INTRAOPERATIVE RADIOTHERAPY FOR SOFT TISSUE SARCOMAS OF THE EXTREMITIES

RESULTS OF THE SPANISH POOLED ANALYSIS

Alfredo Polo (1) & Felipe Calvo (2)

On behalf of the Spanish Sarcoma Pooled Analysis

(1) Ramon y Cajal University Hospital

(2) Gregorio Marañon University Hospital

WHY A SPANISH POOLED ANALYSIS?


Bay of Biscay
Brive-la-Gaillarde
Bordeaux
Valence
Mont-de-Marsan
Montauban
Avignon
Toulouse
Nîmes
Pau
Carcassonne
Montpellier
Narbonne
Perpignan
Andorra
Girona
Viveiro
Gijón
A Coruña
Santander
Bilbao
Donostia
Carballo
Lugo
Oviedo
Santiago de Compostela
Vitoria-Gasteiz
Ponferrada
León
Pamplona
Burgos
Ourense
Vigo
Logroño
Viana do Castelo
Valladolid
Zaragoza
Lleida
Barcelona
Porto
Reus
Vilanova i la Geltrú
Salamanca
Aveiro
Viseu
Madrid
Coimbra
Talavera de la Reina
Castelló de la Plana
Balearic Sea
Ciutadella de Menorca
Portugal
España
Spain
Cáceres
València
Palma
Maó-Mahón
Santarém
Badajoz
Felanitx
Ibiza
Lisboa
Ciudad Real
Albacete
Évora
Alacant
Setúbal
Murcia
Córdoba
Jaén
Lorca
Sevilla
Cartagena
Huelva
Granada
Portimão
Faro
Jerez de la Frontera
Almería
Málaga
Esteponao
Alboran Sea
Gibraltar
الجزائر
Algiers
تيزي وزو
Tizi Ouzou
بجاية
Bejaia
الشلف
Chlef
وهران
Oran
Relizane
المدية
Médéa
البويرة
Bouira
Setif
طنجة
Tangier
برج بوعريريج
Bordj Bou Arreridj
تطوان
Tetouan
الناظور
Nador
وجدة
Oujda
سيدي بلعباس
Sidi Bel Abbes
الجلفة
Djelfa
تاوريرت
سعيدة

SPANISH POOLED ANALYSIS - SARCOMA

Aim: pooled data analysis of patients treated with multimodal concept consisting of maximal resection and IOERT with or without postoperative irradiation

RadioOnkologie

Behandeln
Forschen
Lehren

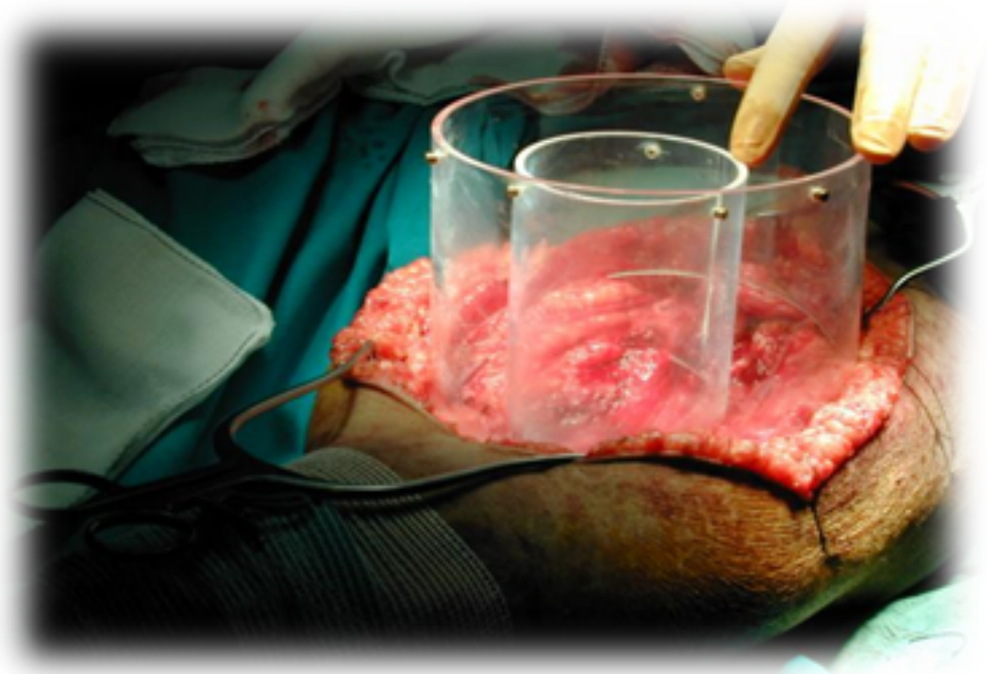
UniversitätsKlinikum Heidelberg

Intraoperative Radiation Therapy (IORT) for primary and recurrent retroperitoneal soft tissue sarcoma: First results of a poole analysis

Krempien R[1], Roeder F[1], Buchler MW[1], Di Paoli A[2], Bertola G[2], Boz G, [2]
Garcia-Sabrido JL[3], Calvo FA[3]

On behalf of the European Working Party of the International Society of Intraoperative Radiotherapy (ISIORT)

[1]University of Heidelberg, Germany, [2]National Cancer Institute, CRO Aviano, Italy,
[3]University Hospital Gregorio Maranon, Madrid, Spain



1991-2007, 320 patients, Heidelberg, Marañón, CRO Aviano

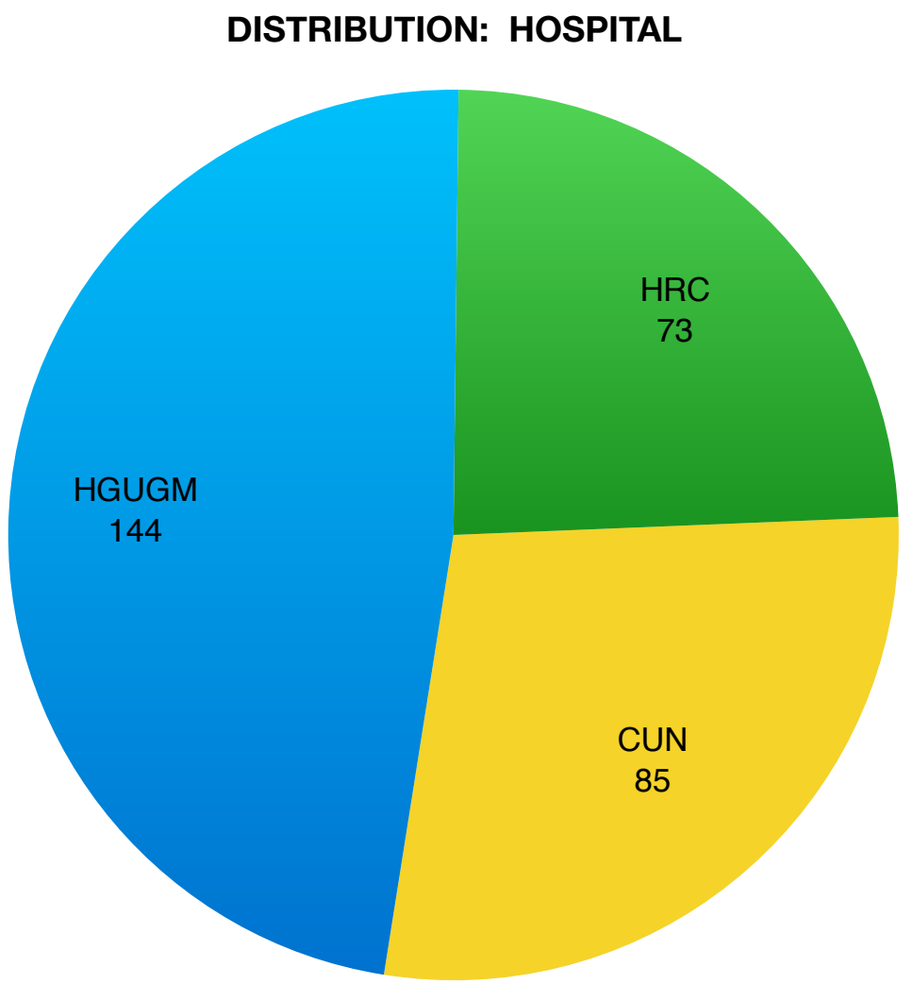
Local control 82% (5-y), survival @ 5-y R2 23% vs 75% p<0,01

Local control ≥ 15Gy (p<0,05), R2 45% vs 77% (p<0,01)

2008

POOLED ANALYSIS

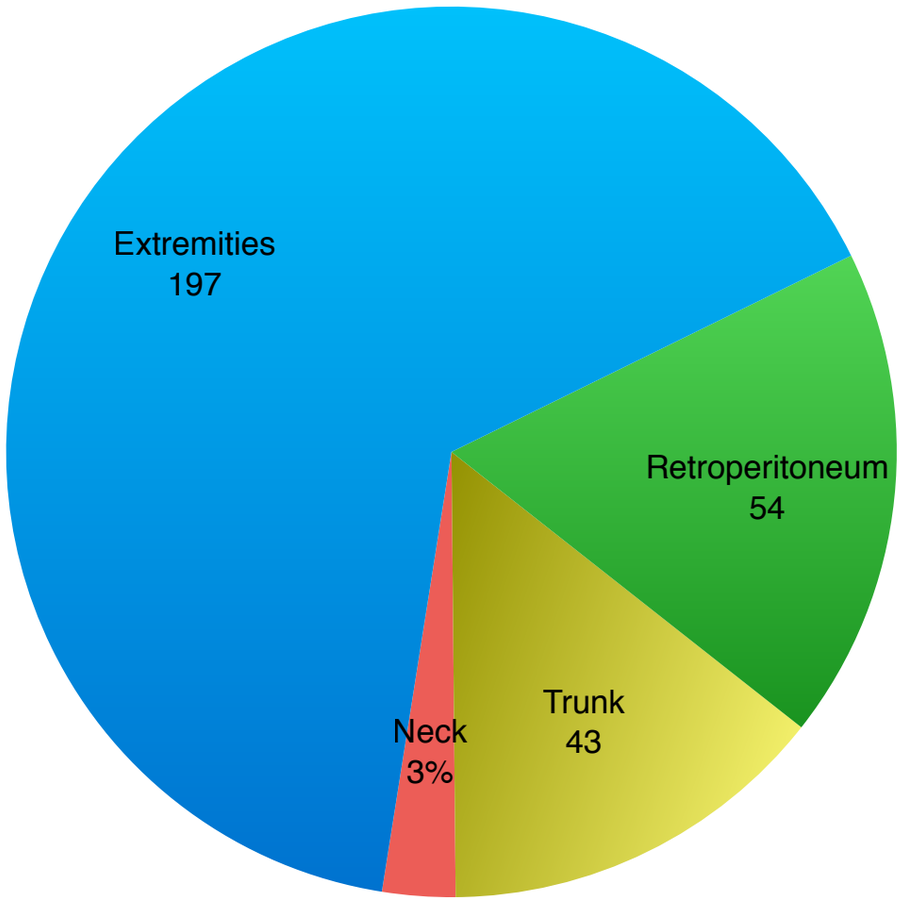
SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)



302 patients treated from 1985 to 2011

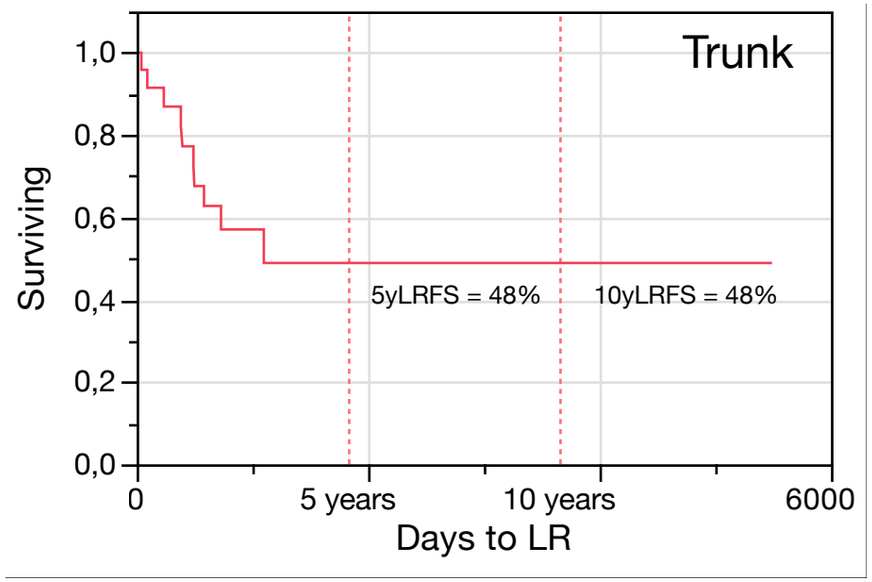
SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)

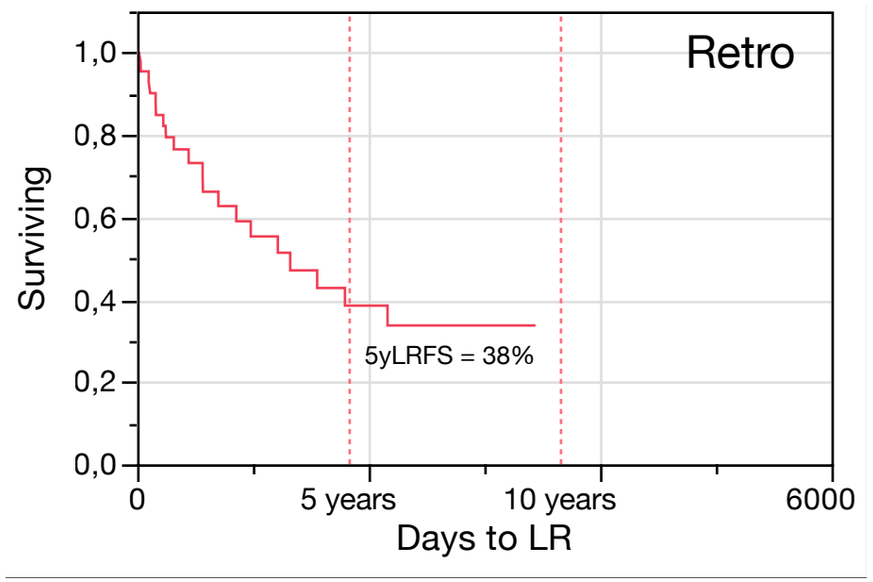
DISTRIBUTION: TUMOR LOCATION

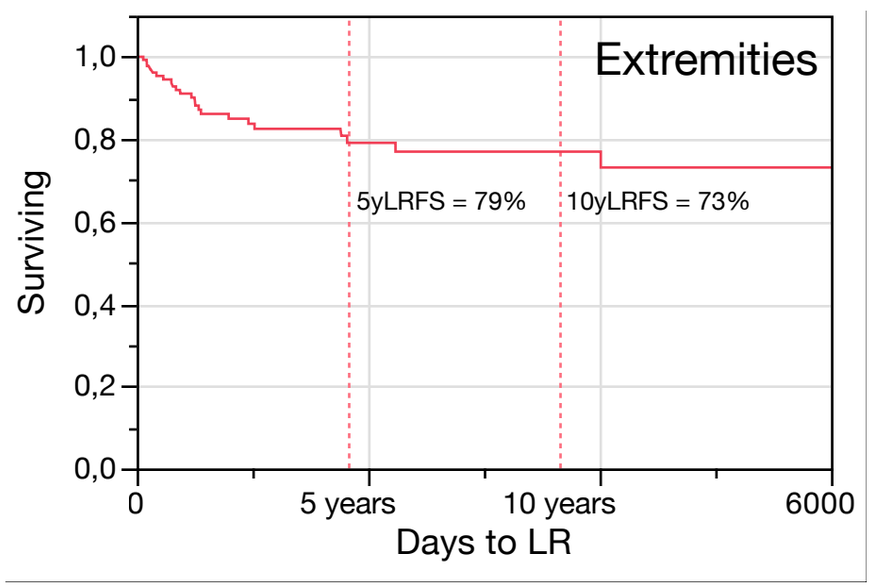


SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)

LOCAL RELAPSE FREE SURVIVAL







- Calvo FA, Sole CV, Polo A et al. Limb-sparing management with surgical resection, external-beam and intraoperative electron-beam radiation therapy boost for patients with primary soft tissue sarcoma of the extremity : A multicentric pooled analysis of long-term outcomes. Strahlenther Onkol. 2014

- Calvo FA, Sole CV, Cambeiro M et al. Prognostic value of external beam radiation therapy in patients treated with surgical resection and intraoperative electron beam radiation therapy for locally recurrent soft tissue sarcoma: a multicentric long-term outcome analysis. Int J Radiat Oncol Biol Phys. 2014;88:143-150.

- Sole CV, Calvo FA, Polo A et al. Anticipated intraoperative electron beam boost, external beam radiation therapy, and limb-sparing surgical resection for patients with pediatric soft-tissue sarcomas of the extremity: a multicentric pooled analysis of long-term outcomes. Int J Radiat Oncol Biol Phys. 2014;90:172-180.

- Sole CV, Calvo FA, Cambeiro M et al. Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue sarcomas. Clin Transl Oncol. 2014

Clin Transl Oncol
DOI 10.1007/s12094-014-1157-y

RESEARCH ARTICLE

Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue sarcomas

C. V. Sole · F. A. Calvo · M. Cambeiro · A. Polo · A. Montero · R. Hernanz · C. Gonzalez · M. Cuervo · D. Perez · M. S. Julian · R. Martinez-Monge

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Clinical Investigation

Anticipated Intraoperative Electron Beam Boost, External Beam Radiation Therapy, and Limb-Sparing Surgical Resection for Patients with Pediatric Soft-Tissue Sarcomas of the Extremity: A Multicentric Pooled Analysis of Long-Term Outcomes

Claudio V. Sole, MD,*,†,‡ Felipe A. Calvo, MD, PhD,*,† Alfredo Polo, MD, PhD,§ Mauricio Cambeiro, MD, PhD,|| Ana Alvarez, MD,¶ Carmen Gonzalez, MD,¶ Jose Gonzalez, MD,# Mikel San Julian, MD,** and Rafael Martinez-Monge, MD, PhD§

*Department of Oncology, ¶Traumatology

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Clinical Investigation: Sarcoma

Prognostic Value of External Beam Radiation in Patients Treated With Surgical Resection a Intraoperative Electron Beam Radiation Thera Recurrent Soft Tissue Sarcoma: A Multicentr Long-Term Outcome Analysis

Felipe A. Calvo, MD, PhD,*,† Claudio V. Sole, MD,*,†,‡ Mauricio Angel Montero, MD,|| Alfredo Polo, MD, PhD,|| Carmen Gonzal Miguel Cuervo, MD,# Mikel San Julian, MD,** Jose L. Garcia and Rafael Martinez-Monge, MD, PhD§

*Department of Oncology, Hospital General Universitario Gregorio Marañón, Madrid Complutense University, Madrid, Spain; ‡Service of Radiation Oncology, Instituto d §Service of Radiation Oncology, Clínica Universitaria, Universidad de Navarra, Pam Oncology, Hospital Universitario Ramón y Cajal, Universidad de Alcala, Madrid, S Hospital General Universitario Gregorio Marañón, Madrid, Spain; #Service of Orth General Universitario Gregorio Marañón, Madrid, Spain; **Service of Orthopedics Universitaria, Universidad de Navarra, Pamplona, Spain; and ††Service of Gener Universitario Gregorio Marañón, Madrid, Spain

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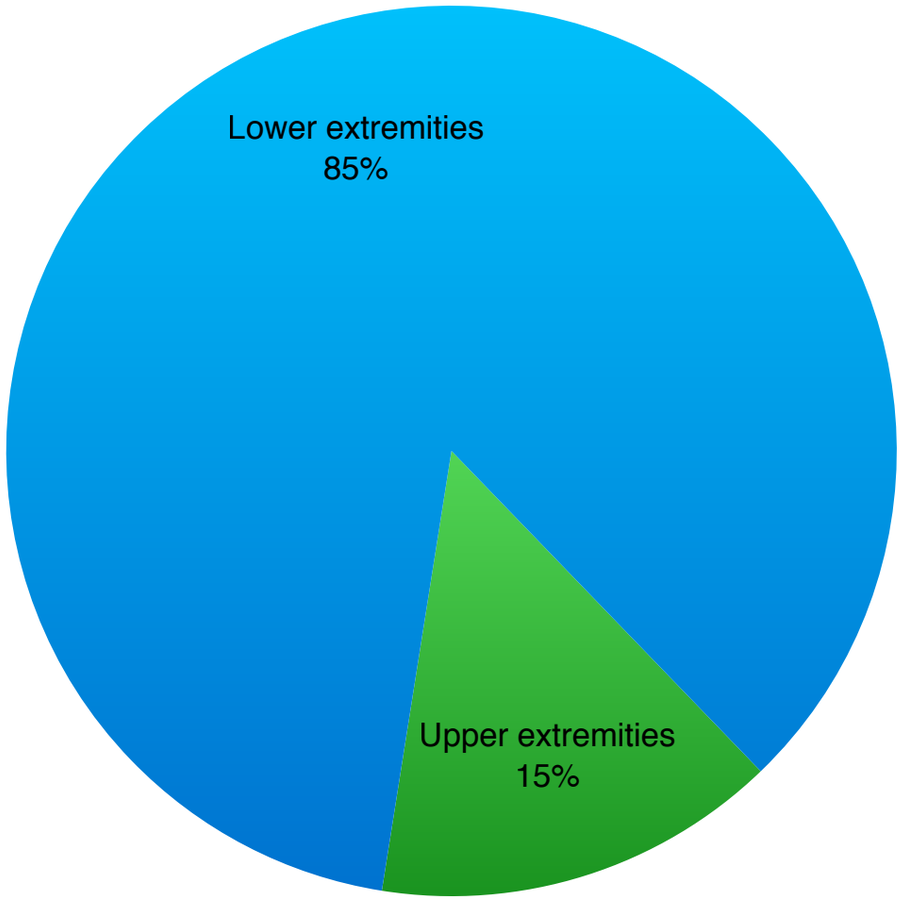
RESULTS OF THE POOLED ANALYSIS FOR THE EXTREMITIES SUBGROUP

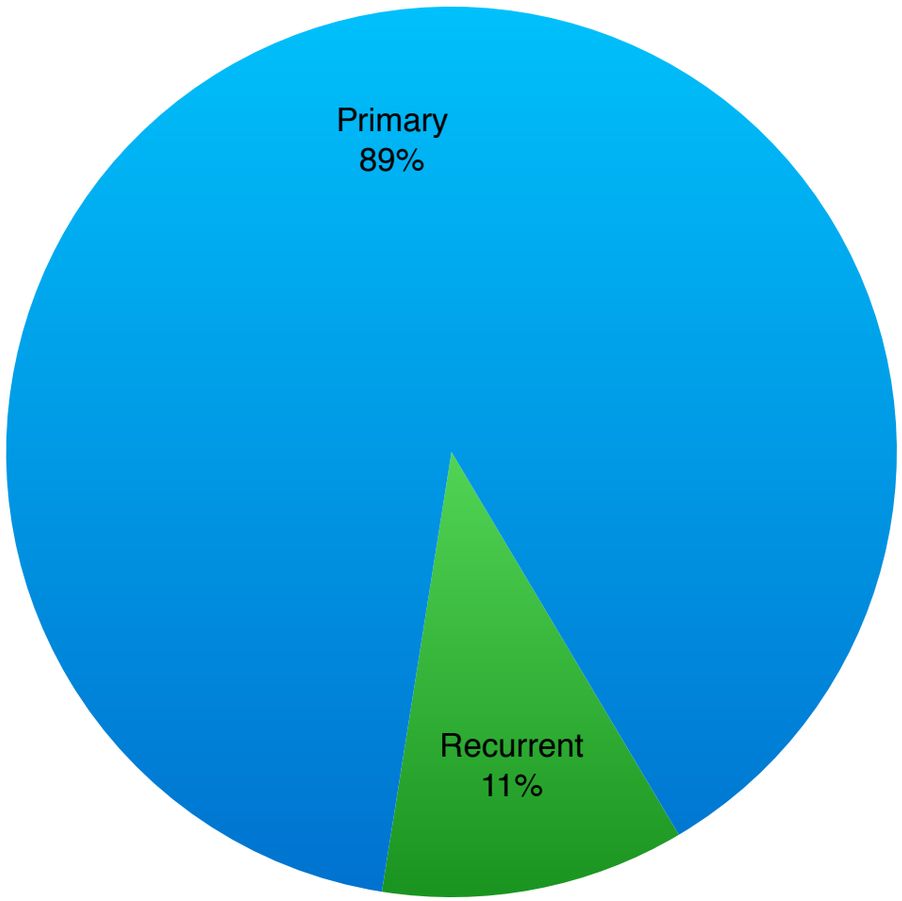
SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)

DISTRIBUTION: TUMOR LOCATION



SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)

DISTRIBUTION: PRIMARY vs. RECURRENT



SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)

PATIENT AND TUMOR CHARACTERISTICS

CHARACTERISTIC		VALUE
Gender	Male	66 (48%)
	Female	72(52%)
Age at diagnosis	Median	52 y.
Histologic type	Synovial sarcoma	16
	Leiomyosarcoma	20
	Malignant fibrous histiocytoma	40
	Liposarcoma	54
	Sarcoma NOS	12
	Other	55
Histologic grade	G1	39(19%)
	G2	51 (25%)
	G3	87 (44%)
	G4	2 (1%)
Largest tumor diameter	Median	10 cm.
	Range	1 - 33 cm.
AJCC stage	IA	4
	IB	36
	IIA	13
	IIB	38
	III	60
	IV	5
Tumor location	Upper extremities	29 (14%)
	Lower extremities	168 (86%)
Primary vs. Recurrent	Primary	159 (80%)
	Recurrent	38 (19%)

SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)

TREATMENT CHARACTERISTICS

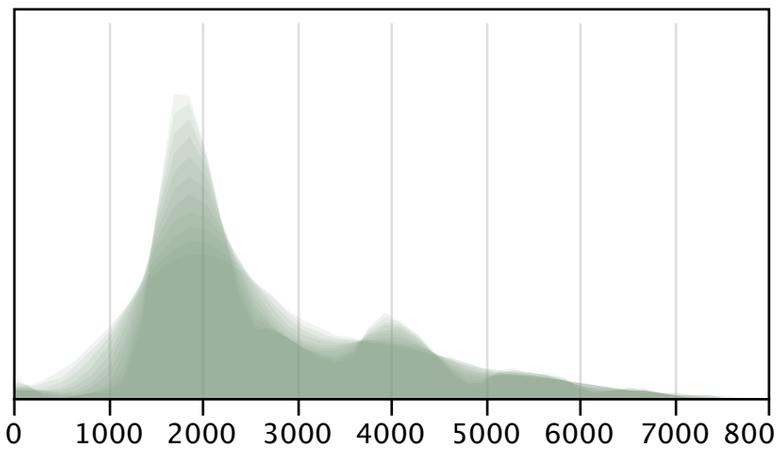
CHARACTERISTIC		VALUE
Resection type	R0	158 (80.2%)
	R1	27 (13.7%)
	R2	11 (5.5%)
EBRT dose (Gy)	Median	50 Gy
	Range	25.2 - 60.4 Gy
IORT dose (Gy)	Median	12.5 Gy (HRC: 15Gy; HGUGM: 10Gy; CUN: 15Gy)
	Range	7.5 - 20 Gy
Total physical dose	Median	60 Gy
	Range	32.7 - 72.9
Chemotherapy	Yes	37 (21%)
	No	155 (79%)

SPANISH POOLED ANALYSIS - SARCOMA
(SUBGROUP - EXTREMITIES ONLY)

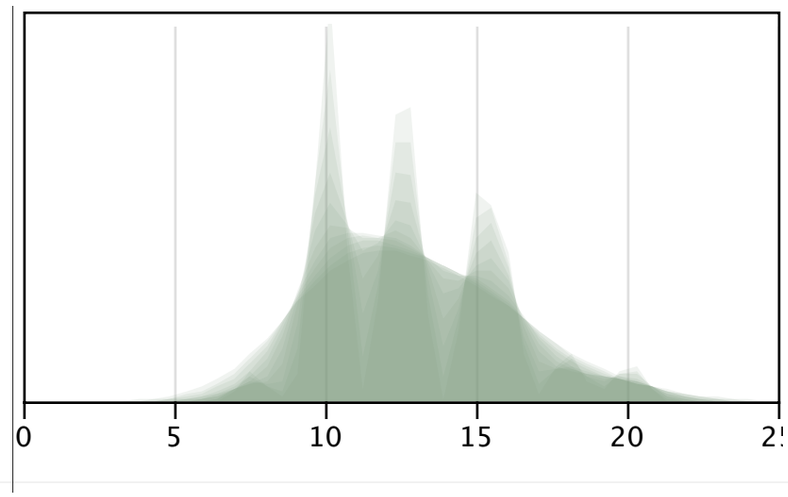
IORT CHARACTERISTICS

PARAMETER		VALUE
Electron energy (MeV)	4	13
	6	69
	8	22
	9	5
	10	7
	12	18
	15	3
	18	1
Aplicator diameter (cm)	5	2
	6	13
	7	8
	8	5
	9	27
	10	19
	12	22
	15	8
IORT fields	1	104
	2	31
	3	1
	4	2
Monitor units	Mean	2224
	Range	1083 - 6775

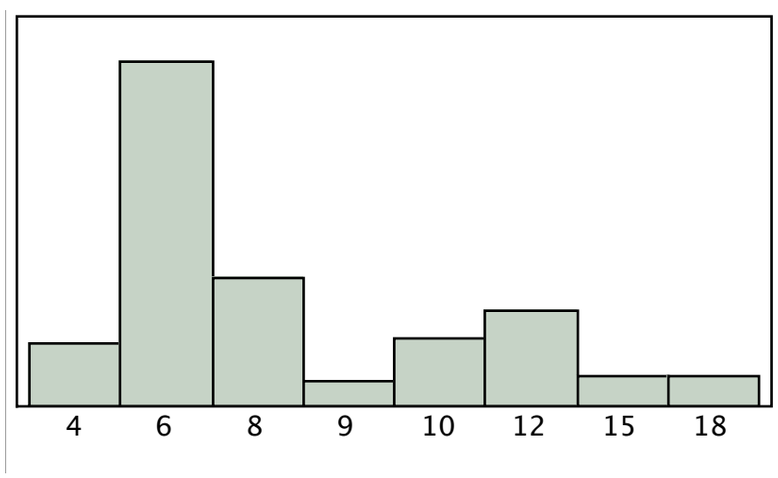
IORT - MONITOR UNITS



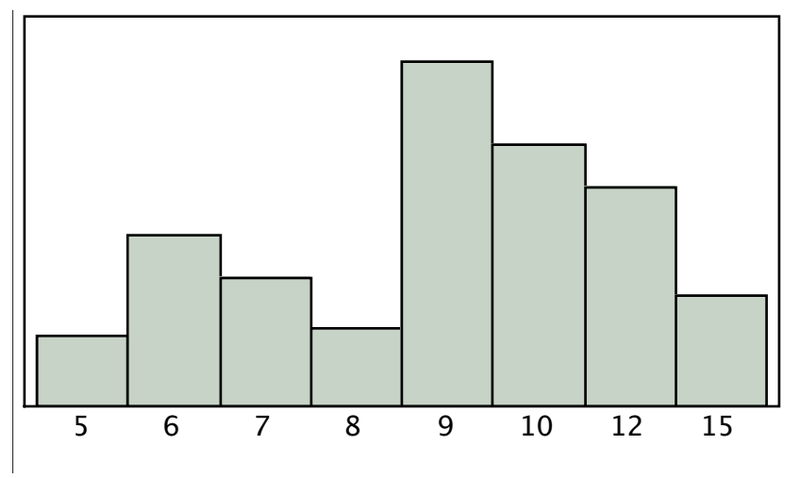
IORT - NOMINAL DOSE (Gy)

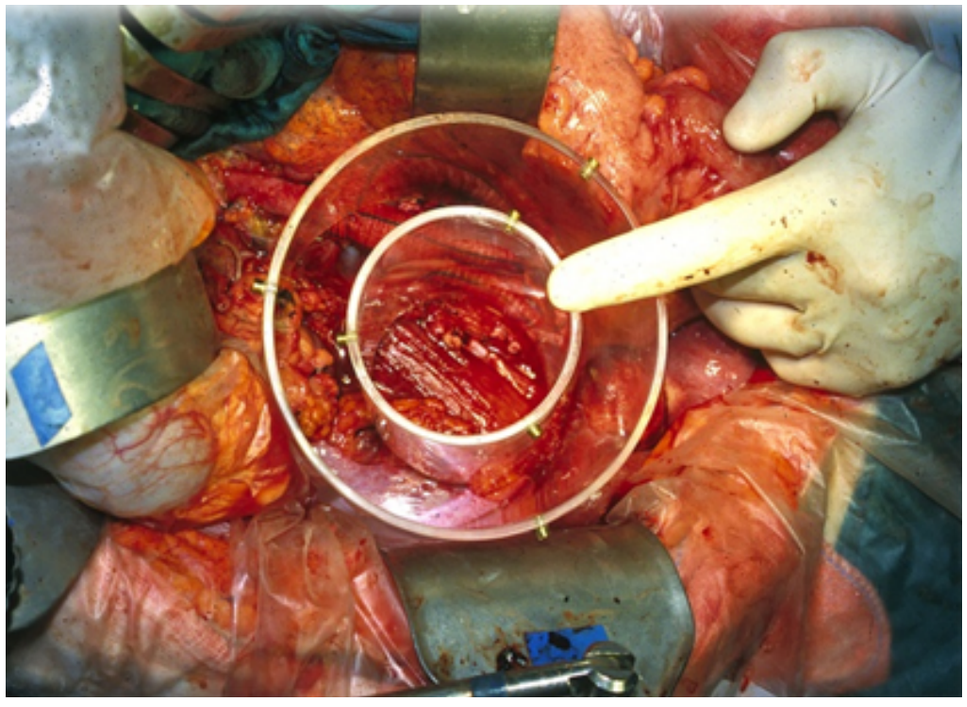


IORT - ELECTRON ENERGY (MeV)

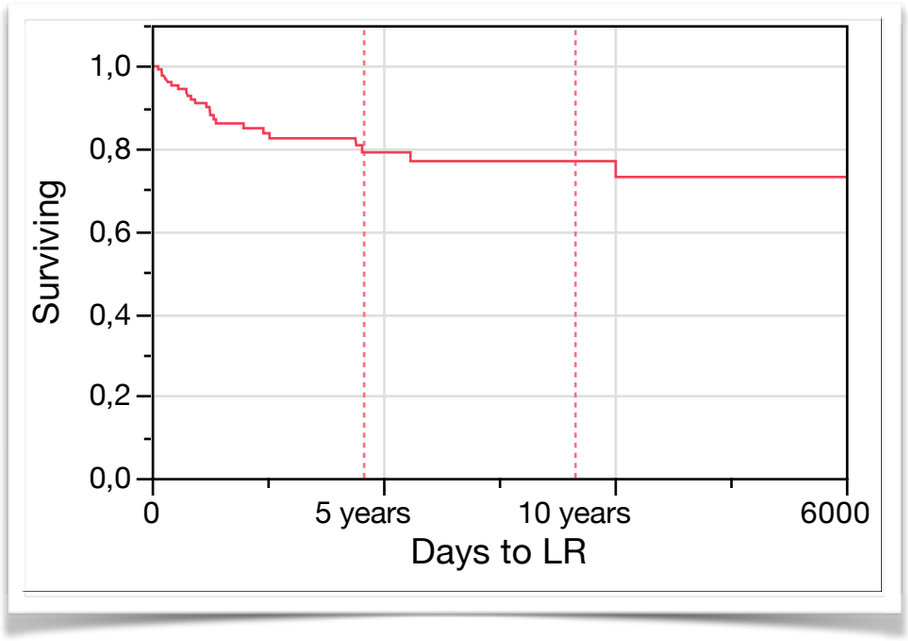


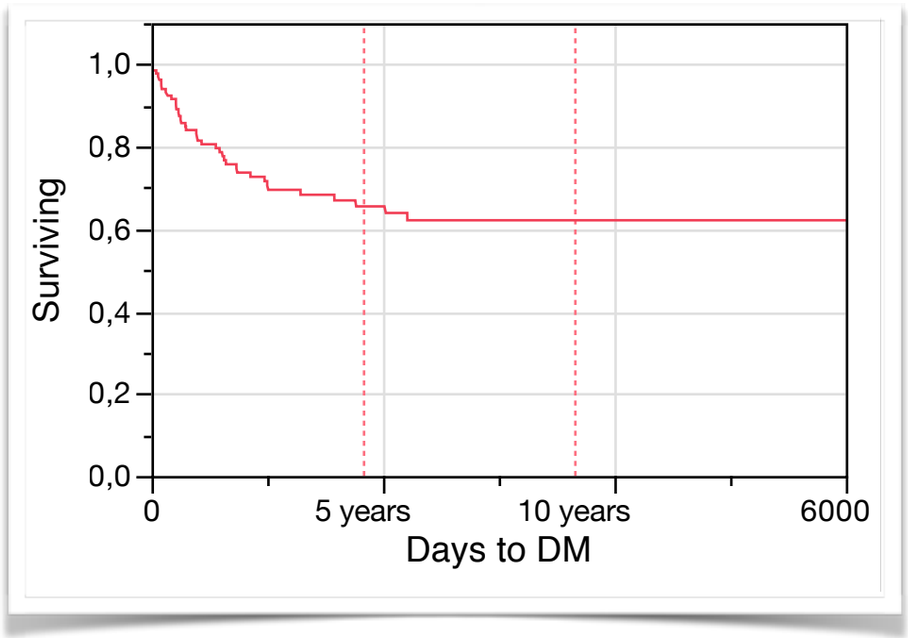
IORT - APPLICATOR SIZE (cm.)

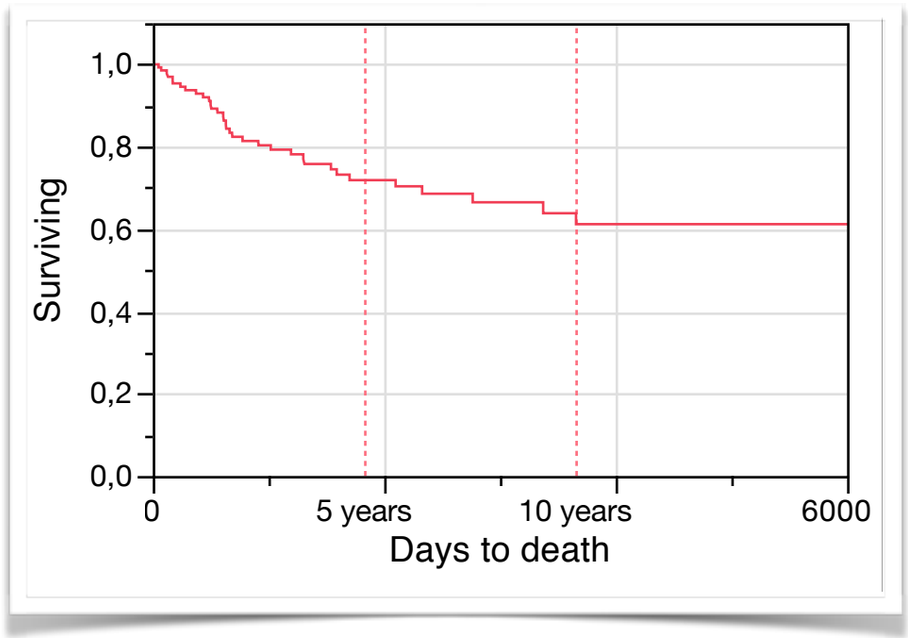




- Median FU = 3.6 y.
- Median FU (CUN) = 7.3 y.
- Median FU (HGUGM) = 5.0 y.
- Median FU (HRC) = 1.5 y.



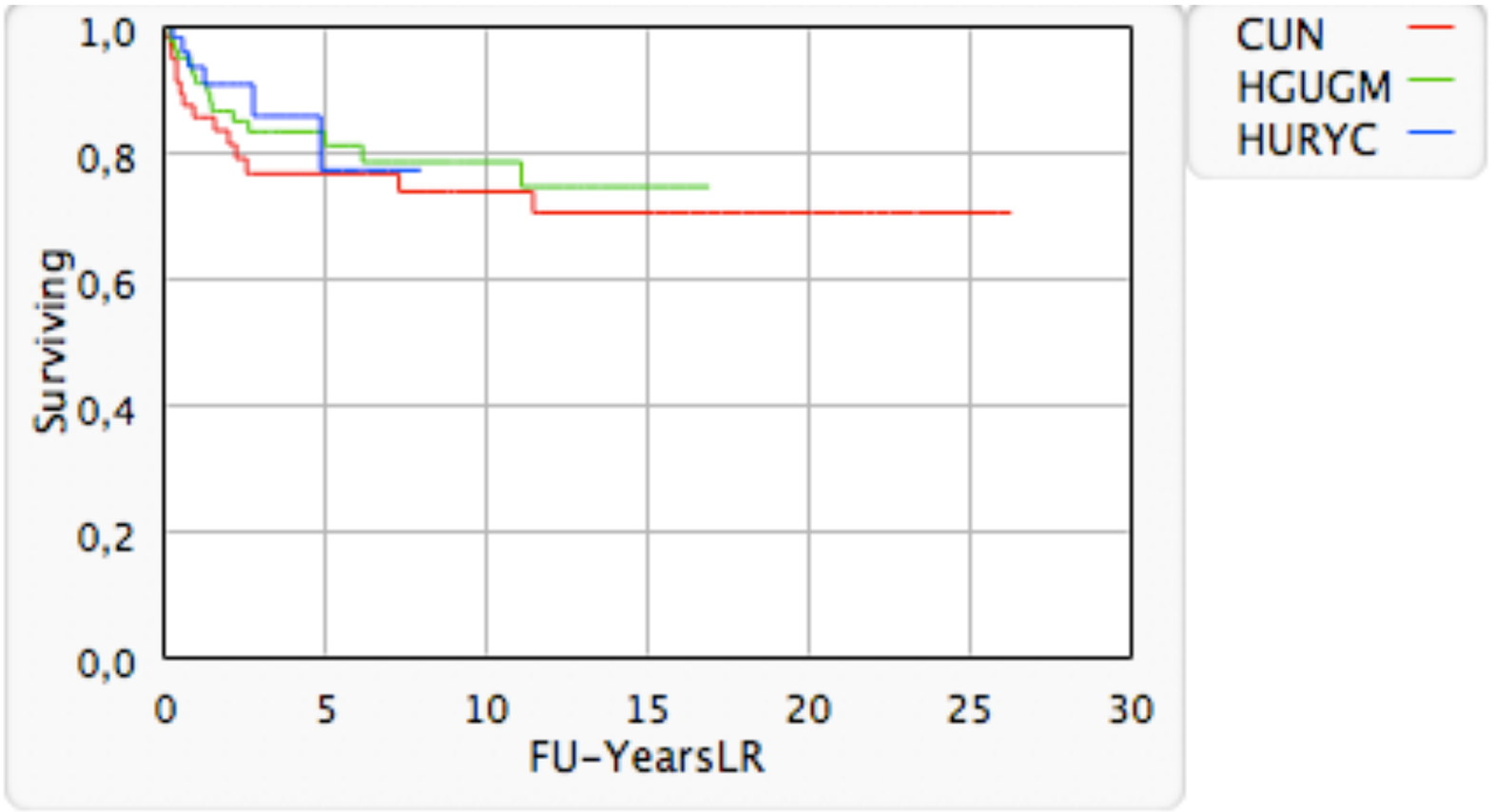




	LRFS	DMFS	OS
5y	79%	65%	71%
10y	76%	62%	61%

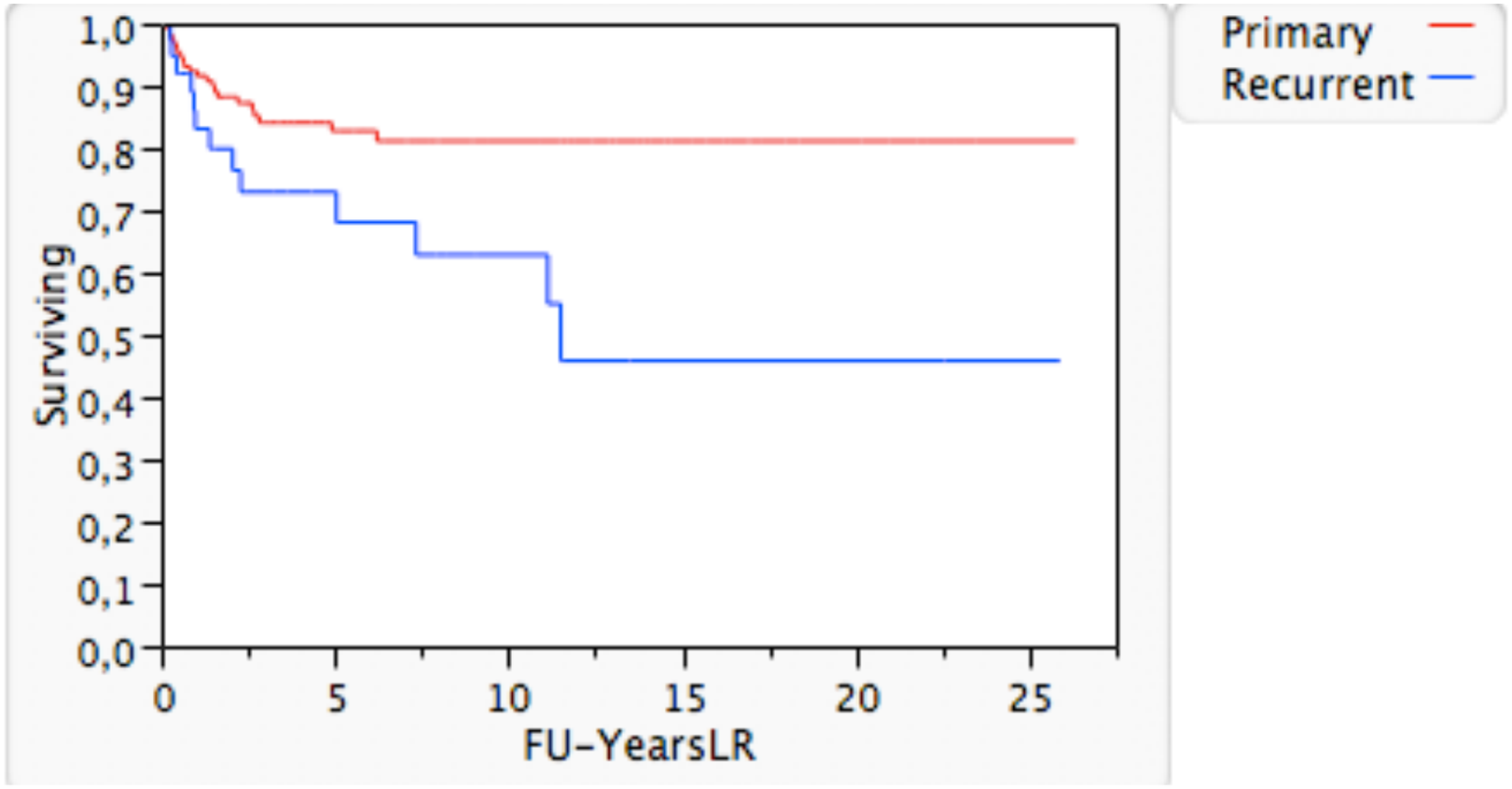
FACTORS AFFECTING LRFS

IMPACT OF HOSPITAL ON LOCAL RELAPSE



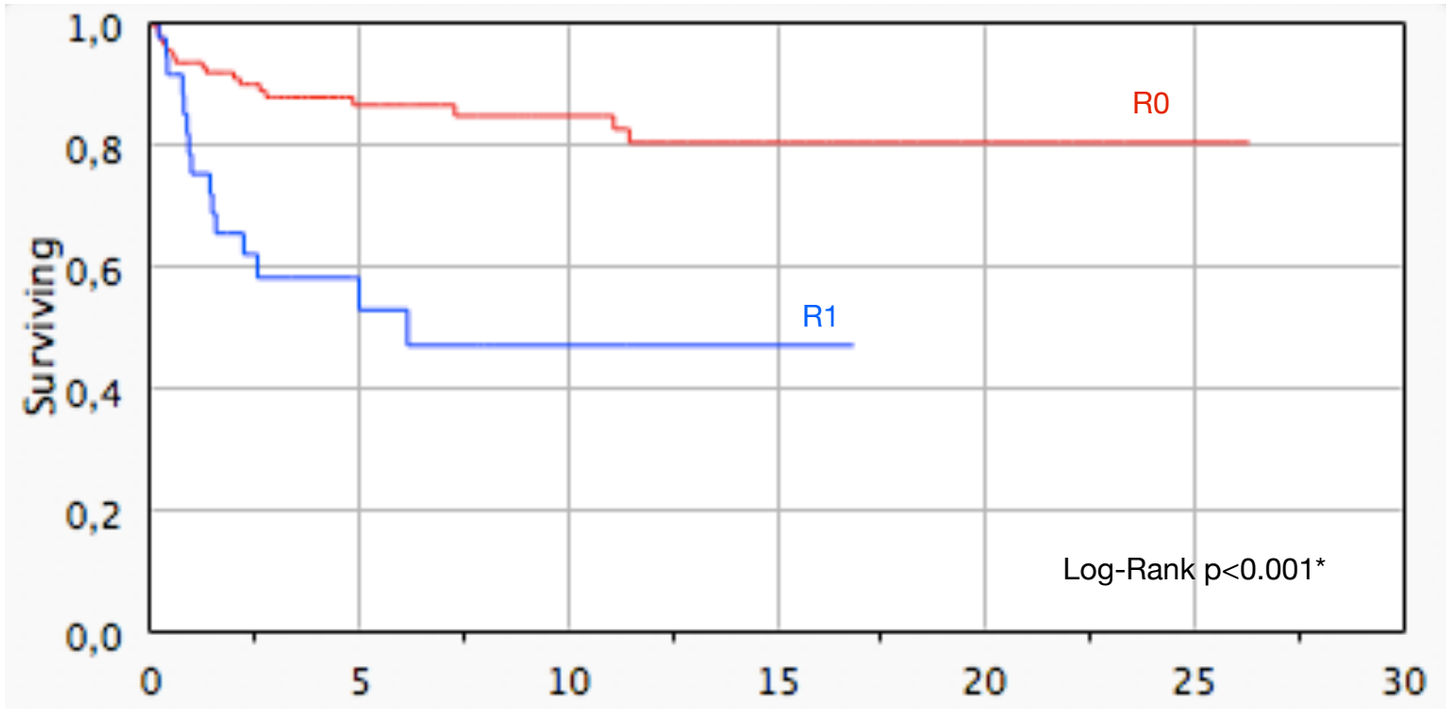
	HGUGM	CUN	HRC
5yLRFS	81%	76%	76%
10yLRFS	78%	73%	-
20yLRFS	-	70%	

PRIMARY vs. RECURRENT TUMOR



	Primary	Recurrent
5yLRFS	83%	81%
10yLRFS	72%	62%

RESECTION STATUS: R0 vs. R1

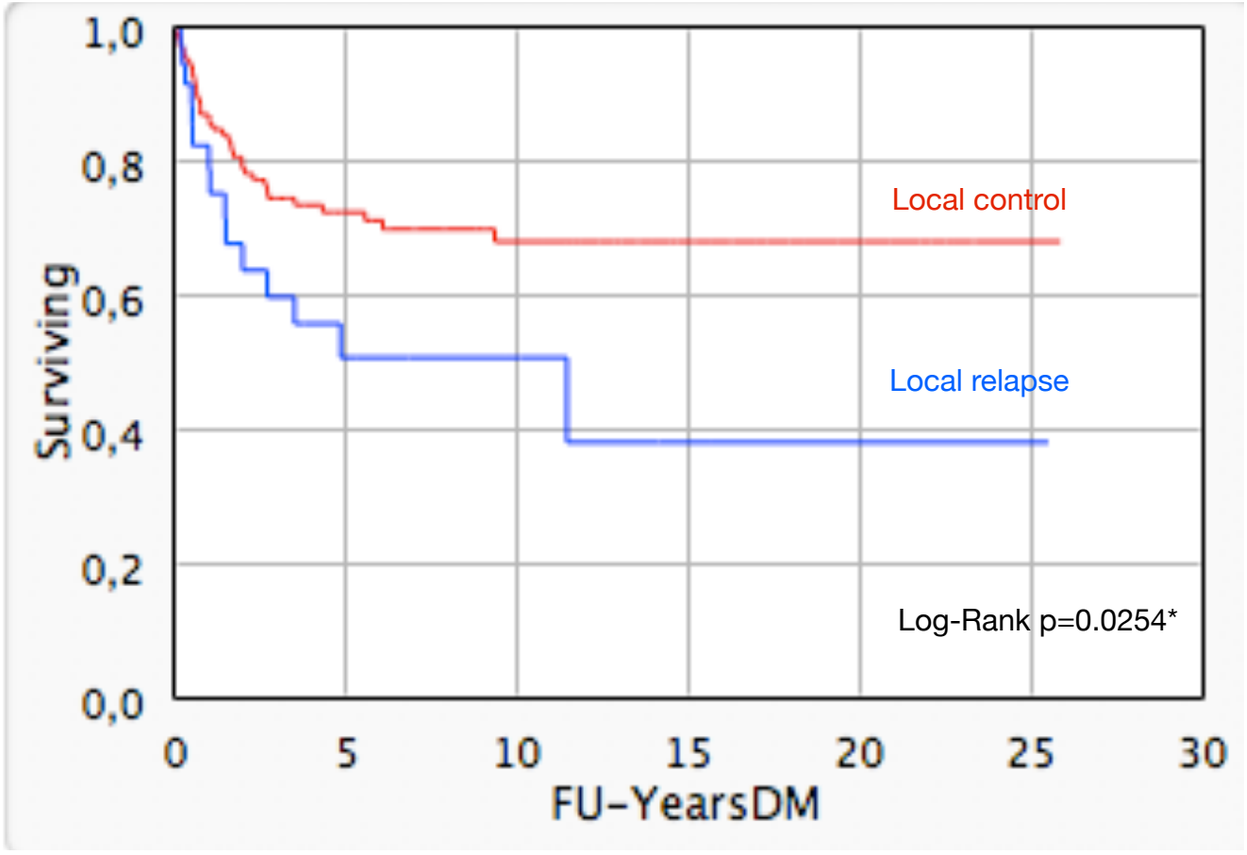


	R0	R1
5yLRFS	86%	57%
10yLRFS	85%	47%
20yLRFS	80%	-

- Only factor in multivariate analysis

FACTORS AFFECTING DMFS

DISTANT METASTASES FREE SURVIVAL

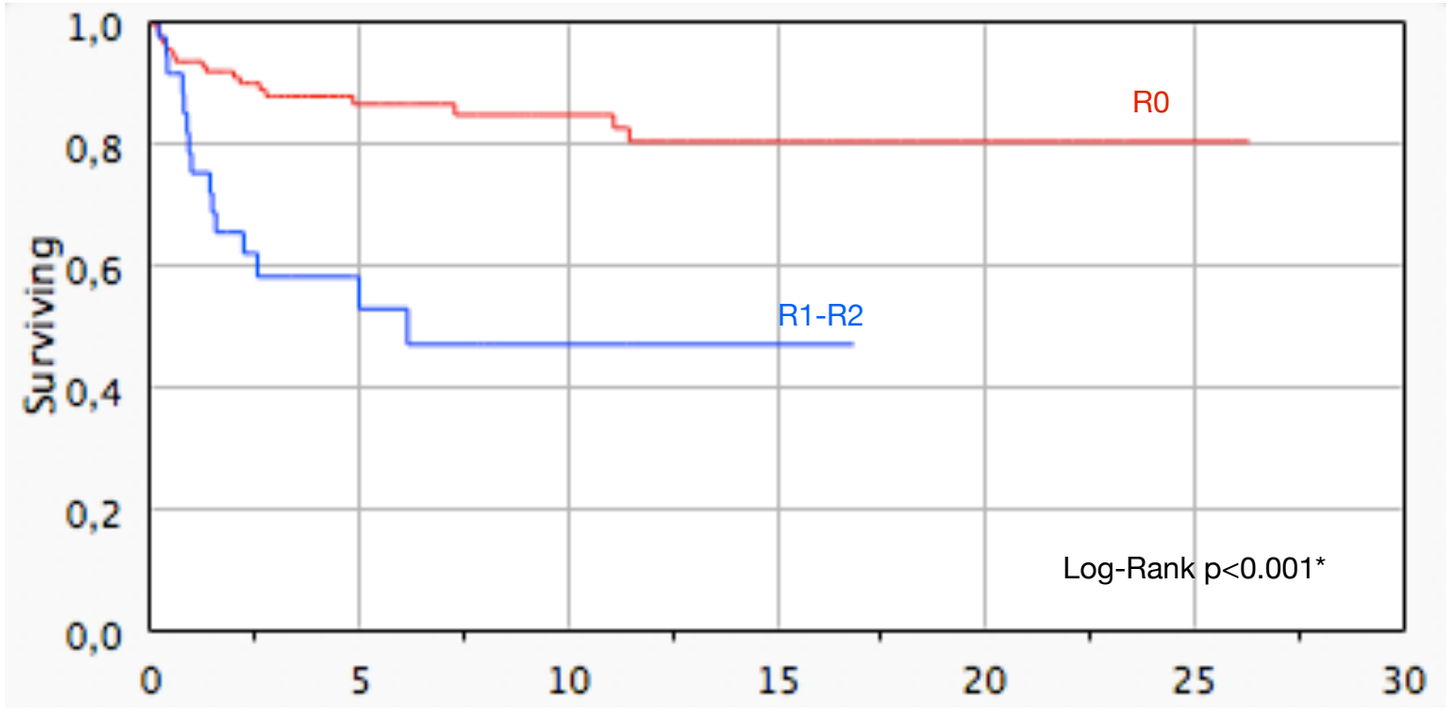


	Local control	Local relapse
5yLRFS	72%	51%
10yLRFS	68%	51%

DOSE - RESPONSE

SARCOMA (SUBGROUP - EXTREMITIES)
DOSE - RESPONSE ANALYSIS

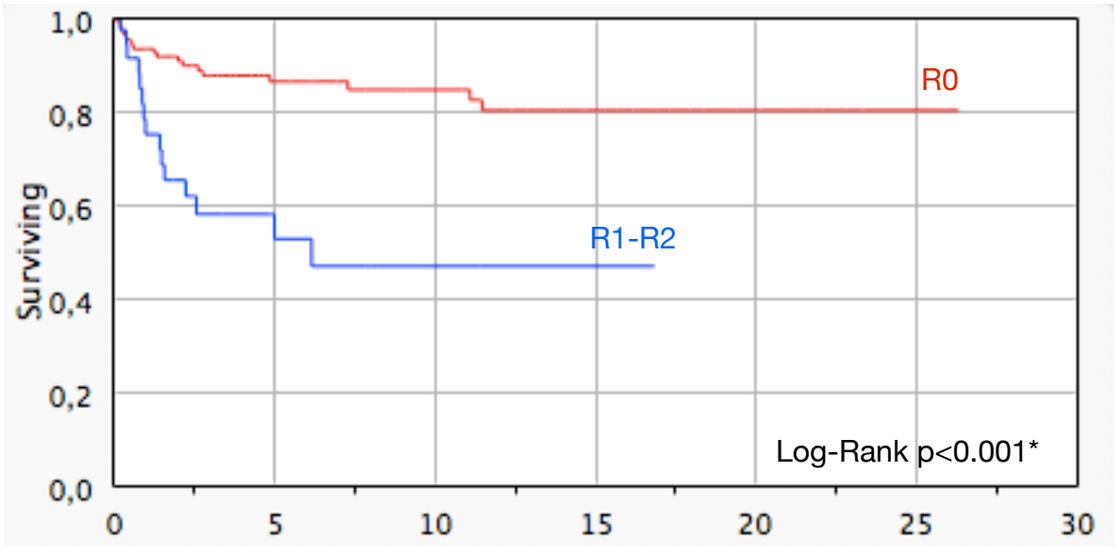
RESECTION STATUS: R0 vs. R1-R2



	R0	R1-R2
5yLRFS	86%	57%
10yLRFS	85%	47%
20yLRFS	80%	-

SARCOMA (SUBGROUP - EXTREMITIES)
DOSE - RESPONSE ANALYSIS

RESECTION STATUS: R0 vs. R1-R2



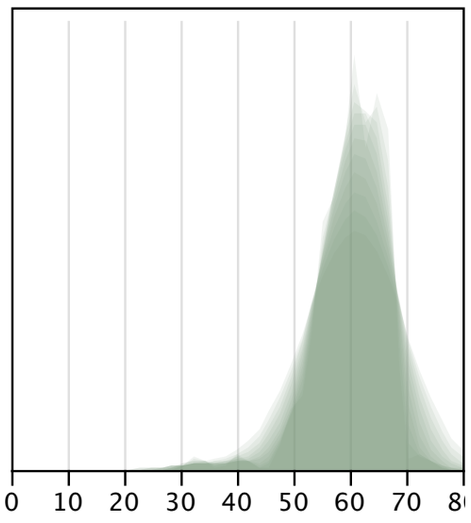
Years

	R0	R1-2
5yLRFS	86%	57%
10yLRFS	85%	47%
20yLRFS	80%	-

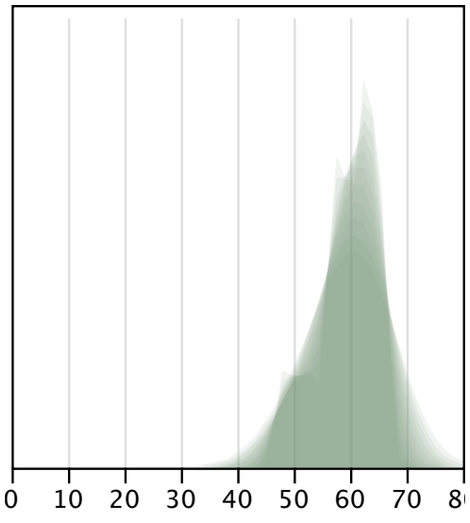
DOSE STATISTICS: R0 vs. R1-R2

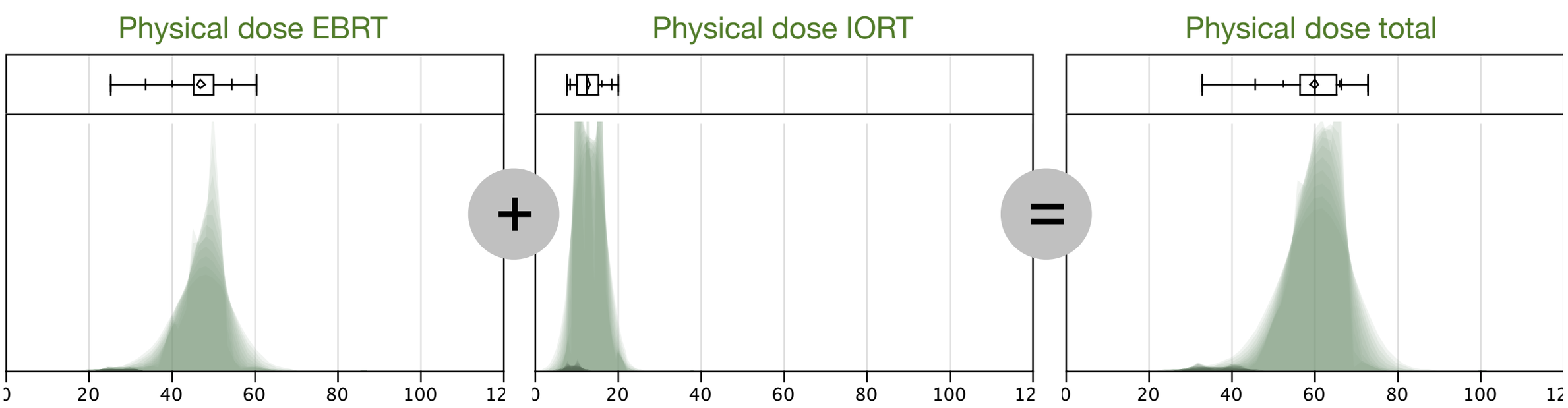
	R0	R1-2
Median dose IORT (Gy)	12.5	12.5
Median dose EBRT (Gy)	50	50
Median total dose (Gy)	60	60

PHYSICAL DOSE - R0



PHYSICAL DOSE - R1-R2




Physical dose EBRT
Physical dose IORT
Physical dose total
+
=
0
20
40
60
80
100
12

Int. J. Radiation Oncology Biol. Phys., Vol. 46, No. 2, pp. 507–513, 2000

0360-3016/00/$–see front matter

ELSEVIER

PII S0360-3016(99)00330-2

PHYSICS CONTRIBUTION

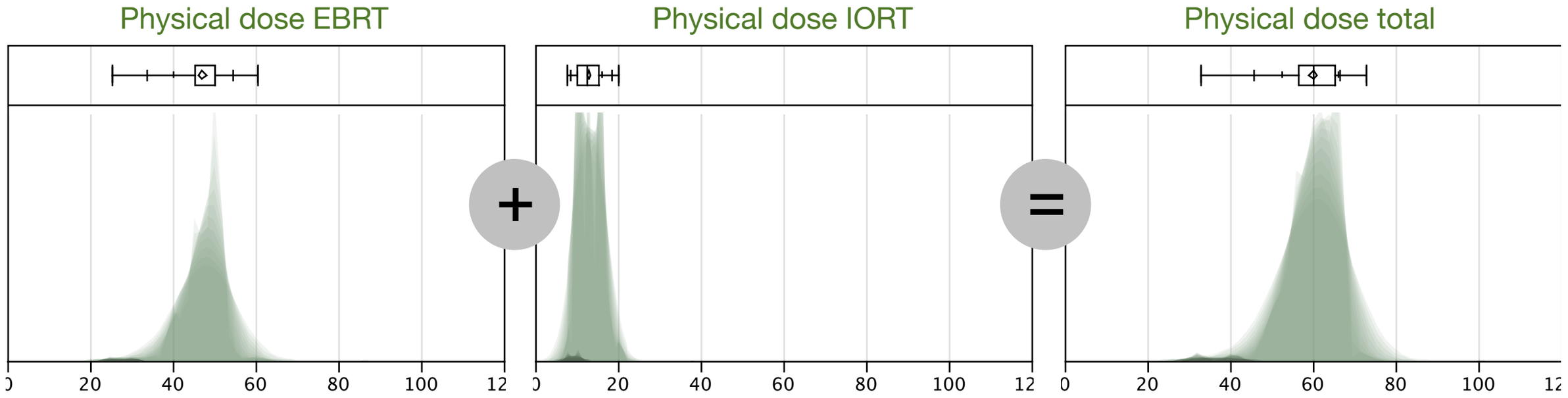
A SIMPLE METHOD OF OBTAINING EQUIVALENT DOSES FOR USE IN HDR BRACHYTHERAPY

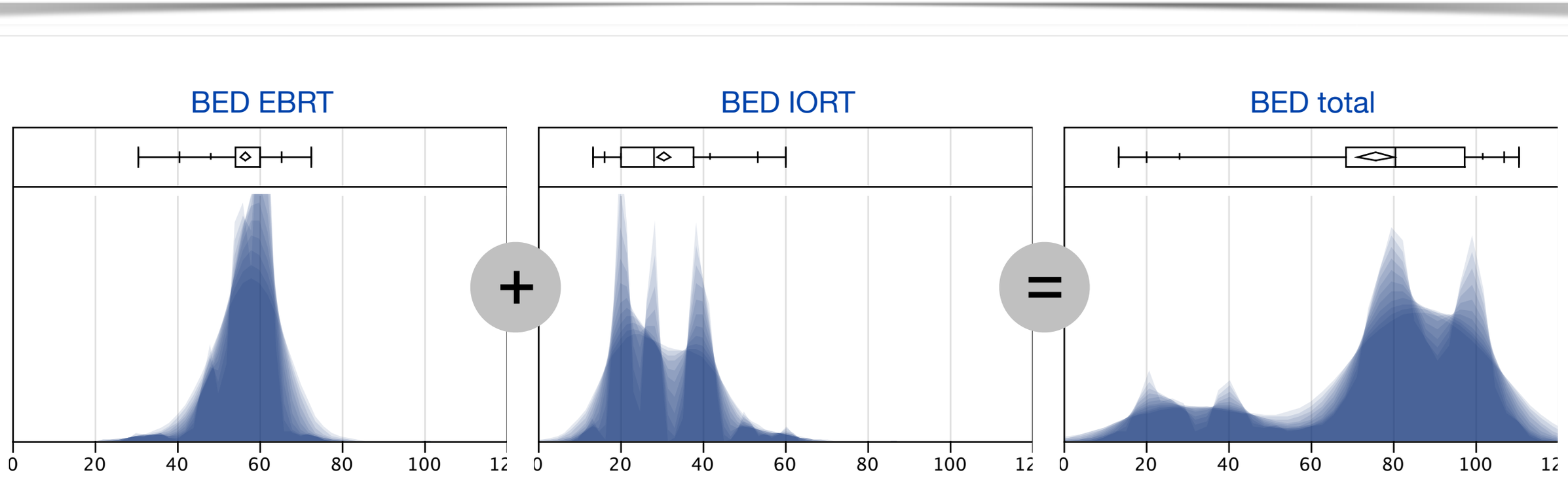
SUBIR NAG, M.D., AND NILENDU GUPTA, PH.D.

Division of Radiation Oncology, Arthur G. James Cancer Hospital and Research Institute, Ohio State University, Columbus, OH

$$\mathrm{BED} = nd\left[1 + \frac{\mathrm{d}}{(\alpha/\beta}\right] \qquad (1)$$

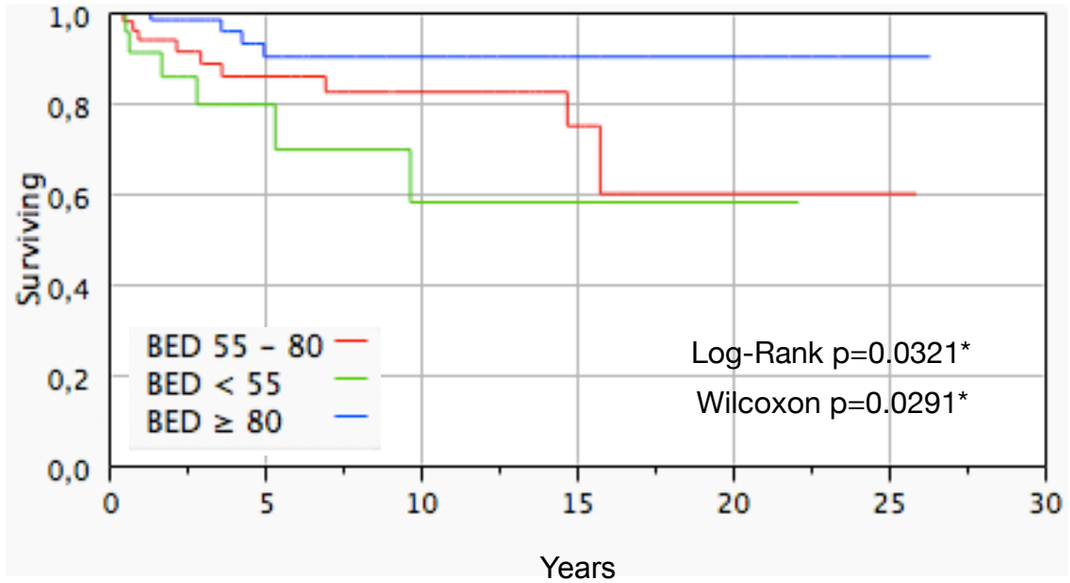
$$\mathrm{D_{Eq}} = \frac{\mathrm{BED}}{\left(1 + \frac{\mathrm{d_{REF}}}{(\alpha/\beta)}\right)} \qquad (2)$$


Physical dose EBRT
Physical dose IORT
Physical dose total
+
=
0
20
40
60
80
100
12


BED EBRT
BED IORT
BED total
+
=
0
20
40
60
80
100
12

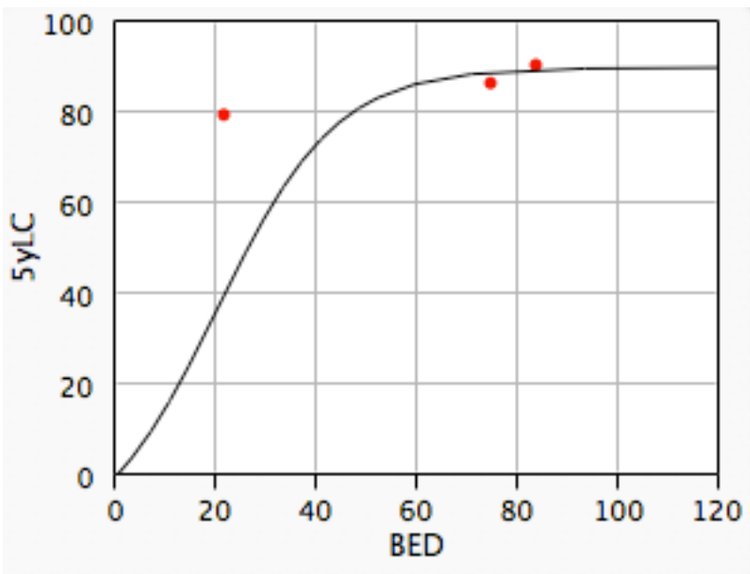
SARCOMA (SUBGROUP - EXTREMITIES)
DOSE - RESPONSE ANALYSIS

MARGIN STATUS - R0

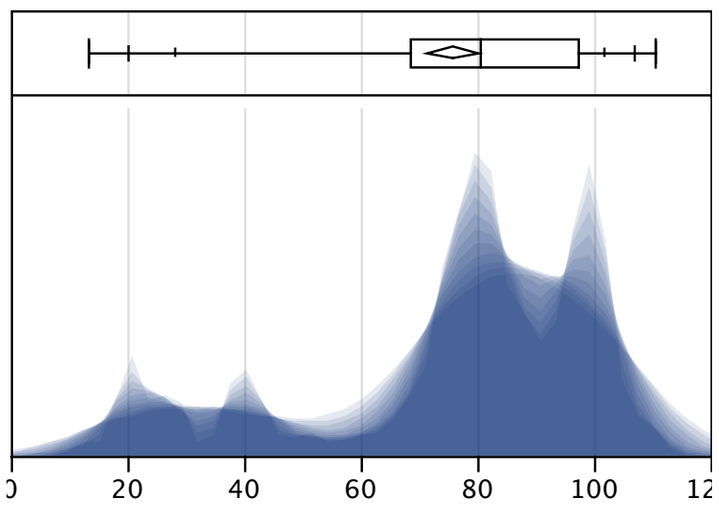


	5yLC	10yLC	20yLC
BED ≥ 80	90%	90%	90%
BED 55 - 80	86%	82%	58%
BED < 55	80%	60	58%

NONLINEAR FIT (LOGISTIC 4p) - R0

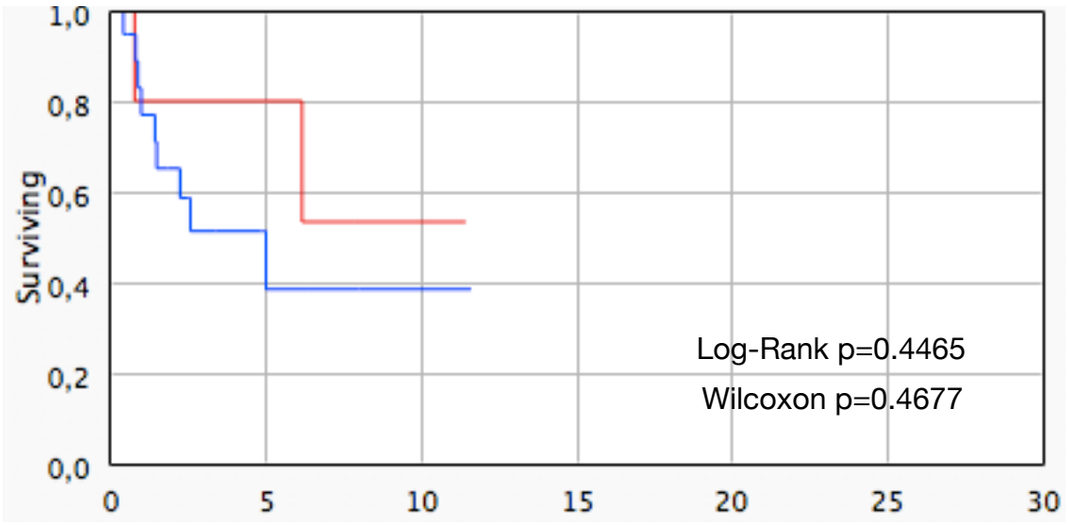


BED TOTAL



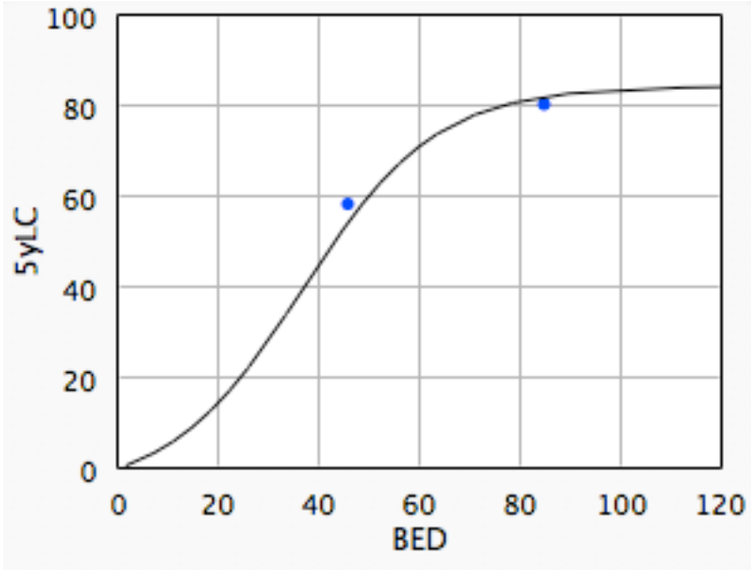
SARCOMA (SUBGROUP - EXTREMITIES)
DOSE - RESPONSE ANALYSIS

MARGIN STATUS - R1

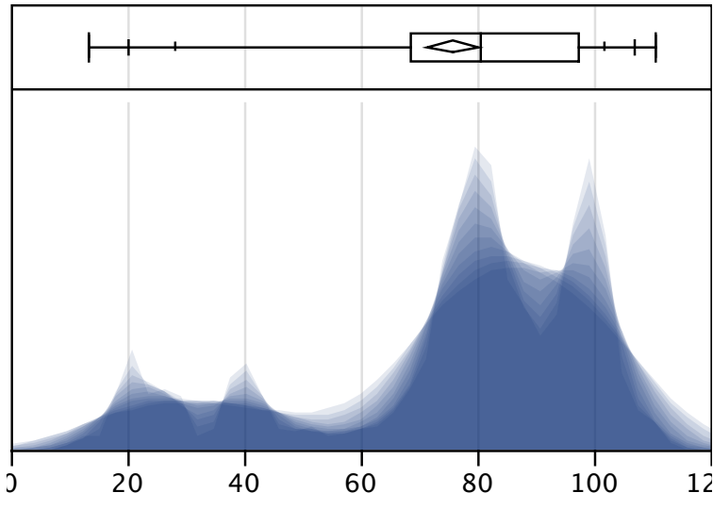


	5yLC	10yLC	20yLC
BED ≥ 65	80%	53%	-
BED < 65	51%	38%	-

NONLINEAR FIT (LOGISTIC 4p) - R1

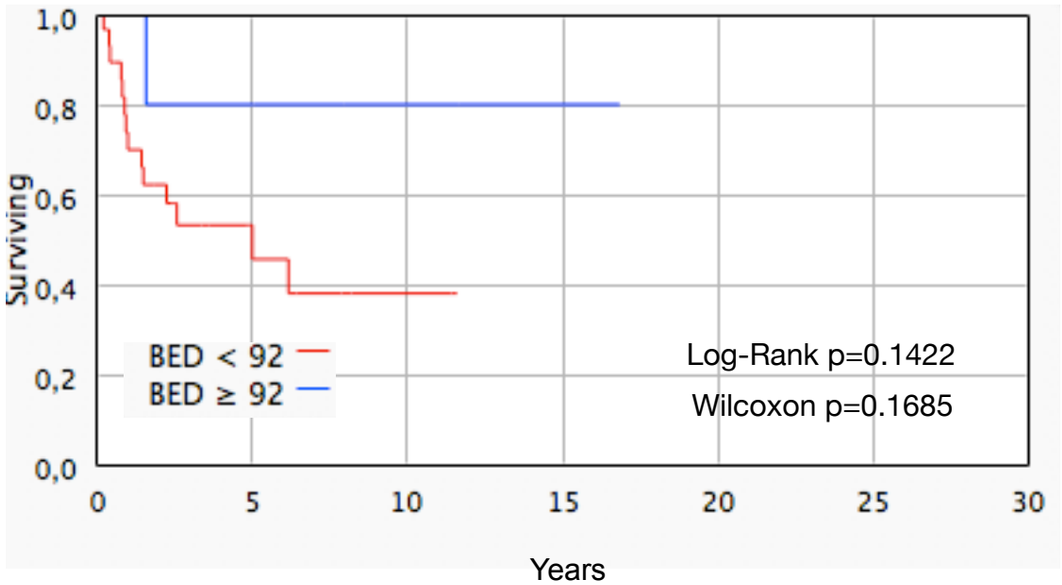


BED TOTAL



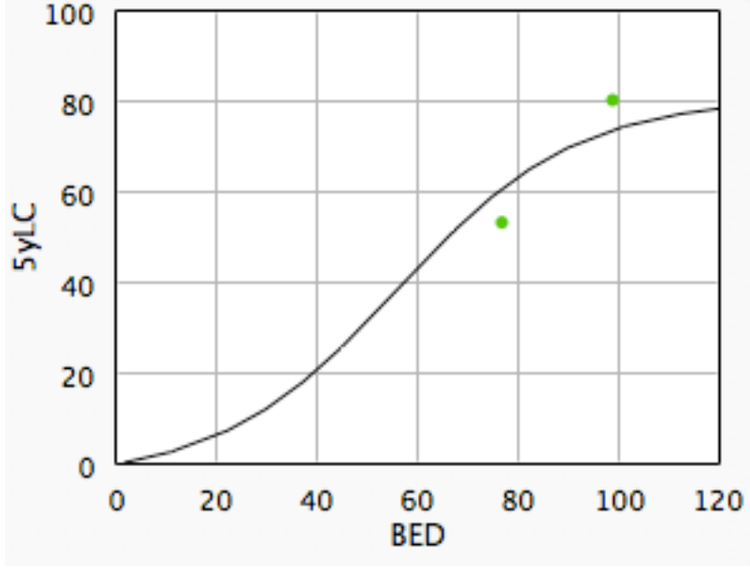
SARCOMA (SUBGROUP - EXTREMITIES)
DOSE - RESPONSE ANALYSIS

MARGIN STATUS - COMBINED R1 and R2

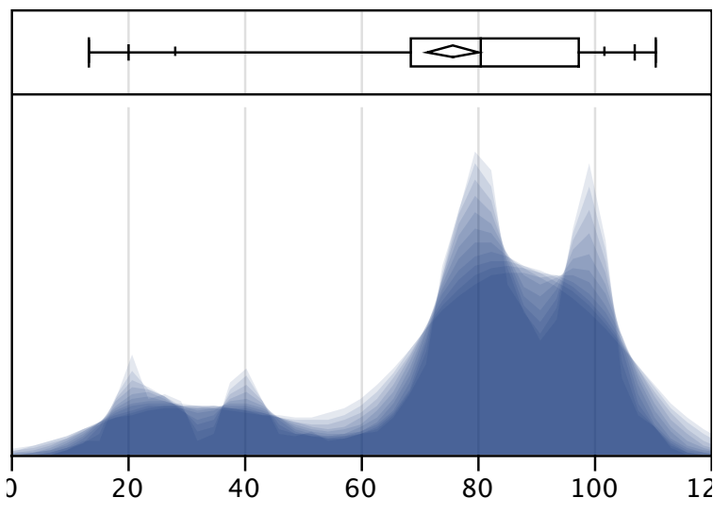


	5yLC	10yLC	20yLC
BED ≥ 92	80%	80%	-
BED < 92	58%	38%	-

NONLINEAR FIT (LOGISTIC 4p) - COMBINED R1-R2



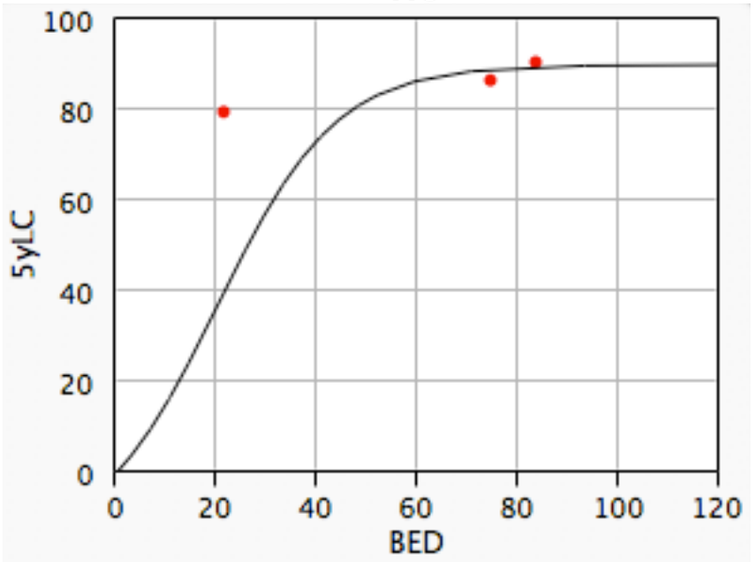
BED TOTAL



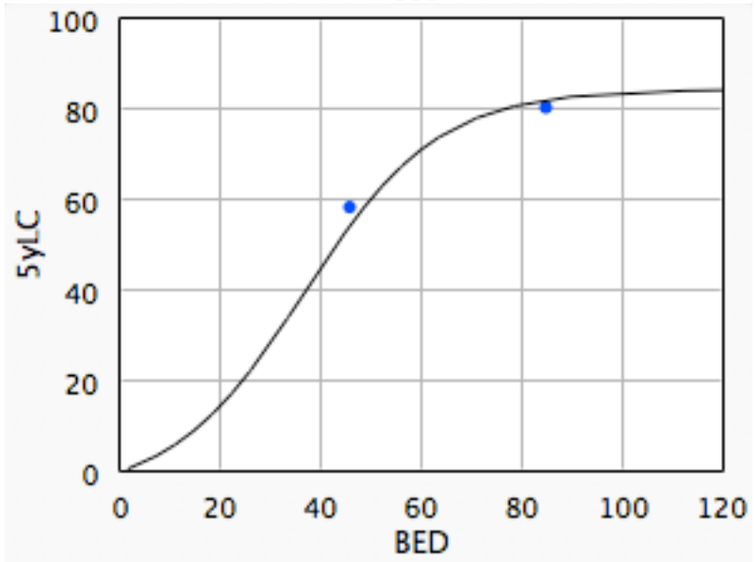
SARCOMA (SUBGROUP - EXTREMITIES)
DOSE - RESPONSE ANALYSIS

SUMMARY - LOGISTIC FIT

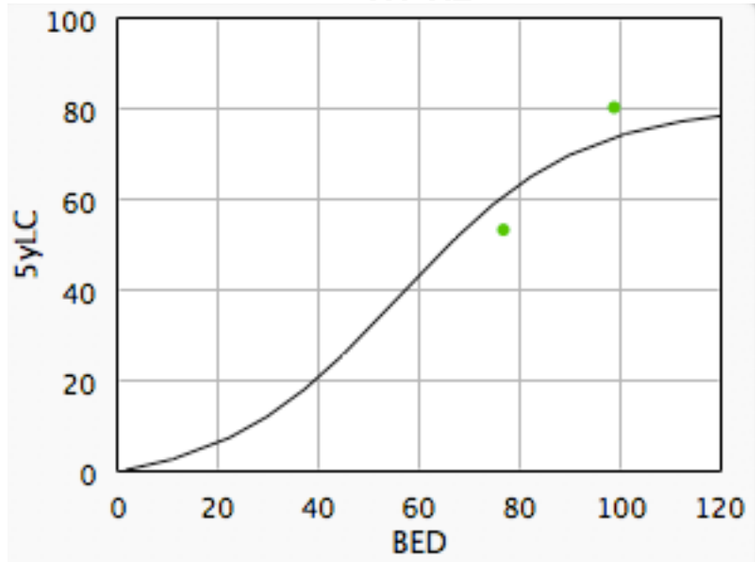
RO



R1



R1-R2

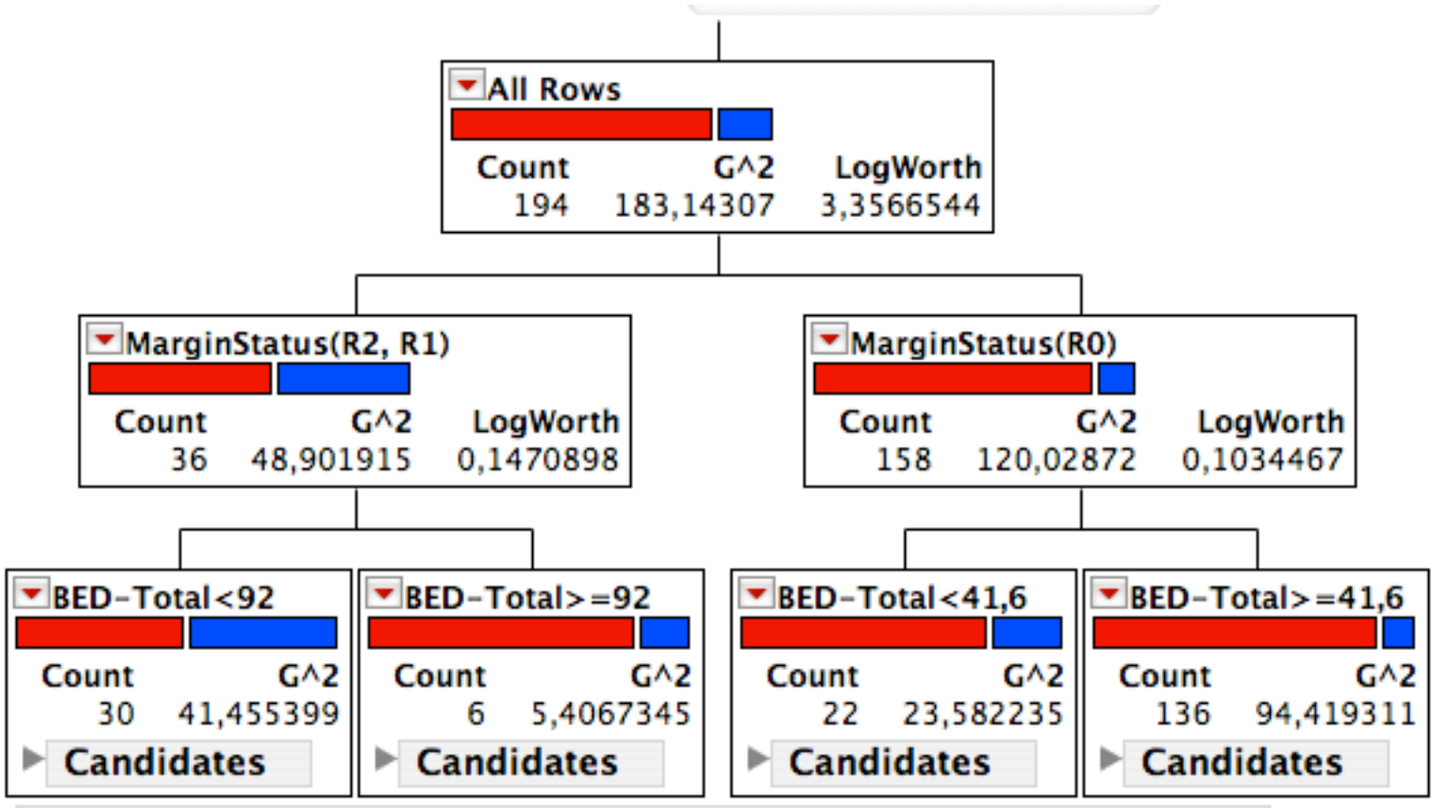


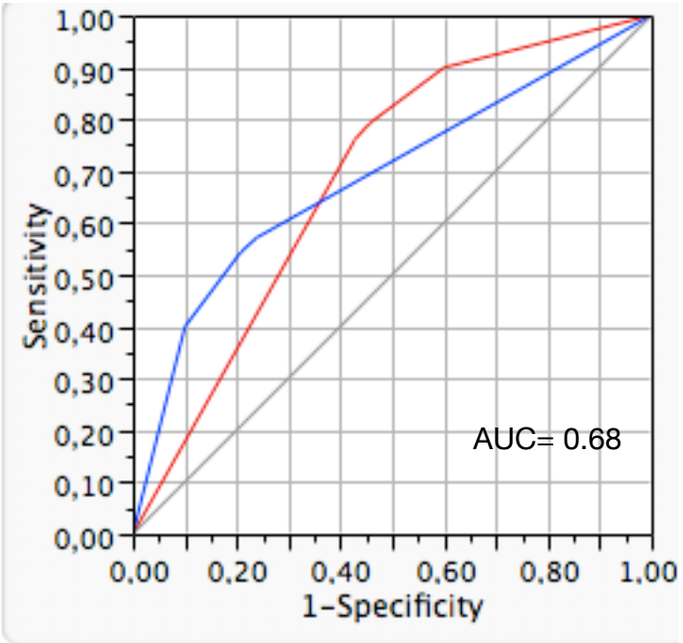
	R0	R1	R1-R2
TCD50	20,75	37,02	56,32
σ50	0,0849	0,075	0,057
γ50	1,76	2,77	3,21

PREDICTIVE MODELS

RECURSIVE PARTITIONING ANALYSIS

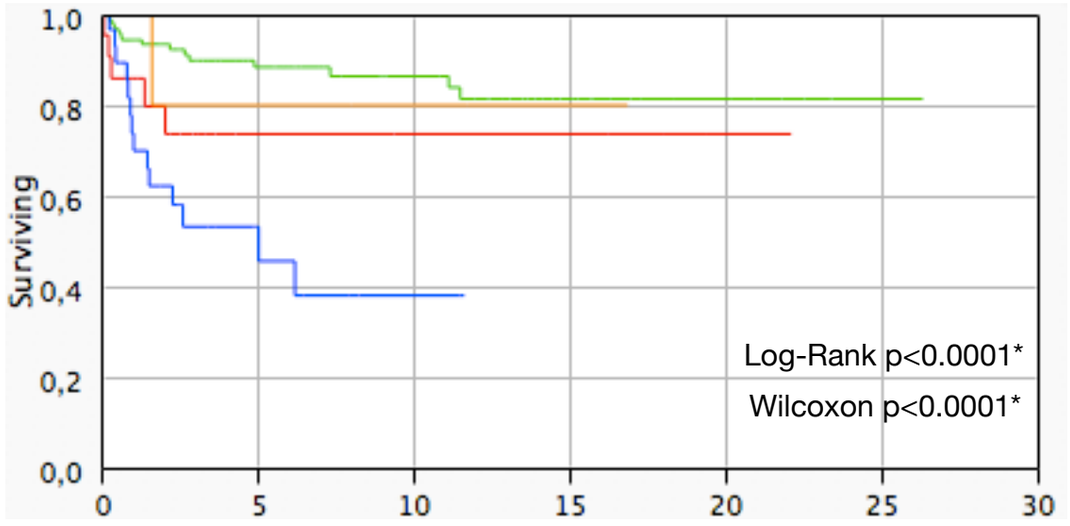
MODEL 1 - UNSUPERVISED





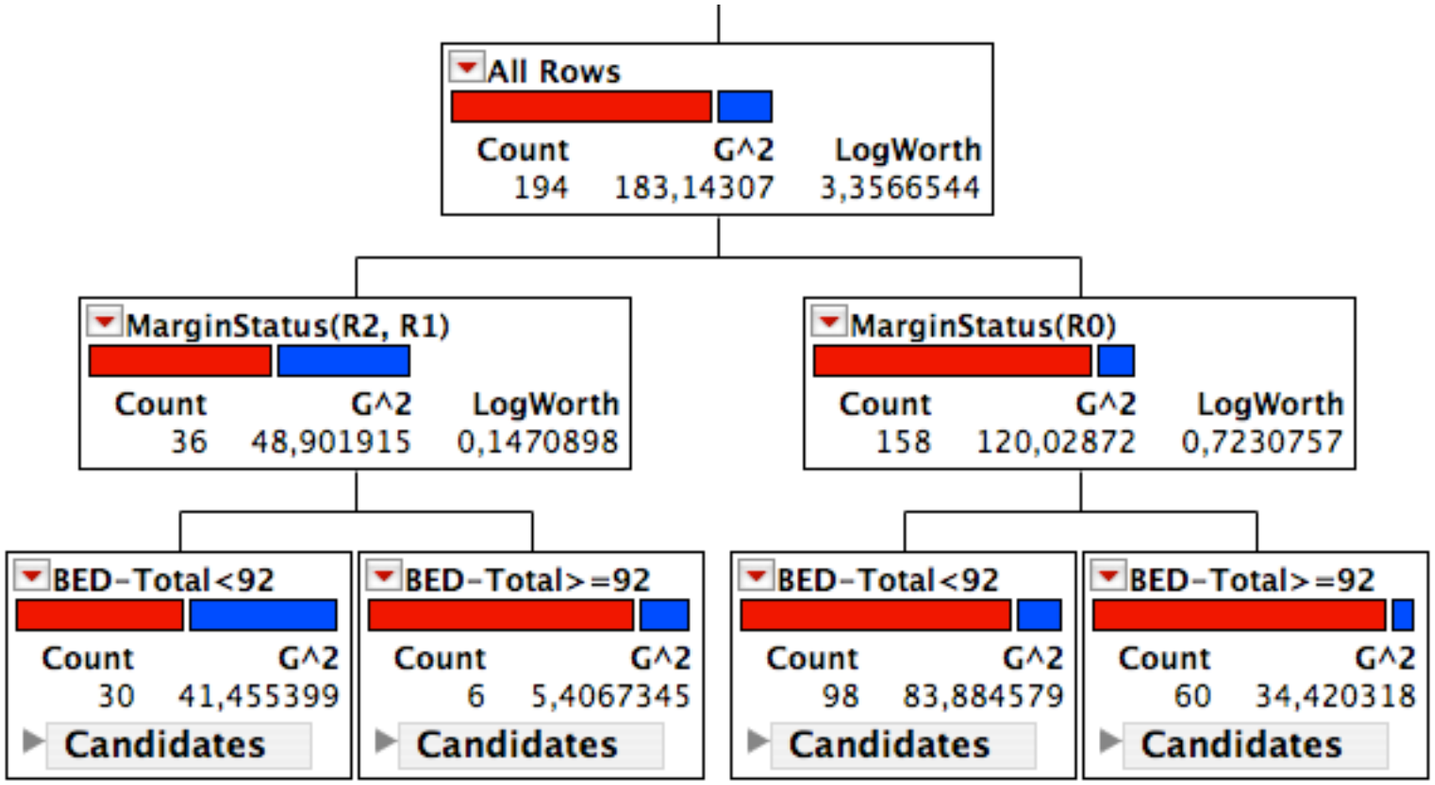
RECURSIVE PARTITIONING ANALYSIS

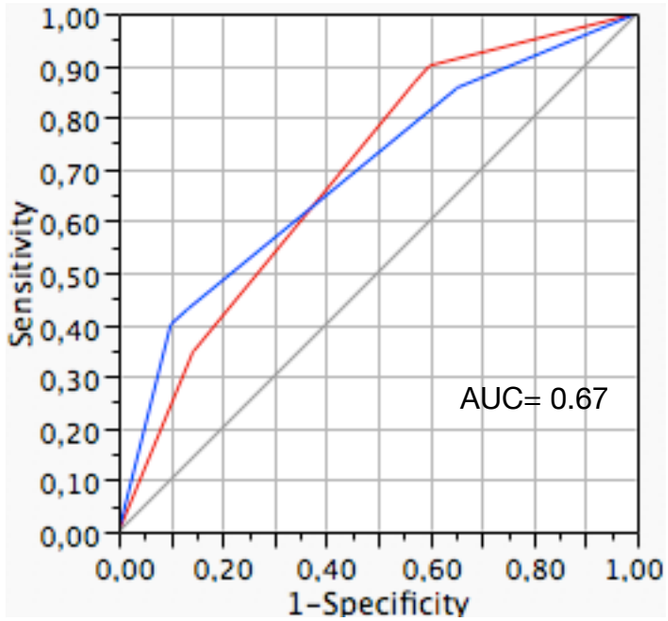
MODEL 1 - UNSUPERVISED



RECURSIVE PARTITIONING ANALYSIS

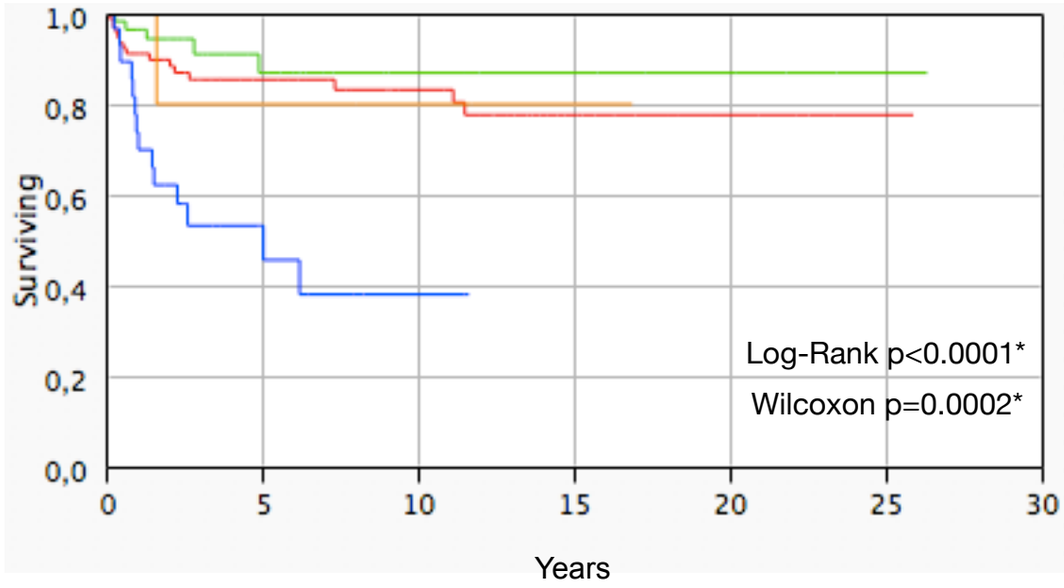
MODEL 2 - SUPERVISED





RECURSIVE PARTITIONING ANALYSIS

MODEL 2 - SUPERVISED



DISCUSSION

ELSEVIER

Seminars in
RADIATION
ONCOLOGY

The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction

David J. Brenner, PhD, DSc

The tool most commonly used for quantitative predictions of dose/fractionation dependencies in radiotherapy is the mechanistically based linear-quadratic (LQ) model. The LQ formalism is now almost universally used for calculating radiotherapeutic isoeffect doses for different fractionation/protraction schemes. In summary, the LQ model has the following useful properties for predicting isoeffect doses: (1) it is a mechanistic, biologically based model; (2) it has sufficiently few parameters to be practical; (3) most other mechanistic models of cell killing predict the same fractionation dependencies as does the LQ model; (4) it has well-documented predictive properties for fractionation/dose-rate effects in the laboratory; and (5) it is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction. To date, there is no evidence of problems when the LQ model has been applied in the clinic.
Semin Radiat Oncol 18:234-239

Dimopoulos JC, Potter R, Lang S et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. Radiother Oncol. 2009;93:311-315.

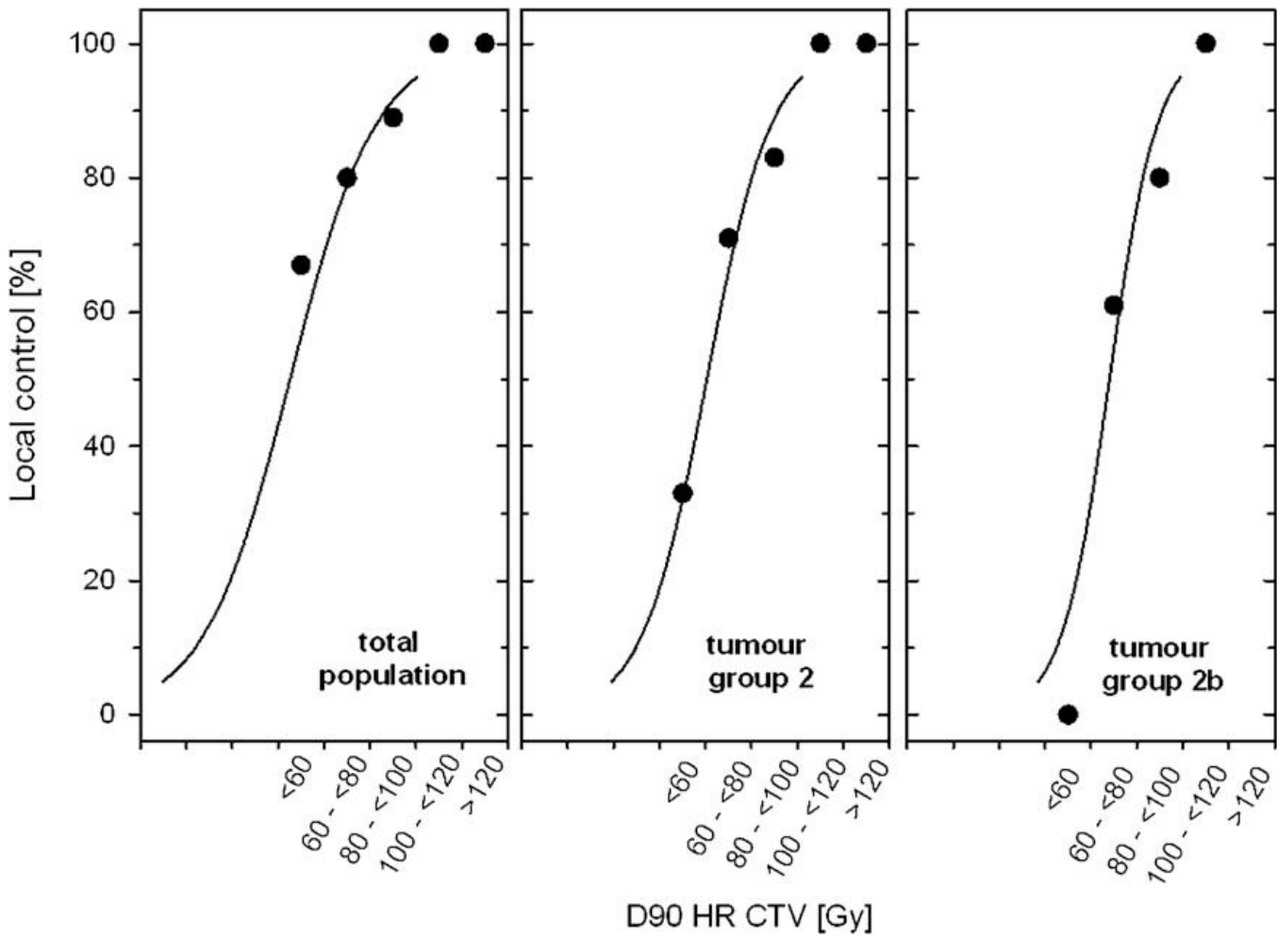
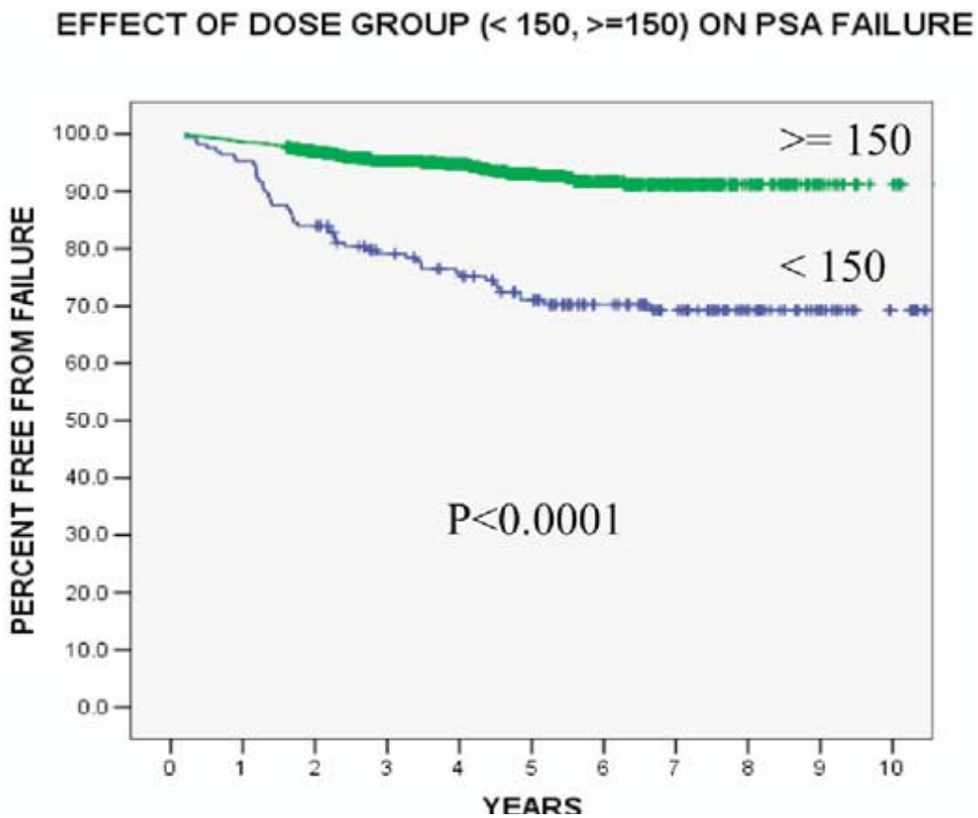
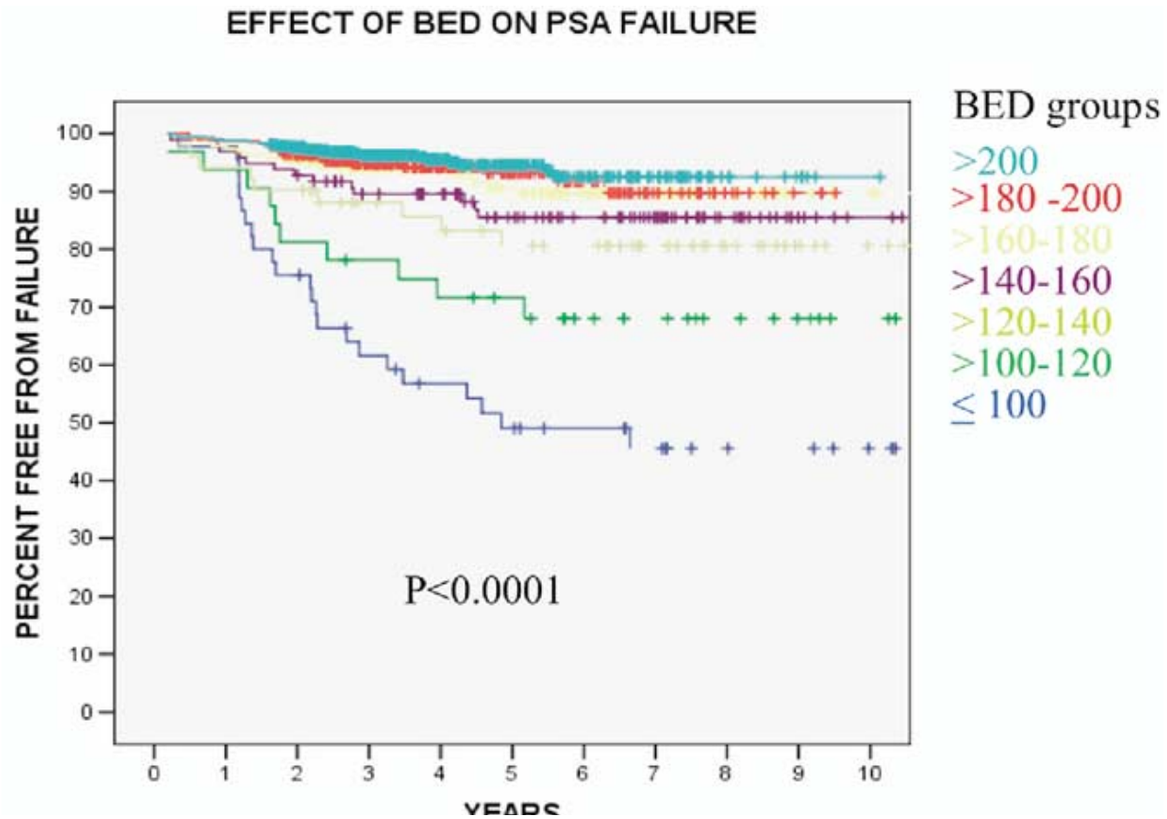


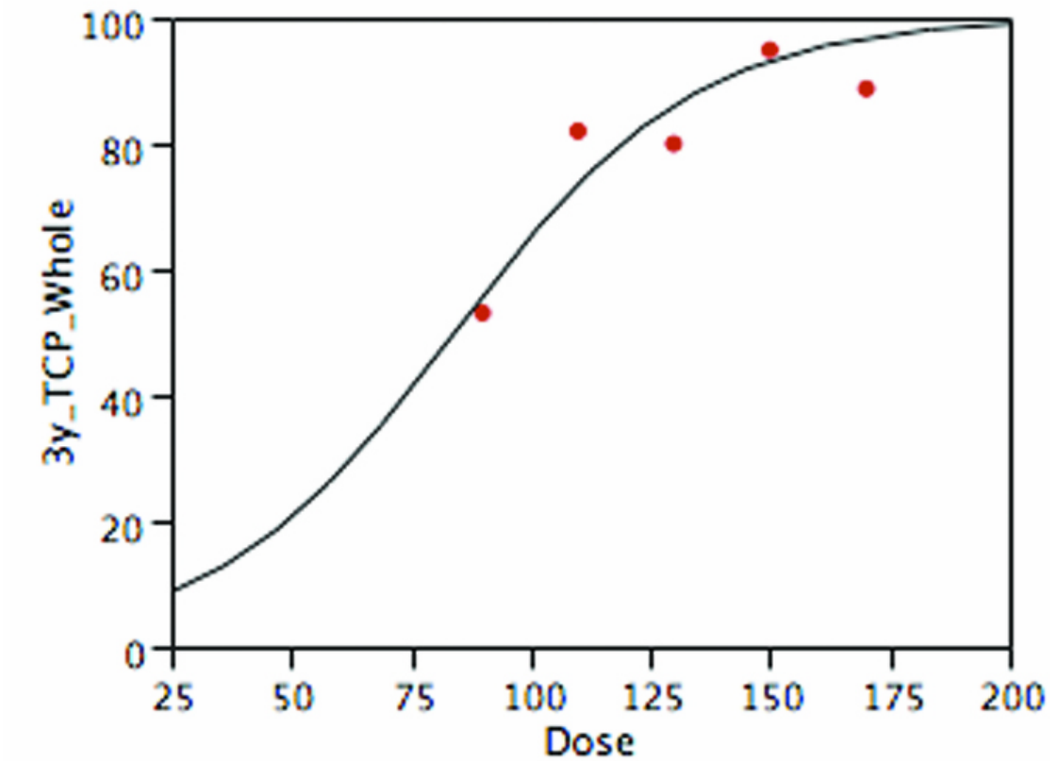
Fig. 1. Dose–response relationships (D90 in the HR CTV) for local control in the total patient population (left panel), for group 2 (large tumours, middle panel) and for group 2b (large, non-responding tumours, right panel). Particular values of the curves are presented in Table 3.

Stock RG, Stone NN, Cesaretti JA, Rosenstein BS. Biologically effective dose values for prostate brachytherapy: effects on PSA failure and posttreatment biopsy results. Int J Radiat Oncol Biol Phys. 2006;64:527-533.



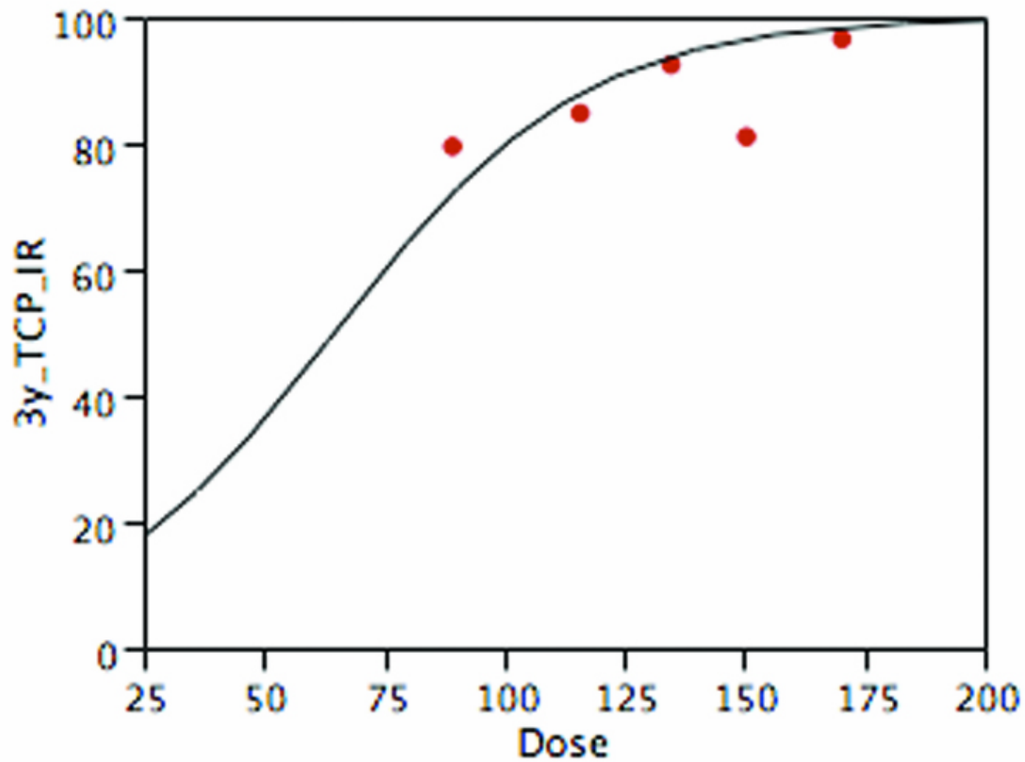


Stock R, et al. A Dose-response study for I-125 prostate implants. IJRO 1998; 41: 101



TCD50 = 84.19 Gy
σ50 = [-0.0397]

Our series



TCD50 = 80.60 Gy
σ50 = [-0.0312]

Martinez AA, Gonzalez J, Ye H et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2011;79:363-370.

Table 3. Patient follow-up times by dose bin

Dose group	Group	No. of cases (n = 472)	Mean follow-up (years)	Median follow-up (years)	Range (years)	BED (α/β of 1.2) P-EBRT plus HDR
Low dose	5.5 Gy x 3 fractions	26	11.2	11.2	2.1–17.0	215 Gy
	6.0 Gy x 3 fractions	21	10.3	10.9	1.1–16.1	231 Gy
	6.5 Gy x 3 fractions	32	10.5	10.9	2.0–15.0	248 Gy
	8.25 Gy x 2 fractions	44	8.2	8.9	1.5–13.3	253 Gy
	8.75 Gy x 2 fractions	44	8.7	9.3	3.4–12.3	268 Gy
High dose	9.50 Gy x 2 fractions	111	8.3	9.7	1.2–11.9	292 Gy
	10.5 Gy x 2 fractions	125	6.2	7.0	0.4–11.0	327 Gy
	11.5 Gy x 2 fractions	69	6.0	6.2	0.4–9.3	366 Gy
All cases		471	7.8	8.2	0.4–17.0	

Martinez AA, Gonzalez J, Ye H et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2011;79:363-370.

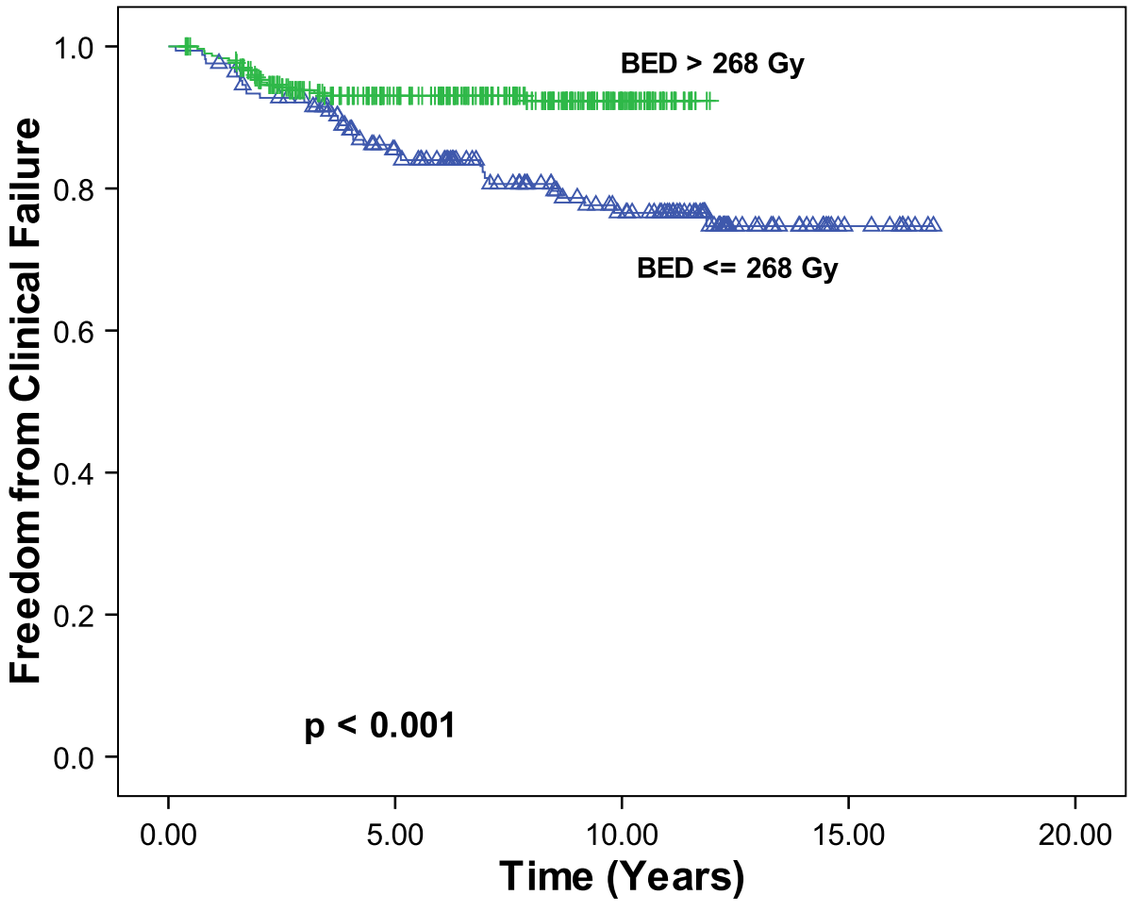


Fig. 2. Freedom from clinical failure by HDR dose level for all cases (n = 472).

- The Linear-Quadratic model has widespread use
- LQ model can be applied also to large doses per fraction
- Dose-response relationship can be obtained for cervix and prostate model
- Uncertainties in parameter selection must be considered
- Sensitivity analysis is needed
- More data are needed to validate our results

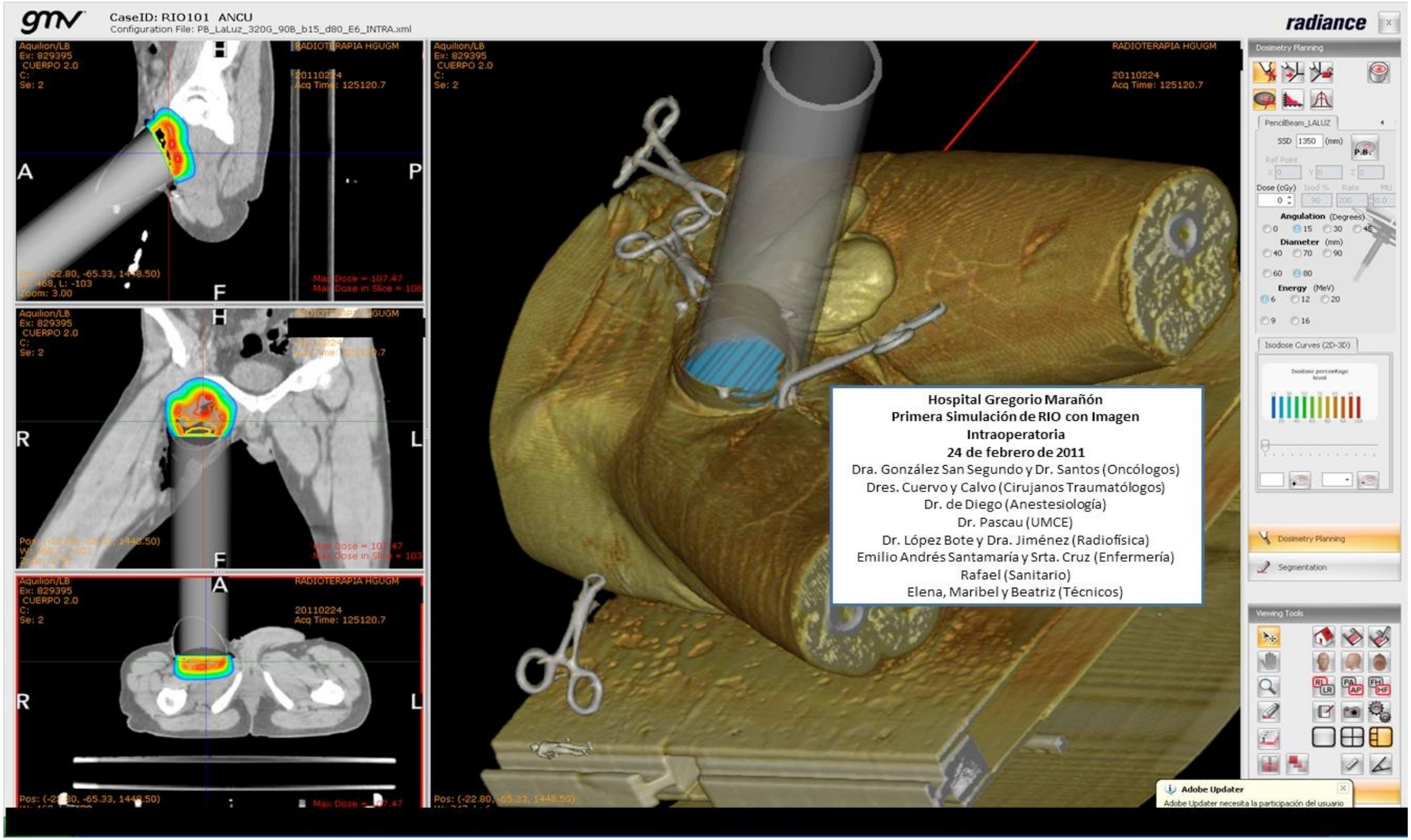
CONCLUSION

- A validated tool for dose manipulation has been presented
- A dose-response relationship has been described for sarcoma of the extremities
- More clinical data are needed to fine-tune the curve
- Sensitivity analysis id needed (different alfa-beta, repair halftimes, and irradiation time)
- External data are needed to validate the model

WHAT IS NEXT? ROADMAP

- Sensitivity analysis to fit the model to an optimal parameter set
- Validation of the model against an external data set (anyone in the room?)
- Include volumetric data (Vref, D90... using Radiance)

WHAT IS NEXT? VOLUMETRIC ANALYSIS



CUN	HRC	HGUGM
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THANKS FOR YOUR ATTENTION!