



Asociación Médica Argentina
Sociedad Argentina de Terapia
Radiante Oncológica



**7º Curso de Actualización en
Protección Radiológica
para Médicos Radioterapeutas**

Hipofraccionamiento Extremo: Próstata – Pulmón - Oligometástasis

Dr. Gustavo Ferraris



**CENTRO MEDICO
DEAN FUNES**
TECNOLOGIA DEL NUEVO MILENIO
ASOCIADO A 21ST CENTURY ONCOLOGY

Objetivos

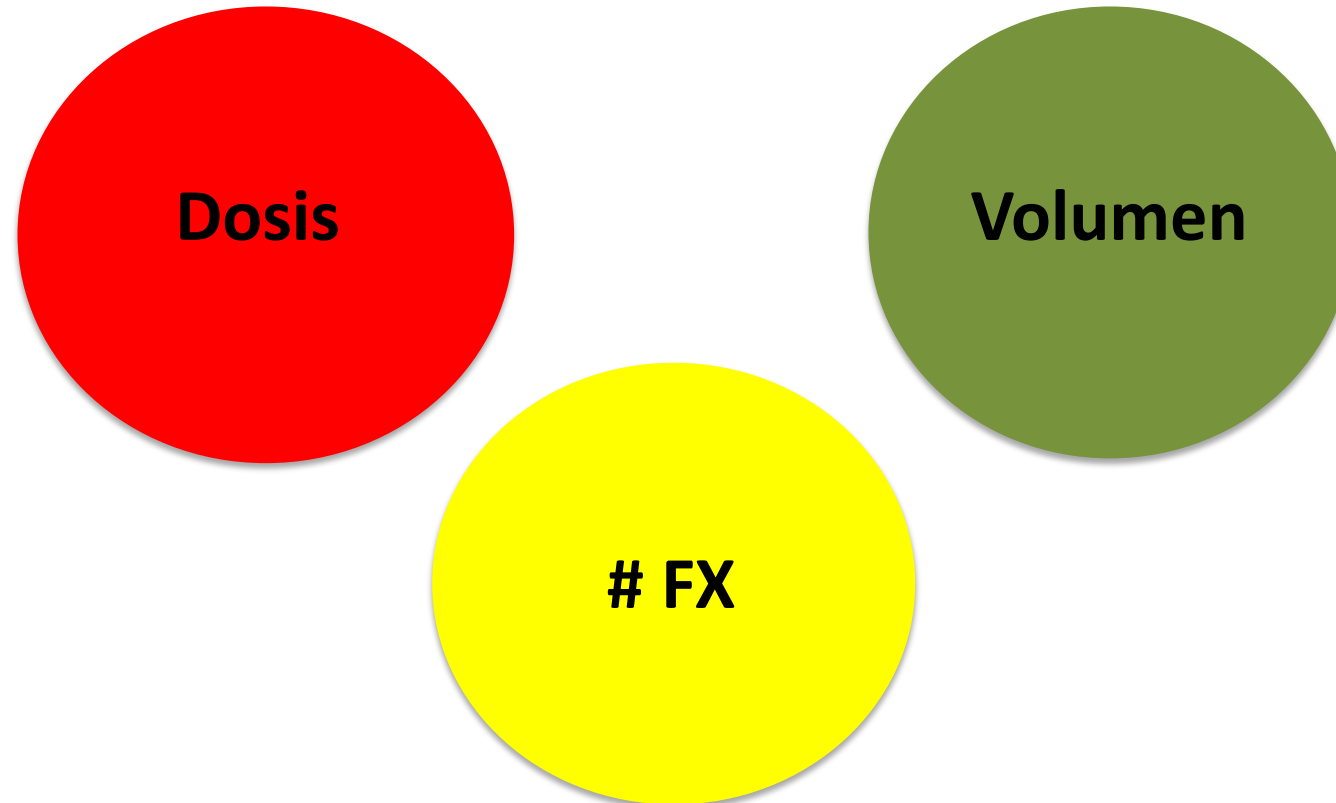
- Mostrar un resumen de **indicaciones y complicaciones** reportadas en trabajos de investigación con SBRT
- Presentar estrategias para **mitigar el riesgo**, ya que las restricciones de dosis están disponibles en la web

Escenario General

- **Órganos o estructuras seriales**
 - PTV muy próximo a OAR o superpuesto
 - Re-irradiación
- **Órganos o estructuras paralelas**
 - Volumen inadecuado para mantener la función del órgano
 - Órgano enfermo/ tejido restante inadecuado para mantener su función: Hígado y Pulmón

Radioprotección: Evitar Toxicidad

- Toxicidad no está relacionada a una técnica per se, pero si a:



Márgenes en general

- **GTV=CTV**
- **Márgenes adicionales dependen de las sistemas de inmovilización, manejo de movimiento de órganos y equipo IGRT**
- **ITV para movimiento**
- **PTV para variabilidad de set-up, mínimo 3-5 mm**
- **BED > 100**

Evaluación del plan

Gradientes de dosis

- Puede llegar a ser un desafío
- Isodosis prescripción: 95% cobertura PTV
- Conformidad: Ratio entre la isodosis del volumen de prescripción (PIV) y el volumen del PTV
- Ideal < 1.2
- **Áreas con $>105\%$ de la prescripción dentro del PTV**

Estrategias Generales

- Delineación de **TODOS** los Órganos a Riesgo (OAR) relevantes
- PRV para algunos OAR: médula, duodeno
- Piel
- Múltiples blancos: órganos paralelos/seriales
- Fraccionamientos más prolongados
- Fraccionamiento diario/días alternos

Pulmón (primario/oligo MTTTS)

ASTRO Guidelines

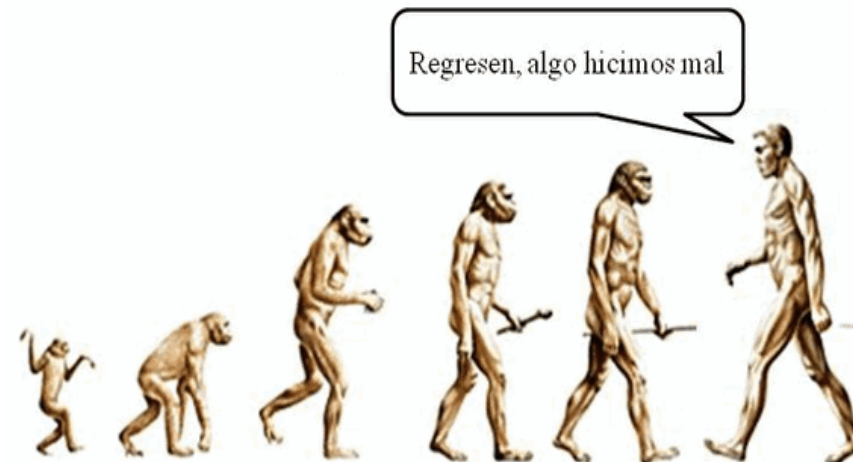
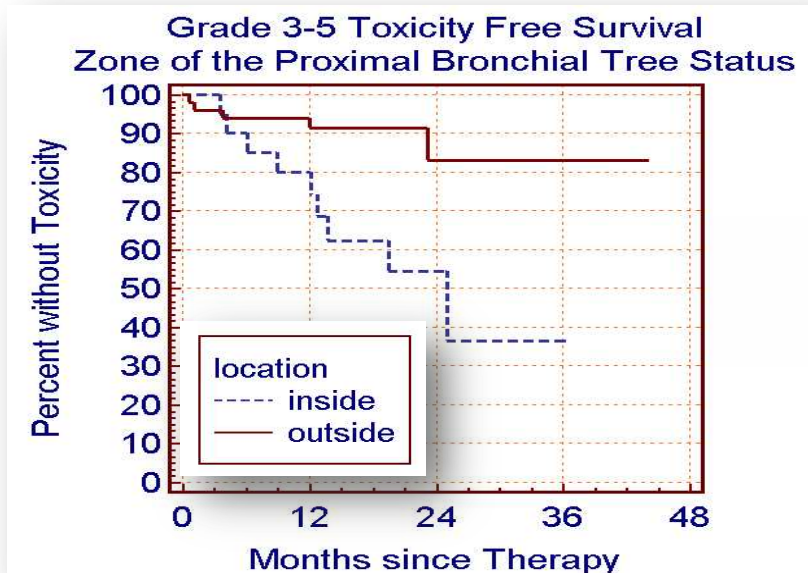
Special Article

Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline

Gregory M.M. Videtic MD, CM, FRCPC, FACR ^{a,*}, Jessica Donington MD ^b, Meredith Giuliani MBBS ^c, John Heinzerling MD ^d, Tomer Z. Karas MD ^e, Chris R. Kelsey MD ^f, Brian E. Lally MD ^g, Karen Latzka ^h, Simon S. Lo MB, ChB, FACR ⁱ, Drew Moghanaki MD, MPH ^j, Benjamin Movsas MD ^k, Andreas Rimner MD ^l, Michael Roach MD ^m, George Rodrigues MD, PhD, FRCPC ⁿ, Shervin M. Shirvani MD, MPH ^o, Charles B. Simone II MD ^p, Robert Timmerman MD ^q, Megan E. Daly MD ^r

Universidad Indiana: Fase II

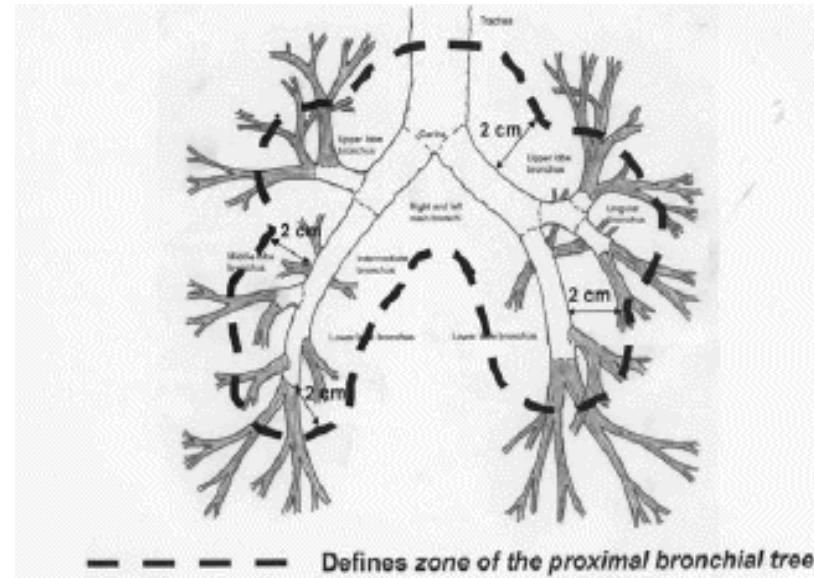
- 60-66 Gy en 3 Fracciones. 70 pts. (<7 cm)
- Toxicidad Grado 3-5
- Tumores centrales (27% vs 10%)
- 6 muertes toxicas (4 centrales)



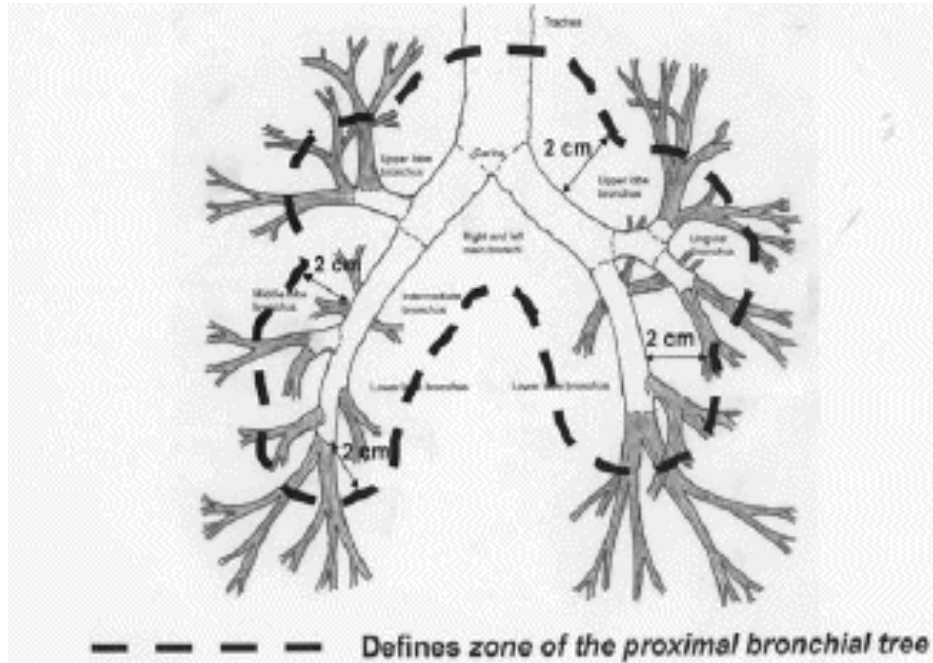
Tórax

- Predictores de toxicidades Grado 3-5:
- Localización hilar/pericentral (riesgo **↑** 11 veces)
- Volumen tumoral >10 ml (riesgo **↑** 8 veces)

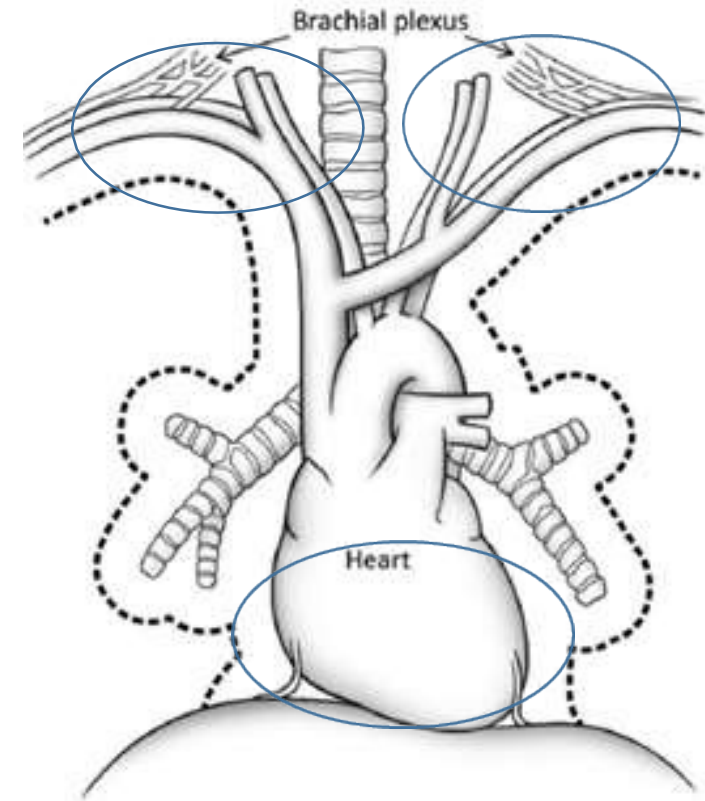
**Definición RTOG
Tumores Centrales**



Tumores Centrales

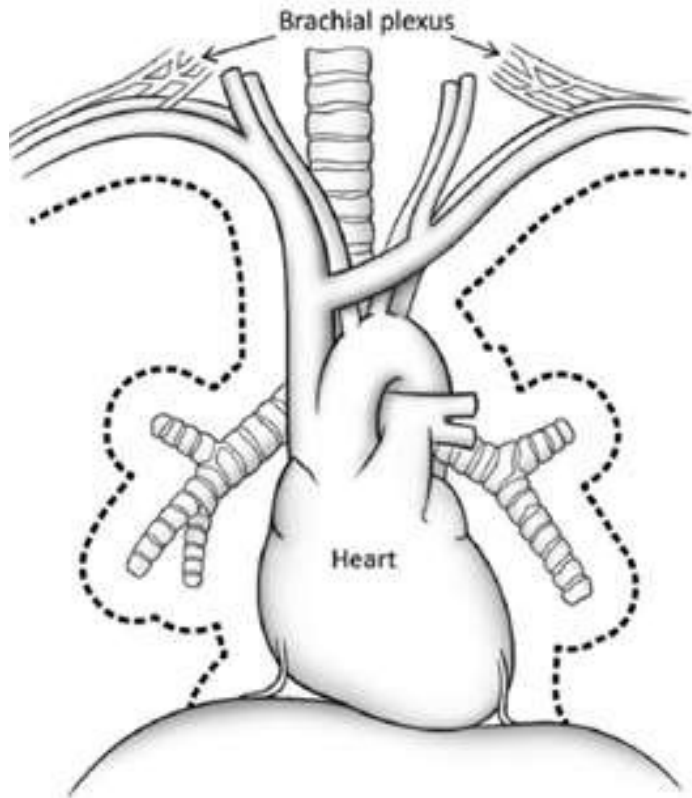


Proximal Bronchial Tree (PBT) = Distal 2cm trachea to the beginning of segmental bronchi (Timmerman)



**RTOG 0813:
Tumour within or touching the zone of PBT or PTV touching med pleura/ pericardium**

Tumores Ultra-Centrales



Central

GTV abuts PBT

Mihai ASTRO 2018



ITV abuts the proximal bronchial tree

Sunybrook

**PTV contacts/ overlaps PBT,
Oesophagus, trachea, pulmonary vein/artery**

Princess Margaret

Tumores Centrales

- **Delinear vías aéreas mayores y grandes vasos**
- **Utilizar fraccionamientos más prolongados:**
- **50-60 Gy en 5 Fxs (más común 50 Gy en 5 Fxs)**
- **48-50 Gy en 4 Fxs**
- **60 Gy en 8 Fxs**
- **60 Gy en 12 fxs**

Fraccionamientos: Diario vs Alternos

Quality of life

Lung stereotactic body radiation therapy (SBRT) delivered over 4 or 11 days: A comparison of acute toxicity and quality of life ☆☆☆



Suneil Jain^a, Ian Poon^b, Hany Soliman^b, Brian Keller^b, Anthony Kim^b, Fiona Lochray^b, Latifa Yeung^c, Patrick Cheung^{b,*}

^aCentre for Cancer Research and Cell Biology, Queens University Belfast, United Kingdom; ^bSunnybrook Odette Cancer Centre, Department of Radiation Oncology;

^cRouge Valley Health System, Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, Institute of Health Policy Management & Evaluation, University of Toronto, Canada

54 pacientes
48 – 52 Gy en 4 Fx

Fraccionamientos: Diario vs Alternos

Disnea > Grado 2 y síntomas respiratorios empeoraron con fraccionamiento diario

Table 4

CTCAE v4 grade 2 or higher dyspnea and respiratory symptoms corrected for baseline symptoms.

Symptom	Grade 2 or higher (percent)								p-Values
	4 day				11 day				
	Post-treatment	One month	Four month	Any time post-treatment	Post-treatment	One month	Four month	Any time post-treatment	
Dyspnea	14.8	14.8	14.8	25.9	3.7	7.4	3.7	11.1	0.15
Respiratory toxicity	14.8	14.8	18.5	29.6	7.4	7.4	7.4	14.8	0.16

Winner

Pneumonitis actínica

	Grade 2–4 pneumonitis (%)	<i>p</i> value
MLD		
≤4 Gy	4.3	0.02
>4 Gy	17.6	
V20		
>20 %	8.9	0.67
V10		
≤12 %	5.7	0.1
>12 %	15	
V20		
≤4 % (Median)	4.3	0.03
>4 %	16.4	
≤10 % (RTOG)	9.6	0.42
>10 %	15.8	
V10		
>48 mL	13	0.18
Tumor location		
Upper lobe	9	0.59
Lower/middle lobe	12	
COPD		
No	5.7	0.36
Yes	12	

Lo et al. Normal Tissue Constraints.
In: Stereotactic Body Radiation
Therapy (Editors: Lo, Teh, Lu,
Schefter). Springer 2012

Toxicidad Pulmonar Radio-inducida

Clinical Investigation

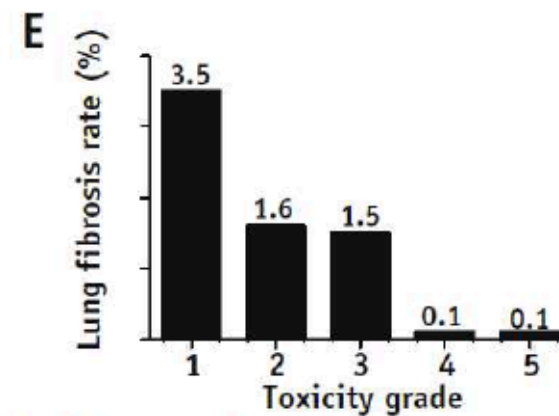
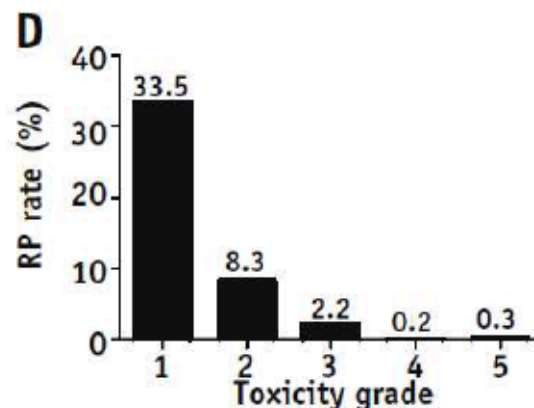
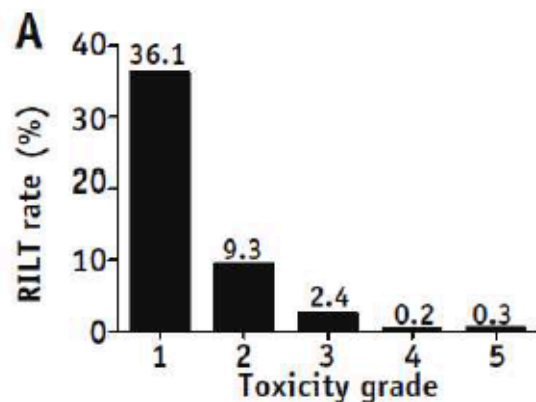
Simple Factors Associated With Radiation-Induced Lung Toxicity After Stereotactic Body Radiation Therapy of the Thorax: A Pooled Analysis of 88 Studies

Jing Zhao, MD, PhD,^{*,†} Ellen D. Yorke, PhD,[‡] Ling Li, MD, PhD,^{*,§}
Brian D. Kavanagh, MD,^{||} X. Allen Li, PhD,[¶] Shiva Das, PhD,[#]
Moyed Miften, PhD,^{||} Andreas Rimner, MD,^{**} Jeffrey Campbell, PhD,^{*}
Jinyu Xue, PhD,^{††} Andrew Jackson, PhD,[‡] Jimm Grimm, PhD,^{‡‡}
Michael T. Milano, MD, PhD,^{§§} and
Feng-Ming (Sprina) Kong, MD, PhD,^{*,§§§}

88 estudios – 7752 pacientes

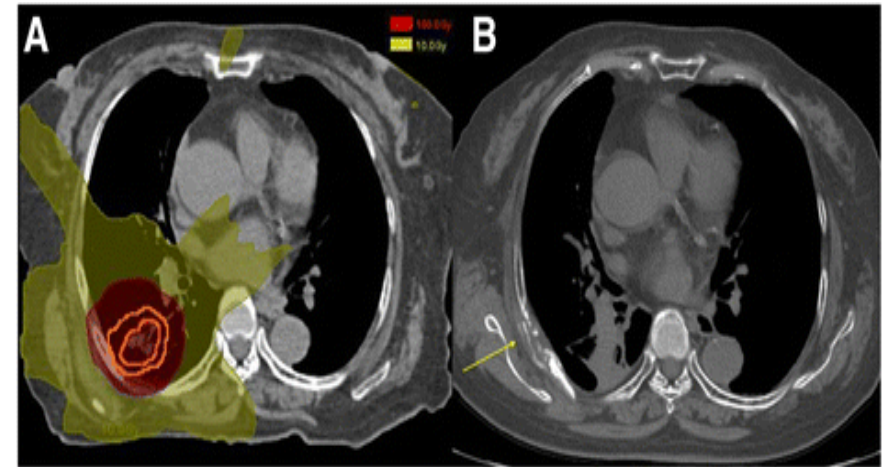
Factores de riesgo:

- Edad mayor
- Tumores grandes
- Dosis (V20 y MLD)



Pared Costal

- Dolor costal (5-10%)
 - Miositis
 - Fibrosis
 - Fractura costal (< 5%)
-
- Puede ser transitoria o crónica
 - Intervalo de presentación 8-12 meses



Pared Costal

**CHEST WALL VOLUME RECEIVING >30 GY PREDICTS RISK OF SEVERE PAIN AND/
OR RIB FRACTURE AFTER LUNG STEREOTACTIC BODY RADIOTHERAPY**

NEAL E. DUNLAP, M.D.,* JING CAI, PH.D.,* GREGORY B. BIEDERMANN, M.D.,* WENSHA YANG, PH.D.,*
STANLEY H. BENEDICT, PH.D.,* KE SHENG, PH.D.,* TRACEY E. SCHEFTER, M.D.,†
BRIAN D. KAVANAGH, M.D.,† AND JAMES M. LARNER, M.D.*

Tratar de reducir el volumen que reciba >30 Gy a < 30 CC

Solo 10-15% de pacientes de MDACC y MSKCC pudieron lograrlo

Variables:

- Proximidad a la pared costal
- Depende del seguimiento
- Como se contornea la pared
- Otros factores: obesidad -diabetes

OBESITY INCREASES THE RISK OF CHEST WALL PAIN FROM THORACIC STEREOTACTIC BODY RADIATION THERAPY

JAMES WELSH, M.D.,* JIMMY THOMAS, M.D.,* DEEP SHAH, B.S.,* PAMELA K. ALLEN, PH.D.,*
 XIONG WEI, PH.D.,* KEVIN MITCHELL, B.S.,* SONG GAO, PH.D.,† PETER BALTER, PH.D.,†
 RITSUKO KOMAKI, M.D.,* AND JOE Y. CHANG, M.D., PH.D.*

Departments of *Radiation Oncology and †Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

$$IMC = \frac{PESO}{ALTURA^2}$$

BMI	G2+ CWpain	%	Sign
< 29	13/196	6.7%	P=0.01
≥ 29	9/66	13.6%	

SBRT central: Meta-analysis 2019

	N	p value	
3-Year OS Rate			
All	389	50.5 (39.4-61.5)	
BED _{10Gy} <100	108	51.4 (12.7-88.5)	
BED _{10Gy} ≥100	259	53.0 (44.1-61.8)	.949
1-Year LC Rate			
All	385	91.3 (83.2-95.7)	
BED _{10Gy} <100	98	75.9 (66.5-83.4)	
BED _{10Gy} ≥100	287	93.6 (89.7-96.0)	<.001
2-Year LC Rate			
All	382	82.2 (71.7-89.4)	
BED _{10Gy} <100	98	62.8 (52.8-71.8)	
BED _{10Gy} ≥100	284	86.7 (82.2-90.3)	<.001
3-Year LC Rate			
All	295	72.2 (55.0-84.7)	
BED _{10Gy} <100	116	66.3 (34.7-87.9)	
BED _{10Gy} ≥100	179	77.6 (65.2-86.5)	.441
Complication Grade ≥3			
All	442	9.1 (5.4-15.0)	
BED _{10Gy} <100	116	2.8 (0.4-16.4)	
BED _{10Gy} ≥100	300	10.8 (6.2-18.1)	.162

Outcomes of Stereotactic Ablative Radiotherapy for Centrally Located Early-Stage Lung Cancer

*Cornelis J. A. Haasbeek, MD, PhD, Frank J. Lagerwaard, MD, PhD, Ben J. Slotman, MD, PhD,
and Suresh Senan, MRCP, FRCR, PhD*

63 pacientes

Tumores en no fly zone

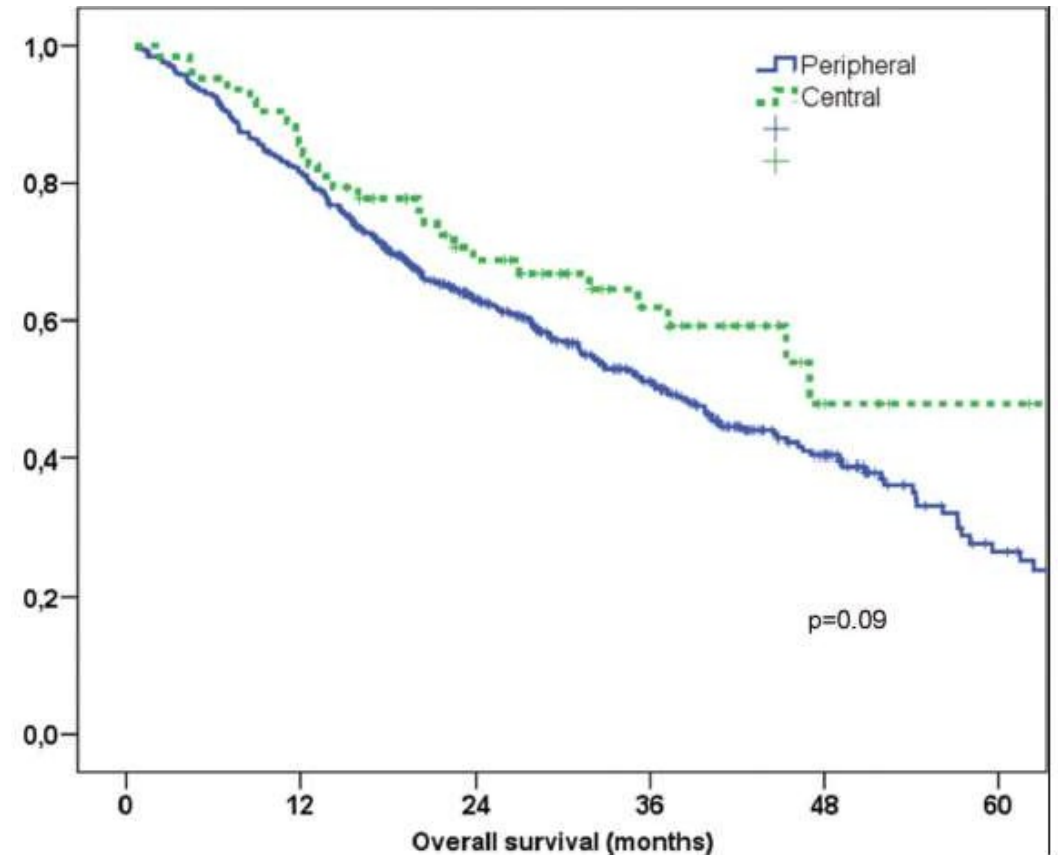
o ≤ 1 cm desde corazón o mediastino

PTV = ITV +3mm

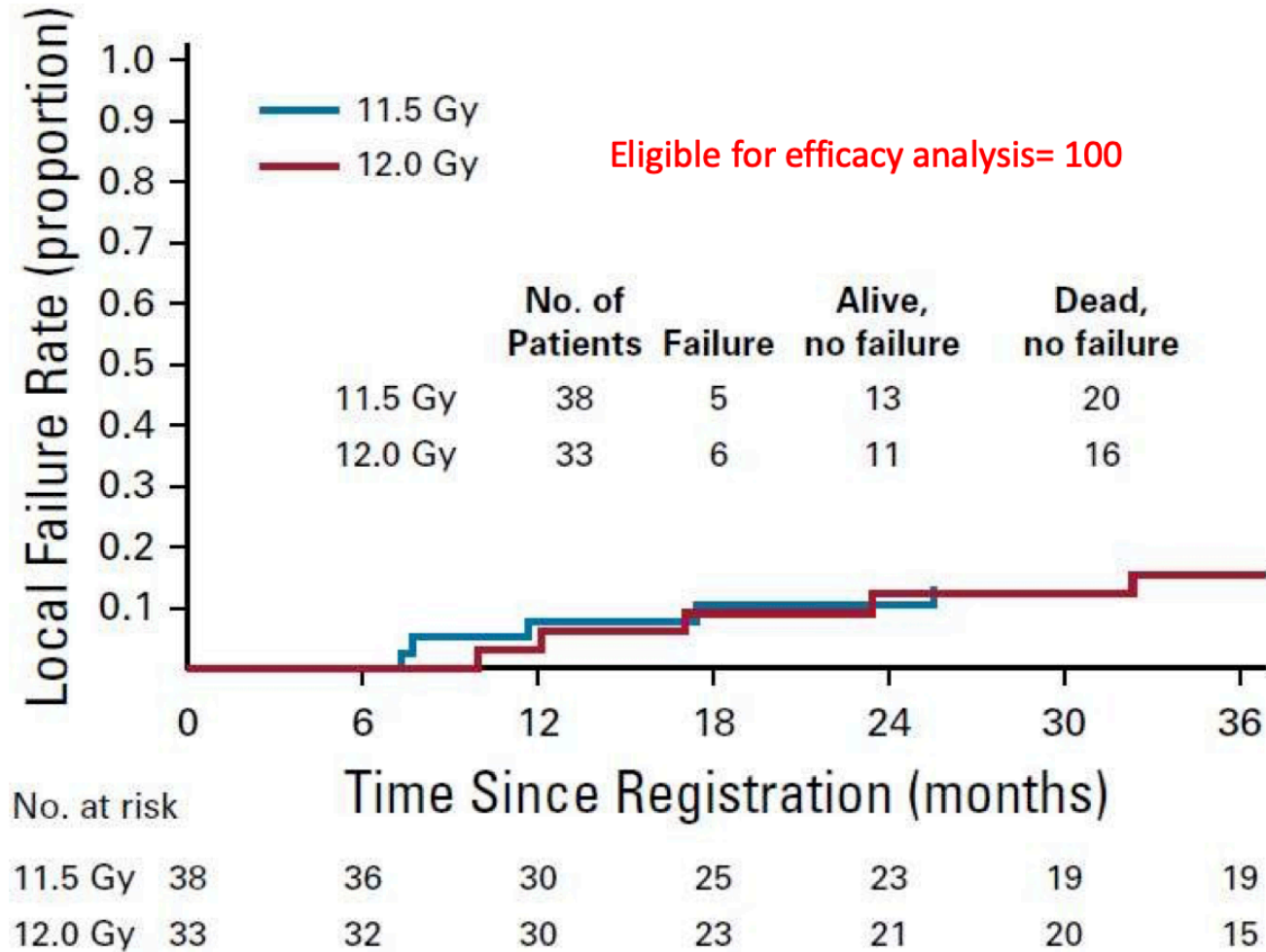
60Gy/8 (7.5Gy/fracción) Rx 80% isodose

Toxicidad: 8% grado 3 No grado 4/5

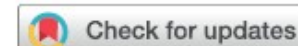
Control local: 92.6% 3 años



RTOG 0813: Escala de dosis NSCLC



ORIGINAL ARTICLE



Is stereotactic body radiotherapy for ultra-central lung tumor a feasible option? A systemic review and meta-analysis


Chai Hong Rim^a , Young Kim^b, Chul Yong Kim^c, Won Sup Yoon^a, and Dae Sik Yang^d

Table 3. Pooled rates of primary endpoints among patients with UC tumors.

Outcome	Study (<i>n</i>)	Patients (<i>n</i>)	<i>p</i> , heterogeneity	<i>I</i> ² (%)	Egger's test, <i>p</i>	Events (%) (95% CI)
Two-year LC	4	126	.751	0	.483	96.7 (91.0–98.9)
Two-year OS	4	160	<.001	87.8	.781	57.7 (32.0–79.8)
Complications ≥ grade 3	7	205	<.001	75.7	.184	23.2 (11.8–40.5)

CI: confidence interval; LC: local control; OS: overall survival.

PTV vs cobertura OAR

Seleccionar restricciones
RTOG vs. EORTC


Restricciones
OK

Tratamiento

Restricciones
no cumplidas

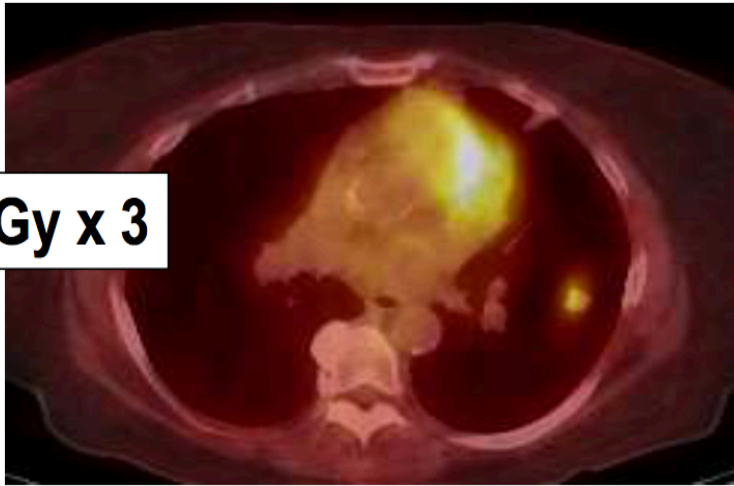
RT convencional

Compromiso de cobertura
de PTV y/o bajar dosis
para respetar OAR

Reducir dosis de PTV en
porción crítica de PTV
Dose painting 

Fraccionamientos
Reducir hot spot
Minimizar ITV

18 Gy x 3



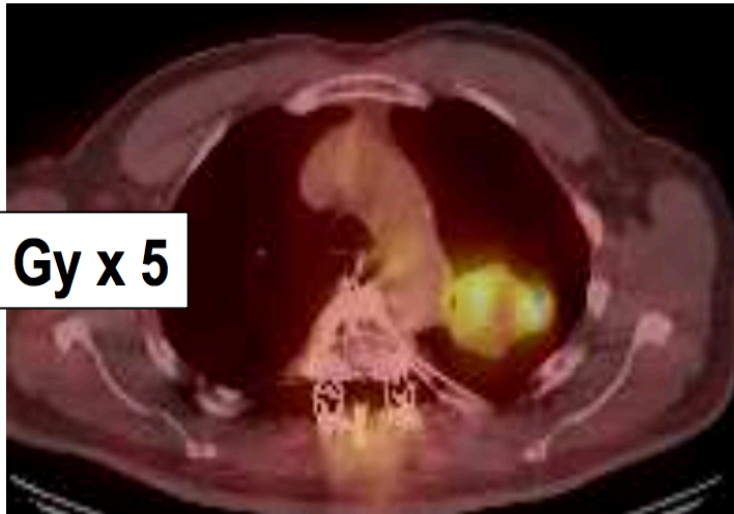
Peripheral

12 Gy x 5



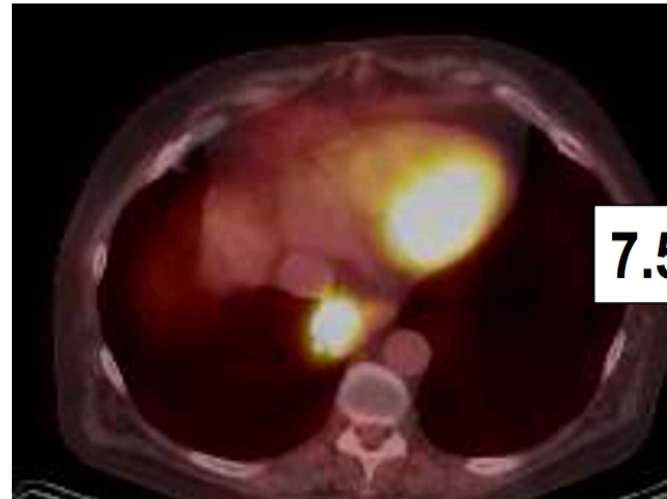
Very peripheral

11 Gy x 5



Central

7.5 Gy x 8



"Supercentral"

Tumores pulmonares múltiples: Escenarios

👉 **Primarios sincrónicos T1-T2 NSCLC**

👉 **Nódulos separados NSCLC**

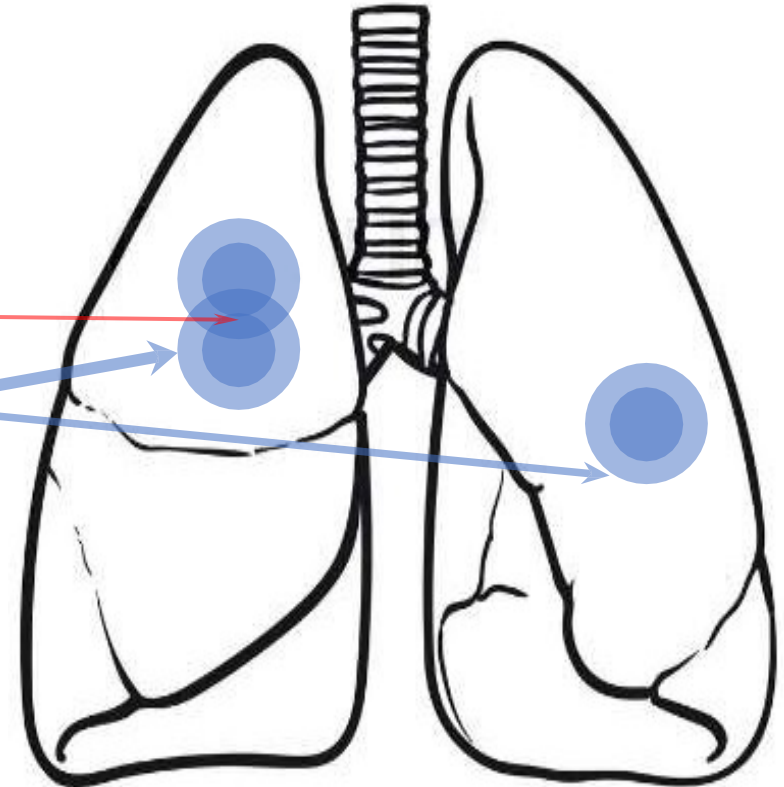
- T3 (mismo lóbulo)
- T4 (mismo pulmón, lóbulos diferentes)

👉 **Oligometastasis**

Exposición tejidos sano

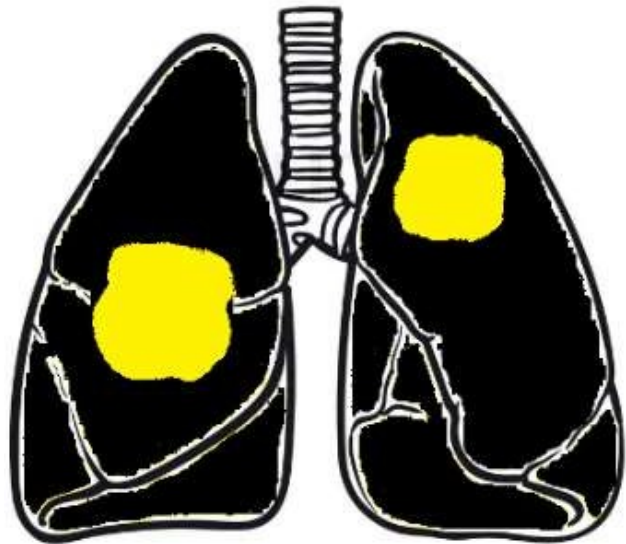
vs. blanco único...

- ↑ volumen de alta dosis
- ↑ volumen baja/moderada dosis



Volumen Absoluto de pulmón ahorrado

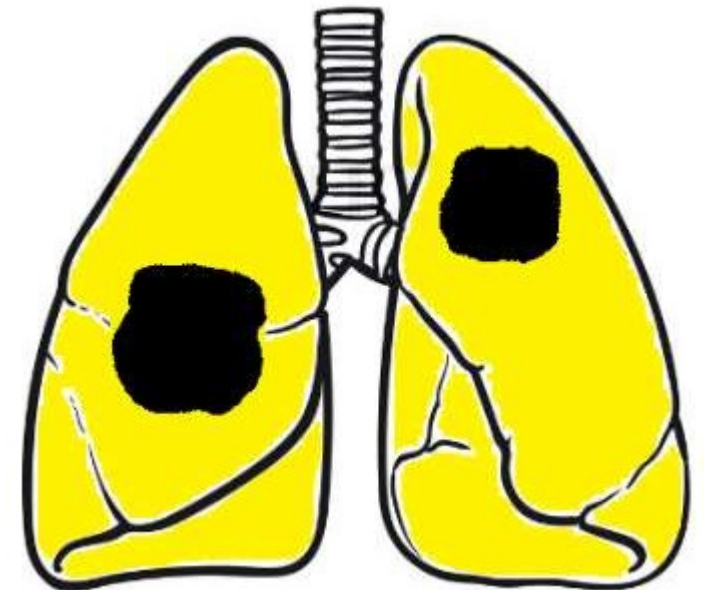
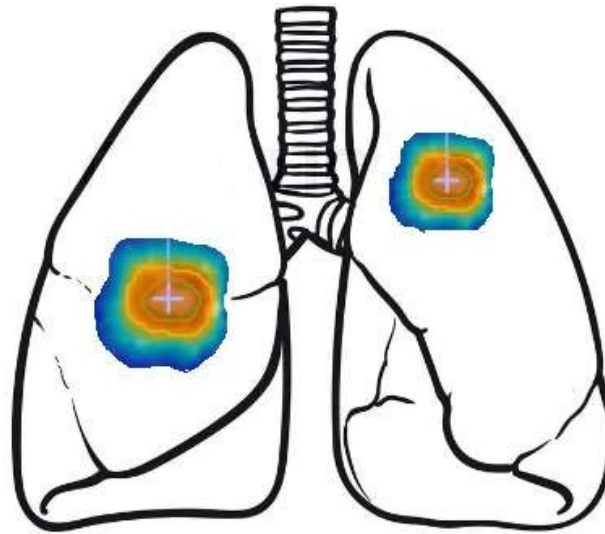
(Volumen crítico <12.5 Gy)



o

Volumen Relativo de pulmón irradiado

(lung V20)



Restricciones de dosis: NRG

- NRG oligometastasis : BR001, BR002 and LU002
- SABR-COMET-3 &-10 (1-3 & 4-10 mets)

Toxicity	Critical Volume	1-fraction	3 fractions	5 fractions
Pneumonitis	>1000 cc	7.4 Gy	11.4 Gy	13.5 Gy
↓ lung function	>1500 cc	7.0 Gy	10.5 Gy	12.5 Gy
Toxicity	Threshold	1-fraction	3 fractions	5 fractions
Pneumonitis	<37%	V8	V11	V13.5

Restricciones de dosis: NRG

- **STEREO-SEIN** (1-5 oligometástasis cancer de mama)

Toxicity	Threshold	4-9 fractions
Pneumonitis	≤35%	V15
Pneumonitis	<10%	V20

Inst. Gustave Roussy

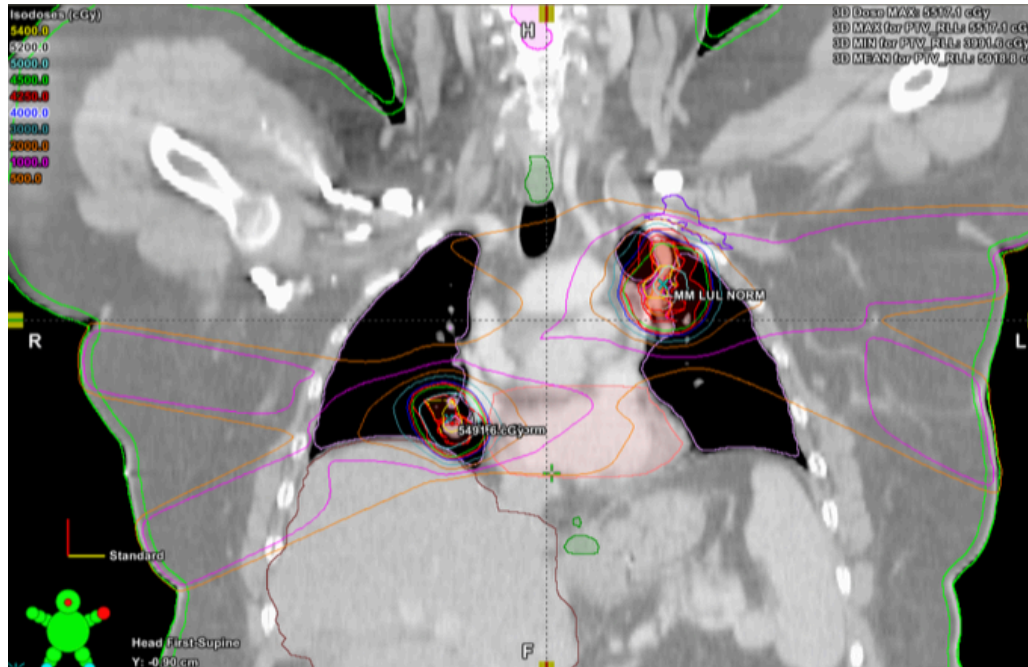
- **SAFRON II/TROG 13.01** (1-3 oligometástasis de pulmón)

Toxicity	Threshold	1-fraction	4 fractions
Pneumonitis	<1000 cc	V5	V5
Toxicity	Critical Volume	1-fraction	4 fractions
Pneumonitis	>66% lung	7.4 Gy	12.4 Gy

Soluciones prácticas + 2 lesiones

- **Isocentro único vs múltiple**
- **Haces modulados**
 - **Volume Modulated Arc Radiotherapy (VMAT)**
- **Generar plan suma (*si hay isocentros separados*)**
- **Fraccionamiento convencional/hipofraccionado moderado**
 - *Compromiso control local??*
- **Reducir márgenes PTV**
 - *Compromiso control local?*
- **Tratar las lesiones en días alternos (*UK Consensus*)**
 - *Reduce dosis diaria a todo el pulmón*

Múltiples sitios



Oligo-metástasis pulmonares:

SBRT

45 Gy/5Fx a lesión Derecha

40 Gy/5 Fx a lesión Izquierda

Siempre realizar un plan suma si se van a tratar múltiples lesiones

En caso de estructuras paralelas

Tener en cuenta VOLUMEN

En caso de estructuras seriales

Tener en cuenta DOSIS MAXIMA

Toxicidad Esofágica

Clinical Investigation

Esophageal Dose Tolerance to Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors for Late Toxicity



Kevin L. Stephans, MD,* Toufik Djemil, PhD,* Claudiu Diaconu, MD,[†]
Chandana A. Reddy, MS,* Ping Xia, PhD,* Neil M. Woody, MD,*
John Greskovich, MD,* Vinit Makkar, MD,[‡] and
Gregory M.M. Videtic, MD, CM, FRCPC*

Int J Radiation Oncol Biol Phys, Vol. 90, No. 1, pp. 197–202, 2014

Toxicidad Esofágica

Max Point Dose

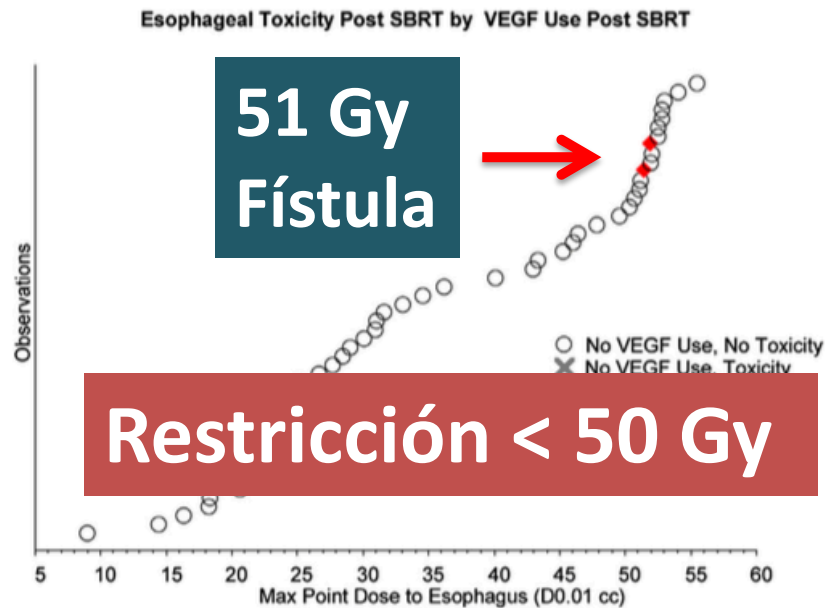


Fig. 1. Esophageal toxicity by maximum esophageal point dose and post-stereotactic body radiation therapy vascular endothelial growth factor use.

Dosis 1 CC

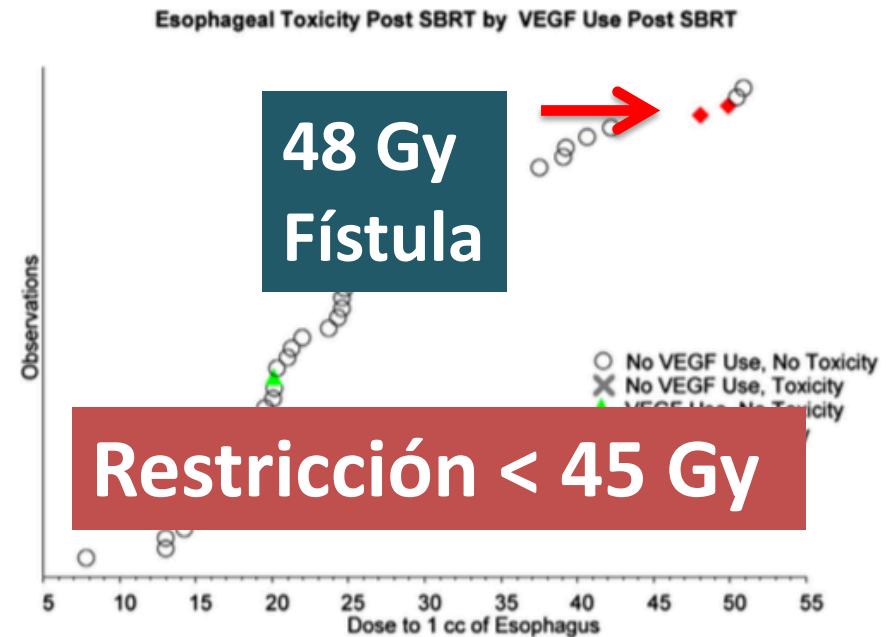


Fig. 2. Esophageal toxicity by dose to 1 cc of esophagus and post-stereotactic body radiation therapy vascular endothelial growth factor use.

~~VEGF~~

Toxicidad Esofágica: Dosis única

Clinical Investigation: Thoracic Cancer

Esophageal Toxicity From High-Dose, Single-Fraction Paraspinal Stereotactic Radiosurgery

Brett W. Cox, MD,^{*} Andrew Jackson, PhD,[†] Margie Hunt, MS,[†] Mark Bilsky, MD,[‡]
and Yoshiya Yamada, MD^{*}

Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, pp. e661–e667, 2012

Toxicidad Esofágica: Dosis única

Restringir dosis $2.5 \text{ cm}^3 < 14 \text{ Gy}$ \longrightarrow Toxicidad Grado 3 $< 5\%$

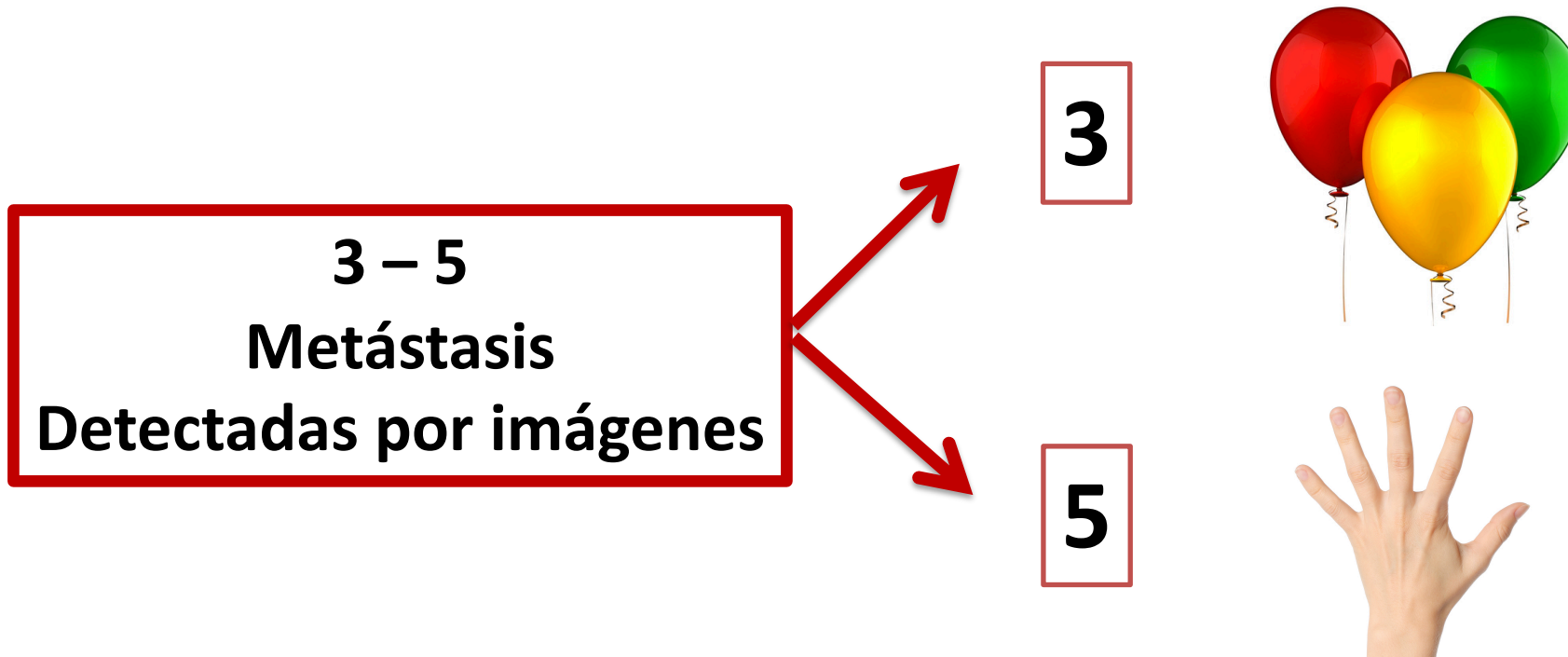
Table 4 Dosimetric and volumetric predictors of grade ≥ 3 esophageal toxicity

Dosimetric variable	Median split	Toxicity incidence below median split		Toxicity incidence above median split		RR grade ≥ 3 toxicity	P
		n	%	n	%		
D2.5 cm ³	14.02 Gy	2/102	2	12/102	12	12/2 = 6	.01
V10 Gy	4.77 cm ³	4/102	4	10/102	10	10/4 = 2.5	.16
V12 Gy	3.78 cm ³	3/102	3	11/102	11	11/3 = 3.7	.05
V15 Gy	1.87 cm ³	1/102	1	13/102	13	13/1 = 13	.0013
V20 Gy	0.11 cm ³	2/102	2	12/102	12	12/2 = 6	.01
V22 Gy	0.0 cm ³	1/102	1	13/102	13	13/1 = 13	.0013

Abbreviation: RR = relative risk.

Oligometástasis

Definición Oligometástasis



➤ Definición de oligo-metástasis no basada en evidencia

Estimate of oligometastasis at presentation/year

Over 14,000 Oligometastatic Breast Cancer Patients

Over 50,000 Oligometastatic Lung Cancer Patients

Nearly 10,000 Oligometastatic Prostate Cancer Patients

Over 14,000 Oligometastatic Colorectal Cancer Patients

Ashworth A, et al. Lung Cancer 82(2):197-203 (2013).
Cancer Facts & Figures 2017. ©2017, American Cancer Society, Inc.

Engels B, et al. Radiat Oncol 2012;7:34.

Fong Y, et al. Ann Surg 1999;230(3):309-318.

Jain SK, et al. J Clin Oncol. 2012;30 Suppl; abstr e11512.

Khan AJ, et al. Radiother Oncol 81(2):163-7 (2006).

Khatri VP, et al. J Clin Oncol 2005;23(33):8490-8499.

Mehta N, et al. Int J Oncol 25(6):1677-83 (2004).

Miller KD, et al. CA Cancer J Clin. 66(4):271-289.

Muacevic et al. Urol Oncol 31(4):455-60;2013

Sridharan S, et al. Radiother Oncol 121:98-102, 2016

NCT02364557/NRG-BR003.

Parikh RB, et al. IJROBP 89(4):880-7 (2014).

Sakai K, et al. Thor Cancer 7(6):670-75 (2016).

Senkus E. Breast. 23(1) 2014.

Siegel RL, et al. CA Cancer J Clin 66(1):7-30.

Singh D, et al. IJROBP 58(1):3-10;2004

Takeda A, et al. World J Gastroenterol 2014;20(15):4220-4229.

Vichapat V, et al. Br J Cancer 2012. 10;107(2):221-223.

Walters S, et al. Thorax 68(6):551-64 (2013).

Waselenko JK and Dawson NA. Oncology 11(10):1551-60;1997

Eficacia Local SBRT

	Lesiones	Control Local@2 A
Mama	33	97%
NSCLC	148	83%
CRC	133	86%
RCC	56	91%
Sarcoma	20	70%
Esófago	15	93%
Melanoma	15	87%
Otros	105	89%
Total	525	87%



➤ **70 – 97% control local independiente de la histología**

Objetivos tratamiento local

Cura

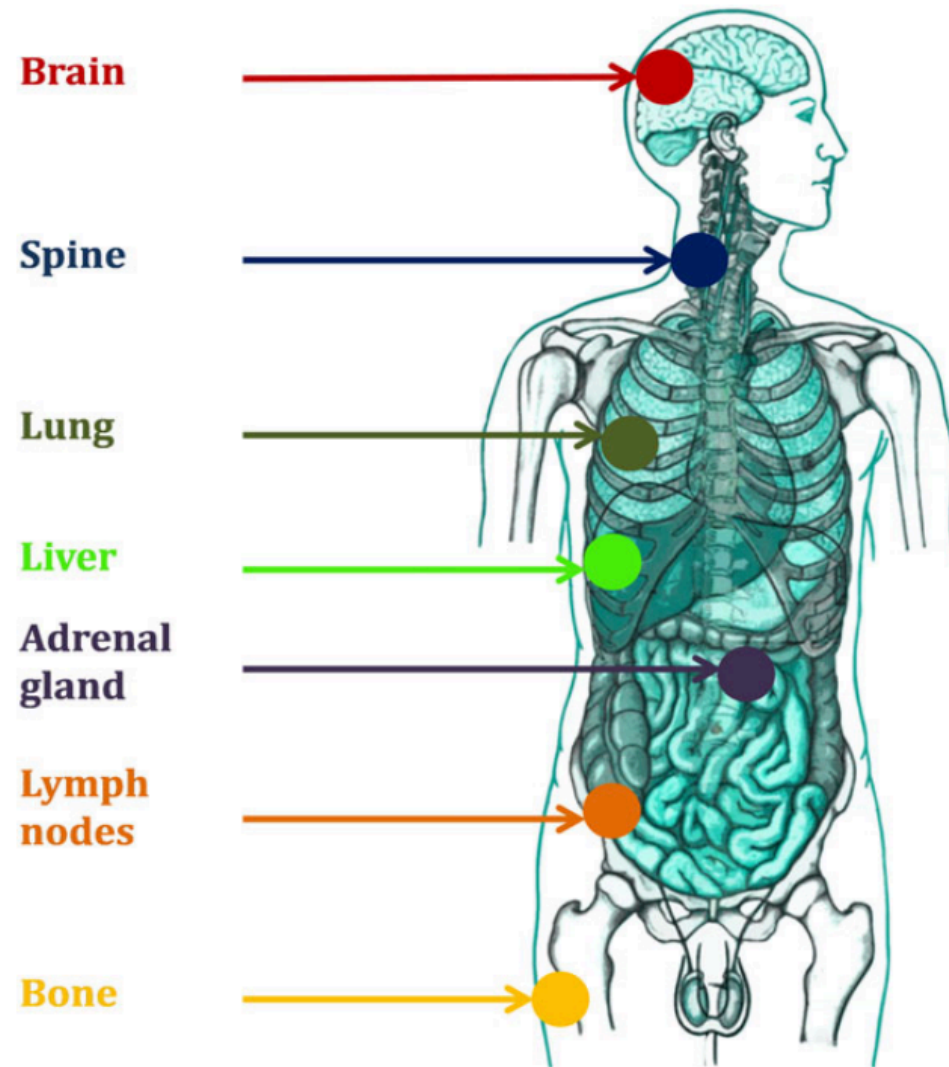
Retraso inicio terapia sistémica

Paliación a largo plazo/Prevención de síntomas

Inmuno-modulación

Tratamiento extendido mas allá de oligoprogresión

Donde SBRT?





Advancing Research. Improving Lives.™

NRG-BR001: A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

Steven J Chmura, MD, PhD¹, Kathryn A Winter, MS², Joseph K Salama, MD³, Clifford Robinson, MD⁴, Thomas M. Pisansky, MD⁵, Virginia Borges, MD⁶, Hania Al-Hallaq, PhD¹, Martha Matuszak, PhD⁷, Sean S Park, MD⁵, Victor Gonzalez, MD⁸, Yasmin Hasan, MD¹, Jose Bazan, MD⁹, Philip Wong, MD¹⁰, Harold A Yoon, MD¹¹, Janet K Horton, MD³, Gregory N Gan, MD PhD¹², Michael T Milano, MD, PhD¹³, Elin Ruth Sigurdson, MD¹⁴, Jennifer Moughan, MS², Julia White, MD⁹

¹ University of Chicago Comprehensive Cancer Center; ² NRG Oncology Statistics and Data Management Center/ACR; ³ Duke University Medical Center; ⁴ Washington University in St. Louis; ⁵ Mayo Clinic; ⁶ University of Colorado – Anschutz Medical Center; ⁷ University of Michigan; ⁸ University of Arizona Medical Center – University Campus; ⁹ Ohio State University Comprehensive Cancer Center; ¹⁰ Centre Hospitalier de l'Université de Montréal; ¹¹ Heartland Cancer Research NCORP; ¹² University of New Mexico Comprehensive Cancer Center; ¹³ University of Rochester; ¹⁴ Fox Chase Cancer Center

ASTRO Annual Meeting: 10/24/2018

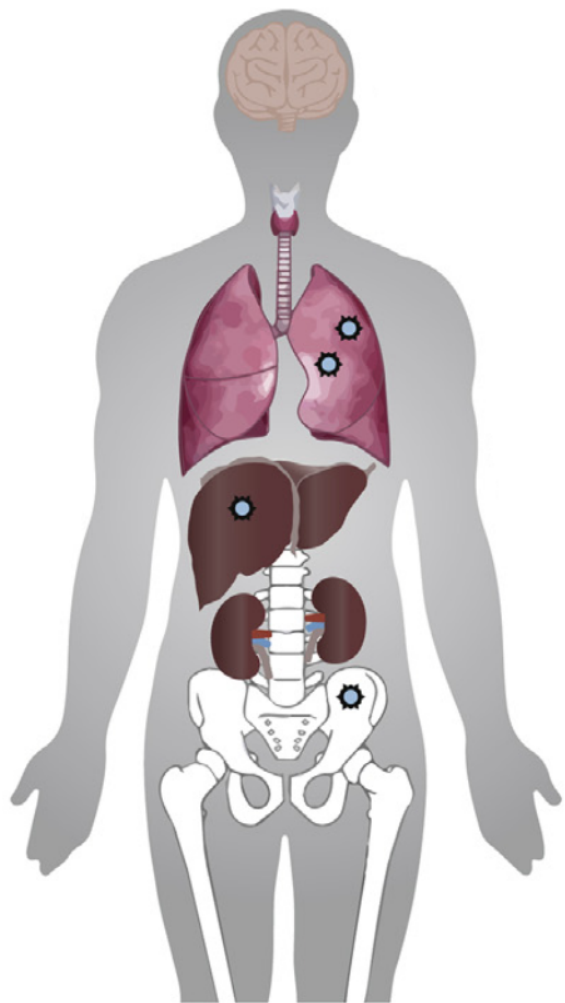


SBRT Dosing NRG

ONCOLOGY

Advancing Research. Improving Lives.™

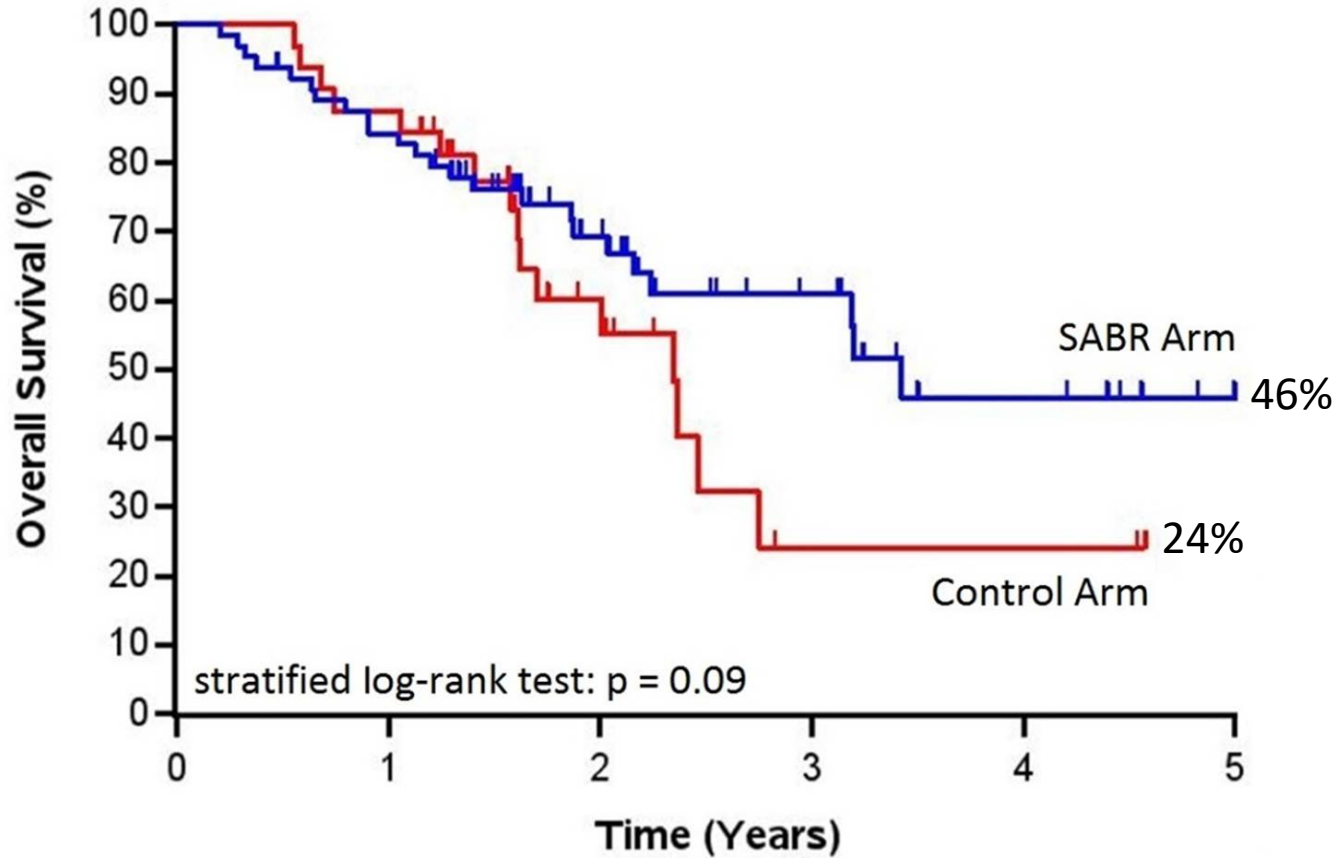
Metastatic Location	Initial Starting Dose	Dose De-escalation
Lung – Peripheral	45 Gy (3 fxs)	42 Gy (3 fxs)
Lung – Central	50 Gy (5 fxs)	47.5 Gy (5 fxs)
Mediastinal/Cervical Lymph Node	50 Gy (5 fxs)	47.5 Gy (5 fxs)
Liver	45 Gy (3 fxs)	42 Gy (3 fxs)
Spinal/Paraspinal	30 Gy (3 fxs)	27 Gy (3 fxs)
Osseous	30 Gy (3 fxs)	27 Gy (3 fxs)
Abdominal-pelvic	45 Gy (3 fxs)	42 Gy (3 fxs)



SABR-COMET: Stereotactic Radiation for the Comprehensive Treatment of Oligometastatic Cancers – Results of a Randomized Study

D. Palma, R. Olson, S. Harrow, S. Gaede, A. Louie,
C. Haasbeek, L. Mulroy, M. Lock, G. Rodrigues, B.
Yaremko, D. Schellenberg, B. Ahmad, G. Griffioen,
S. Senthil, A. Swaminath, N. Kopeck, M. Liu, K. Moore, S.
Currie, G. Bauman, A. Warner, S. Senan

Sobrevida Total



SV Media

Rama Control: 28 meses
(95% CI: 19-33 meses)

Rama SABR: 41 meses
(95% CI: 26 meses no alcanzada)

Number at risk:

	0	1	2	3	4	5
Control	33	28	12	2	2	
SABR	66	53	29	15	7	1

Oligometástasis Abdominales

- **Toxicidad Hepática**
- **Toxicidad gástrico/duodenal**

Toxicidad Hepática

- **Índices de toxicidad son bajos en los trabajos prospectivos con metástasis hepáticas**
- **Mayor toxicidad en pacientes con hepatocarcinoma, especialmente pacientes Child-Pugh B con score >8**
- **Es prudente utilizar diferentes restricciones: metástasis # HCC**

RILD

Enfermedad Hepática Radio-inducida

- **Síndrome caracterizado por:**
 - **Ascitis anictérica**
 - **Elevación de FAL y Transaminasas**
 - **Entre 2 semanas y 4 meses post RT**
 - **Fallo hepático y muerte**

Selección de Pacientes: Metástasis

Selection criteria	Patients categories		
	Suitable	Cautionary	Unsuitable
Lesion number	<3	4	>4
Lesion diameter (cm)	1-3	>3 and ≤6	>6
Distance from OARs (mm)	>8	5-8	<5
Liver function	Child A	Child B	Child C
Free liver volume (cc)	>1,000	<1,000 and ≥700	<700

SBRT, stereotactic body radiation therapy; OARs, organs at risk.

Toxicidad Hepática: Metástasis

Table 1. — Summary of Dose-Volume Constraints for Liver With Conversion to Biologic Equivalent Dose (BED) and Single-Fraction Equivalent Dose (SFED)

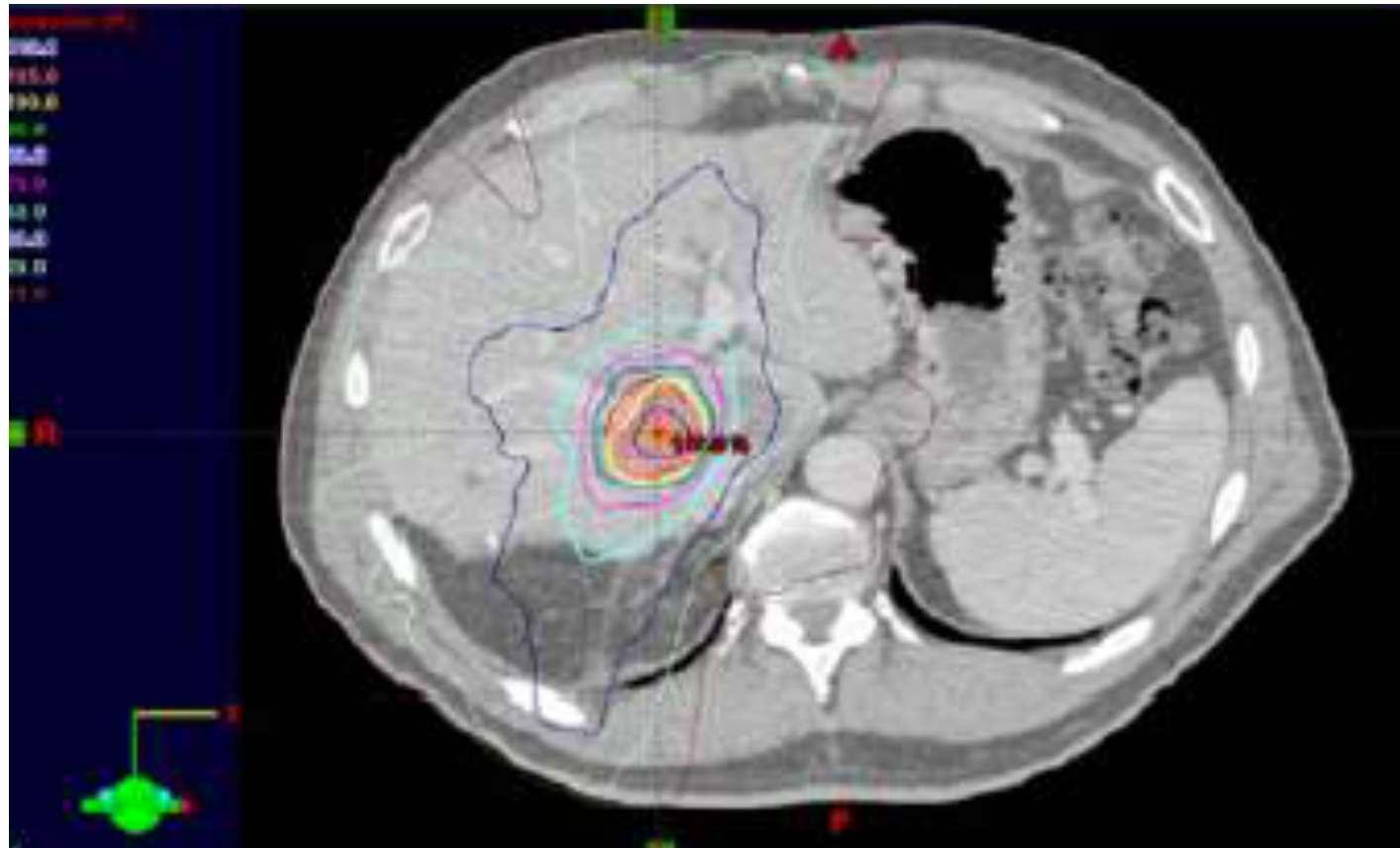
Study	Dose-Volume Constraint (as reported)	Dose-Volume Constraint (converted to V_{Gy})	BED (Gy_3)		SFED	
			1 fx	3 fx	1 fx	3 fx
Herfarth et al ¹⁹	12 Gy to 30% 7 Gy to 50%	$V_{12} \leq 30\%$ $V_7 \leq 50\%$	$V_{60} \leq 30\%$ $V_{29.3} \leq 50\%$		$V_{12} \leq 30\%$ $V_7 \leq 50\%$	
Wulf et al ²¹ Wulf et al ²³	D30 < 7 Gy D50 < 5 Gy	$V_7 \leq 30\%$ $V_5 \leq 50\%$	$V_{23.3} \leq 30\%$ $V_{13.3} \leq 50\%$	$V_{12.4} \leq 30\%$ $V_{7.8} \leq 50\%$	$V_7 \leq 30\%$ $V_{2.8} \leq 30\%$	$V_5 \leq 50\%$ $V_{0.8} \leq 50\%$
Schefter et al ²⁰ Kavanagh et al ⁸	700 cm ³ < 15 Gy	$V_{\leq 15} \geq 700 \text{ cm}^3$	$V_{\leq 40} \geq 700 \text{ cm}^3$		$V_{\leq 10.8} \geq 700 \text{ cm}^3$	
Hoyer et al ²²	10 Gy total < 30%	$V_{10} < 30\%$	$V_{21.1} < 30\%$		$V_{5.8} < 30\%$	
Méndez Romero et al ¹⁸	D33 < 21 Gy D50 < 15 Gy	$V_{21} \leq 33\%$ $V_{15} \leq 50\%$	$V_{70} \leq 33\%$ $V_{40} \leq 50\%$	$V_{50.4} \leq 33\%$ $V_{30} \leq 50\%$	$V_{16.8} \leq 33\%$ $V_{12.6} \leq 33\%$	$V_{10.8} \leq 50\%$ $V_{6.6} \leq 50\%$
Tse et al ²⁴ *	mean dose < 22 Gy*	N/A mean dose	< 49.6 Gy_3		mean dose < 11.5	

* This study determined liver dose constraint based on a previously reported normal tissue complication probability model described in the appendix. In this appendix it was noted that the constraint was “usually mean dose < 22 Gy.”

Take Home Pearls

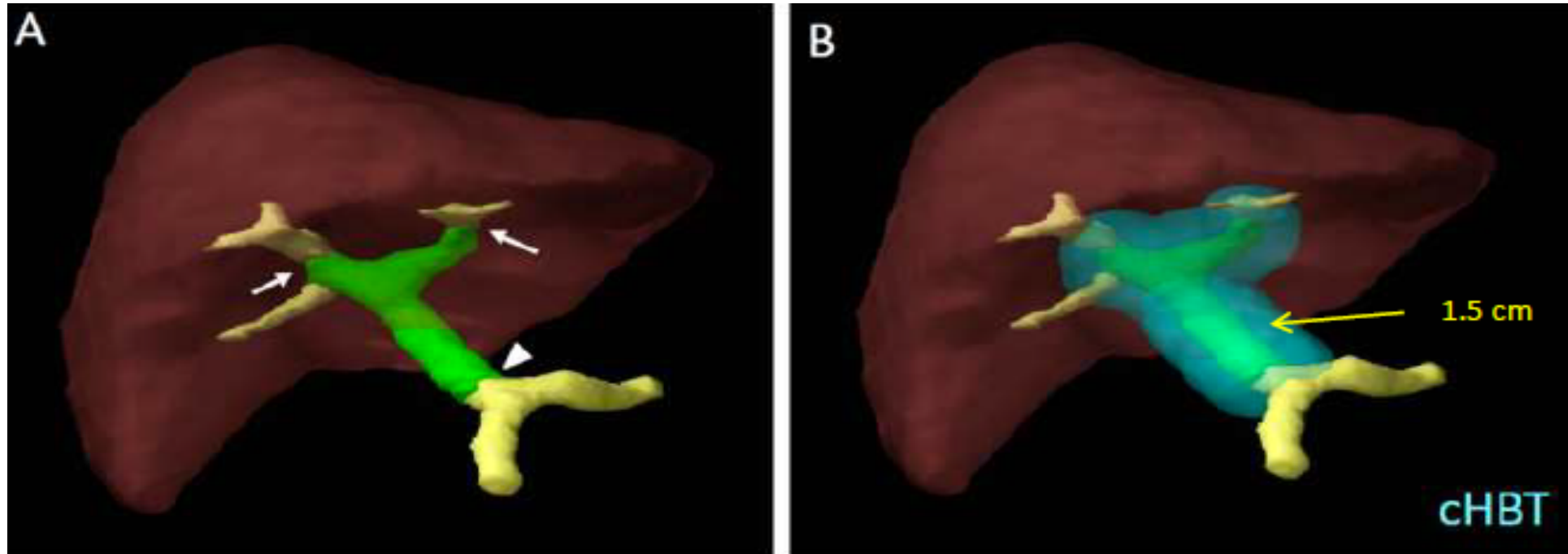
- **Dosis iguales o mayores 45-50 Gy, 3-5 Fx**
- **35 Gy FX única en localización periférica**
- **2-3 fracciones por semana**
- **Utilizar restricciones conservadoras**
- **15 Gy < 700 cc³ hígado**

Toxicidad Hepática Central



SBRT segmento VIII

Toxicidad Hepática Central



$VBED_{10} 72 \geq 21 \text{ cm}^3$, $VBED_{10} 66 \geq 24 \text{ cm}^3$, and
 $D_{\text{mean}}BED_{10} \text{ cHBT} \geq 14 \text{ Gy} \rightarrow \text{cHBT toxicity}$
5 fractions: $V_{40} < 21 \text{ cm}^3 / V_{37.7} < 24 \text{ cm}^3$
3 fractions: $V_{33.8} < 21 \text{ cm}^3 / V_{32} < 24 \text{ cm}^3$

Intestino Delgado

Int J Colorectal Dis (2013) 28:1707–1713

DOI 10.1007/s00384-013-1717-6

ORIGINAL ARTICLE

Severe intestinal toxicity after stereotactic ablative radiotherapy for abdominopelvic malignancies

**Sun Hyun Bae · Mi-Sook Kim · So Young Kim · Won Il Jang ·
Chul Koo Cho · Hyung Jun Yoo · Kum Bae Kim · Dong Han Lee ·
Chul Ju Han · Ki Young Yang · Sang Bum Kim**

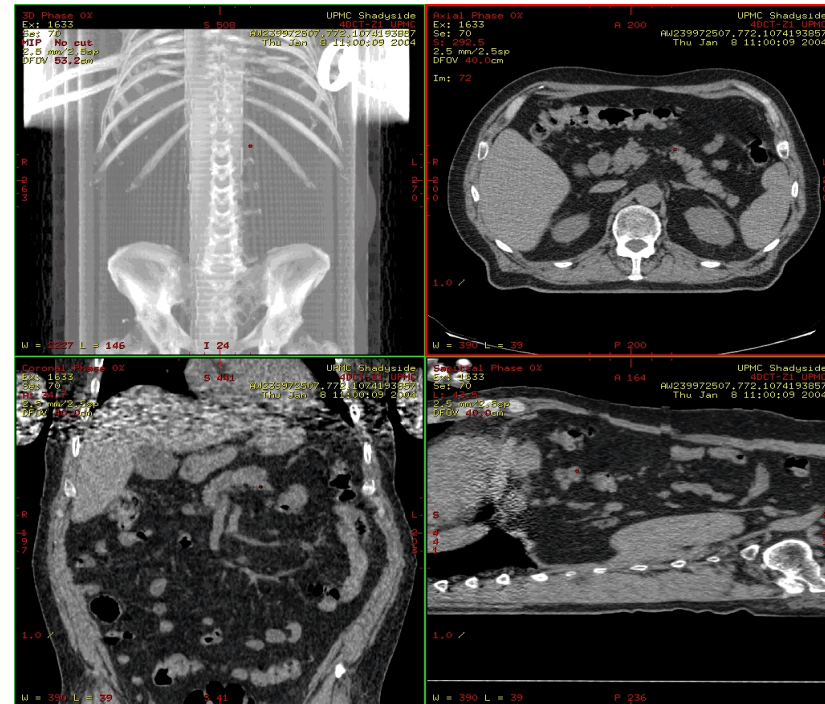
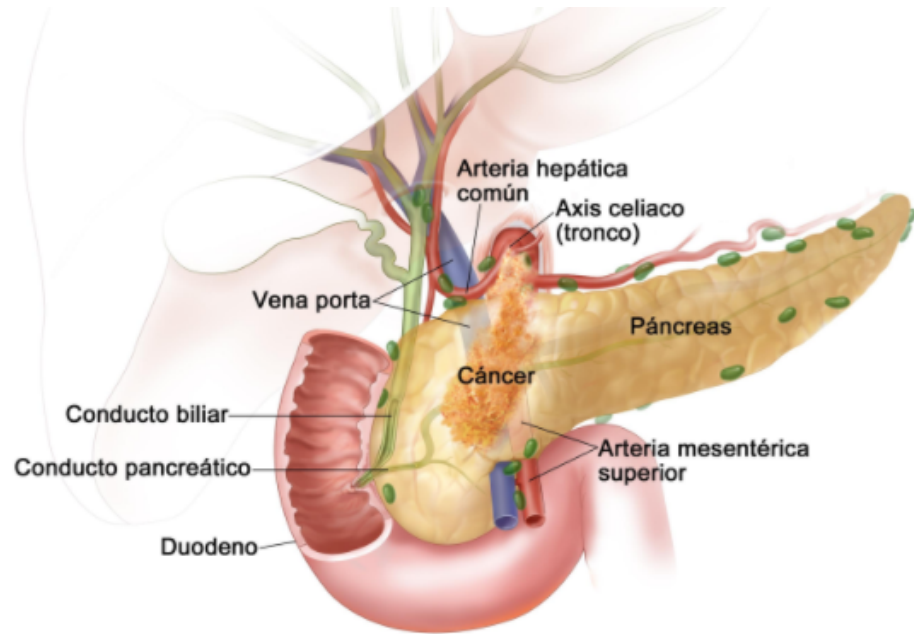
Intestino Delgado

- **Objetivo: Daño Intestinal**
- **N=202**
- **SBRT abdomen/pelvis: 33-60 Gy en 3 Fxs**
- **QD vs QOD** $V_{25} < 20 \text{ ml}$ - Max Point Dose $< 30 \text{ Gy}$
- **Toxicidad intestinal severa disminuyó en pacientes que recibieron SBRT en 4-8 días respecto a días consecutivos**
- **0% vs 18%, $p= 0.037$ – Mayor predictor de daño**

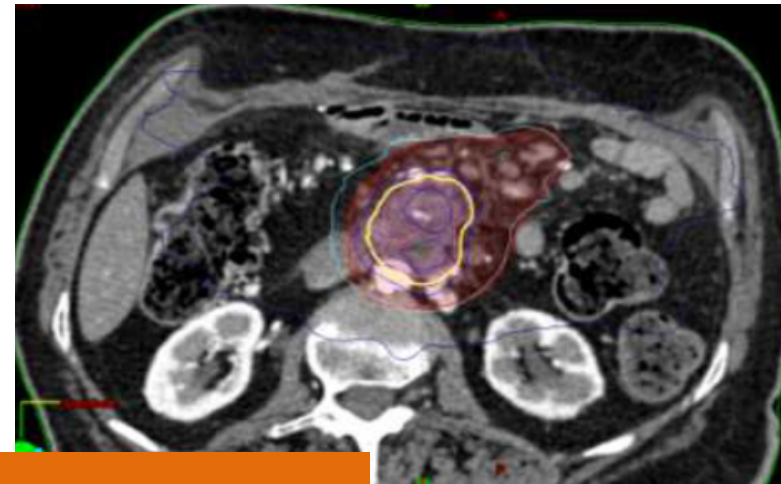
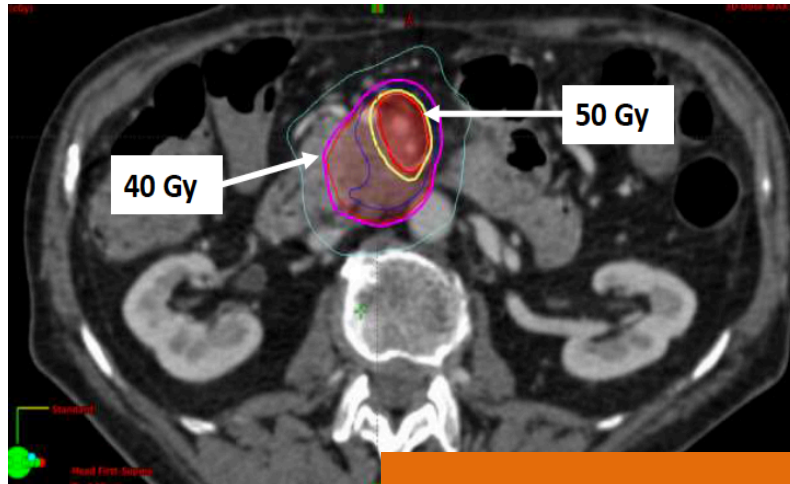
Intestino Delgado

- **Riesgo incrementado de toxicidad intestinal con el uso de inhibidores de crecimiento vascular (VEGF-I) post SBRT abdominal**
- **Incremento estadístico luego de 3 y hasta 6 meses post SBRT (38-33% vs 0%) HR: 16.7**

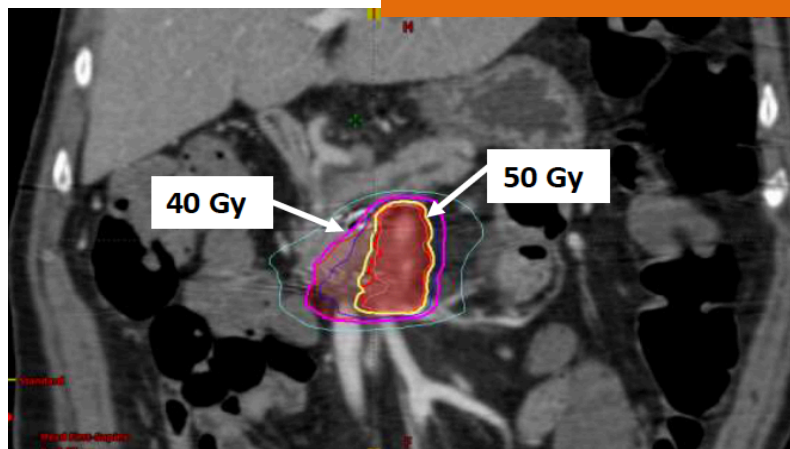
Toxicidad Gastro-duodenal



Estructuras adyacentes: Dose Painting

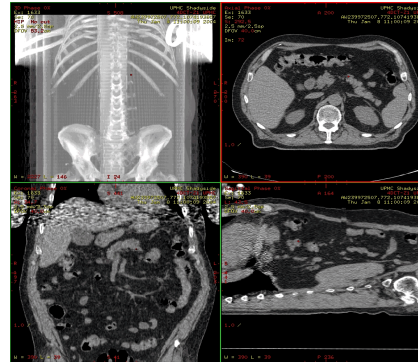


Duodeno: PRV 2-3 mm



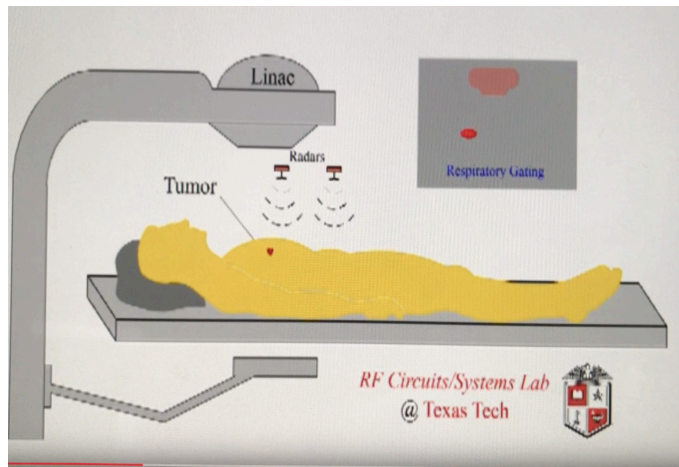
Resolviendo el desplazamiento

Tomografía 4D (4DCT)



Movimiento > 5 – 10 mm

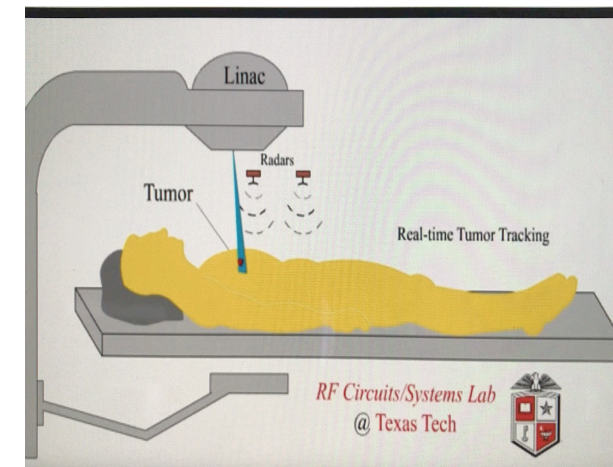
Gaiting Respiratorio



Compresión Abdominal



Tracking





Les prometo que ya termino!!!!!!!!!!

Columna

- **Mielitis radiante**
- **Fractura/compresión vertebral**
- **Flare (aumento dolor)**
- **Plexopatías**

Columna

Spine

SPINE Volume 41, Number 20S, pp S238–S245
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METASTATIC SPINE TUMORS

Stereotactic Body Radiotherapy for Spinal Metastases

iscargar

What are the Risks and How Do We Minimize Them?

Joe H. Chang, MD,* John H. Shin, MD,[†] Yoshiya J. Yamada, MD,[‡] Addisu Mesfin, MD,[§]
Michael G. Fehlings, MD, PhD,[¶] Laurence D. Rhines, MD,^{||} and Arjun Sahgal, MD*

Recommendation 1

Clinicians might evaluate patients for stabilization prior to SBRT if the following risk factors are observed: baseline VCF, significant lytic tumor burden, spinal malalignment, SINS score indicating potentially or frankly unstable spine, mechanical pain, and/or planned SBRT with ≥ 20 Gy per fraction.

Columna

Spine

SPINE Volume 41, Number 20S, pp S238–S245
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Stereotactic Body Radiotherapy for Spinal Metastases

iscargar

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Michael G. Fehlings, MD, PhD,[¶] Laurence D. Rhines, MD,^{||} and Arjun Sahgal, MD*

Recommendation 2

Clinicians might limit the Dmax to the thecal sac (as a surrogate structure for the spinal cord) for de novo SBRT to an EQD2 of ≤ 44.6 Gy.

- Tratamiento primario de
- oligometastásis (RTOG 0631)
 - Menos del 50% de compromiso de vertebra
 - No fragmentos óseos en el canal
 - Columna estable
- Postoperatorio
- Recurrencia post RT

Figure 1: Diagram of Eligible Metastatic Lesions

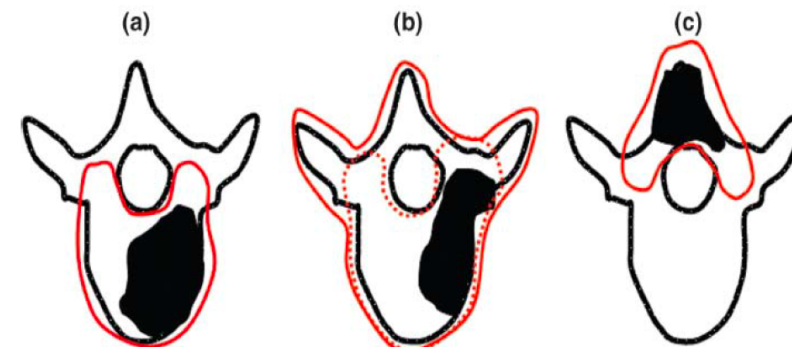
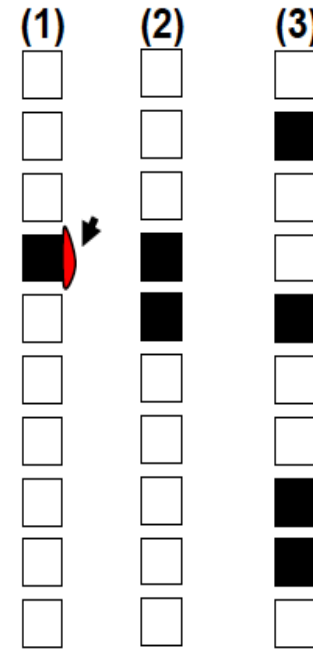


Figure 2: Diagram of Spine Metastasis and Target Volume

Spinal Instability Neoplastic Score: An Analysis of Reliability and Validity From the Spine Oncology Study Group

Daryl R. Fourney, Evan M. Frangou, Timothy C. Ryken, Christian P. DiPaola, Christopher I. Shaffrey, Sigurd H. Berven, Mark H. Bilsky, James S. Harrop, Michael G. Fehlings, Stefano Boriani, Dean Chou, Meic H. Schmidt, David W. Polly, Roberto Biagini, Shane Burch, Mark B. Dekutoski, Aruna Ganju, Peter C. Gerszten, Ziya L. Gokaslan, Michael W. Groff, Norbert J. Liebsch, Ehud Mendel, Scott H. Okuno, Shreyaskumar Patel, Laurence D. Rhines, Peter S. Rose, Daniel M. Sciubba, Narayan Sundaresan, Katsuro Tomita, Peter P. Varga, Luiz R. Vialle, Frank D. Vrionis, Yoshiya Yamada, and Charles G. Fisher

Spine Instability Neoplastic Score (SINS)

SINS Component	Description	Score
Location	Junctional (Occ-C2, C7-T2, T11-L1, L5-S)	3
	Mobile (C3-6, L2-4)	2
	Semirigid (T3-10)	1
	Rigid (S2-5)	0
Pain	Yes*	3
	Occasional non-mechanical pain	1
	No	0
Bone Lesion	Lytic	2
	Mixed	1
	Blastic	0
Alignment	Subluxation / translation	4
	De novo deformity	2
	Normal	0
Vertebral Body	>50% collapse	3
	<50% collapse	2
	No collapse with >50% VB involved	1
	None of above	0
Posterolateral Involvement	Bilateral	3
	Unilateral	1
	None	0

Tallied Score from 6 components

Stable	Potentially Unstable	Unstable
0-6	7-12	13-18



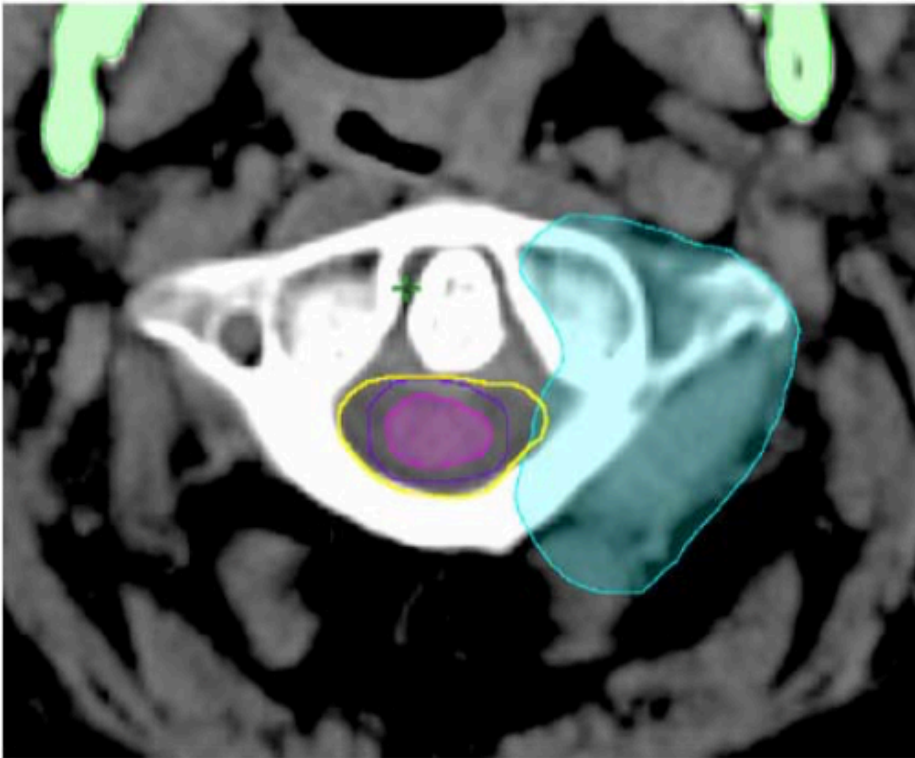
Fisher CG, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine 35(22):E1221-9, 2010

Restricciones: Saco Tecal

Porqué el saco tecal? (márgen anatómico seguro)

- El saco tecal es equivalente a 1.5-2 mm de márgen del planning organ at risk (PRV) por fuera de médula
- El uso del saco tecal como OAR representa el peor escenario de dosis a la médula.
 - Compensa pequeñas incertaezas del software de fusión
 - Compensa movilidad medular
 - Compensa pequeños variaciones intrafracción

PRV médula



La práctica más común es
Agregar 1.5-2mm a la
Médula delineada en secuencia T2
De RMN o Mielograma de TAC



Fig. 1. Axial view of a C1 vertebra involved by metastatic non-small-cell lung carcinoma. The spinal cord is shaded in magenta, the planning organ-at-risk volume (spinal cord + 0.2 cm) is outlined in purple, and the thecal sac is outlined in yellow.

Fractura/compresión vertebral

VOLUME 31 · NUMBER 27 · SEPTEMBER 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Vertebral Compression Fracture After Spine Stereotactic Body Radiotherapy: A Multi-Institutional Analysis With a Focus on Radiation Dose and the Spinal Instability Neoplastic Score

Arjun Sahgal, Eshetu G. Atenafu, Sam Chao, Ameen Al-Omair, Nicholas Boehling, Ehsan H. Balagamwala, Marcelo Cunha, Isabelle Thibault, Lilyana Angelov, Paul Brown, John Suh, Laurence D. Rhines, Michael G. Fehlings, and Eric Chang

2-3 meses

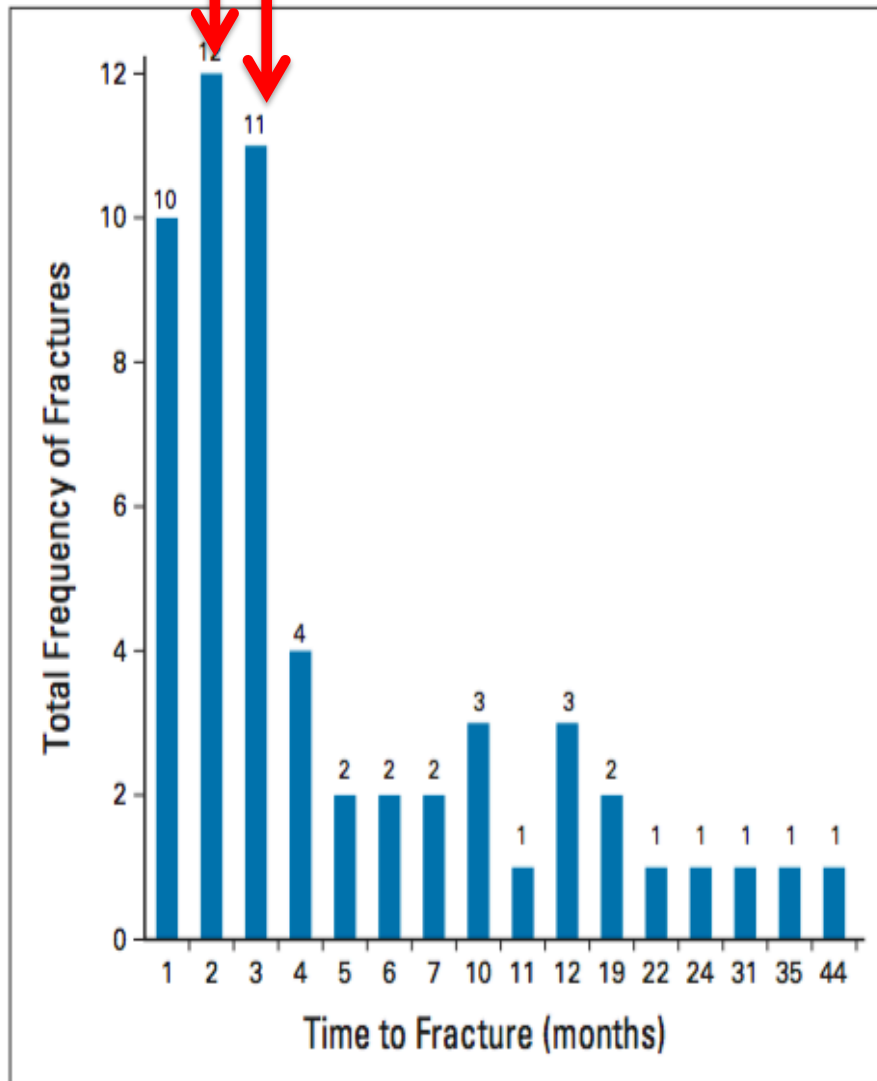


Fig 1. Distribution of the events of vertebral compression fracture over time in 1-month time intervals after spine stereotactic body radiotherapy.

Table 3. Significant Predictors of VCF on Univariate and Multivariate Analysis

Factor	Univariate <i>P</i>	Multivariable Fine and Grey Model		
		<i>P</i>	HR	95% CI
Vertebral body collapse	< .001	Global, < .001		
≥ 50% VCF		.0189	6.92	1.38 to 34.77
< 50% VCF		< .001	8.98	4.48 to 18.00
No VCF but > 50% of vertebral body involved		< .001	4.46	2.08 to 9.57
Dose/fraction, Gy	< .001	Global, < .001		
≥ 24		< .001	5.25	2.29 to 12.01
20-23		< .001	4.91	1.96 to 12.28
Alignment	.0027	< .001	2.99	1.57 to 5.70
Bone lesion type	< .001	.0022	3.53	1.58 to 7.93
Paraspinal/epidural extension	.0036	NS		

NOTE. For vertebral body collapse, the reference is no VCF and less than 50% vertebral body involvement; for dose/fraction, the reference is ≤ 19 Gy/fraction; the reference for alignment was normal, and yphosis/scoliosis and subluxation/translation were grouped as only one patient had subluxation; and the reference for bone lesion was grouped according to mixed and osteoblastic tumor versus osteolytic, given that the majority of VCFs occurred in lytic tumors.

Abbreviations: HR, hazard ratio; NS, not significant; VCF, vertebral compression fracture.

Fractura/compresión vertebral

Precauciones

- Dosis > 20 Gy fracción
- Tumores líticos
- Fractura/compresión vertebral de base (>50%)
- Seguimiento frecuente: 2/3 dentro de 4 meses
- **Utilidad Spinal Instability Neoplastic Score**
 - Estable (0=6)
 - Potencialmente inestable (7-12)
 - Inestable > 12

Flare

Clinical Investigation: Central Nervous System Tumor

Pain Flare Is a Common Adverse Event in Steroid-Naïve Patients After Spine Stereotactic Body Radiation Therapy: A Prospective Clinical Trial

Andrew Chiang, MD,^{*,†} Liang Zeng, MD(C),^{*} Liying Zhang, PhD,^{*} Fiona Lochray, MRTT,^{*} Renee Korol, PhD,^{*} Andrew Loblaw, MD,^{*} Edward Chow, MBBS, PhD,^{*} and Arjun Sahgal, MD^{*,†}

Flare

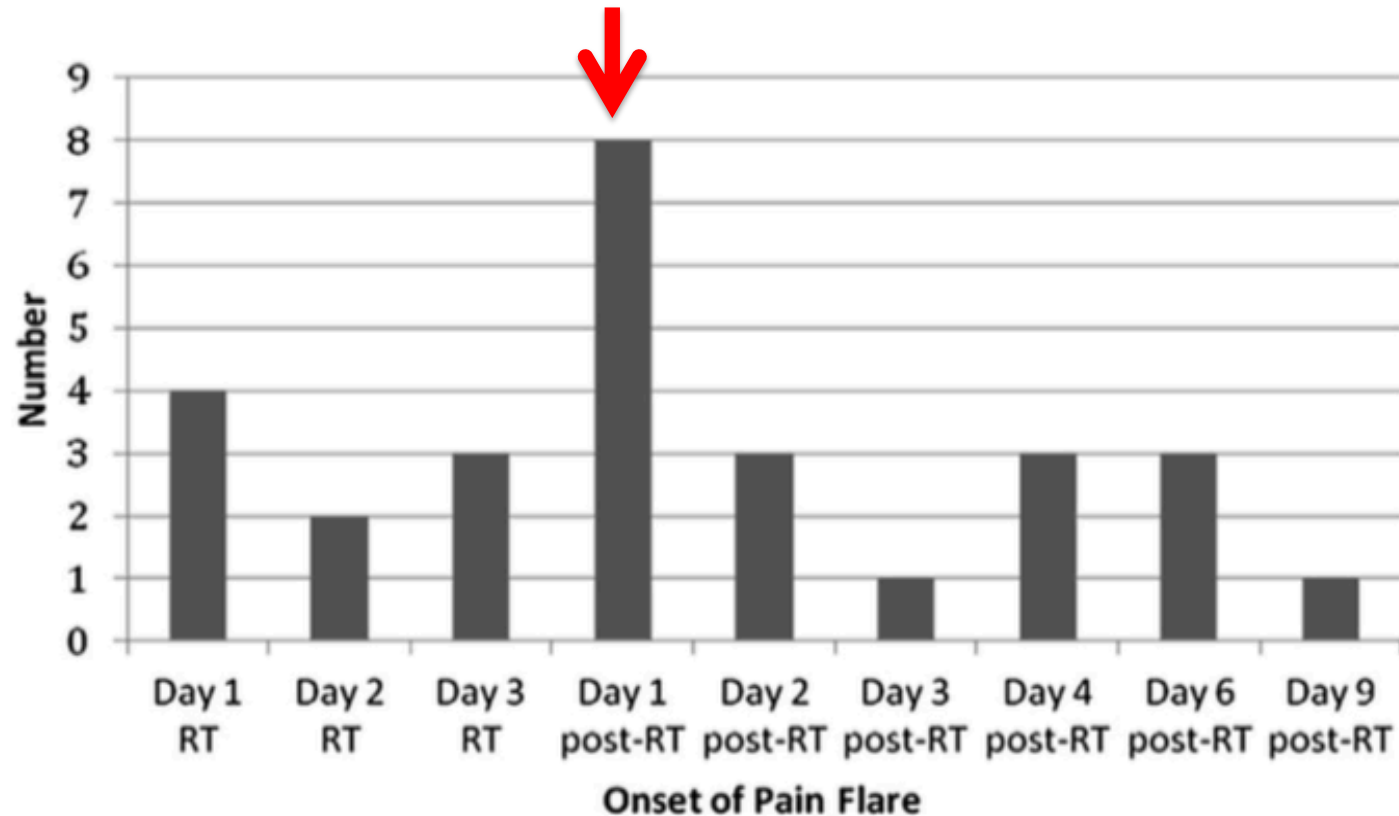


Fig. 1. Day of pain flare onset during and after spine stereotactic body radiation therapy (RT) (n=28 pain flares).

→ **68.3%**

Table 2 Significant predictors of pain flare on multivariate logistic regression analysis

Predictive factor	<i>P</i>	Odds ratio (95% confidence interval)
Karnofsky performance status	.02	1.16 (1.03-1.31)
Spine location:	.033	
Lumbar vs thoracic	.02	28.79 (1.8-461.4)
Cervical vs thoracic	.049	11.30 (1.00-127.3)

Los esteroides funcionan

Recomendación:
 Profilaxis con esteroides
 Con disminución precoz

Corroborado en trabajo
 Plenaria ASTRO 2015

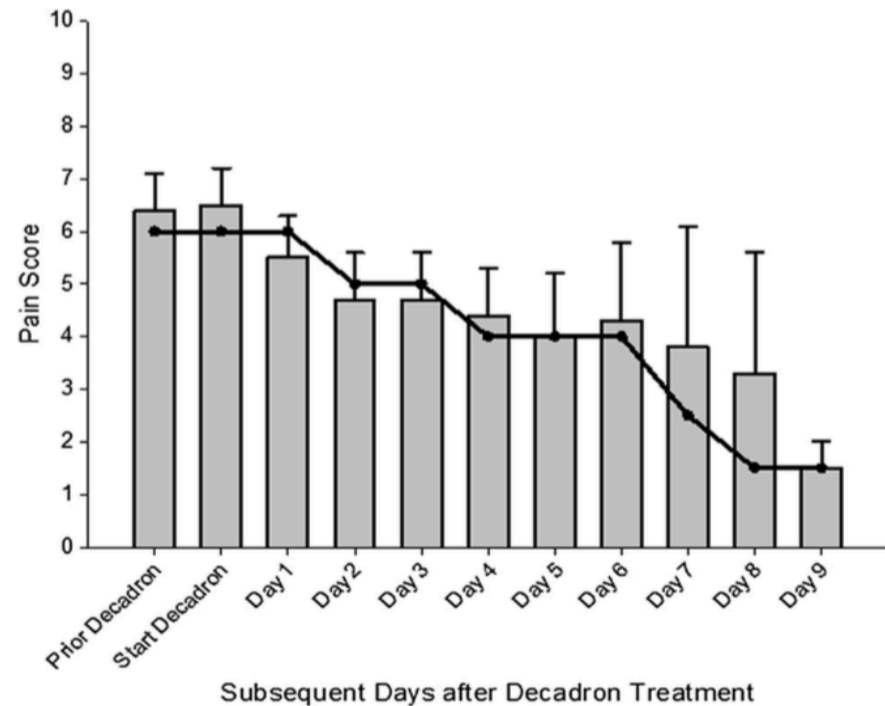


Fig. 2. Change in pain scores after initiation of dexamethasone (n=11 patients). The bars highlight change in mean worst pain scores (standard error) over time, whereas the dotted line represents the change in median worst pain scores over time.

- Late-breaking Abstract Number 1
 Dexamethasone vs Placebo in the Prophylaxis of Radiation-induced Pain Flare Following Palliative Radiation Therapy for Bone Metastases: A Double-blind Randomized, Controlled, Superiority Trial

Plexopatas

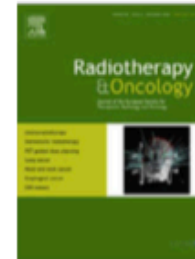
Radiotherapy and Oncology 93 (2009) 408–413



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Lung cancer SBRT

Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: Dose-limiting toxicity in apical tumor sites

Jeffrey A. Forquer^a, Achilles J. Fakiris^{a,*}, Robert D. Timmerman^b, Simon S. Lo^c, Susan M. Perkins^d, Ronald C. McGarry^e, Peter A.S. Johnstone^a

^a Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, USA

^b Department of Radiation Oncology, UT Southwestern School of Medicine, Dallas, USA

^c Department of Radiation Oncology, The Ohio State University, Columbus, USA

^d Division of Biostatistics, Indiana University School of Medicine, Indianapolis, USA

^e Department of Radiation Medicine University of Kentucky, Lexington, USA



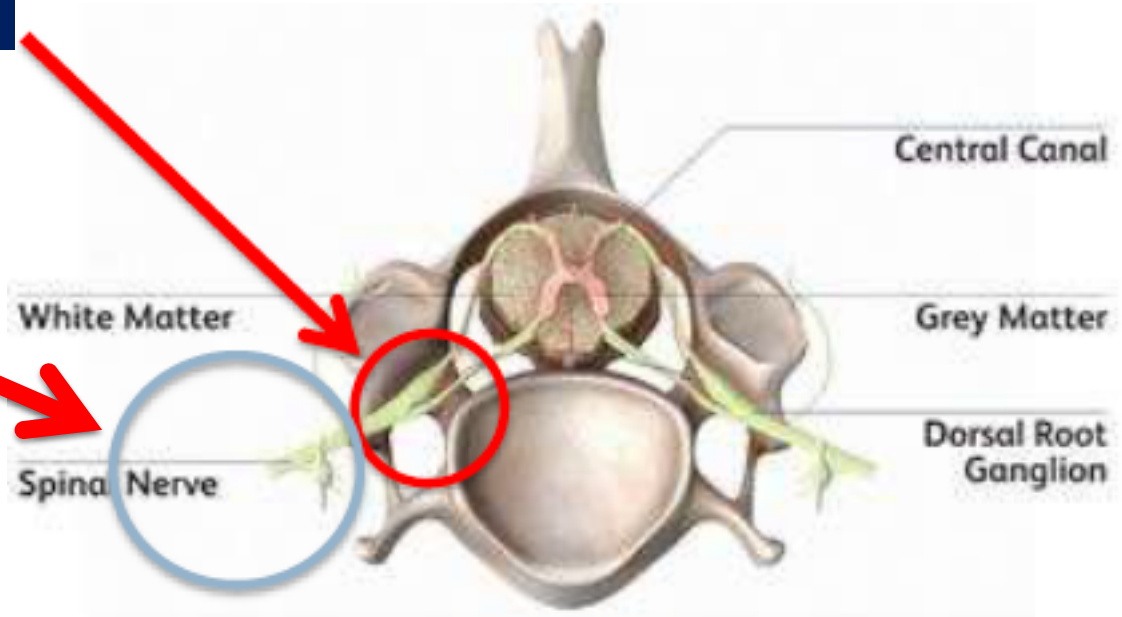
Table 3.3 Normal Tissue Constraints used by RTOG trials (www.rtog.org)*

Organ at Risk	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	RTOG 0631 and 0915: 14 Gy (< 0.03 cc or maximum)/10 Gy (< 0.35 cc)/7 Gy (< 1.2 cc) (only for RTOG 0915)	RTOG 0236 and 0618: 18 Gy (maximum) RTOG 1021: 21.9 Gy (maximum)/18 Gy (< 0.35 cc)/12.3 Gy (< 1.2 cc)	RTOG 0915: 26 (maximum)/20.8 (< 0.35 cc)/13.6 (< 1.2 cc)	RTOG 0813: 30 Gy (maximum)/22.5 Gy (< 0.25 cc)/13.5 Gy (< 0.5 cc)
Brachial plexus	RTOG 0631 and 0915: 17.5 Gy (< 0.03 cc or maximum)/14 Gy (< 3 cc)	RTOG 0236 and 0618: 24 Gy (maximum) RTOG 1021: 24 Gy (maximum)/20.4 Gy (< 3 cc)	RTOG 0915: 27.2 Gy (maximum)/23.6 Gy (< 3 cc)	RTOG 0813: 32 Gy (maximum)/30 Gy (< 3 cc)
Cauda equina	RTOG 0631: 16 Gy (< 0.03 cc)/14 Gy (< 5 cc)	Not available	Not available	Not available
Sacral plexus	RTOG 0631: 18 Gy (< 0.03 cc)/14.4 Gy (< 5 cc)	Not available	Not available	Not available

Plexopatias MMII

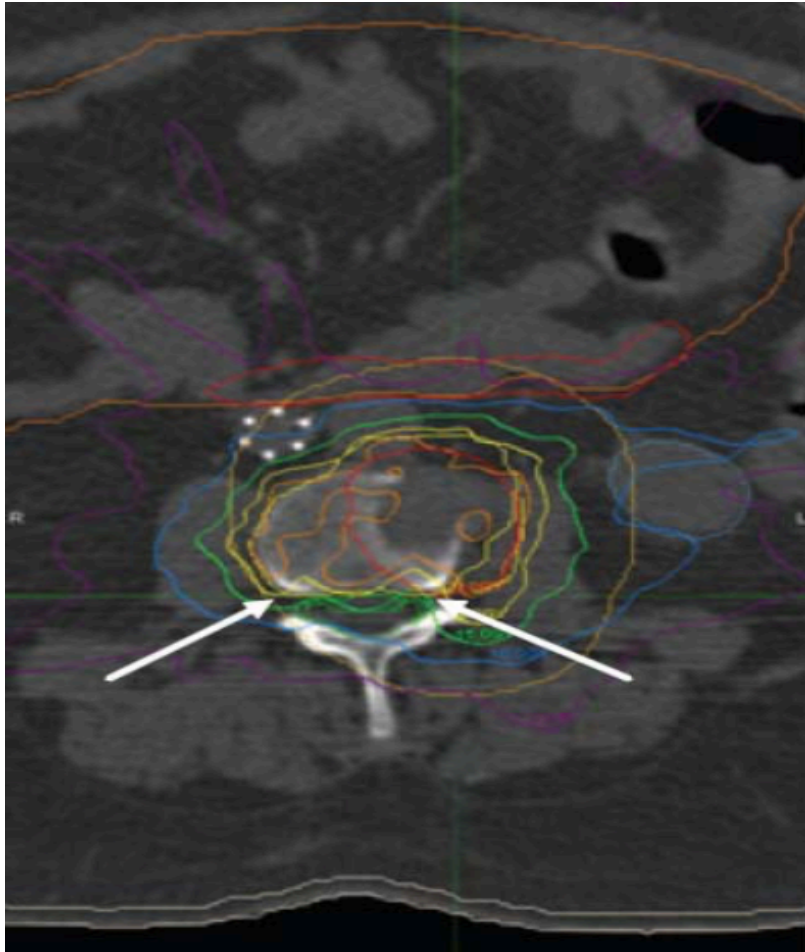
**Raíz Nerviosa:
Radiculopatía**

**Más allá de raíz nerviosa:
Plexopatía**

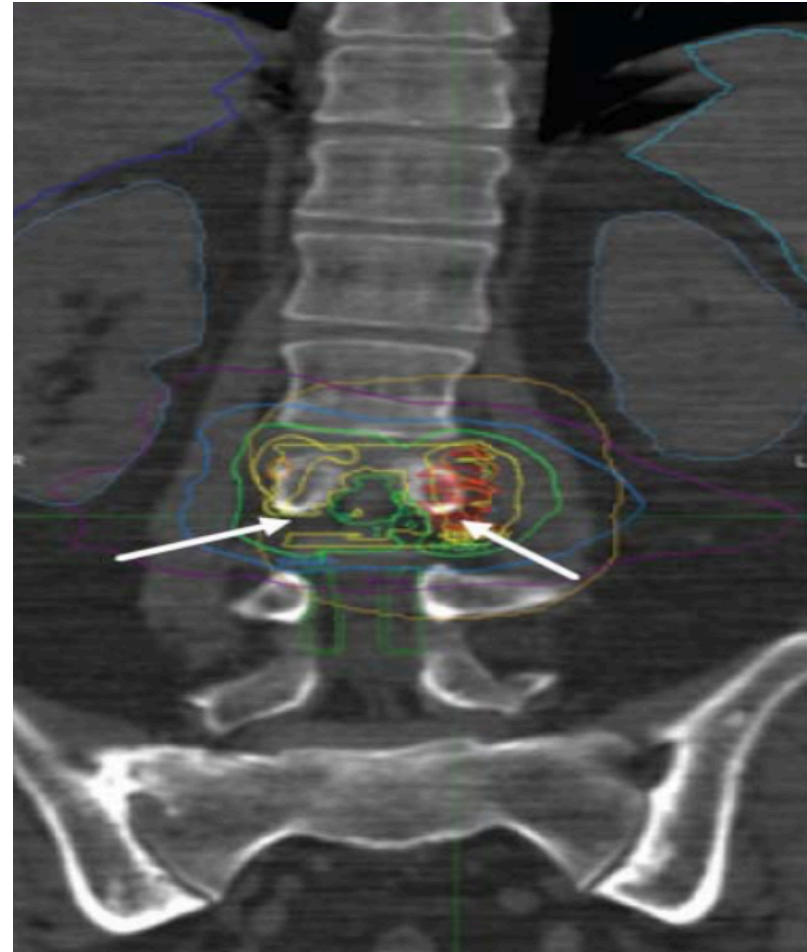


Riesgo < 5%

Plexopatias MMII

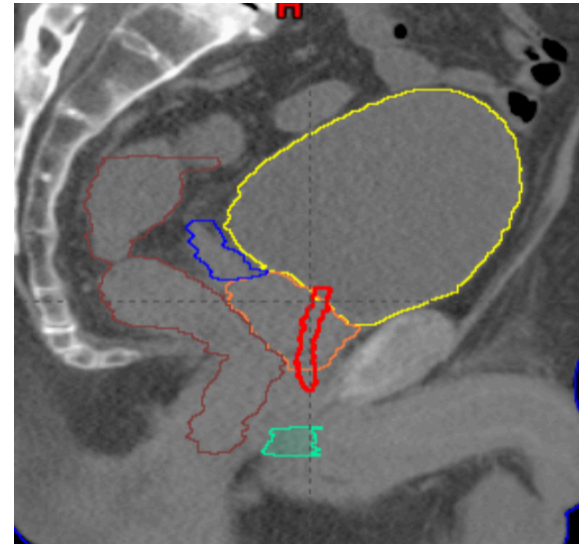
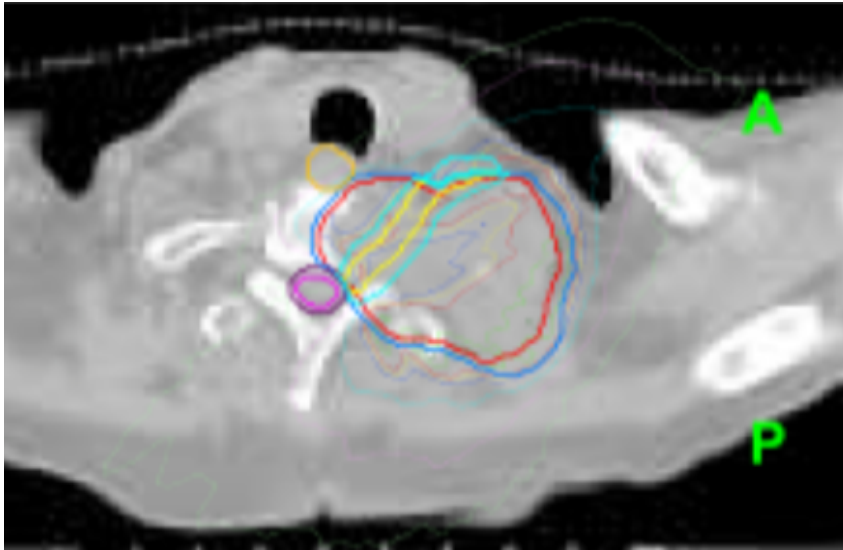


Delinear raíces nerviosas y plexos que inervan las extremidades



Regiones de altas dosis en raíces nerviosas causan radiculopatías

OAR dentro de PTV



Plexo Nervioso - Uretra

Delinear OAR en PTV

Evitar puntos calientes en OAR

SBRT Próstata



PRINCIPLES OF RADIATION THERAPY

Table 1: Regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms, and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.

Regimen for Definitive Therapy	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
	Very-Low ^a	Low ^a	Favorable or good prognostic ^b intermediate	Unfavorable, or poor prognostic ^b , intermediate	High and Very-High ^c	Node Positive
Beam Therapies						
72 Gy to 80 Gy at 2 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5-3 y ADT	✓ with ADT
75.6 Gy to 81.0 Gy at 1.8 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5-3 y ADT	✓ with ADT
70.2 Gy at 2.7 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5-3 y ADT	✓ with ADT
70 Gy at 2.5 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5-3 y ADT	✓ with ADT
60 Gy at 3 Gy per fraction	✓	✓	✓	✓ with 4 mo ADT	✓ with 1.5-3 y ADT	✓ with ADT
51.6 Gy at 4.3 Gy per fraction	✓	✓	✓			
37 Gy at 7.4 Gy per fraction	✓	✓	✓			
40 Gy at 8 Gy per fraction	✓	✓	✓			
36.25 Gy at 7.25 Gy per fraction	✓	✓	✓			

Evidencia Nivel I

Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial



Douglas H Brand, Alison C Tree*, Peter Ostler, Hans van der Voet, Andrew Loblaw, William Chu, Daniel Ford, Shaun Tolan, Suneil Jain, Alexander Martin, John Staffurth, Philip Camilleri, Kiran Kancherla, John Frew, Andrew Chan, Ian S Dayes, Daniel Henderson, Stephanie Brown, Clare Cruickshank, Stephanie Burnett, Aileen Duffton, Clare Griffin, Victoria Hinder, Kirsty Morrison, Olivia Naismith, Emma Hall, Nicholas van As, on behalf of the PACE Trial Investigators*



Toxicidades Rectales y GU

CLINICAL INVESTIGATION

Genitourinary Cancer

LONG-TERM OUTCOMES FROM A PROSPECTIVE TRIAL OF STEREOTACTIC BODY RADIOTHERAPY FOR LOW-RISK PROSTATE CANCER

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Toxicidad Rectal y GI

Table 2. Comparison of late urinary (GU) and late rectal (GI) RTOG toxicity between consecutive daily treatments (QD) vs. those delivered three times a week on alternating days (QOD)

GU toxicity	QD	QOD	<i>p</i> value*
RTOG Gr. 0	37% (6/16 pts)	80% (33/41 pts)	0.003
RTOG Gr. 1	50% (8/16 pts)	12% (5/41 pts)	0.004
RTOG Gr. 2	6% (1/16 pts)	5% (2/41 pts)	1
RTOG Gr. 3	6% (1/16 pts)	2% (1/41 pts)	0.48
RTOG Gr. 1-2	56% (9/16 pts)	17% (7/41 pts)	0.007

GI toxicity	QD	QOD	<i>p</i> value*
RTOG Gr. 0	56% (9/16 pts)	95% (39/41 pts)	0.001
RTOG Gr. 1	37% (6/16 pts)	5% (2/41 pts)	0.0004
RTOG Gr. 2	6% (1/16 pts)	0% (0/41 pts)	0.28
RTOG Gr. 1-2	44% (7/16 pts)	5% (2/41 pts)	0.001

Fase II SBRT Próstata

Dosis:
36.25 en 5 Fx

N= 57

QD:
Más toxicidad GU y GI

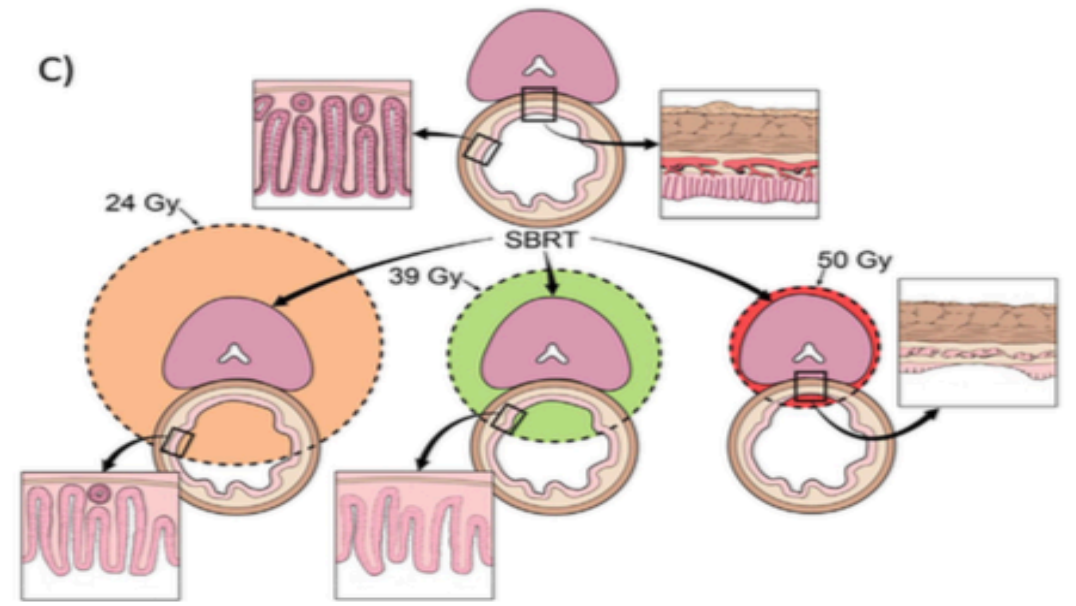
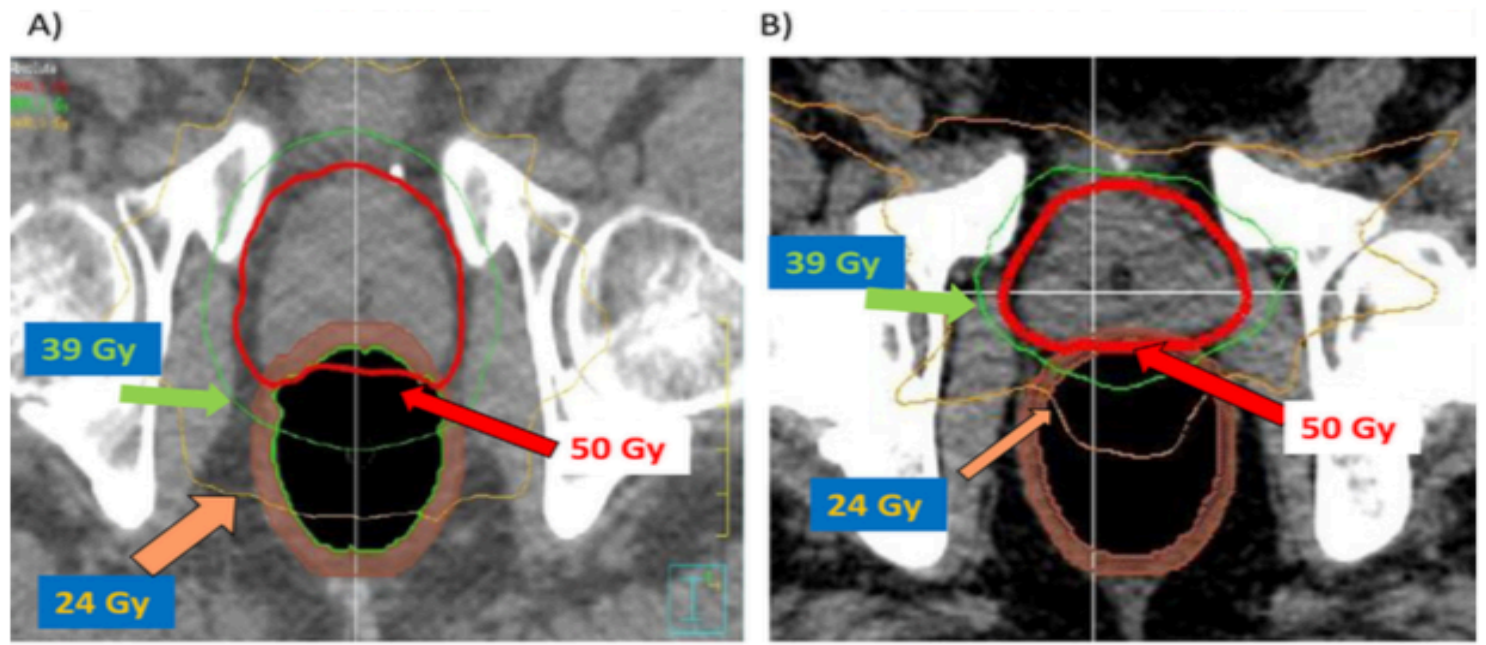
Toxicidad Rectal

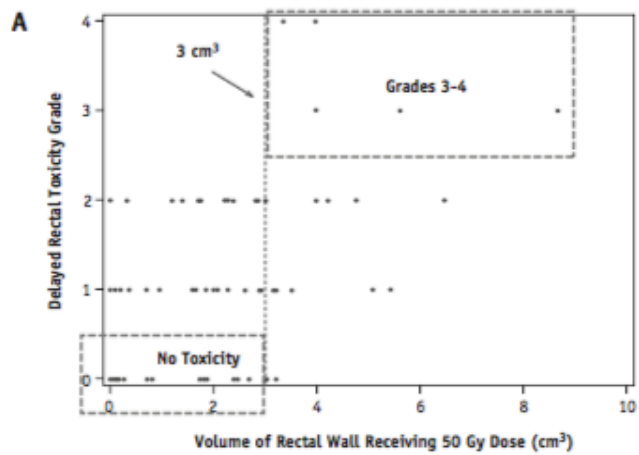
Clinical Investigation: Genitourinary Cancer

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

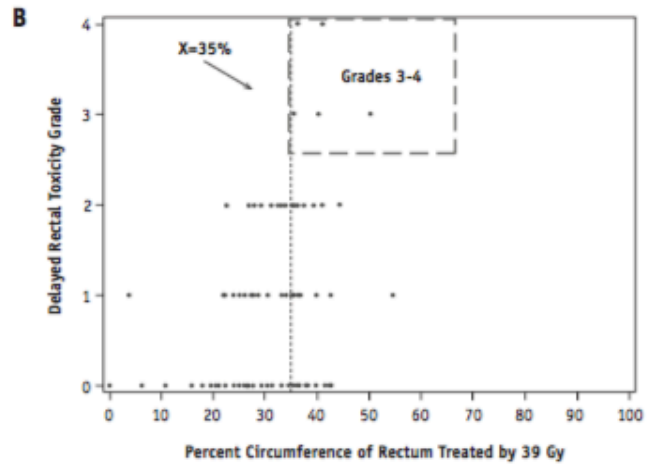


**D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,[†] Christopher Straka, BS,*
Alana Christie, MS,[‡] Yair Lotan, MD,[§] David Pistenmaa, MD,* Brian D. Kavanagh, MD,^{||}
Akash Nanda, MD, PhD,[¶] Patrick Kueplian, MD,[#] Jeffrey Brindle, MD,**
Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD,^{||} Xian-Jin Xie, PhD,[‡]
and Robert D. Timmerman, MD***

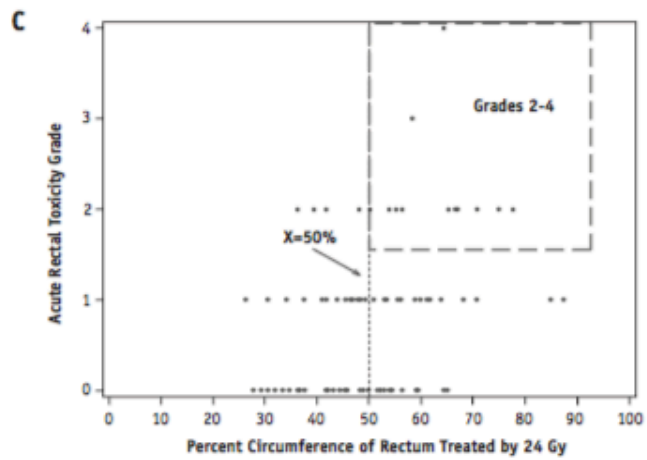




Volumen de pared rectal V50 < 3CC



% circunferencia 39 Gy < 35%



% circunferencia 24 Gy < 50%

Próstata: Estrategias

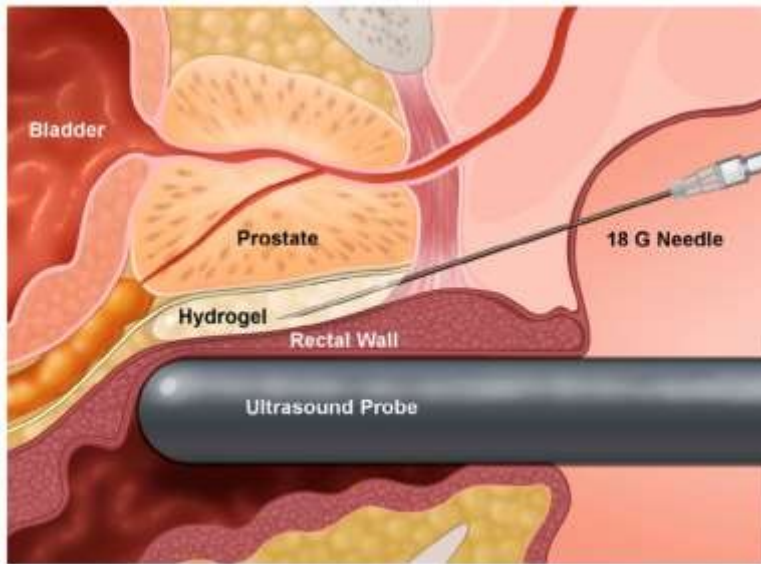


- Respetar los umbrales de dosis de HDV, incluyendo dosis moderadas y bajas



- Evitar puntos calientes
- Evitar dosis altas (no respuesta > 40 Gy)
- Días alternos
- Enemas previos, balón rectal, biogel (spacer)
- Dibujar uretra y evitarla

Espaciador Rectal: < dosis



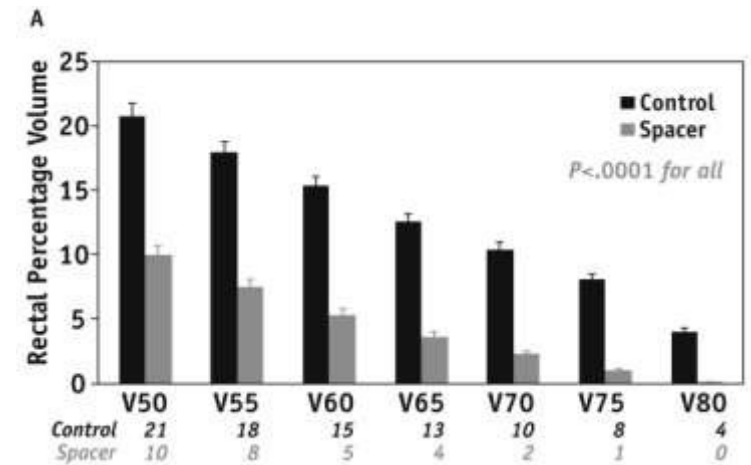
Hydrogel inyectable



Imagen TAC



Imagen RMN



Reducción en dosis
rectal con espaciador

Conclusiones

- **El conocimiento sobre tolerancia de OAR a dosis ablativa es limitado, falta seguimiento**
- **Los límites de tolerancia de dosis son estimados usando modelos LQ y deben ser validados por datos clínicos**
- **Lo más seguro es usar dosis límites de tolerancia provenientes de estudios randomizados**
- **Factores de riesgo han sido identificados y deben usarse técnicas y maniobras para mitigar estas posibles complicaciones**

