

### 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<sup>1</sup>, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M.

<u>Emami B', Lyman J, Brown A, Cola L, Goltein IVI, Munzenriger JE, Shank B, Solin LJ, Wessolf M,</u>

#### 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 dosevolume 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.

- IQV	1	D 5/5 Volume			TD 50/5 Volum	6	
Organ	1-/	23	3	13	2	3	Selected endpoint
Kidney I	5000	3000*	2300		4000*	2800	Clinical nephritis
Bladder	NIA	0000					control inepitites
	NA	8000	6500	N/A	8500	8000	Symptomatic bladder contractur
Bone:	100						and volume loss
T-M joint mag dible	12	124	5200				
1 out joint mandible	6500	6000	6000	7700	-	6500	Necrosis
Rib care			1.9	1100	/200	7200	Marked limitation
Skin	5000		-	6500			of joint function
JKII	JU cm	30 cm <sup>2</sup>	100 cm <sup>2</sup>	10 cm <sup>2</sup>			Pathologic fracture
	7000	8000	5000	-	30 cm*	100 cm <sup>2</sup>	Talanti
Brain		0000	5500	-	-	6500	relangiectasia
orall	6000	5000				7000	Necrosis
Brain stam			4500	7500	6500		Ulceration
Optic nerve L & II	6000	5300	6000		0000	6000	Necrosis
Chiasma	No partia	l volume	5000	-	-		Infarction
Spinal cont	No partia	l volume	5000	-		6500	Necrosis Information
Cont	5 cm	10 cm	5000	No parti	al volume	6500	Blindness
Cauda equina	No v-1	5000	4700	3 cm	10 cm	6500	Blindness
Brachial -1	NO VOLUI	ne effect	6000	7000	7000	20 cm	Muslish
solucinal plexus	6200	6100		No volu	me effect	7500	wyenus necrosis
Eye lens I and II		6100	6000	7700		/500	Clinically apparent
and II	No partie	Volume		//00	7600	7500	nerve damage
Eye retina I and II		rolume	1000			/300	Clinically apparent
Ear mid/external	No partia	l volume			-	1800	nerve damage
Ear mid/external	3000	3000	4500			1800	Cataract requiring
Devilie	5500	\$500	3000*	4000	-	6500	intervention
Parotid* I and II		0000	5500*	6500	4000	40000	Blindness
Inner	-	3200*		0000	6500	4000*	Acute serous
Larvax	7000		3200*	-		0200*	Chronic services otitis
Lung I	/900)*	7000*		(TD 100)	4600+	1000	otitis
Lung II	4500	4500	7000*	9000*	5 is 5000)	4000*	Xerostonia
Heart	4300	3000	4500*	- AND	8000*	0.000	otonna
Esophagus	6000		1750	6500	-	8000*	Cartilan
	6000	4500	1000	~~~~	4000	8000*	Larvnage necrosis
Stomach		5800	4000	7000		2450	Pneumocal edema
Smith .	6000		5500	7200	5500		incumonitis
Small intestine		5500	5000		7000	5000	Paris
Colon	5000		-000	7000		6800	Climinarditis
			4000*		6700		contrical stricture/
	5500		1000	6000		6500	Ula
Rectum			4500				Derformine.
	Volu		- 00	6500		5500	Obstation
Live	No volu	100 cm3				SECO	Derforme
	.010	me effect	6000			3200	Obstration/fistula
	5000			Volume	100 cm3		Performation
		3500	3000	No volur	ne effect	8000	ulceration/
			20.00				

QUANTEC represents an evolution from the Emami tahlog

Organ-Specific Papers

#### Each with 10 sections

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.

1. Clinical Significance- Describes the clinical situations where 1. Brain the organ is irradiated, and the incidence/significance of Caution About QUAN ideoints often Limitations inherent in extracting data from literature Limitations in predictive models Evolving fractionation schedules Combined modality therapy > Host factors predictive > Follow-up duration Dose/Volume Limits- The available Vision Papers information is condensed into meaningful dose/volume True Dose limits, with associated risk rates, to apply clinically. Imaging 9. Future Toxicity Studies- Describes areas in need of future Biomarkers Data Sharing Lessons of QUANTEC 10. Toxicity Scoring- Recommendations on how to score organ

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

#### Historical Development of Stereotactic Ablative Radiotherapy



### 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

2

3

fraction (Gy)

2

2

Gy dose

fractions

60 Gy/30 Fr<sup>a</sup>

60 Gy/30 Fr<sup>a</sup>

60 Gy/30 Fr<sup>a</sup>

Caution About BED ONCOLOGY April 2016 BED Dose Tolerance for Stereotactic Body Radiation Therapy CrossMark 180. pected outcome like NICP. II every patient's tumor contra 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 dosetolerance 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

Caution About

RADIATION

### 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.

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



© 2009

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.



evaluation for stereotactic body radiotherapy Grimm et al

Dose tolerance limits and dose volume histogram

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

abert D. runnie	T TTELETE																	
						Vol.	Vol.	Vol. Limit i	l ax l mit	#AE	# pts # pts in provide the pts # pts	45						
		( 000T			Organ fx	cc	%	(Gy)	(iy) Refs	. ≥G3	dose stu	dy .		Notes	and a second secolor			
Table 2 Mostly Unvalidated Normal	lissue Dose Constraints	tor SBRI			1	0.1		6.9	13 7,70	7 1	7.	2	Ipsilateral hemi	iplegia and con	tralateral pain			
Serial Tissue	Volume (mL) Volun	ne Max (Gy) Max Point Dose (Gy)	Endpoint (≥Grade	e 3)	1				2 71 0.6 86,8	7 1	7	2	After 5 months,	, classic Brown	-Sequard syndro	ome		
	SINGLE-FRAC	TION TREATMENT				0.1		8.5	86,8 0 7,88,8	7 I 89	7	2	After 5 months,	, classic Brown	-Sequard syndro	ome		
Optic pathway	<0.2	8 10	Neuritis		1	1	00%	8	7									
Cochlea		12	Hearing loss THRFF.FR	ACTION TREATMENT	i	0.35	10076	10	24,2	5			RTOG 0631&0	1915				
Spinal cord	<0.25	Ontio nathway	<0.2	15 (5 Cu/fe) 19 5 (6 5 Cu/fe)	NL I	0.25		10	8 90			2000						
opinal colu	<1.2	Cochlea	<b>~0.2</b>	20 (6 67 Gy/fz)	He I	2.6		8	70					· · · ·				
Cauda equina	<5	Brainstem	<1	18 (6 Gy/fz) 23 (7.67 Gy/fz)	Ci	1.7		8	8,24,2	25		3 W.	RTOG 0631 SB	BRT only, RTO	G 0915			
Sacral plexus	<3	Spinal cord	< 0.25	18 (6 Gy/fx) 22 (7.33 Gy/fx)	M	0.02		8	86,8	7 3	7	1.00	Ref (86) reports	s higher doses f	for 2 of these 3			
Esophagus*	<5		<1.2	11.1 (3.7 Gy/fx)	2				5.6 86,8	8 1	1.07	11 11	Bilateral leg we	eakness & urina	ary retention			
Ipsilateral brachial plexus	<3	Cauda equina	<5	21.9 (7.3 Gy/fx) 24 (8 Gy/fx)	Nt Spinal Cord (cont'd.) 2	0.1		24.7	86,8	8 1		( ) C	Bilateral leg we Posterior colum	eakness & uring an dysfunction.	ary retention motor weaknes			
Heart/pericardium	<15	Sacral plexus	<3	22.5 (7.5 Gy/fx) 24 (8 Gy/fx)	Nt 3	0.1		27.8	86,87,	90 1		5	Posterior colum	nn dysfunction,	motor weaknes	5		
Great vessels	<10	Esophagus*	<5	21 (7 Gy/fx) 27 (9 Gy/fx)	St 3	1.7		24	87.9	0 1	5	-	Posterior colum	an dysfunction.	motor weaknes	s		
Skin	<10	Ipsilateral brachial plexus	<3	22.5 (7.5 Gy/fx) 24 (8 Gy/fx)	Nr 3				4 39		r U.V.		For 'extreme ca	ases <sup>†</sup> only				
Stomach	<10	Heart/pericardium	<15	24 (8 Gy/fx) 30 (10 Gy/fx)	Pe				51,6	, ``	3	-	Based on BED3	3=45Gy, but BI	ED1=55Gy			
Duodenum*	<5	Great vessels	<10	39 (13 Gy/fx) 45 (15 Gy/fx)	Ar 3	0.25		18	8.6 7				Median doses q	uoted, not limi	ts			
Jejunum/ileum*	<5	Frachea and ipsilateral bronchus	<4	15 (5 Gy/fx) 30 (10 Gy/fx)	St 3	0.1		16.3	7				Adadian dorme o	moted not limit				
Colon*	<20	Stomach	<10	22.5 (7.5 Gy/ft) 24 (8 Gy/ft) 21 (7 Gy/fz) 24 (8 Gy/ft)	UI 3												<b>(</b> )	110
Rectum*	<20	Duodenum*	<5	15 (5 Gy/fz) 24 (8 Gy/fz)	3												<u> </u>	110
Bladder wall	<15	Jeiunum/ileum*	<5	16.2 (5.4 Gy/fz) 27 (9 Gy/fz)	Er						11 M							
Penile build	< 3	Colon*	<20	20.4 (6.8 Gy/fx) 30 (10 Gy/fx)	C	Sto	ran	tacti	c hod	v radia	tion t	horan	V. Ih	a rong	nrt ot	ΔΔΡΜ Τα	ek Grau	n 10
Renal hilum/vascular trunk	<2/3 volume	Rectum*	<20	20.4 (6.8 Gy/fx) 30 (10 Gy/fx)	Pr 4	OLC	160	ιασι		y raula		nerap	$y_{\tau} = 110$	elepu			ar arou	ip iu
Parallal Tissus Cri	tical Valuma (ml.)	Bladder wall	<15	15 (5 Gy/fx) 30 (10 Gy/fx)	C) 4	1	utot među	anay	<0.5 cc	10	15	18 (0 UVTX)	23.1 (7.7 59/13)	23 (4.5 Gy/IX)	31 (6.2 Gyitx)	neuropathy		•
Parallel Tissue Cri	tical volume tites	Penile bulb	<3	21.9 (7.3 Gy/fx) 42 (14 Gy/fx)		10%	- Spinal con	rd II-	<0.35 cc	10	14	18 (6 Gy/tx)	21.9 (7.3 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis		
Lung (right and left)	1,500	Femoral heads (right and left)	<10	21.9 (7.3 Gy/fx)	i .	10%	Spinal con	rd	<1.2 cc	1		12.3 (4.1 Gy/R)		14.5 (2.9 Gy/fx)				
Lung (right and left)	700	Renal hilum/vascular trunk	<2/3 volume	18.6 (6.2 Gy/fx)	5 Spinal Cord 1 0.9	·	subvolum	e	3 -105					-				
Renal cortex (right and left)	200	Parallel Tissue Crit	tical Volume (mL)	Critical Volume Dose Max (Gy)	10		and below	v level	of				1					
Sorial Tiesuo	Volume (ml.) Volum	Lung (right and left)	1,500	10.5 (3.5 Gy/fx)			treated per Canda con	er Ryu) uina	subvolume <5 cc	10	14	18 (6 Gy/fx) 21.9 (7.3 Gy/fs)	21.9 (7.3 Gy/fx) 24 (8 Gy/fx)	23 (4.6 Gy/fx) 30 (6 Gy/fx)	30 (6 Gy/fx) 32 (6.4 Gy/fx)	Myelitis Neuritis		
Senar Tissue	Volume they Volum	Lung (right and left)	1,000	11.4 (3.8 Gy/fx)	Pneumonitis		Sacral ple	xus	<5 cc	14.4	16	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gyifx)	Neuropathy		
		Liver	700	17.1 (5.7 Gy/fx)	Basic liver function	14.0	Esophague Brachial p	s" plexus	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx) 20.4 (6.8 Gy/fx)	25.2 (8.4 Gy/fx) 24 (8 Gy/fx)	19.5 (3.9 Gy/fx) 27 (5.4 Gy/fx)	35 (7 Gy/fx) 30.5 (6.1 Gy/fx)	Stenos is/fistula Neuropathy		
		Renal cortex (right and left)	200	14.4 (4.8 Gy/fx)	Basic renal function	11/5	Heart/peri	icardium	<15 cc	16	22	24 (8 Gy/fx)	30 (10 Gy/fx)	32 (6.4 Gy/fx)	38 (7.6 Gyntx)	Pericarditis		
					V LVZ O	MO	Great vess Trachea a	sels ind large	<10 cc	31	37	39 (13 Gyfx)	45 (15 Gy/fx)	47 (9.4 Gy/fs)	53 (10.6 Gy/fx)	Aneurysm		
						0-	bronchus <sup>b</sup>		<4 cc	10.5	20.2	15 (5 Gy/fx)	30 (10 Gy/fx)	16.5 (3.3 Gy/fx)	40 (8 Gy/fx)	Stenosis/fistula		
					dit.		airways	-smaller	<0.5 cc	12.4	13.3	18.9 (6.3 Gy/fx)	23.1 (7.7 Gyffx)	21 (4.2 Gy/fx)	33 (6.6 Gyifx)	with atelectasis		
					2 U1		Rib	30	<1 cc	22	30	28.8 (9.6 Gy/fx)	36.9 (12.3 Gy/fx)	35 (7 Gy/fx)	43 (8.6 Gyifx)	Pain or fracture		
					00		Skin	~	<10 cc	23	26	30 (10 Gy/K) 30 (10 Gy/K)	33 (11 Gy/fx)	36.5 (7.3 Gy/fx)	39.5 (7.9 Gy/fx)	Ulceration		
					1.20	10.	Stomach		<10 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula		
				23	- allO	171	Dicoentin	n	<10 cc	9	12.4	11.4 (3.8 Gy/fx)	22.2 (74 Optio)	12.5 (2.5 Gy/fx)	32 (6.4 Gynx)	Utoration		
					101.	67.	Television II				14.1	177 (60 (5-6))	25.2 (0.1 (2-17-)	10.5 (2.0.0-20)	25 (7 (2-10-)	Enteritis/		
				52	Pro Pr		Colon <sup>b</sup>	ream	<20 cc	14.3	15.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx) 28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Colitis/fistula		
				010.	-101		Rectumb		<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Proctitis/fistula Outbie/fistula		
					- 19-		Penile bal	lb	<15 cc <3 cc	11.4	18.4	21.9 (7.3 Gy/fx)	42 (94 Gyfts) 42 (14 Gy/fs)	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence		
				C.(V)*			Femoral h	heads				210 (72 (20))		20 (6 (2 - (6 - )		Manuala		
		Ch Ch			- Di-		eright and Renal	1000	<10 cc	14		21.9 (7.3 Gy/fx)		30 (6 G9/IX)		merosis		
		/ 1. ( ))			011		hilum/vase	cular	<2/3	10.6	18.6 (6.2 Gulbr)			23 (4.6 Ge/fe)		Malignant		
				~~	1		tradk.		*Junie	10.0	10.0 (0.2 Oyun)			20 (40 Gyrld)		albertana		

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



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





Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. 83–89, 2010 Copyright © 2010 Elsevier Inc. Printed in the USA. All rights reserved 0360-3016/10/8-see front matter

> Società Italian WATERIALENC

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.,<sup>†</sup> Joseph O. Deasy, Ph.D.,<sup>‡</sup> Avi Eisbruch, M.D.,<sup>§</sup> Andrew Jackson, Ph.D.,<sup>||</sup> Lawrence B. Marks, M.D.,<sup>¶</sup> Randall K. Ten Haken, Ph.D.,<sup>§</sup> and Ellen D. Yorke, Ph.D.<sup>||</sup>

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



Seminars in RADIATION ONCOLOGY

CrossMark

#### Introduction and Clinical Overview of the DVH Risk Map

Sucha O. Asbell, MD, Jimm Grimm, PhD,<sup>†</sup> Jinyu Xue, PhD, Meng-Sang Chew, PhD,<sup>‡</sup> 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



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



**Figure 4** Creation of a DVH Risk Map: interpolating risk level estimates from the published dose-response model: the arrow shows that for  $D_{2 \text{ cc}} = 49.8$  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**



### **DVH Risk Maps**



		L	ow Risk Lim	its	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	
										Nex	

### DVH Risk Maps Examples: H&N



### Spinal cord

#### QUANTEC: DRGAN 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.,<sup>†</sup> 2010 AND TIMOTHY E. SCHULTHEISS, PH.D.<sup>‡</sup>

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

#### **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.<sup>‡</sup>

Institution (ref.)	Cases of myelopathy/total patients	Total dose (Gy)	Dose/fraction (Gy)	Dose to cord (Gy)	BED to cord (G <sub>3</sub> )	patients previously irradiated to involved segment of spine	
Stanford and Pittsburgh (50)	6/1075	12.5–25 25 20 21 24 20	5-25 12.5 10 10 8 2	D <sub>max</sub> : 3.6–30 D <sub>max</sub> : 26.2 D <sub>max</sub> : 19.2 D <sub>max</sub> : 13.9 D <sub>max</sub> : 29.9 D <sub>max</sub> : 8.5	Range: 24–141 Gy <sub>3</sub> D <sub>max</sub> : 141 D <sub>max</sub> : 81 D <sub>max</sub> : 46 D <sub>max</sub> : 129 D <sub>max</sub> : 33	>55%	
Henry Ford (7)	1/86*	<10-18	20 <10-18	$\begin{array}{c} D_{max}: 10 \\ \underline{Mean \pm SD} \\ D_{max}: 12.2 \pm 2.5 \\ D1: 10.7 \pm 2.3 \\ D10: 8.6 \ 2.1 \\ \underline{Maximum} \\ D & = 19.2 \end{array}$	$D_{max}: 43$ <u>Mean ± SD</u> $D_{max}: 62 \pm 4.6$ D1: 49 ± 4.1 D10: 33 ± 3.6 <u>Maximum</u> D : 142	0%	
94	epor	5 <sub>18<sup>†</sup></sub>	rd	$\begin{array}{c} D_{max}, 19.2\\ D1; 15.8\\ 010; 13\\ \underline{Mea} \pm \underline{SD}\\ D_{max}; 14.8 \pm 2.2\\ D1; 12.4 \pm 1.9\\ D10; 9.8 \pm 1.5\\ \end{array}$	$D_{max} = 142 D1: 99 D10: 69 Mean \pm SD D_{max}: 77 \pm 3.8 D1: 61 \pm 3.1 D10: 42 \pm 2.3 \\D10: 42 \pm 2.3 \\D10: 42 \pm 2.3 \\D10: 42 \pm 2.3 \\D10: 42 \pm 2.3 \\D$		2001
Korea (49)	P 2/9 Ge t		BRT	Dmax:14. DI: 13.0 DI0: 9.5 Ma.aan D <sub>max</sub> :32.9 D25:11.0 Range	Dmax:88 D1:69 D10:40 <u>Median</u> D <sub>max</sub> :106 D25:21 Range	33%	RIPT
9	wit	-30 -33	10	Dmax: 11–37 D25: 1.2–24 Dmax: 35.2 D25: 15.5 Dmax: 32.9 D25: 24.0	D <sub>max</sub> : 19–172 D25: 1–88 D <sub>max</sub> :172 D25: 42 153 88	RIALL	
NYMC (51) <sup>3</sup> UCSF (52)	3/31 0/38	Median: 10 100 12 20 24	Median: 5 50 12 5 8	Median: 6.0 <u>Median</u> D <sub>0.1cc</sub> : 10.5	$\frac{\text{Median}}{D_{0.1cc}}$	Unknown 62%	
Spinal cord	Parti Parti Parti	al organ al organ al organ		3 3 3	D-CRT D-CRT D-CRT		Mye Mye Mye
	Parti Parti	al organ al organ		S	RS (single f RS (hypofr	fraction) action)	Mye Mye

for partial cord irradiation as part of spine radiosurgery, a naximum cord dose of 13 Gy in a ingle fraction or 20 Gy in three ractions appears associated with <1% risk of injury

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

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

						_				( Q.D <sup>O</sup> _3070
				Vol.	Max			# pts	# pts	(a) (a)
	#	Vol.	Vol.	Limit	Limit		#AE	rx this	în	
Organ	fx	cc	%	(Gy)	(Gy)	Refs.	$\geq G3$	dose	study	Notes
	1	0.1		6.9		86.87	1		72	Insilateral heminlegia and contralateral pain
	1	0.1		0.5	13	7.70			12	ipsnateral nomplegia and contratateral pain
	ĩ				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			2	
	1	0.25	100%	10		2122		1001	0	PTOC 0(21 80015
	1	0.35		10		24,25		NO	)	R10G 0031&0915
	1	0.23		10		90	5.0	Db.	. 6	
	1	2.6		8		70	1000		RIFF	
	1	1.7		8		91	HO-	C	1V	
	1	1.2		7		8,24,25		~00-		RTOG 0631 SBRT only, RTOG 0915
	1	0.02		8		86,87	3.00	05	72	Ref (86) reports higher doses for 2 of these 3
	1				5 帐	-50	RIK			
	2			24.7	25.6	86,88	11 G			Bilateral leg weakness & urinary retention
	2	0.1		24.7	- (190.0	86,88				Bilateral leg weakness & urinary retention
Spinal Cord (cont d.)	3	0.1		27.0	0030.9	86,87,90	1		55	Posterior column dysfunction, motor weakness
( )		8		$\frac{27.0}{16.5}$		6	1		55	Postenoi column dysfunction, motor weakness
10	3	1.7		24	INTE	87.90	1		55	Posterior column dysfunction, motor weakness
(Be	13-1				24	39				For 'extreme cases' only
1	- 3				22	8				
	3				21	51,67				Based on BED3=45Gy, but BED1=55Gy
	3	P. 22			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		8.5		8				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
	2				10	,27,39,45,46				PTOG 0618
	3				18 5	3,62,63,64,65				K100 0018
	3				15	26,54,68				
	4				26	25				RTOG 0915
	4	1		20	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
-										



Seminars in RADIATION ONCOLOGY

CrossMark

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

Jimm Grimm, PhD,<sup>\*</sup> Arjun Sahgal, MD,<sup>†</sup> Scott G. Soltys, MD,<sup>‡</sup> Gary Luxton, PhD,<sup>‡</sup> Ashish Patel, MD,<sup>§</sup> Scott Herbert, MD,<sup>I</sup> Jinyu Xue, PhD,<sup>§</sup> Lijun Ma, PhD,<sup>‡</sup> Ellen Yorke, PhD,<sup>#</sup> John R. Adler, MD,<sup>\*\*</sup> and Iris C. Gibbs, MD, FACR<sup>‡</sup>

Image-guided robotic radiosurgery for spinal metastases

200 papers

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

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

### **DVH Elaboration and Modeling Methods**



### **DVH Maps Construction**





		Low Risk Limits										
< 1%	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%							
		Societa Italiana	di Radiobium di Radiobium Non RIPRODUCIBILE									

	(1 A)	Sur all			
	$\langle \mathcal{B} \mathcal{B} \rangle$	MATERO	ligh Risk Limit	ts	
< 3 %	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

	R	MATERIALE MATERIALE	lisorders								
	Grade										
Adverse Event	har har 1 min	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



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.,<sup>†</sup> Lawrence B. Marks, M.D.,<sup>‡</sup> John Flickinger, M.D.,<sup>§</sup> Jiho Nam, M.D.,<sup>‡</sup> and John Kirkpatrick, M.D., Ph.D.<sup>¶</sup>

#### 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* 

					(ADD)		NOD.		
	#	Vol.	Vol. Vol. Limit	Max Limit	ED.	#AE	# pts rx this	# pts in	
Organ	fx	cc	% (Gy)	(Gy)	Refs.	$\geq G3$	dose	study	Notes
	1 1			15 13	10 17 72	NRIPP	9	50	77.8% chance of RON above 15Gy
	1			12	73 20	2	29	215	7% chance of RON above this, 1.1% chance below
17	1			-041	74				
sie -	/1	(O)		- 10	8,17,72,75	4	15	50	No RON below 10Gy, 27% RON from 10-15Gy
	- (12)	No.		8 D	8				tradition, dose tolerance not fully appreciated
	1	0.2	8	610	8,72,73,76				
51-	- Ins	- Y	μ	7.5	82				
	2	0.03	10		83				
	2	Nº Labor		10	39				
	2	a alara		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





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

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

#### Methods and Materials

- ✓ RETROSPECTIVE ANALYSIS (Stanford University, 2000-2013)
- "<u>Perioptic</u>" 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**



- → 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



### **Estimated RION Risk level**



		1	Low Risk Limit	8	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

. She

Number o Fractions	f 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	00010 21.9	24.2
3	20.9	24.2	DUCIBILE 26.3	29.1
4	23.7	27.5 RIP	29.9	33.1
5	26.1	MATERIALD 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:

Francesca Maurizi, Elisa D'Angelo, Francesca Cucciarelli, Sara Costantini, Lo Sardo Pierluigi, Melissa Scricciolo, Enrico Raggi, Alessandra Guido, Damiano Balestrini, Lisa Vicenzi, Marco Valenti, Giorgia Timon, Massimo Giannini, Giulia Ghigi Giovanna Mantello e a tutto il gruppo AIRO ERM

verso ... i "nuovi" limiti di dose per OARs in radioterapia ipofrazionata



#### A cura del

GRUPPO AIRO REGIONALE EMILIA ROMAGNA MARCHE (coordinatore Giovanna Mantello)

