Associazione Italiana Radioterapia Oncologica

Società Italiana di Radiobiologia

Associazione Italiana Radioterapia Oncologica

Farmaci innovativi e ipofrazionamento

PALACONGRESSI DI RIMINI
30 settembre, 1-2 ottobre 2016

Radioterapia Ipofrazionata del distretto testa collo: come cambiano i constraints di dose?

Ciammella P.

S.C. Radioterapia
IRCCS – Azienda ospedaliera Santa Maria Nuova, Reggio Emilia

Int J Radiat Oncol Biol Phys. 1991 May 15;21(1):109-22.

Tolerance of normal tissue to therapeutic irradiation.

Emami B[1], Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M.

Limitations of the Emami tables:

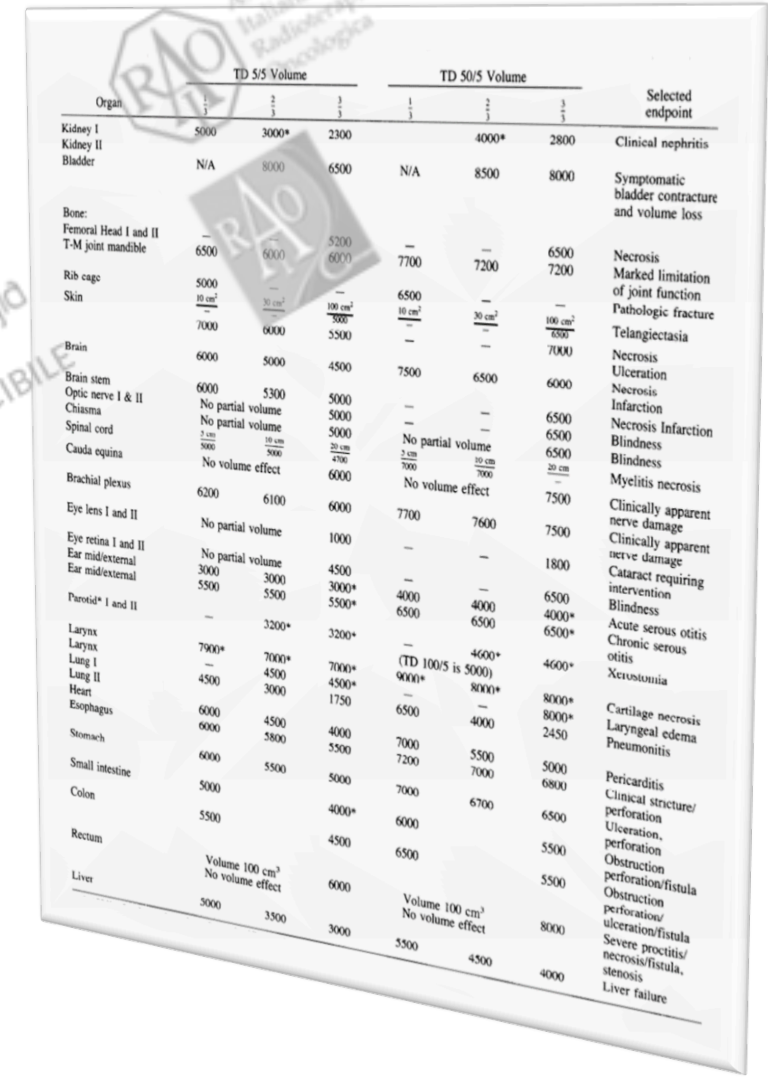
➢ It was a literature review up to 1991.

➢It completely pre-dated the 3D-CRT-IMRT- IGRT era. Even at that time dose-volume histograms were not in routine clinical use.

➢It was a tabulation of the estimates for three arbitrary volumes (1/2, 1/3, whole organ)

➢It was only for external beam radiation with conventional fractionation.

➢Only one severe complication was chosen as an endpoint.

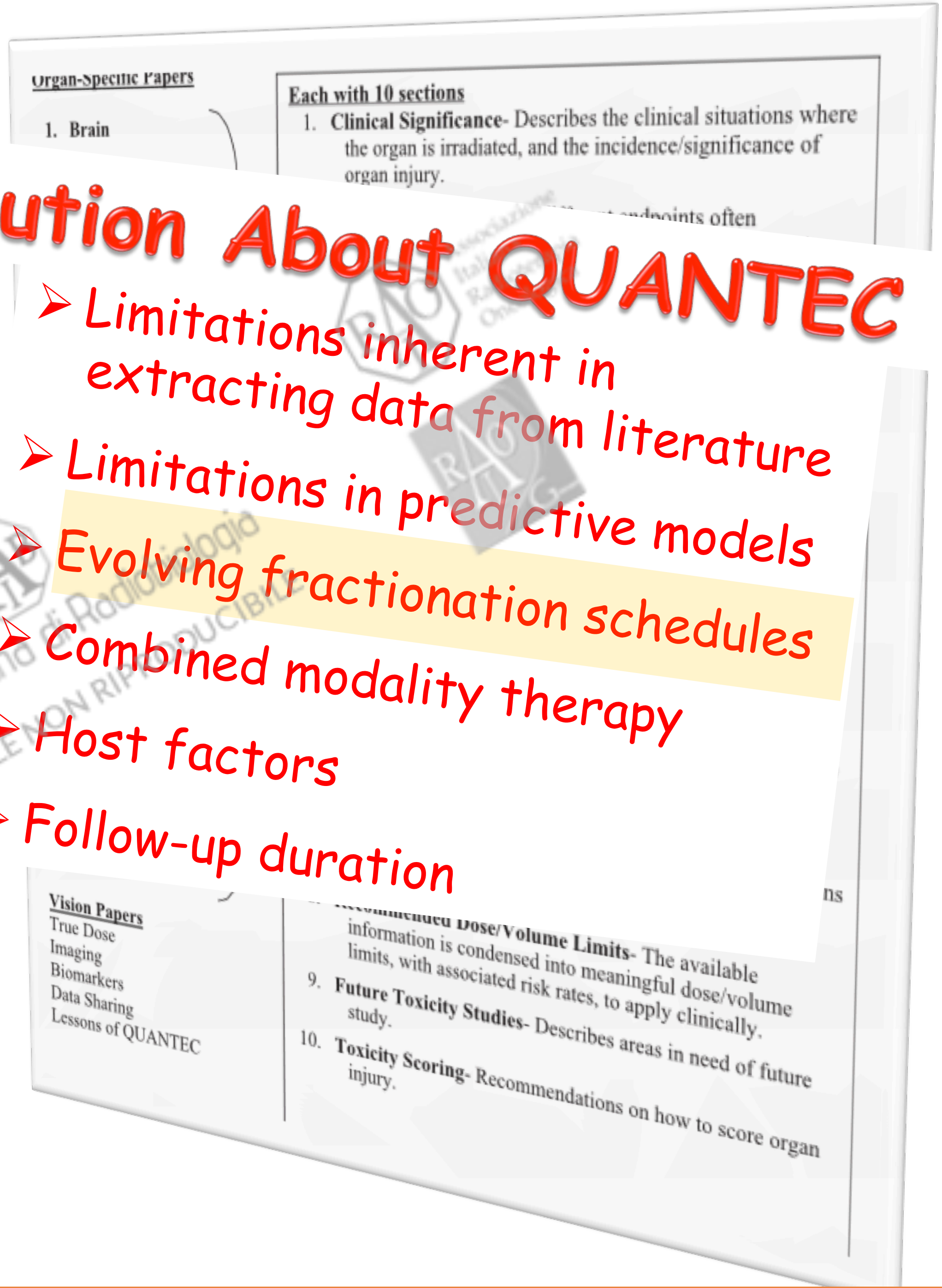


Organ	TD 5/5 Volume 1/3	2/3	3/3	TD 50/5 Volume 1/3	2/3	3/3	Selected endpoint
Kidney I	5000	3000*	2300		4000*	2800	Clinical nephritis
Kidney II							
Bladder	N/A	8000	6500	N/A	8500	8000	Symptomatic bladder contracture and volume loss
Bone:							
Femoral Head I and II	–	–	5200	–	–	6500	Necrosis
T-M joint mandible	6500	6000	6000	7700	7200	7200	Marked limitation of joint function
Rib cage	5000	–	–	6500	–	–	Pathologic fracture
Skin	10 cm² / –	30 cm² / –	100 cm² / 5000	10 cm² / –	30 cm² / –	100 cm² / 6500	Telangiectasia
	7000	6000	5500	–	–	7000	Necrosis Ulceration
Brain	6000	5000	4500	7500	6500	6000	Necrosis Infarction
Brain stem	6000	5300	5000	–	–	6500	Necrosis Infarction
Optic nerve I & II	No partial volume		5000	–	–	6500	Blindness
Chiasma	No partial volume		5000	No partial volume		6500	Blindness
Spinal cord	5 cm / 5000	10 cm / 5000	20 cm / 4700	5 cm / 7000	10 cm / 7000	20 cm / –	Myelitis necrosis
Cauda equina	No volume effect		6000	No volume effect		7500	Clinically apparent nerve damage
Brachial plexus	6200	6100	6000	7700	7600	7500	Clinically apparent nerve damage
Eye lens I and II	No partial volume		1000	–	–	1800	Cataract requiring intervention
Eye retina I and II	No partial volume		4500	–	–	6500	Blindness
Ear mid/external	3000	3000	3000*	4000	4000	4000*	Acute serous otitis
Ear mid/external	5500	5500	5500*	6500	6500	6500*	Chronic serous otitis
Parotid* I and II	–	3200*	3200*	–	4600*	4600*	Xerostomia
				(TD 100/5 is 5000)			
Larynx	7900*	7000*	7000*	9000*	8000*	8000*	Cartilage necrosis
Larynx	–	4500	4500*	–	–	8000*	Laryngeal edema
Lung I	4500	3000	1750	6500	4000	2450	Pneumonitis
Lung II							
Heart	6000	4500	4000	7000	5500	5000	Pericarditis
Esophagus	6000	5800	5500	7200	7000	6800	Clinical stricture/perforation
Stomach	6000	5500	5000	7000	6700	6500	Ulceration, perforation
Small intestine	5000		4000*	6000		5500	Obstruction perforation/fistula
Colon	5500		4500	6500		5500	Obstruction perforation/ulceration/fistula
Rectum	Volume 100 cm³ No volume effect		6000	Volume 100 cm³ No volume effect		8000	Severe proctitis/necrosis/fistula, stenosis
Liver	5000	3500	3000	5500	4500	4000	Liver failure

QUANTEC represents an evolution from the Emami tables

The first goal:
to review the available literature on volumetric/dosimetric information of normal tissue complication and provide a simple set of data to be used by the busy community practitioners of radiation oncology physicists, and dosimetrists.

The second goal:
to provide reliable predictive models on relationships between dose-volume parameters and the normal tissue complications to be utilized during the planning of radiation oncology.

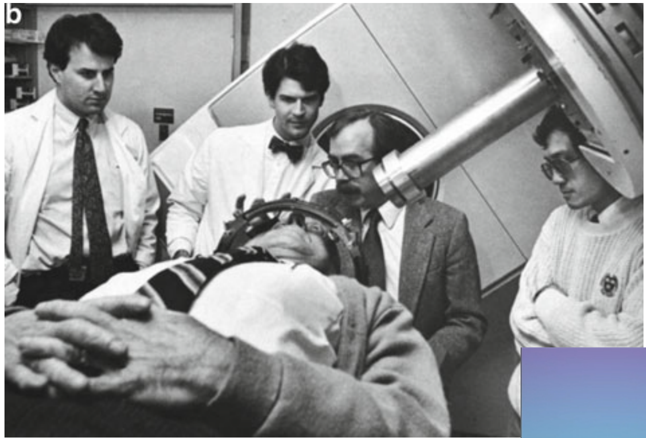


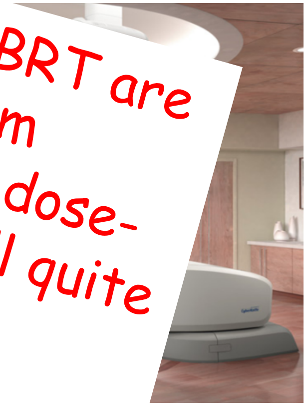
Caution About QUANTEC

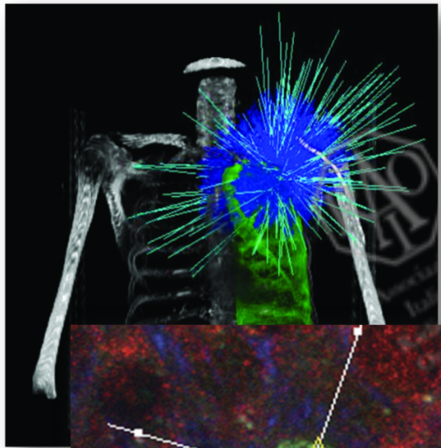
- Limitations inherent in extracting data from literature
- Limitations in predictive models
- Evolving fractionation schedules
- Combined modality therapy
- Host factors
- Follow-up duration

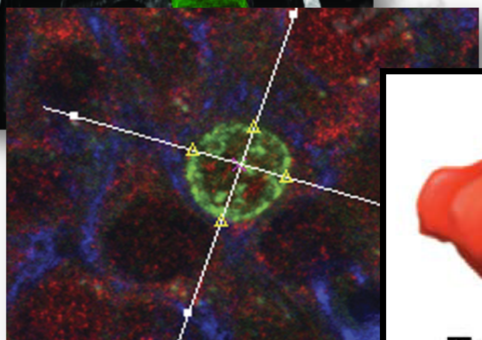
Historical Development of Stereotactic Ablative Radiotherapy

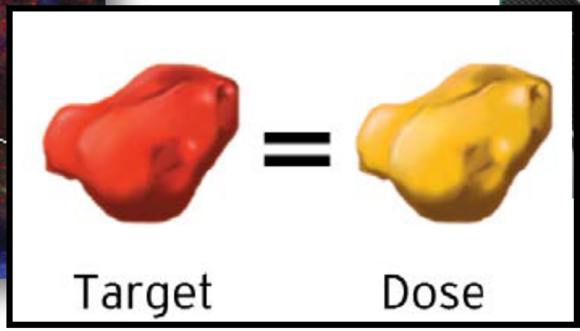
Early SRS treatment at the Brigham and Women's Hospital, 1984











Normal tissue dose limits for SBRT are considerably different from conventional RT due to extreme dose-fractionation schemes and are still quite immature

And normal tissue dose limits for SBRT should not be directly extrapolated from conventional RT data

2016

The Radiobiology of Hypofractionation

In parallel with these technological, computer driven developments, *macroscopic radiobiological models* have been developed that incorporate our extensive knowledge of the dependence of cell killing on total dose, fraction size, interfraction interval, dose rate, the cell cycle, hypoxic status and other factors

Caution About BED

Gy dose/ fractions	Dose/ fraction (Gy)	α/β for brain tissue	BED
60 Gy/30 Fr[a]	2	1	180
60 Gy/30 Fr[a]	2	2	
60 Gy/30 Fr[a]	2	3	

Caution About NTCP

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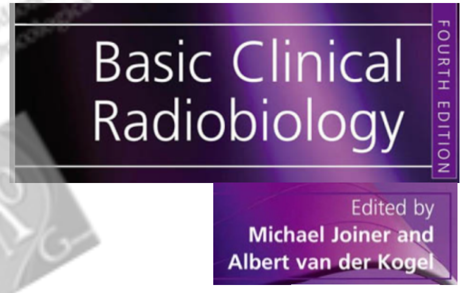
Volume 26, Number 2
Seminars in RADIATION ONCOLOGY
April 2016

Dose Tolerance for Stereotactic Body Radiation Therapy

...pected outcome like NTCP. If every patient's tumor contr... probability (TCP) was 99% or higher, and if every patient's NTCP was 1% or lower, we would not need surrogate metrics like the conformality index, tumor coverage, and dose-tolerance limits. Note that in 3 consecutive sentences, we went from "need" to "ideally" to "if," and in reality TCP and NTCP are often still uncertain, and are rarely as good as 99% and 1%, so we usually are highly dependent on the surrogate metrics of plan quality. In this issue of Seminars, we focus on both clinical practice and rigorous statistics, spending as little time in the middle as possible. Maximum likelihood parameter fitting and other statistical methods are required to obtain reliable estimates of risk, but the focus of this work is on the clinical utility.

The Radiobiology of Hypofractionation

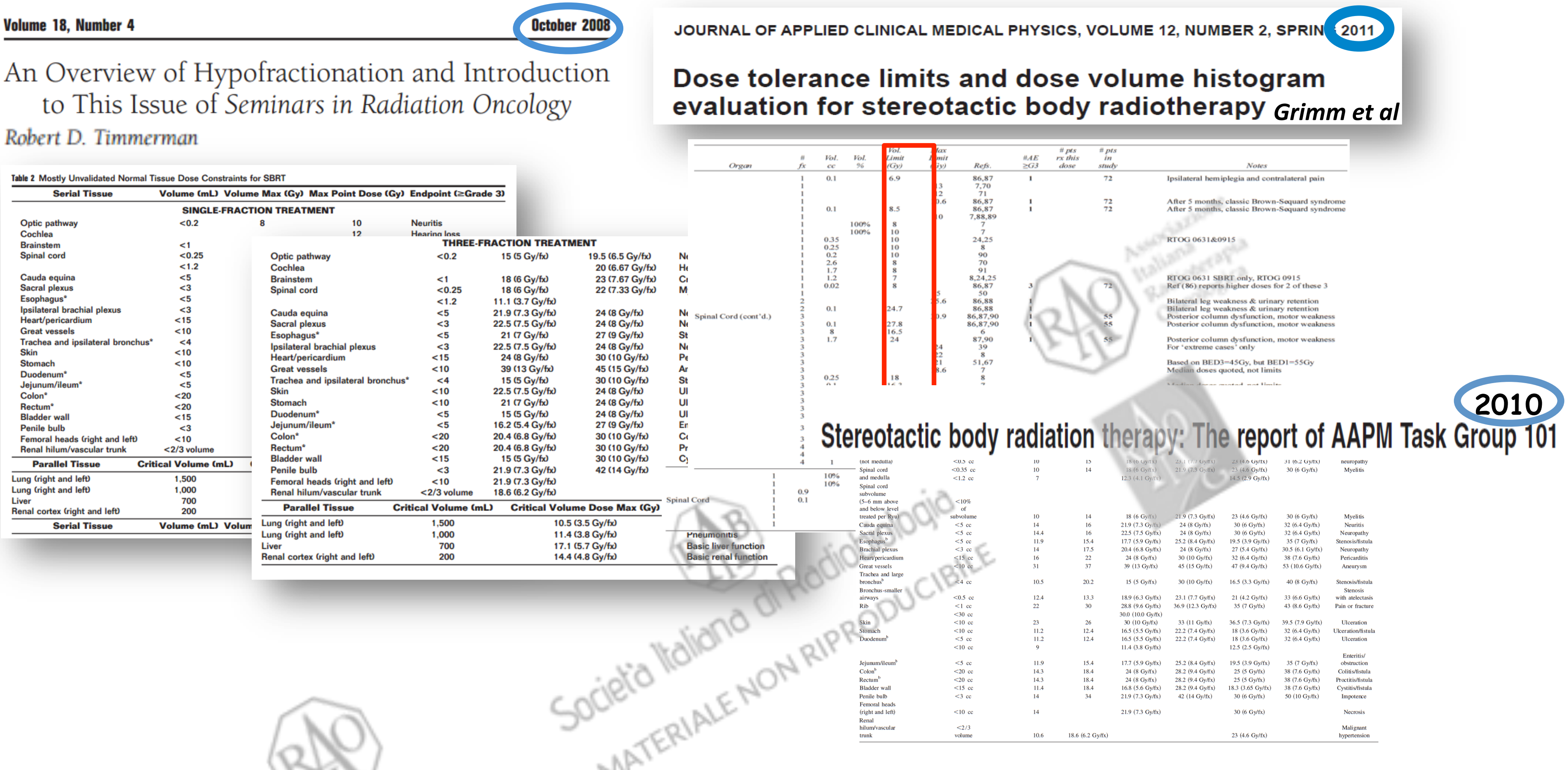
The effects of high doses of RT may be difficult to predict from the linear-quadratic (LQ) model that is very useful for conventional RT.



© 2009

Also, at very high dose per fraction the mathematical form of the LQ model is unlikely to be correct. While the LQ survival curve represents a

allow the estimation of three model parameters. It is difficult to give a specific dose per fraction beyond which the simple LQ model should not be used, but extrapolations beyond 5–6 Gy per fraction are likely to lack clinically useful precision.



Dose tolerance for stereotactic body radiation therapy is still much more uncertain

It grew to 500 dose-tolerance limits and as of 2016 there are well over 1000 published limits, but they are discordant, ever changing, and until now have lacked quantitative estimates of corresponding incidence of complication

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Seminars in RADIATION ONCOLOGY

Volume 26, Number 2 April 2016

Dose Tolerance for Stereotactic Body Radiation Therapy

NTCP results were detailed in the July 2001 issue of Seminars in Radiation Oncology for conventionally fractionated radiation therapy. After 7 years, an extensive collection of stereotactic ablative body radiotherapy (SABR) or stereotactic body radiation therapy (SBRT) dose-tolerance limits was presented in the October 2008 issue of Seminars in Radiation Oncology (QUANTEC), but **estimates of risk were not yet available**.

We now have sufficient data to combine the 2: NTCP for SBRT.

Jimm Grimm, PhD
Bott Cancer Center, Holy Redeemer Hospital, Meadowbrook, PA

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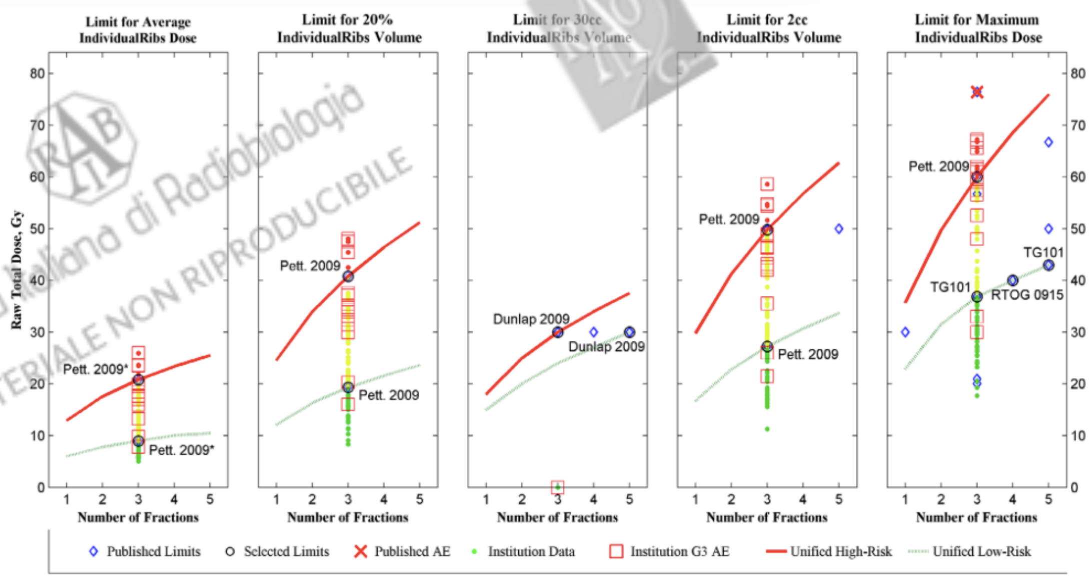
Seminars in RADIATION ONCOLOGY

Introduction and Clinical Overview of the DVH Risk Map

Sucha O. Asbell, MD,* Jimm Grimm, PhD,† Jinyu Xue, PhD,* Meng-Sang Chew, PhD,‡ and Tamara A. LaCouture, MD*

2016

- Review of Literature
- DVH Risk Map Creation
- DVH Risk Map Utilization



	Low Risk Limits					High Risk Limits				
	Dmean Limit (Gy)	D20% Limit (Gy)	D30cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)	Dmean Limit (Gy)	D20% Limit (Gy)	D30cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*6.0*	*12.1*	*15.0*	*16.7*	*22.9*	*12.9*	*24.6*	*18.0*	*29.8*	*35.7*
2 fx	*7.8, 5.0%*	*16.3, 5.0%*	*20.0*	*22.8, 5.0%*	*31.5, 5.0%*	*17.6, 50.0%*	*33.9, 50.0%*	*25.0*	*41.3, 50.0%*	*49.7, 50.0%*
3 fx	**9.0, 5.0%**	**19.3, 5.0%**	*24.0*	**27.2, 5.0%**	**36.9, 4.5%**	**20.8, 50.0%**	**40.8, 50.0%**	**30.0**	**49.8, 50.0%**	**60.0, 49.9%**
4 fx	*10.0, 5.1%*	*21.6, 5.0%*	*27.0*	*30.7, 5.0%*	**40.0, 3.9%**	*23.4, 50.0%*	*46.4, 50.0%*	*34.0*	*56.8, 50.0%*	*68.6, 50.0%*
5 fx	*10.5*	*23.6*	**30.0**	*33.7*	**43.0**	*25.5*	*51.2*	*37.5*	*62.8*	*76.0*

Next

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Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S3–S9, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.09.040

INTRODUCTORY PAPER

QUANTITATIVE ANALYSES OF NORMAL TISSUE EFFECTS IN THE CLINIC (QUANTEC): AN INTRODUCTION TO THE SCIENTIFIC ISSUES

Søren M. Bentzen, Ph.D., D.Sc.,* Louis S. Constine, M.D.,† Joseph O. Deasy, Ph.D.,‡ Avi Eisbruch, M.D.,§ Andrew Jackson, Ph.D.,|| Lawrence B. Marks, M.D.,¶ Randall K. Ten Haken, Ph.D.,§ and Ellen D. Yorke, Ph.D.||

Selection criteria for QUANTEC: all data must already exist in the peer-reviewed literature

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Seminars in RADIATION ONCOLOGY

Introduction and Clinical Overview of the DVH Risk Map

Sucha O. Asbell, MD,* Jimm Grimm, PhD,† Jinyu Xue, PhD,* Meng-Sang Chew, PhD,‡ and Tamara A. LaCouture, MD*

2016

Selection citeria for this issue of Seminars: each of these articles after the introduction presents new data and dose-response modeling from an Institution, for a critical structure that previously did not have many published dose-response models for SBRT or where an additional new model could supplement the information that had been sparse

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Seminars in RADIATION ONCOLOGY

Introduction and Clinical Overview of the DVH Risk Map

Sucha O. Asbell, MD,[*] Jimm Grimm, PhD,[†] Jinyu Xue, PhD,[*]
Meng-Sang Chew, PhD,[‡] and Tamara A. LaCouture, MD[*]

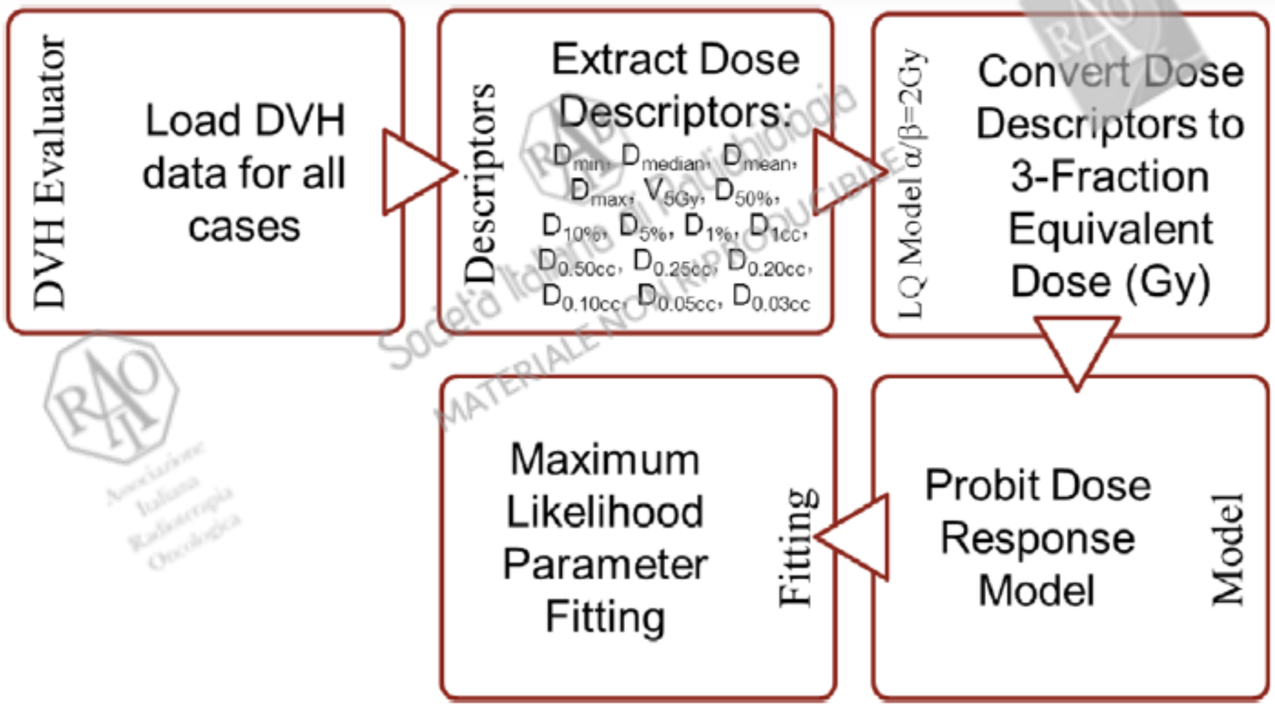
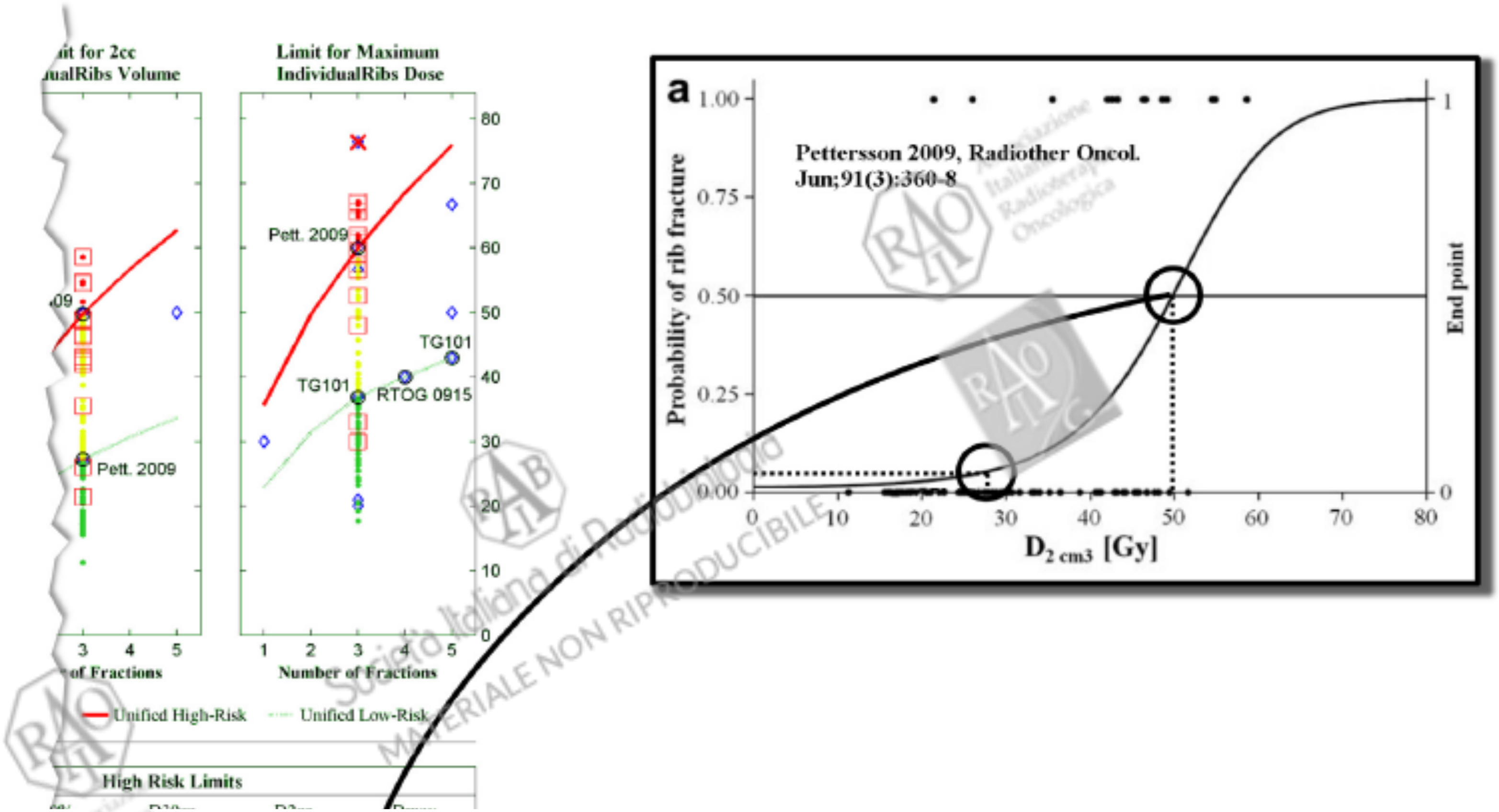


Figure 1 Flowchart of dose-response modeling process. (Color version of figure is available online.)

DVH Risk Map



$$NTCP(D_V) = \frac{1}{1 + e^{4\gamma_{50,V}\frac{(\frac{D_{50,V}}{3}+\frac{\alpha}{\beta})}{(\frac{2D_{50,V}}{3}+\frac{\alpha}{\beta})}[1-\frac{D_V}{D_{50,V}}\frac{(\frac{D_V}{3}+\frac{\alpha}{\beta})}{(\frac{D_{50,V}}{3}+\frac{\alpha}{\beta})}]}}$$

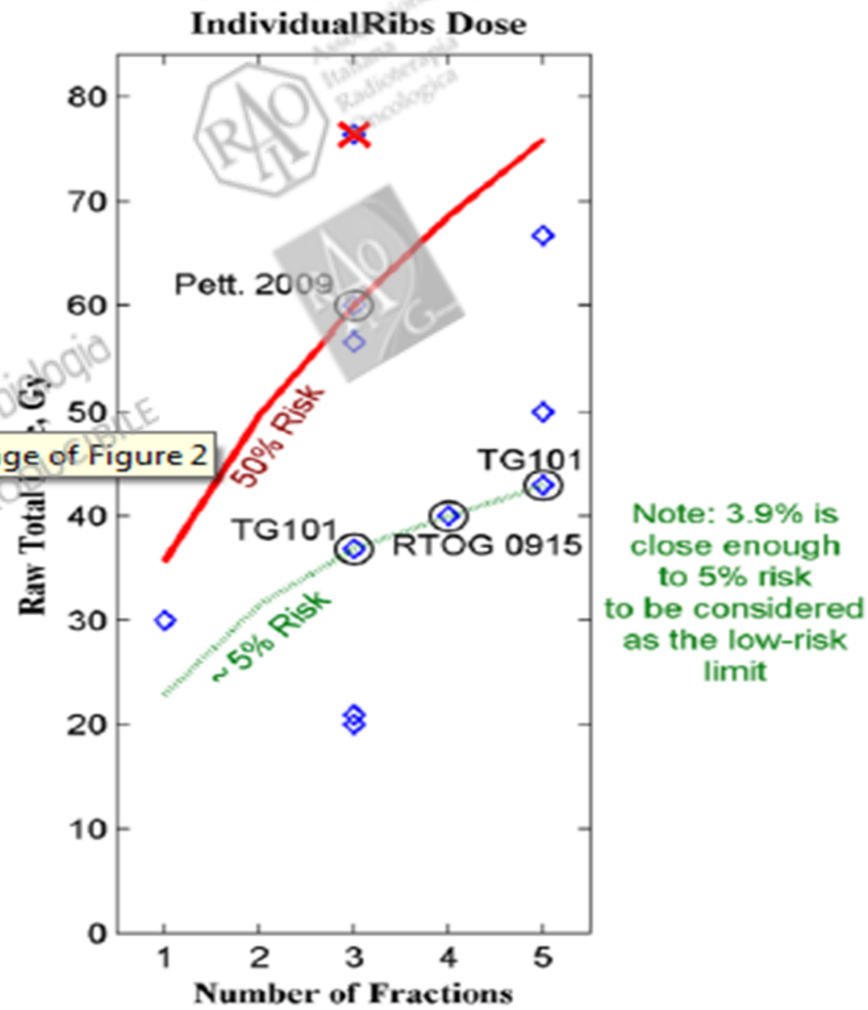
Figure 4 Creation of a DVH Risk Map: interpolating risk level estimates from the published dose-response model: the arrow shows that for $D_{2\ cc}$ = 49.8 Gy in 3 fractions, the estimated risk level was 50% and this was placed in the table for a 3-fraction high-risk limit. Similarly, the 5% risk level for D_{2cc} = 27.2 Gy in 3 fractions was interpolated and placed as the low-risk limit. All other dose-volume constraints were interpolated from corresponding models using the same methodology. (Color version of figure is available online.)

Risk Levels

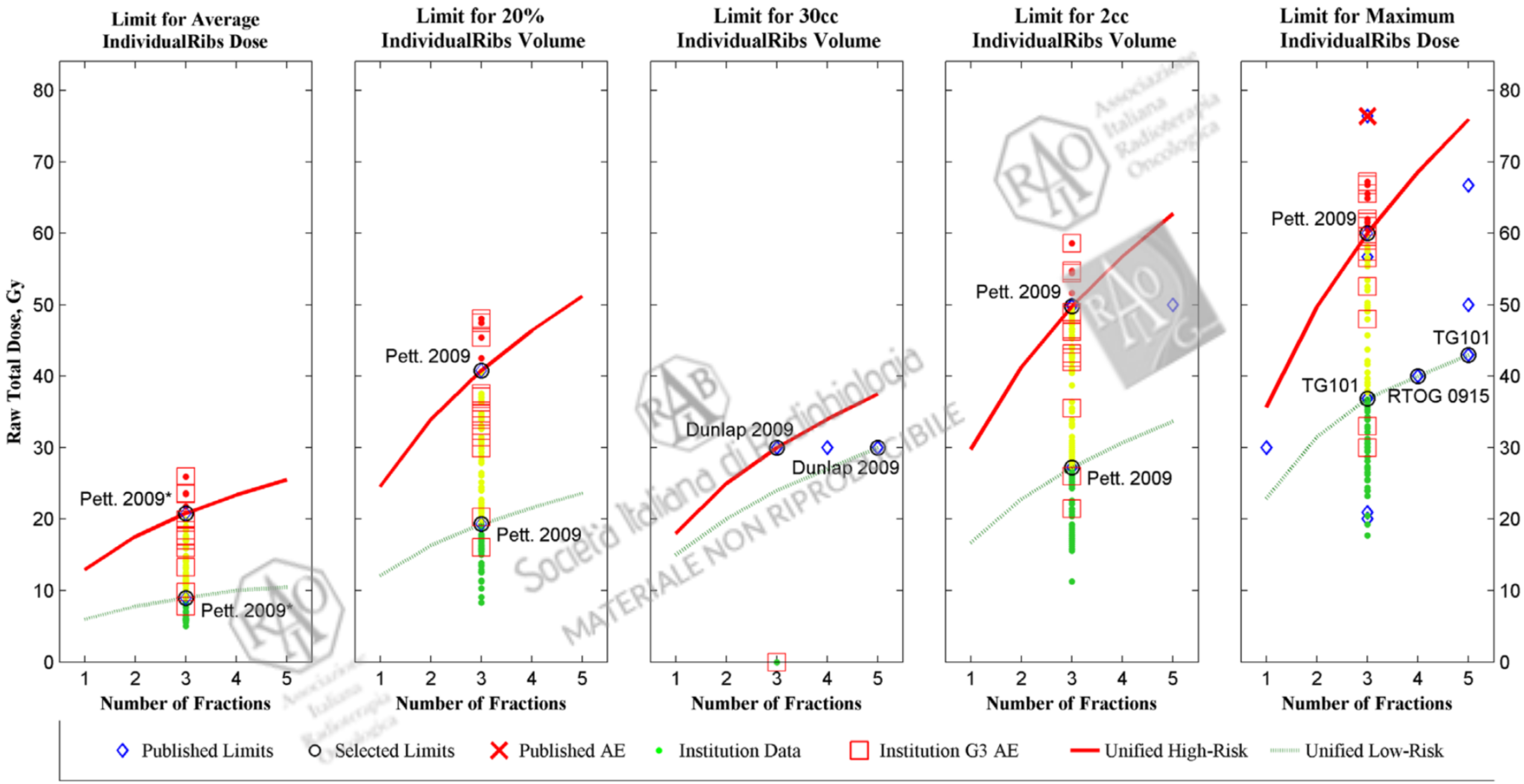
published dose-tolerance limits

near the 5% or 50% risk levels

dose at which a published complication occurred



DVH Risk Maps



	Low Risk Limits					High Risk Limits				
	Dmean Limit (Gy)	D20% Limit (Gy)	D30cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)	Dmean Limit (Gy)	D20% Limit (Gy)	D30cc Limit (Gy)	D2cc Limit (Gy)	Dmax Limit (Gy)
1 fx	6.0	12.1	15.0	16.7	22.9	12.9	24.6	18.0	29.8	35.7
2 fx	7.8, 5.0%	16.3, 5.0%	20.0	22.8, 5.0%	31.5, 5.0%	17.6, 50.0%	33.9, 50.0%	25.0	41.3, 50.0%	49.7, 50.0%
3 fx	**9.0, 5.0%**	**19.3, 5.0%**	24.0	**27.2, 5.0%**	**36.9, 4.5%**	**20.8, 50.0%**	**40.8, 50.0%**	**30.0**	**49.8, 50.0%**	**60.0, 49.9%**
4 fx	10.0, 5.1%	21.6, 5.0%	27.0	30.7, 5.0%	**40.0, 3.9%**	23.4, 50.0%	46.4, 50.0%	34.0	56.8, 50.0%	68.6, 50.0%
5 fx	10.5	23.6	**30.0**	33.7	**43.0**	25.5	51.2	37.5	62.8	76.0

Next

DVH Risk Maps Examples: H&N

- ✓Spinal cord

- ✓Optic nerves and chiasm

Spinal cord

QUANTEC: ORGAN SPECIFIC PAPER — Central Nervous System: Spinal Cord

RADIATION DOSE–VOLUME EFFECTS IN THE SPINAL CORD

John P. Kirkpatrick, M.D., Ph.D.,* Albert J. van der Kogel, Ph.D.,† and Timothy E. Schultheiss, Ph.D.‡

2010

Three clinical scenarios for the development of myelopathy:

- De novo irradiation of the complete spinal cord cross-section via conventionally fractionated external beam RT

- Reirradiation of the complete spinal cord cross-section after a previous course of conventional external beam RT

- Irradiation of a partial cross-section of the cord using high-dose/fraction stereotactic radiosurgery

Endpoint: myelopathy defined as a Grade 2 or higher myelitis per CTCAE v3.0

QUANTEC: ORGAN SPECIFIC PAPER — Central Nervous System: Spinal Cord

RADIATION DOSE–VOLUME EFFECTS IN THE SPINAL CORD

John P. Kirkpatrick, M.D., Ph.D.,* Albert J. van der Kogel, Ph.D.,† and Timothy E. Schultheiss, Ph.D.‡

Institution (ref.)	Cases of myelopathy/total patients	Total dose (Gy)	Dose/fraction (Gy)	Dose to cord (Gy)	BED to cord (Gy_3)	Proportion of patients previously irradiated to involved segment of spine
Stanford and Pittsburgh (50)	6/1075	12.5–25	5–25	D_{max}: 3.6–30	Range: 24–141 Gy_3	>55%
		25	*12.5*	*D_{max}: 26.2*	*D_{max}: 141*	
		20	*10*	*D_{max}: 19.2*	*D_{max}: 81*	
		21	*10.[illegible]*	*D_{max}: 13.9*	*D_{max}: 46*	
		24	*8*	*D_{max}: 29.9*	*D_{max}: 129*	
		20	*2*	*D_{max}: 8.5*	*D_{max}: 33*	
		[illegible]	*20*	*D_{max}: 10*	*D_{max}: 43*	
Henry Ford (7)	1/86*	<10–18	<10–18	Mean ± SD D_{max}: 12.2 ± 2.5 D1: 10.7 ± 2.3 D10: 8.6 2.1 Maximum D_{max}: 19.2 D1: 15.8 D10: 13	Mean ± SD D_{max}: 62 ± 4.6 D1: 49 ± 4.1 D10: 33 ± 3.6 Maximum D_{max}: 142 D1: 99 D10: 69	0%
		18†	[illegible]8	Mean ± SD D_{max}: [illegible].8 ± 2.2 D1: 12.[illegible] ± 1.9 D10: 9.8 ± 1.5	Mean ± SD D_{max}: 77 ± 3.8 D1: 61 ± 3.1 D10: 42 ± 2.3	
		16	*[illegible]6*	*Dmax:14.[illegible]* *D1: 13.0* *D10: 9.[illegible]*	*Dmax:88* *D1:69* *D10: 40*	
Korea (49)	2/9	[illegible]–44	[illegible]5	Median D_{max}:32.9 D25:11.0 Range Dmax: 11–37 D25: 1.2–24	Median D_{max}:106 D25:21 Range D_{max}: 19–172 D25: 1–88	33%
		30	*10*	*D_{max}: 35.2* *D25: 15.5*	*D_{max}:172* *D25: 42*	
		33	*11*	*D_{max}: 32.9 D25: 24.0*	*153* *88*	
NYMC (51)‡	3/31	Median: 10	Median: 5	Median: 6.0	12	Unknown
		100	*50*			
		12	*12*			
		20	*5*			
UCSF (52)	0/38	24	8	Median $D_{0.1cc}$: 10.5	Median $D_{0.1cc}$: 23	62%

9 published reports of spinal cord dose tolerance with SBRT

Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50
	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1

For partial cord irradiation as part of spine radiosurgery, a maximum cord dose of 13 Gy in a single fraction or 20 Gy in three fractions appears associated with a <1% risk of injury

JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, VOLUME 12, NUMBER 2, SPRING 2011

Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy

Grimm et al

Organ	# fx	Vol. cc	Vol. %	Vol. Limit (Gy)	Max Limit (Gy)	Refs.	#AE ≥G3	# pts rx this dose	# pts in study	Notes
	1	0.1		6.9		86,87	1		72	Ipsilateral hemiplegia and contralateral pain
	1				13	7,70				
	1				12	71				
	1				10.6	86,87	1		72	After 5 months, classic Brown-Sequard syndrome
	1	0.1		8.5		86,87	1		72	After 5 months, classic Brown-Sequard syndrome
	1				10	7,88,89				
	1		100%	8		7				
	1		100%	10		7				
	1	0.35		10		24,25				RTOG 0631&0915
	1	0.25		10		8				
	1	0.2		10		90				
	1	2.6		8		70				
	1	1.7		8		91				
	1	1.2		7		8,24,25				RTOG 0631 SBRT only, RTOG 0915
	1	0.02		8		86,87	3		72	Ref (86) reports higher doses for 2 of these 3
	1				5	50				
	2				25.6	86,88	1			Bilateral leg weakness & urinary retention
	2	0.1		24.7		86,88	1			Bilateral leg weakness & urinary retention
Spinal Cord (cont'd.)	3				30.9	86,87,90	1		55	Posterior column dysfunction, motor weakness
	3	0.1		27.8		86,87,90	1		55	Posterior column dysfunction, motor weakness
	3	8		16.5		6				
	3	1.7		24		87,90	1		55	Posterior column dysfunction, motor weakness
	3				24	39				For 'extreme cases' only
	3				22	8				
	3				21	51,67				Based on BED3=45Gy, but BED1=55Gy
	3				18.6	7				Median doses quoted, not limits
	3	0.25		18		8				
	3	0.1		16.3		7				Median doses quoted, not limits
	3	1.2		11.1		8				
	3	1		8.5		7				Median doses quoted, not limits
	3	2		6.9		7				Median doses quoted, not limits
	3	5		4.1		7				Median doses quoted, not limits
	3				18	6,27,39,45,46 53,62,63,64,65				RTOG 0618
	3				15	26,54,68				
	4				26	25				RTOG 0915
	4				25	27				
	4	1		20		27,28				
	1		10%	10		7,24,85				10% of {cord adjacent to tumor +6mm inf & sup}
	1		10%	9.6		85	1		86	Lower extremity G4/5 weakness
	1	0.9		8		80				
Spinal Cord	1	0.1		13.7		85,86	1		86	Lower extremity G4/5 weakness
	1				14.6	85,86	1		86	Lower extremity G4/5 weakness
	1				14	7,8,25,71				RTOG 0915
	1				13.1	86,87	1		72	Ipsilateral hemiplegia and contralateral pain

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Seminars in RADIATION ONCOLOGY

Estimated Risk Level of Unified Stereotactic Body Radiation Therapy Dose Tolerance Limits for Spinal Cord

Jimm Grimm, PhD,[*] Arjun Sahgal, MD,[†] Scott G. Soltys, MD,[‡] Gary Luxton, PhD,[‡] Ashish Patel, MD,[§] Scott Herbert, MD,[‖] Jinyu Xue, PhD,[§] Lijun Ma, PhD,[¶] Ellen Yorke, PhD,[#] John R. Adler, MD,[**] and Iris C. Gibbs, MD, FACR[‡]

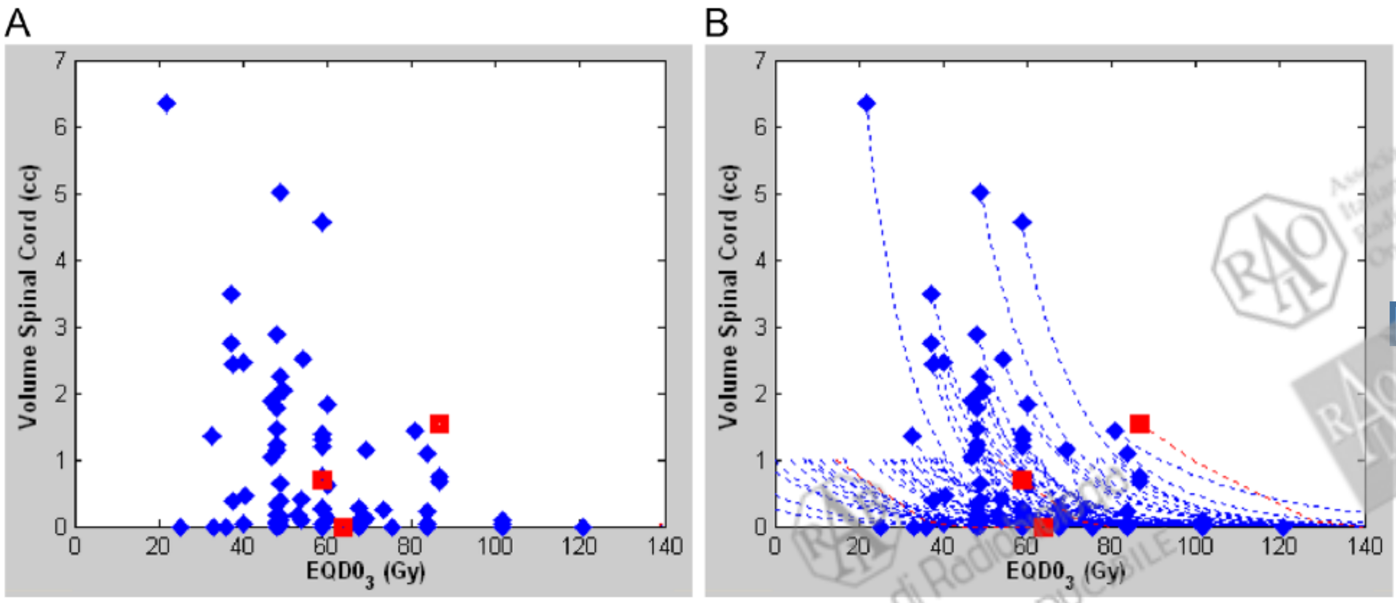
200 papers

Image-guided robotic radiosurgery for spinal metastases

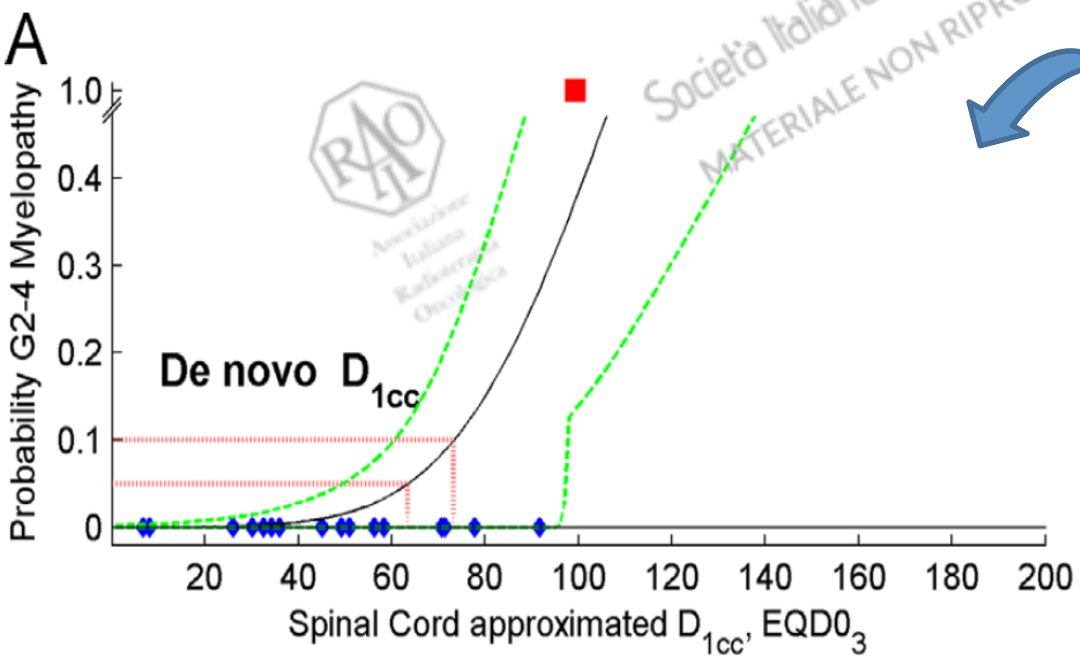
Iris C. Gibbs[a,*], Pimkhuan Kamnerdsupaphon[b], Mi-Ryeong Ryu[c], Robert Dodd[e], Michaela Kiernan[d], Steven D. Chang[e], John R. Adler Jr[e]

Radiotherapy and Oncology 82 (2007) 185–190
www.thegreenjournal.com

DVH Elaboration and Modeling Methods



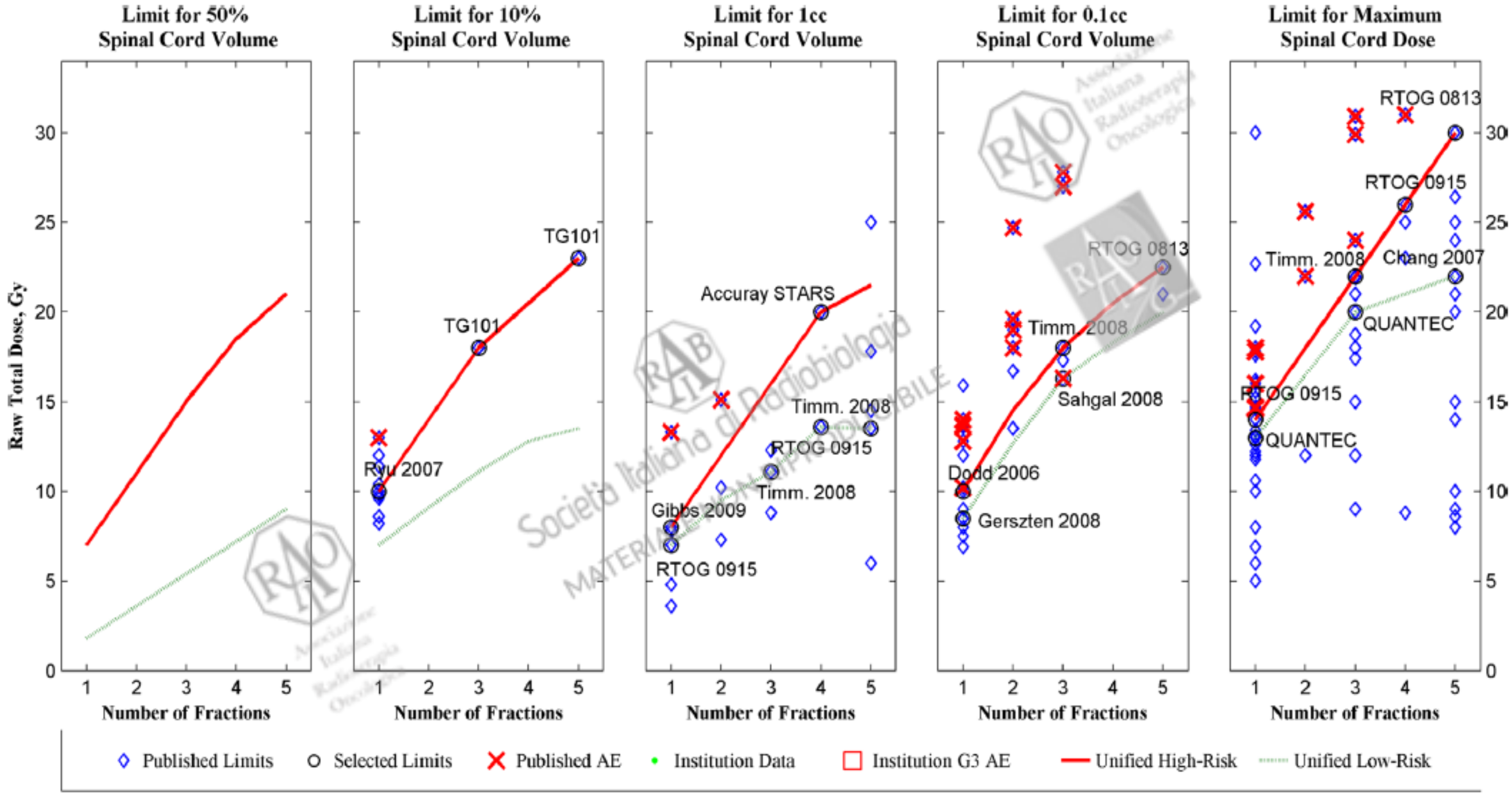
D_{1cc}, $D_{0.1cc}$ and Dmax

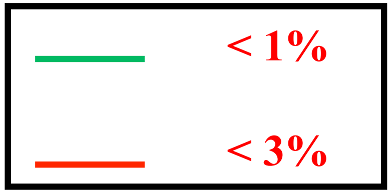


$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx$$

PROBIT MODEL

DVH Maps Construction





< 1%

	Low Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.1cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*1.8*	*7.0*	**7.0, 0.1%**	**8.5, 0.1%**	**13.0, 0.9%**
2 fx	*3.6*	*9.1*	*9.5, 0.1%*	*12.7, 0.1%*	*16.5, 0.6%*
3 fx	*5.4*	*11.1*	**11.1, 0.1%**	**16.3, 0.2%**	**20.0, 0.7%**
4 fx	*7.2*	*12.8*	**13.6, 0.2%**	*18.3, 0.2%*	*21.0, 0.5%*
5 fx	*9.0*	*13.5*	**13.5, 0.1%**	*20.0, 0.2%*	**22.0, 0.4%**

< 3 %

	High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D1cc Limit (Gy)	D0.1cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*7.0*	**10.0**	**8.0, 0.2%**	**10.0, 0.2%**	**14.0, 1.6%**
2 fx	*11.0*	*14.0*	*12.0, 0.4%*	*14.5, 0.3%*	*18.0, 1.1%*
3 fx	*15.0*	**18.0**	*16.0, 0.9%*	**18.0, 0.4%**	**22.0, 1.3%**
4 fx	*18.5*	*20.5*	**20.0, 2.2%**	*20.5, 0.4%*	**26.0, 1.8%**
5 fx	*21.0*	**23.0**	*21.5, 2.0%*	**22.5, 0.4%**	**30.0, 2.6%**

Optic nerves and chiasm

Endpoints

RION (Radiation-induced optic neuropathy)
Vision loss

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)
Publish Date: August 9, 2006

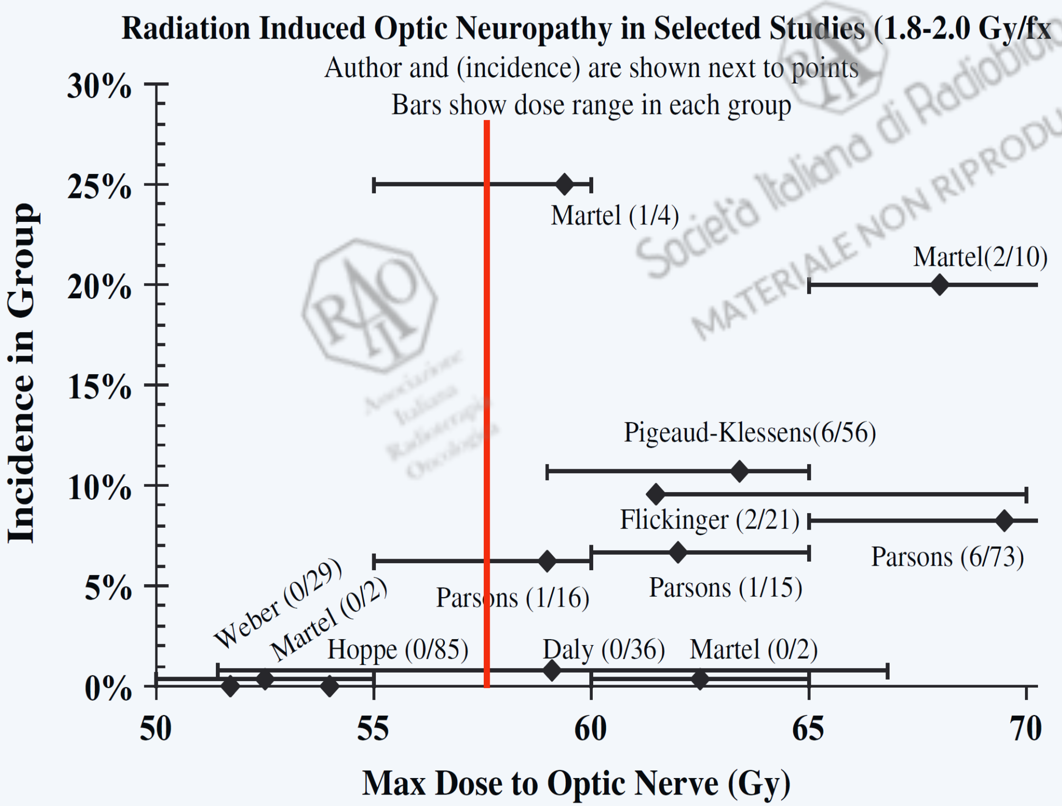
Eye disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-

Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).

Optic nerves and chiasm constraints for conventionally fractionated RT

Emami data	TD5/5	TD50/5
	50 Gy	65 Gy

Quantec data



Risk of toxicity

- < 3% with Dmax < 55 Gy
- 3%-7% with Dmax 55-60 Gy
- > 7% with Dmax > 60 Gy

QUANTEC: ORGAN-SPECIFIC PAPER — Central Nervous System: Optic Nerve/Chiasm

RADIATION DOSE–VOLUME EFFECTS OF OPTIC NERVES AND CHIASM

Charles Mayo, Ph.D.,* Mary K. Martel, Ph.D.,† Lawrence B. Marks, M.D.,‡
John Flickinger, M.D.,§ Jiho Nam, M.D.,‡ and John Kirkpatrick, M.D., Ph.D.¶

Quantec threshold limits are 60 Gy in 1.8 Gy/fraction and 12 Gy for single-fraction SRS

JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, VOLUME 12, NUMBER 2, SPRING 2011

Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy *Grimm et al*

14 Studies

Organ	# fx	Vol. cc	Vol. %	Vol. Limit (Gy)	Max Limit (Gy)	Refs.	#AE ≥G3	# pts rx this dose	# pts in study	Notes
	1				15	17	7	9	50	77.8% chance of RON above 15Gy
	1				13	72				
	1				12	73	2	29	215	7% chance of RON above this, 1.1% chance below
	1				11	74				
	1				10	8,17,72,75	4	15	50	No RON below 10Gy, 27% RON from 10-15Gy tradition, dose tolerance not fully appreciated
	1				8	8				
	1	0.2		8		8,72,73,76				
	1				7.5	82				
	2	0.03		10		83				
	2				10	39				
	2				5	39				Preferred cumulative max
Optic nerve	3				19.5	8				
	3	0.03		15		83				
	3	0.2		15		8				
	3	0.5		10.5		83				
	3				15	39				
	3				5	39				Preferred cumulative max
	5				30	84				Only based on two cases
	5				25	8,72,77,78				

Dose constraints for hypofractionated SRS over 2-5 days for optic nerves have not been well described

ELSEVIER

2016

Seminars in RADIATION ONCOLOGY

Dose-Response Modeling of the Visual Pathway Tolerance to Single-Fraction and Hypofractionated Stereotactic Radiosurgery

Susan M. Hiniker, MD,[*] Leslie A. Modlin, BA,[*] Clara Y. Choi, MD, PhD,[*] Banu Atalar, MD,[†] Kira Seiger, BA,[*] Michael S. Binkley, BA,[*] Jeremy P. Harris, MD, MPhil,[*] Yaping Joyce Liao, MD,[‡] Nancy Fischbein, MD,[§] Lei Wang, PhD,[*] Anthony Ho, PhD,[*] Anthony Lo, MS,[*] Steven D. Chang, MD,[‖] Griffith R. Harsh, MD,[‖] Iris C. Gibbs, MD,[*] Steven L. Hancock, MD,[*] Gordon Li, MD,[‖] John R. Adler, MD,[‖] and Scott G. Soltys, MD[*]

Methods and Materials

- ✓ RETROSPECTIVE ANALYSIS (Stanford University, 2000-2013)
- ✓ "**Perioptic**" tumors (within 3 mm of the optic nerves or chiasm)
- ✓ **262** pts treated with single and hypofractionated SRS:
  - ✓ Benign tumors **236**
  - ✓ Malignant tumors **26**
- ✓ A total of 34 pts (13%) had been treated previously with RT (27 with EBRT and 7 with SRS)

Methods and Materials

DOSE PRESCRIPTION

- 1 Fraction: Median Dose 18 Gy (range 12-25 Gy)
- 3 Fractions: Median Dose 24 Gy (range 18-33 Gy)
- 5 Fractions: Median Dose 25 Gy (range 18-40 Gy)

Dmax to the optic nerve

- 1 Fraction: Median Dmax 7.6 Gy (range 1.9-12.4 Gy)
- 3 Fractions: Median Dmax mediana 13.4 Gy (range 2.7-23.3 Gy)
- 5 Fractions: Median Dmax 19.6 Gy (range 3.8-29.4 Gy)

Results

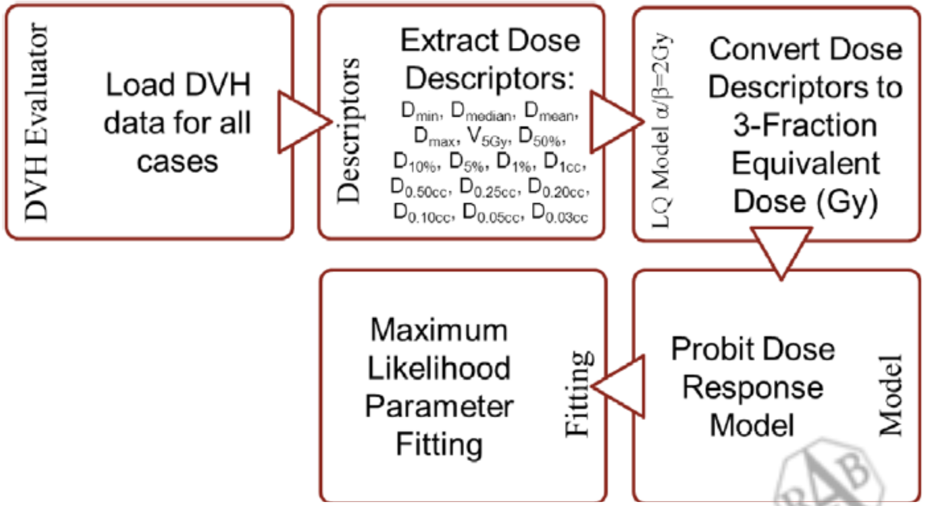
Median Follow-up : 36.8 months (range, 2-142)

- **7 (2.7%)** pts had worsening of vision following RT
  - **5 (1.9%)** due to tumor growth
  - **2 (0.8%)** due to RT (without tumor growth)

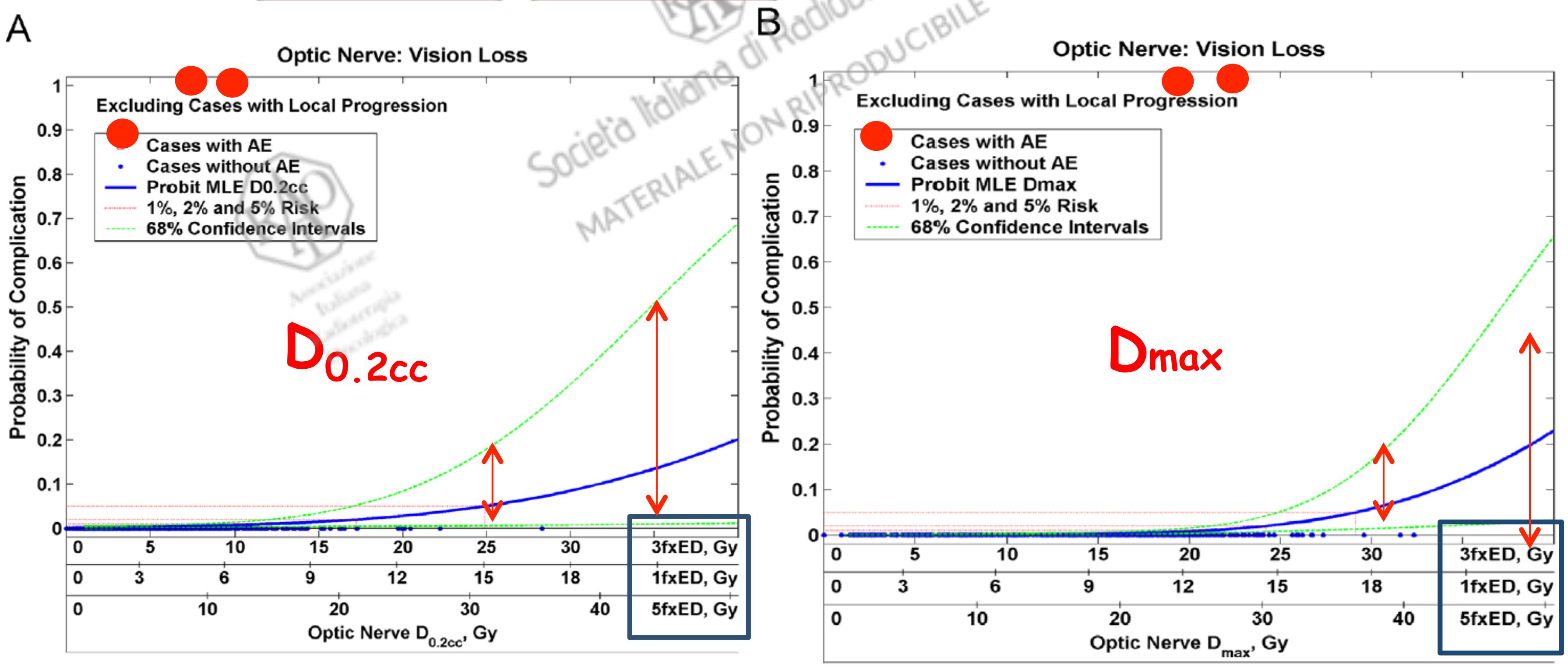
1° treated with 25 Gy in 5 fx, with a maximum dose to the optic nerve of 23.9 Gy

2° treated with 25 Gyin 5 fx to the 78% isodose ; the maximum dose to the optic pathway of 27.7 Gy: BUT the patient had 2 courses of RT previously (EBRT and SRS with 20 Gy in single fx)

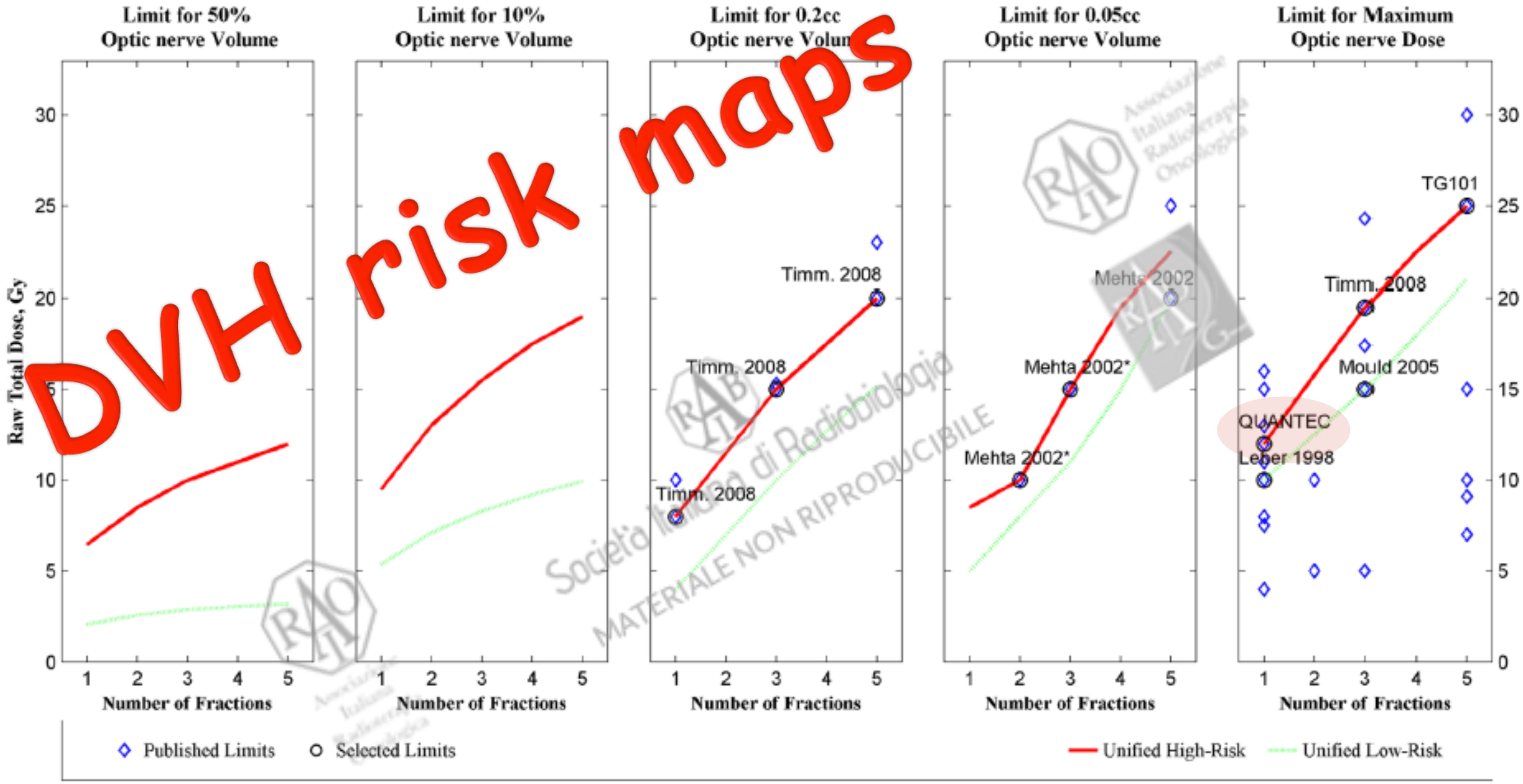
Data Analysis



NTCP curves



Estimated RION Risk level



	Low Risk Limits					High Risk Limits				
	D50% Limit (Gy)	D10% Limit (Gy)	D0.2cc Limit (Gy)	D0.05cc Limit (Gy)	Dmax Limit (Gy)	D50% Limit (Gy)	D10% Limit (Gy)	D0.2cc Limit (Gy)	D0.05cc Limit (Gy)	Dmax Limit (Gy)
1 fx	*2.1, 0.3%*	*5.4, 0.2%*	*4.0, 0.4%*	*5.0, 0.1%*	**10.0, 0.3%**	*6.5, 1.0%*	*9.5, 1.0%*	**8.0, 1.1%**	*8.5, 0.6%*	**12.0, 0.7%**
2 fx	*2.6, 0.3%*	*7.1, 0.2%*	*7.0, 0.6%*	*8.0, 0.2%*	*12.5, 0.2%*	*8.5, 1.0%*	*13.0, 1.0%*	*11.5, 1.2%*	**10.0, 0.4%**	*15.8, 0.6%*
3 fx	*2.9, 0.3%*	*8.3, 0.2%*	*10.0, 0.7%*	*11.0, 0.3%*	**15.0, 0.2%**	*10.0, 1.0%*	*15.5, 1.0%*	**15.0, 1.5%**	**15.0, 0.8%**	**19.5, 0.7%**
4 fx	*3.1, 0.3%*	*9.2, 0.2%*	*12.7, 0.9%*	*15.0, 0.6%*	*18.0, 0.3%*	*11.0, 1.0%*	*17.5, 1.0%*	*17.5, 1.6%*	*19.5, 1.4%*	*22.5, 0.8%*
5 fx	*3.2, 0.3%*	*9.9, 0.2%*	*15.2, 1.0%*	**20.0, 1.1%**	*21.0, 0.4%*	*12.0, 1.0%*	*19.0, 1.0%*	**20.0, 1.7%**	*22.5, 1.6%*	**25.0, 0.8%**

Optic Nerve Dmax Values corresponding to 1%, 2%, 3%, and 5% Risk of RION

Number of Fractions	Dmax for 1% Risk (Gy)	Dmax for 2% Risk (Gy)	Dmax for 3% Risk (Gy)	Dmax for 5% Risk (Gy)
1	12.7	14.6	15.9	17.5
2	17.5	20.2	21.9	24.2
3	20.9	24.2	26.3	29.1
4	23.7	27.5	29.9	33.1
5	26.1	30.3	32.9	36.6

Risk of RION < 1% with maximum point dose of:

12 Gy in 1 Fr
19,5 Gy in 3 Fr
25 Gy in 5 Fr

DVH Risk Maps

"The DVH Risk Maps can be represented a stable bridge between clinical practice and rigorous estimation theory"

… The DVH Risk Maps allow clinicians
to evaluate alternative treatments plans based on acceptable risk levels appropriate for each unique clinical situation to better optimize radiation treatment
and to become more confortable in devising more aggressive regimens when necessary such as radioresistant tumors to improve the effectiveness of treatment

Grazie a:

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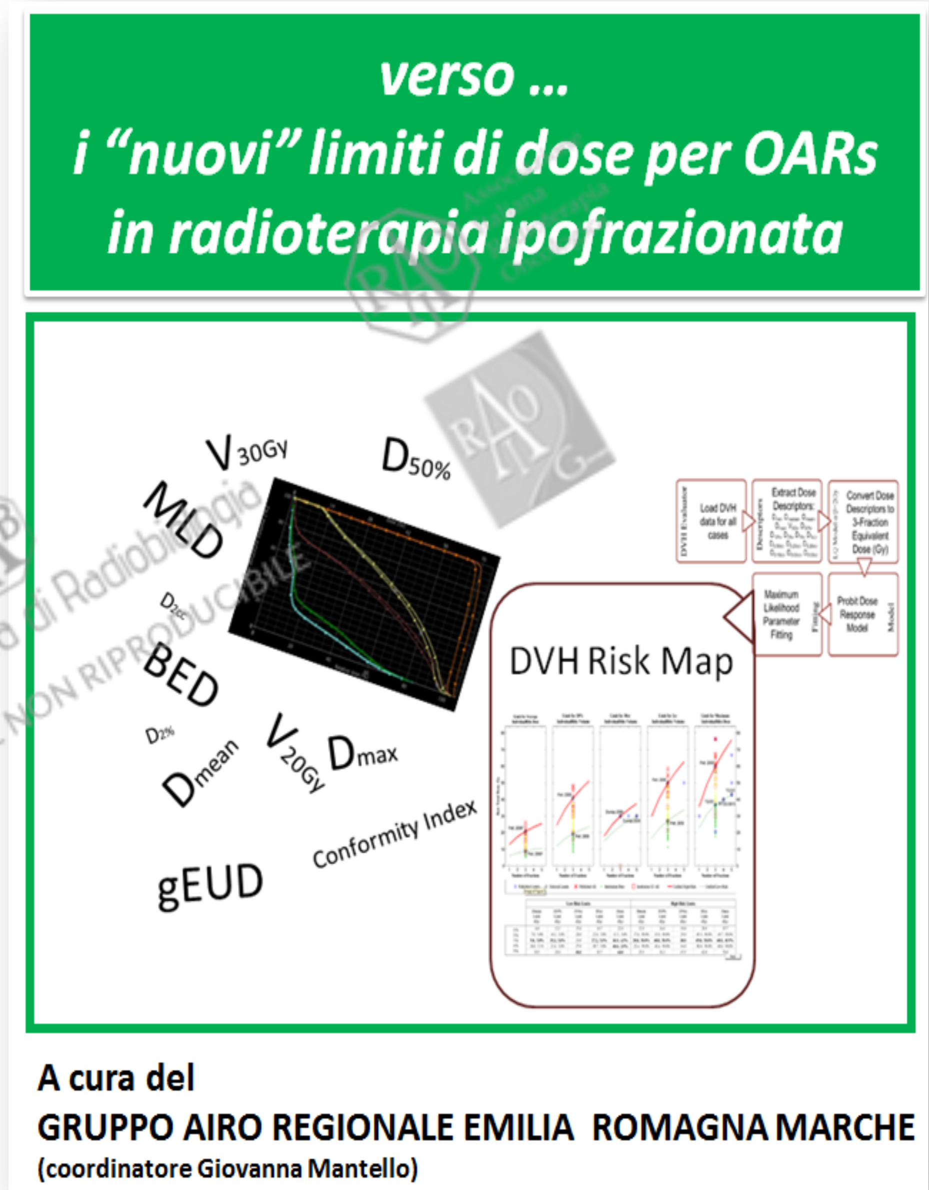
Giovanna Mantello e a tutto il gruppo AIRO ERM




Its long way to go…