1 MAY 15, 1991

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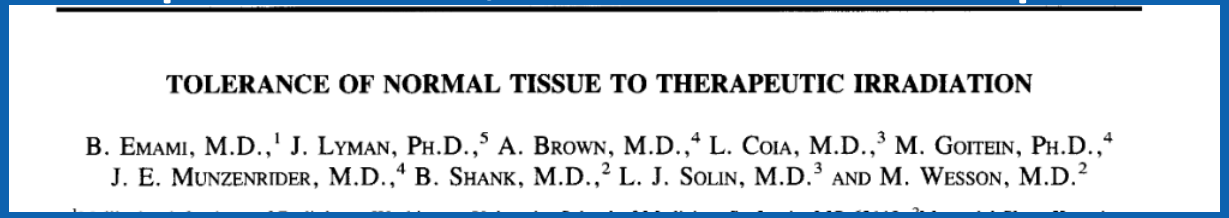
THREE-DIMENSIONAL PHOTON TREATMENT PLANNING
REPORT OF THE COLLABORATIVE WORKING GROUP ON THE EVALUATION
OF TREATMENT PLANNING FOR EXTERNAL PHOTON BEAM RADIOTHERAPY

- Preparing for computerized, 3D treatment planning and delivery



TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

B. EMAMI, M.D.,[1] J. LYMAN, PH.D.,[5] A. BROWN, M.D.,[4] L. COIA, M.D.,[3] M. GOITEIN, PH.D.,[4]
J. E. MUNZENRIDER, M.D.,[4] B. SHANK, M.D.,[2] L. J. SOLIN, M.D.[3] AND M. WESSON, M.D.[2]

- Most severe radiation-induced complication in 28 normal organs
  - The 'Emami paper'
- Conventional fractionation only. Adults only.
- Due to scarce literature-clinicians' consensus recommendations.
- TD5/5 and TD50/5 (dose for 5 and 50% complication by 5 years)

Complication depends on dose and irradiated volume

- Simple dose distribution-uniform dose to whole, 2/3 and 1/3 organ, zero to rest
  - ‘partial organ irradiation’ like parallel opposed

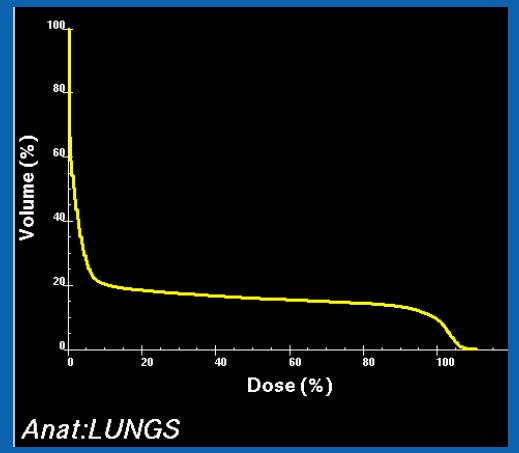


Table 1. Normal tissue tolerance to therapeutic irradiation

Organ	TD 5/5 Volume			TD 50/5 Volume			Selected endpoint
	1/3	2/3	3/3	1/3	2/3	3/3	
Kidney I	5000	3000*	2300	—	4000*	2800	Clinical nephritis
Kidney II							

- Modeled dose-volume complication incidence as sigmoidal curve

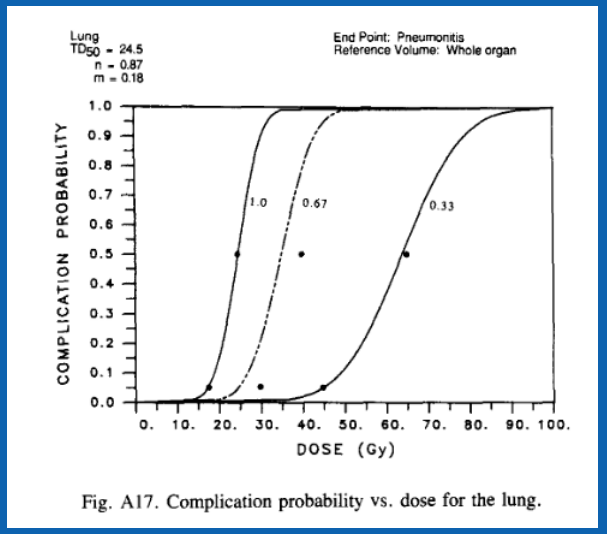


Fig. A17. Complication probability vs. dose for the lung.

FITTING OF NORMAL TISSUE TOLERANCE DATA TO AN ANALYTIC FUNCTION

C. Burman, Ph.D.,[1] G. J. Kutcher, Ph.D.,[1] B. Emami, M.D.[2] and M. Goitein, Ph.D.[3]

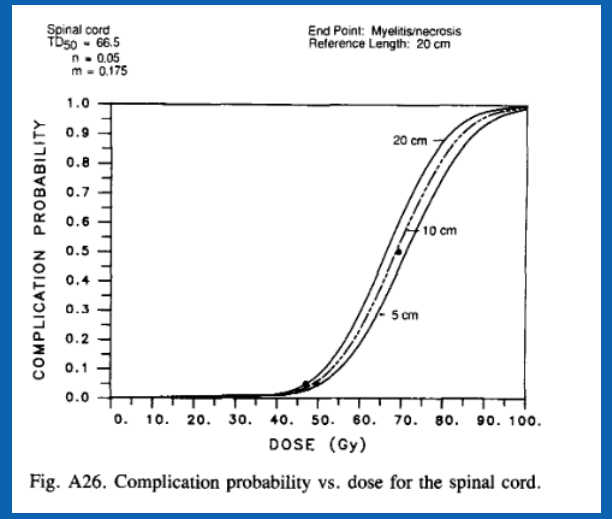


Fig. A26. Complication probability vs. dose for the spinal cord.

Due to major technological changes a new consensus review of normal tissue complications was published in 2010 in **IJROBP**

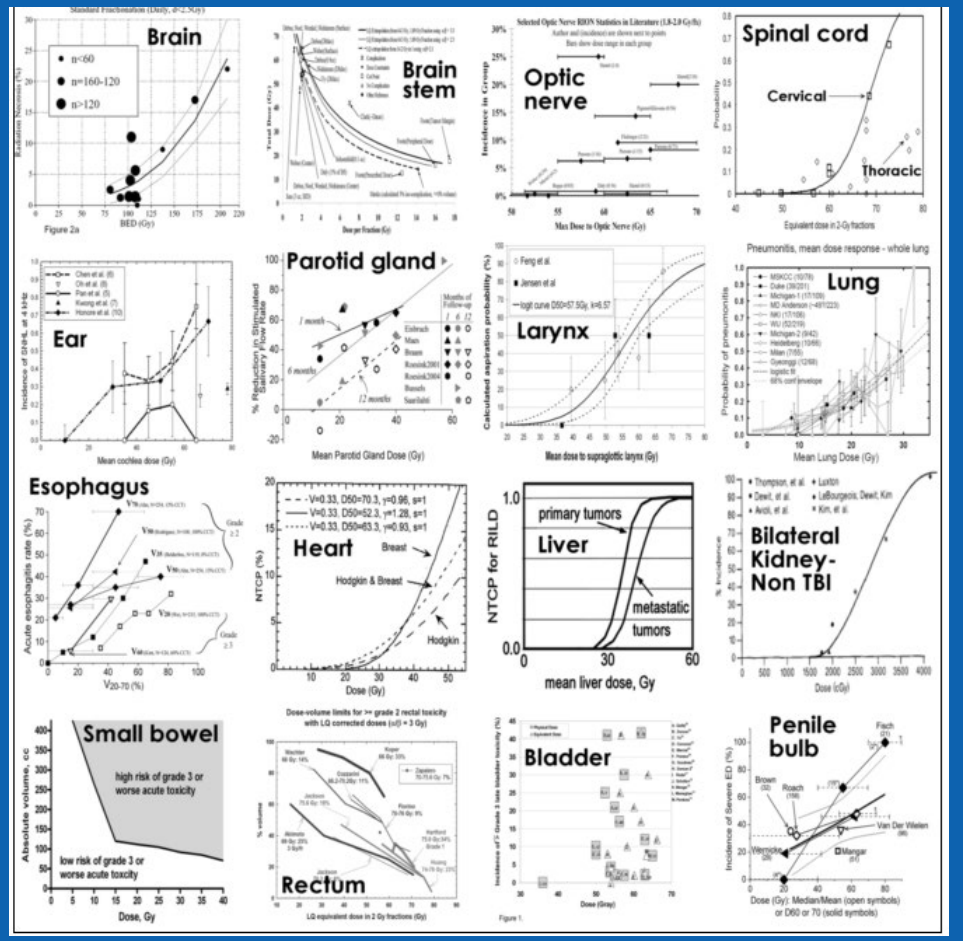
Quantitative Analyses of Normal Tissue Effects in the Clinic

QUANTEC

Volume 76, Issue 3, Supplement,
Pages S1-S160 (1 March 2010)

- **All guidelines from peer-reviewed published data**
- 16 organs, range of complications
- Mostly conventional fractionation
- Table of practical dosimetric guidelines per organ

Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 ≤ 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	

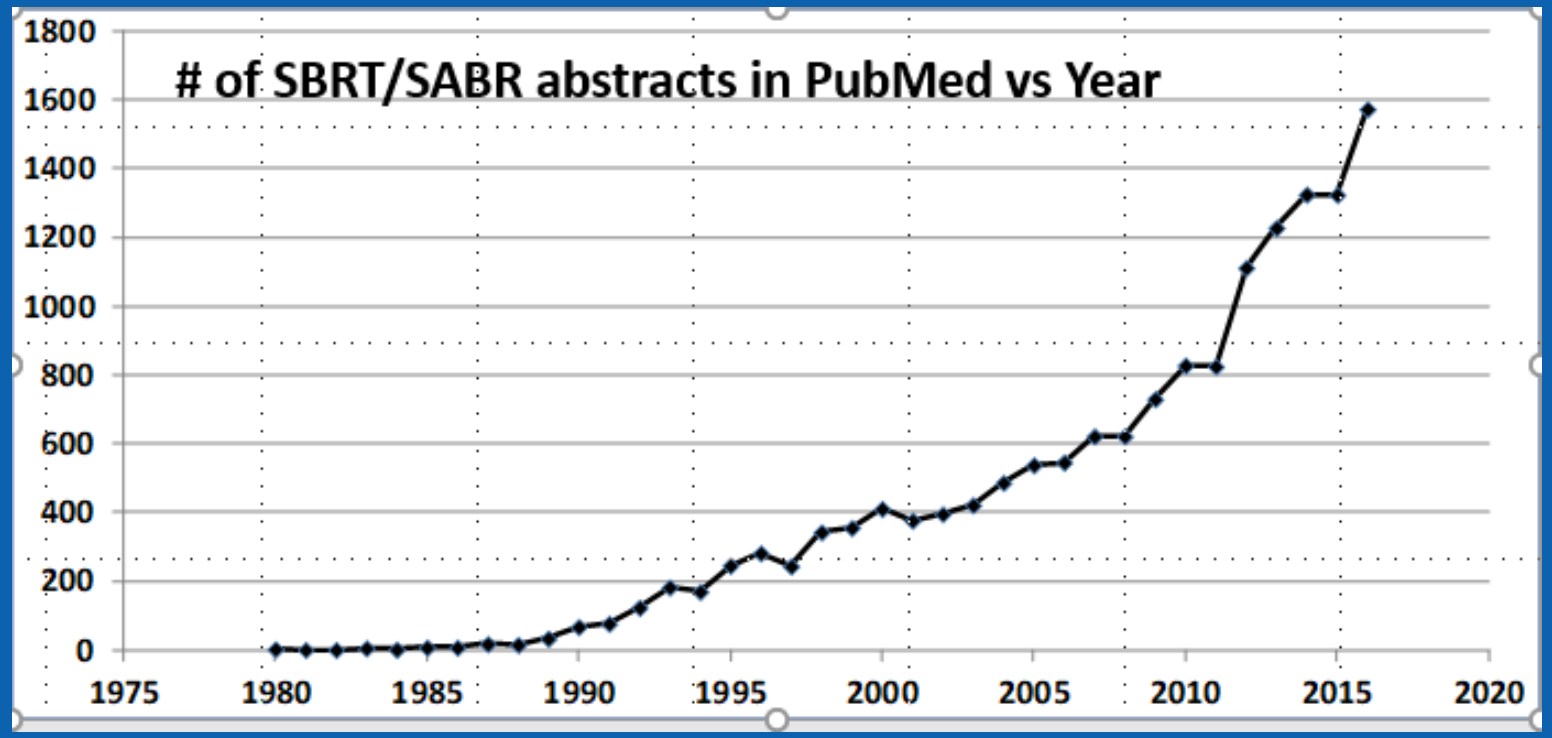


Standard article format

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.
3. **Challenges Defining Volumes**- Describes how the organ is typically defined (or segmented) on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

TIME MARCHES ON

Increasing safe and effective clinical use of stereotactic body radiation therapy -SBRT, aka Stereotactic Ablative Radiotherapy or SABR- for disease sites throughout the body



HyTEC=Hypofractionated Treatment Effects in the Clinic

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Approved in 2011

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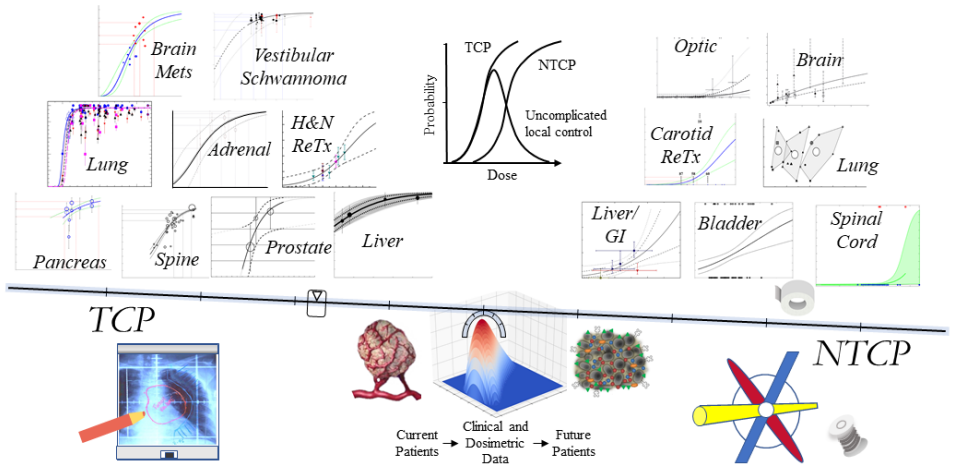
Charge The radiobiology of hypofractionated treatments may differ considerably from that of standard fractionated treatments, in regards to repair, reoxygenation, dose-rate effects, volume effects, fraction size effects, etc. The working group will generate reports, including but not limited to, critically surveying the published data regarding:

1. Tumor response: review of the effect of hypofractionation on local control.
2. Normal tissue response: review of the effect of hypofractionation on normal tissue tolerances.
3. Radiobiology of hypofractionated treatments.
4. Clinical rationales for the diverse prescription schemes in current use (e.g. 20GyX3 vs 24GyX1).
5. Standards for reporting outcome, including endpoints, defining/contouring of target and normal structures, dose definitions.

1. Clinical significance
2. Endpoints
3. Challenges defining and segmenting anatomic volumes
4. Review of outcomes data
5. Factors affecting outcomes
6. Mathematical/biological models
7. Special situations
8. Recommended dose-volume objectives
9. Future studies
10. Reporting standards for outcomes

HyTEC: 'Hy' Dose per Fraction, Hypofractionated Treatment Effects in the Clinic



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AAPM Working Group on SBRT (WGSBRT), Biological Effects Subcommittee (BESC)

- AAPM Working Group, under BESC
- Each article has 10 standard sections
- 9 TPC, 7 NTCP, Introduction, 3 'Vision' papers
- Multiple 'blind' reviewers per paper
  - chosen by steering committee, TPC, Science Council

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HyTEC Introduction

High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC): An Overview

Jimm Grimm, PhD,*,† Lawrence B. Marks, MD,‡ Andrew Jackson, PhD,§ Brian D. Kavanagh, MD,‖ Jinyu Xue, PhD,¶ and Ellen Yorke, PhD‡

A summary of the key dose, volume, and outcome data for the organs and tumors considered in HyTEC is provided in Tables 2 and 3. In generating the table entries, preference was given to providing published clinical data when available. Thus, for situations where both clinical and model-based data were available, the clinical data were favored. Further, the NTCP data shown are largely for patients who have received no prior radiation therapy (RT), and the entries reflecting situations with prior RT are so noted. We recognize and emphasize that the data are imperfect. For many tumor sites, local recurrence is difficult to establish with certainty by noninvasive imaging methods, and there are statistical issues (eg, competing risks, a failure to consistently assess for local failure in patients with systemic disease, and favorable patient selection for both retrospective analyses and prospective studies) that collectively may tend to overestimate the true local control rates across an entire population.

The HyTEC authors took the pragmatic approach of reviewing the available literature and pooling data from publications containing the minimal set of data elements needed for a meaningful analysis (eg, clearly stated dose schedules, prescription practices, critical structure dose reporting, and clinical outcomes for toxicity or tumor control). From these analyses, the subgroups summarized the dose, volume, and outcome data, and when possible, generated associated models, while at the same time acknowledging the uncertainties. We emphasize and acknowledge that the models used in many of these reports are imperfect (eg, the linear-quadratic model is simplistic), but support their use as a tool to try to pool data. Data pooling was often limited by the retrospective nature of much of the published data and by a lack of clarity and inconsistencies/uncertainties regarding critical items such as (1) dose calculation and specification, (2) image segmentation, (3) outcome definitions (for both toxicity and tumor control), and (4) accounting for competing risks and variable follow-up durations. The HyTEC effort also in-

- **All data from selected peer-reviewed publications**
- TCP and NTCP practical guideline tables in Introduction
- **Published clinical data favored over model results**
  - Important for comparing fractionations

Table 2 Summary of NTCP[6] estimates after SRS/SBRT from the HyTEC reports*

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)†	Notes
Brain; for metastasis	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 5\ cm^3$	10%	From Table 3 and Figs. 4 and 5 in paper.
		1	Symptomatic necrosis	$V_{12Gy} \leq 10\ cm^3$	15%	Consistent with QUANTEC.
		1	Symptomatic necrosis	$V_{12Gy} \leq 15\ cm^3$	20%	Prior whole brain RT appears to not markedly increase risks in most reports (with the exception of brain stem).† However, repeat SRS/fSRS to the same area has been associated with markedly increased risks.
		3	Edema or necrosis	$V_{20Gy} \leq 20\ cm^3$	≤ 10%	
		3	Edema or necrosis	$V_{20Gy} \leq 30\ cm^3$	≤ 20%	
		5	Edema or necrosis	$V_{24Gy} \leq 20\ cm^3$	≤ 10%	
		5	Edema or necrosis	$V_{24Gy} \leq 30\ cm^3$	≤ 20%	
Brain; SRS for arteriovenous malformation	Total brain including target	1	Symptomatic necrosis	$V_{12Gy} \leq 10\ cm^3$	≤ 10%	From Figure 2 in paper
Optic pathway	Optic nerves and chiasm	1	Neuropathy	D_{max} < 10-12 Gy	< 1%	From Table 3 in paper. Consistent with QUANTEC. Prior RT exposure of the optic pathway (either whole brain RT or SRS/fSRS) appears to markedly increase risks.
		3	Neuropathy	D_{max} < 20 Gy	< 1%	
		5	Neuropathy	D_{max} < 25 Gy	< 1%	
Carotid artery (re-treatment)	Each carotid artery	5	Grade 3-5 bleeding	D_{max} < 20-30 Gy	< 2-12%	Dose-volume metric shown is for the reirradiation SBRT dose *in patients with prior RT*‡
	Each carotid artery	5	Grade 3-5 bleeding	$D_{0.5cc}$< 20 Gy	< 2-12%	Dose-volume metric shown is for the reirradiation SBRT dose *in patients with prior RT*‡
Lungs	Combined lungs minus target§	3-5	Grade ≥ 2 toxicity§	Mean dose ≤ 8 Gy; V_{20Gy} < 10-15%	10-15%	Preexisting interstitial lung disease appears to increase toxicity risk
Liver; SBRT for primary lesions	Liver minus GTVs‖	3	Grade ≥ 3 liver enzyme change	Mean dose ≤ 13 Gy	<20%	For patients with intact liver function. Various clinical factors (eg, underlying liver impairment per the Child Pugh score, platelet count) can reduce liver tolerance.# Consistent with QUANTEC (that broadly considered radiation induced liver injury; this includes liver enzyme changes).
	Liver minus GTVs‖	6	Grade ≥3 liver enzyme change	Mean dose ≤ 18 Gy	<20%	
Liver; SBRT for metastases	Liver minus GTVs‖	3	Grade ≥3 liver enzyme change	Mean dose ≤ 15 Gy	<20%	
	Liver minus GTVs‖	6	Grade ≥3 liver enzyme change	Mean dose ≤ 20 Gy	<20%	

(continued on next page)

Lightening Tour of Radiobiological Effects for HyTEC

- A dose is more potent when delivered in fewer fractions
- HyTEC pools data from various fractionations (1- >5)
  - Isoeffective Dose (few fractions) < Dose (many fractions)
  - Isoeffective doses have the same Biologically Effective Dose or BED
- Many BED models developed over the years

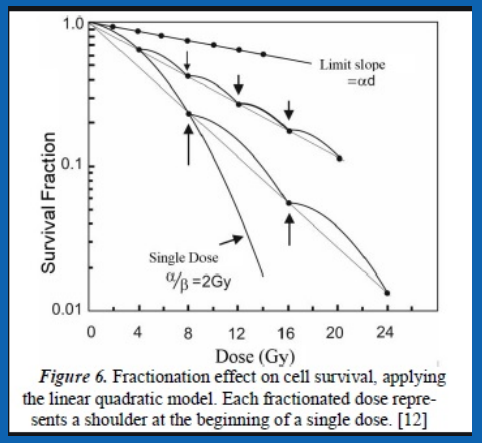
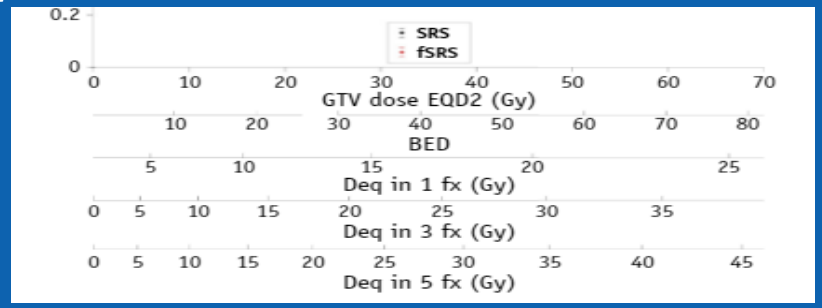
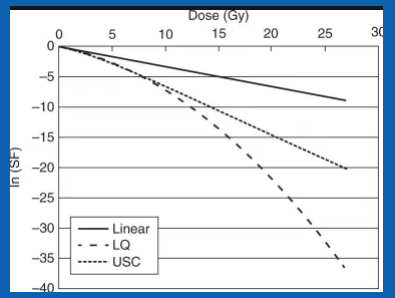


Figure 6. Fractionation effect on cell survival, applying the linear quadratic model. Each fractionated dose represents a shoulder at the beginning of a single dose. [12]

- Widely used: Linear-Quadratic (LQ) model
  - D=total dose, n=# of fractions, α/β = effect-dependent parameter
    - α/β high (≥ 10 Gy) for most TCP, low (≤ 5 Gy) for NTCP
  - **BED=D (1+[D/n]/α/β)**
  - EQD2 = isoeffective dose (same α/β) in 2 Gy fractions
  - HyTEC also uses Equivalent Dose in specified # fractions



- Most HyTEC articles use LQ
  - Imperfect but simple
  - A few compare LQ to other models



HyTEC Organ-Specific Paper: Spinal Cord

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††

- Endpoint: ≥ Grade 3 radiation myelopathy [RM]-highly symptomatic
- PubMed search 1/05-1/18; 40 initial hits triaged to 7 de novo studies, 5 re-irradiation
- No case reports, cauda vs cord or de novo vs reirradiation not separately reported, inadequate followup information
- Due to extreme clinical caution, there are very few RM cases!

Table 1 De novo spine SBRT literature that met the inclusion criteria for this review

Series	No. of patients	Dose reporting structure	Median prescribed dose in Gy (range)/ number of fractions (range)	Median spinal cord D_{max}, Gy	Median spinal cord D_{max} $EQD2_2$, Gy	Median follow-up, mo	No. of cases of RM
Chang 2012[45,*]	131	Thecal sac	Mean $EQD2_2$ 50.7/NS	NS	Mean 48.68 ± 29.97	Mean 23.7	0
Daly 2011[42]	19	Cord	20 (18-30)/1 (1-3)	1 Fx: 22.7 (range, 17.8-30.9); 2 Fx 22.0 (range, 21.3-26.6); 3 Fx: 21.9 (range, 19.7-25.4)	1 Fx: 140.17; 2 Fx: 71.5; 3 Fx: 50.92[†]	33.7	1
Gerszten 2012[53,*]	26	Cord	Mean 16 (12-24)/ 1 (1-3)	Mean 8.7 (range, 4-11.5)	Mean 23.27[†]	32	0
Sahgal 2007[54,*]	12	Thecal sac	21 (10-40)/3 (1-5)	20.9 (range, 4.3-23.1)	46.85[†]	25	0
Sahgal 2009[55,*]	14	Thecal sac	24 (7-40)/3 (1-5)	16.8 (range, 10.7-26)	28 (range, 15-57)	9	0
Sahgal 2013[33,*,‡]	66	Thecal sac	NS / (1-5)	NS	35.69	15	0
Katsoulakis 2017[34]	228	Cord	24 (18-24) / 1	13.85 (range, 9.61-15.21)	54.88 (range, 27.89-65.44)	15	2

Abbreviations: D_{max} = maximum dose; $EQD2_2$ = equivalent dose in 2 Gy fract … = radiation myelopathy; SBRT = stereotactic body radiation therapy.

* The results from only the patients who met the inclusion criteria are reported in this row (instead of the full cohort of patients from the original study).

† Cumulative $EQD2_2$ estimated using summary data presented in paper.

‡ The data presented are the controls, not the cases of radiation myelopathy.

Plus Lord, 19 cases (1 RM), Gibbs[24]

Table 2 Reirradiation spine SBRT literature that met the inclusion criteria for this review

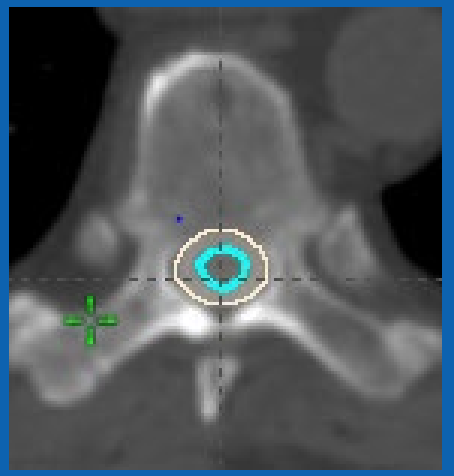
Paper	No. of patients	Dose reporting structure	Median prescribed dose (range) / number of fractions (range)	Median prescribed dose of prior RT (range) / number of fractions (range)
Chang 2012[45,*]	54	Thecal sac	Mean $EQD2_2$ 51.1 / NS	NS
Gwak 2005[44,*]	3	Cord	33 (21-35) Gy / 3	50.4 Gy (30-50.4) Gy/ 28 (10-28)
Sahgal 2009[55,*]	25	Thecal sac	24 (8-30) Gy / 3 (1-5)	36 Gy / 14
Sahgal 2012[43,*,†]	14	Thecal sac	24 (10-30) Gy / 3 (1-5)	$EQD2_2$ = 39.8 (29.0-64.5)
Thibault 2015[35,§]	16	Cord PRV (+1.5 mm)	30 (20-35) Gy / 4 (2-5)	SBRT 24 (20-35)/ 2 (1-5)
Thibault 2015[35,§]	24	Cord PRV (+1.5 mm)	30 (24-35) Gy / 4 (2-5)	cEBRT: 22.5 (20-30); SBRT 24 (20-30)/ 2 (2-5)

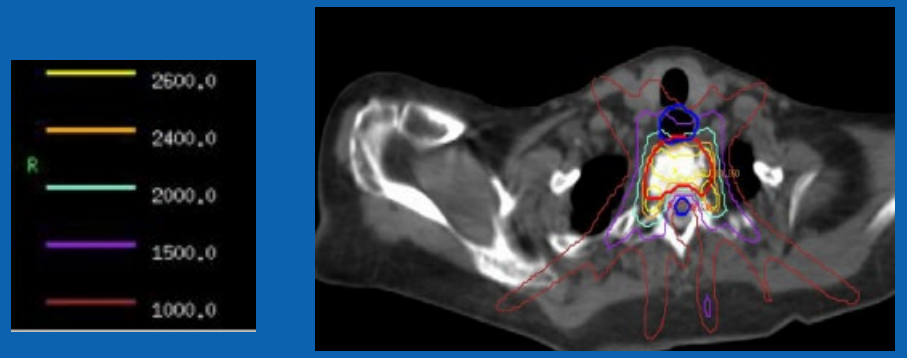
Median spinal cord D_{max}, Gy	Median spinal cord D_{max} $EQD2_2$ for SBRT, Gy	Median cumulative spinal cord D_{max} $EQD2_2$ of all RT, Gy	Median follow-up, mo	No. cases of RM
NS	Mean 46.19 ± 35.21	Mean 83.37	Mean 21.8	0
24.1 (19.9-32.9)	60.45[†]	NS	24	1
12.8 (5.4-27)	18 (10-49)	41.5[†]	7	0
NS	12.5 (1.9-58.7)	52.4 (39.1-111.2)	12	0
NS	21.9 (12.4-25.0)	51.3	6.8	0
NS	21.9 (17.5-26.7)	73.9	6.8	0

Much more data needed for reirradiation

Challenges defining anatomic Volumes

Spinal canal?
Thecal sac?
Spinal cord seen in myelogram or MRI?
Spinal cord with PRV margin ?

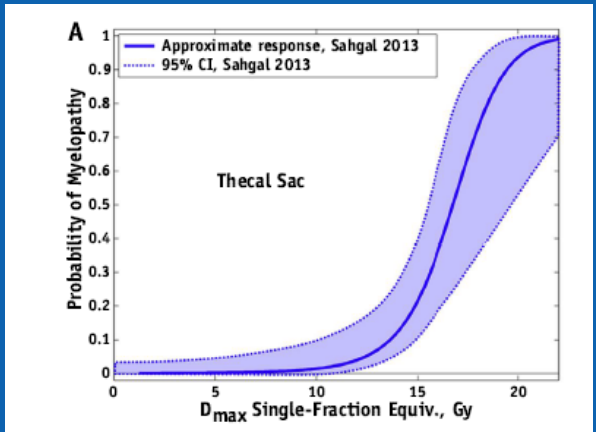


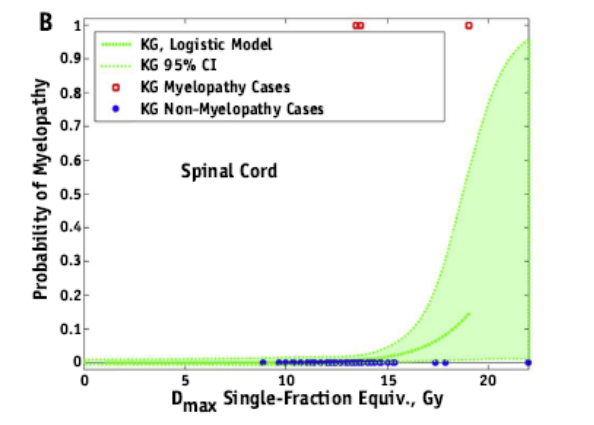


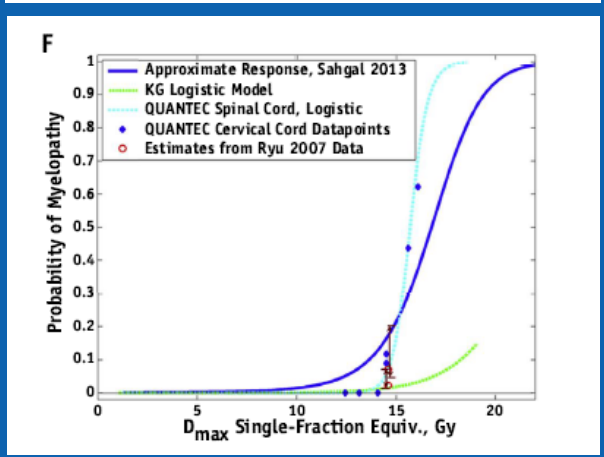
Larger structures may be safer but they penalize paraspinal target coverage

'Whichever approach is used clinically for segmenting the spinal cord, the clinician should be mindful of how past studies have reported spinal cord doses and to what structure the doses were being reported.'

From Figure 1







Sahgal Model

- Thecal Sac
- α/β=2 Gy, 1-5 fraction cases
- 9 Grade 4 RMs from collaborating group + 66 no-RM controls
- Conservative
- Single fraction Thecal Sac Dmax ≤ 12.4 Gy for predicted RM<1-5%

Katsoulakis-Gibbs (K-G) Model

- Spinal cord
- α/β=3 Gy K: 259 single-fraction G: 19 cases, BED(α/β=3 Gy)
- K: 2 RMs G: 1 RM
- Single fraction cord Dmax ≤ 14 Gy for predicted RM<1-5%

Comparison with other published data

"…..steep increases in risk above single fraction Dmax of 15 Gy"

HyTEC Introduction NTCP Table

Table 2 Summary of NTCP[6] estimates after SRS/SBRT from the HyTEC reports*

Organ	Volume segmented	Number of fractions	Endpoint	Dose (Gy) or dose-volume parameters	Rate (%)*	Notes
Spinal cord	Spinal cord, canal, or thecal sac‡‡	1	Myelopathy	D_{max} < 12.4-14 Gy	1-5%	These data are for patients without prior RT (from Table 3 in paper). Information for the setting of re-irradiation are in Table 4 of the paper. Consistent with QUANTEC.
		2		D_{max} < 17-19.3 Gy	1-5%	
		3		D_{max} < 20.3-23.1 Gy	1-5%	
		4		D_{max} < 23-26.2 Gy	1-5%	
		5		D_{max} < 25.3-28.8 Gy	1-5%	

‡‡ A range of doses and complication rates are reported, reflecting the heterogeneity and uncertainty in the data. The spinal cord, canal, and the thecal sac have each been used in different models of radiation myelopathy.

Consistent with other expert Dmax

Table 3 Spinal cord and thecal sac D_{max} values recommended in previous publications compared with model-derived limits

	Existing expert-based recommendations for D_{max}		Model-based limits for D_{max} derived from clinical data		
	AAPM TG101[5]	Kim et al 2017[56]	Sahgal 2013*	Katsoulakis–Gibbs model*	Approximate Risk
			LQ, α/β = 2 Gy	LQ, α/β = 2 Gy	
No. fractions	Gy	Gy	Gy	Gy	of RM, %
1	14	14	12.4	14	1-5
2		18.3	*17*	*19.3*	1-5
3	21.9	22.5	*20.3*	*23.1*	1-5
4		25.6	*23*	*26.2*	1-5
5	30	28	*25.3*	*28.8*	1-5

Abbreviations: AAPM TG101 = American Association of Physicists in Medicine Task Group 101; CT = computed tomography; D_{max} = maximum dose; LQ = linear quadratic; MRI = magnetic resonance imaging; RM = radiation myelopathy.

* The spinal cord itself (from CT myelogram or MRI) was used as the dose reporting structure by Katsoulakis et al[34] and Gibbs et al,[36] and the thecal sac was used as a surrogate structure for the spinal cord by Sahgal et al.[33] Numbers in italics denote LQ-based extrapolations from the single-fraction limit. Note that because of the uncertainties involved, the decimal place may not be meaningful, and an approximately equivalent set of median rounded limits from the recommendations/models would be 14, 18, 22, 26, and 28 Gy for 1 to 5 fractions, respectively.

"It is up to individual physicians to determine their own practice and what limits they wish to apply; all of these tolerance limits are suggestions and are not absolute. **There are significant limitations to the data that cannot be overcome unless large, prospective, multi-institutional cooperative registries of dose tolerance thresholds are created and modelled."**

Now onward:

- **Dr. Anand Mahadevan**: An in-depth look at the HyTEC process with pancreas TCP as the example.
- **Dr. Andrew Jackson**: A physicist's and modeler's perspective on how HyTEC used data from outcomes publications and suggestions as to how future studies can be made more informative.
- **Dr. Larry Marks**: A radiation oncologist's perspective on HyTEC and the future.