Porovnanie predikcie NTCP s klinickými výstupmi hypofrakcionacie v stereorádioterapii a HDR brachyterapii pri použití LQ versus LQ-L modelu

Matula P., Končik J., Jasenčak M.
VOÚ a.s. Košice, SR

Úvod

- Stereotaxia sa stáva rutinnou liečebnou modalitou u vybraných tumorových entít.
- Koncept biologicky efektívnej dávky (BED) je úspešne využívaný po 3 dekády pri porovnávaní rôznych režimov nekonvenčnej frakcionácie a predikcii neskorých účinkov RT na normálne tkanivá.

- Pokročilé (konformné) technológie TO vyvrátili paradigma o nevhodnosti hypofrakcionácie (HF) a vyvolali zvýšený klinický záujem o rádiobiologické modelovanie HF s vysokými d/frakciu

Zistenie diskrepancie !

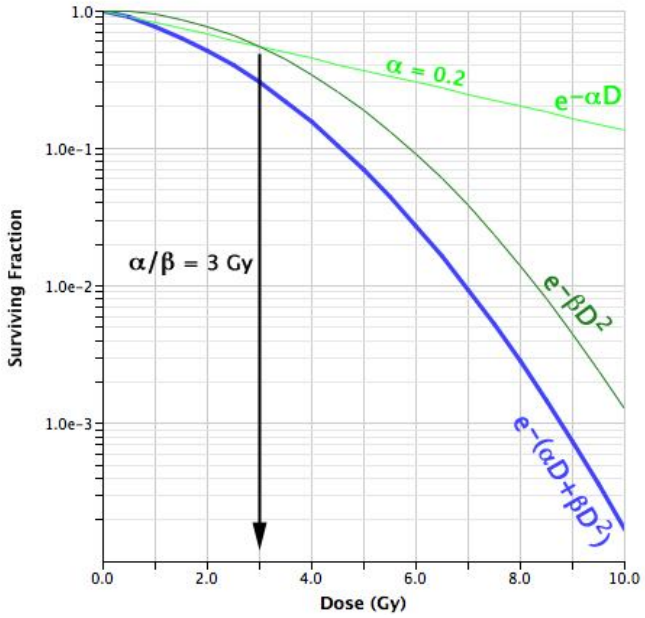
Pri SRT sa ukazuje nižšia frekvencia toxicity oproti predikovaným hodnotám BED , NTCP podľa LQ modelu!

Lineárno – kvadratický model
Biologicky efektívna dávka

$$SF = exp(-\alpha D - \beta D^2)$$

$$E = Nd(\alpha + \beta d)$$

$$E/\alpha = BED = Nd\left[1 + \frac{d}{\alpha/\beta}\right]$$



Biologically effective dose

Total dose

Relative effectiveness

V čom LQ model zlýhava?

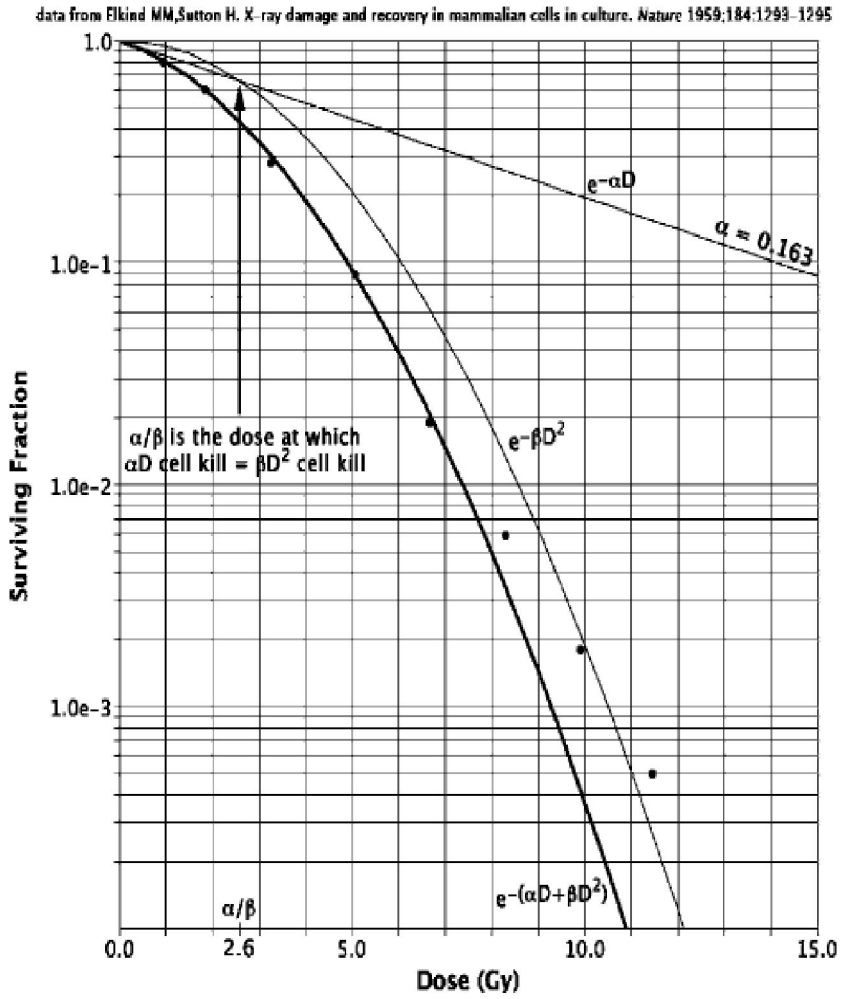
Experimentálne dáta in vitro i klinické výstupy pri hypofrakcionačných režimoch SRT

pri d/fr vyšších ako 6 Gy

odhalili nesúlad

s vypočítanými BED a NTCP !!!

SF (exper.dáta) versus LQ model

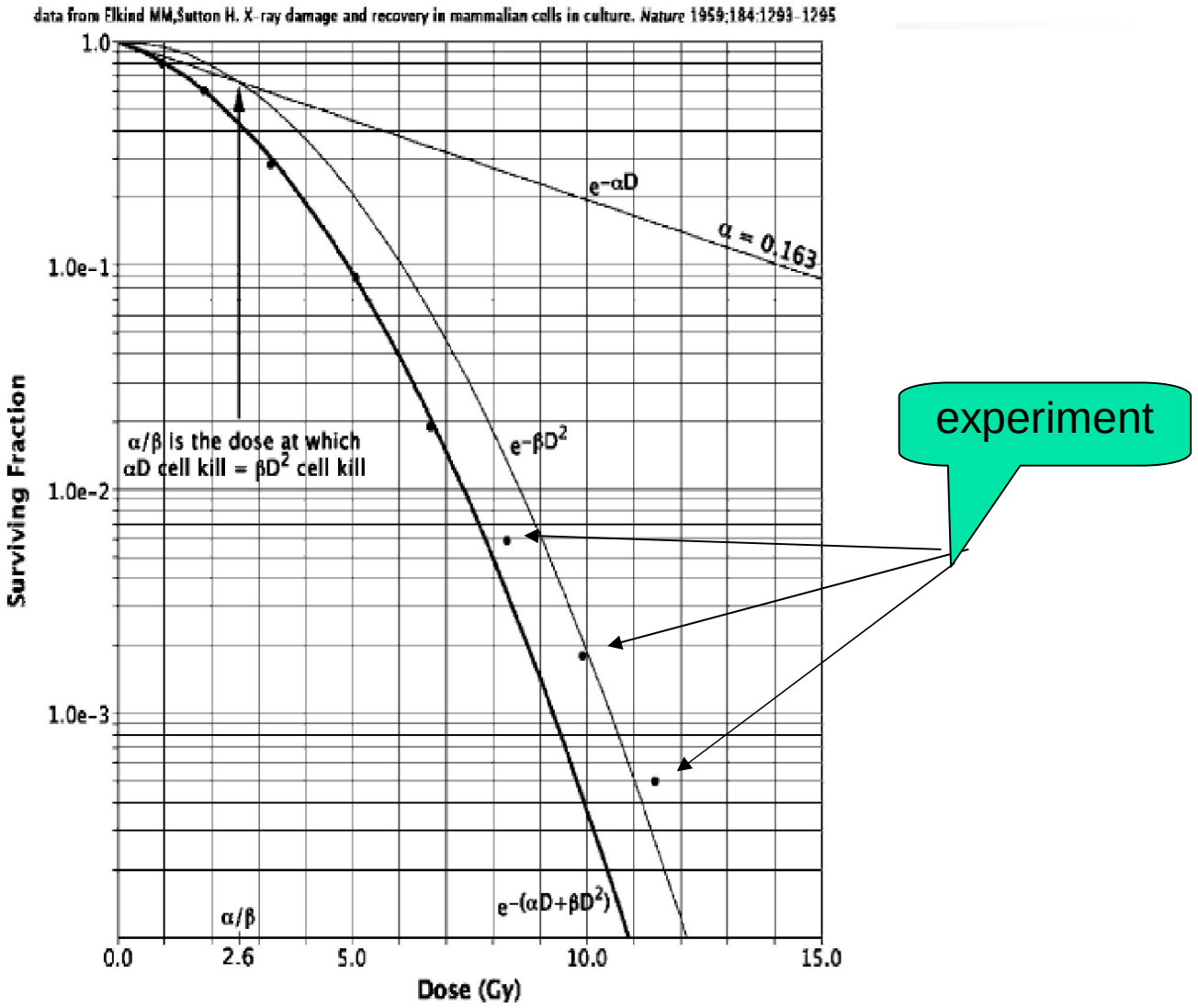


Krivky prežívajúcej frakcie SF pri vyšších d/fr prechádzjú do lineárnej závislosti

Dôsledok:

BED a NTCP falošne predikujú podstatne vyššie komplikácie než sú pozorované v stereorádioterapii

Grafická prezentácia SF



Návrhy na riešenie – modifikácia modelu LQ na LQ-L

- M. Guerrero , X.Li (2004)
- Park C. (2008)
- Astrahan M. (2008)

Cieľ príspevku

1. **Popísať nový model „LQ-L“**
2. **Kvantifikovať zmeny v predikcii neskorých účinkov na normálne tkanivá v modalitách :**

   - stereochirurgie SRS

   - frakcionovanej SRT

   - HDR brachyterapie

Metódy a materiál
SF v LQ-L modeli

$$SF = e^{-(\alpha D + \beta d^2)} \qquad D \le D_T$$

$$SF = e^{-(\alpha D_T + \beta D_T^{\,2} + \gamma (D - D_T))} \qquad D \ge D_T$$

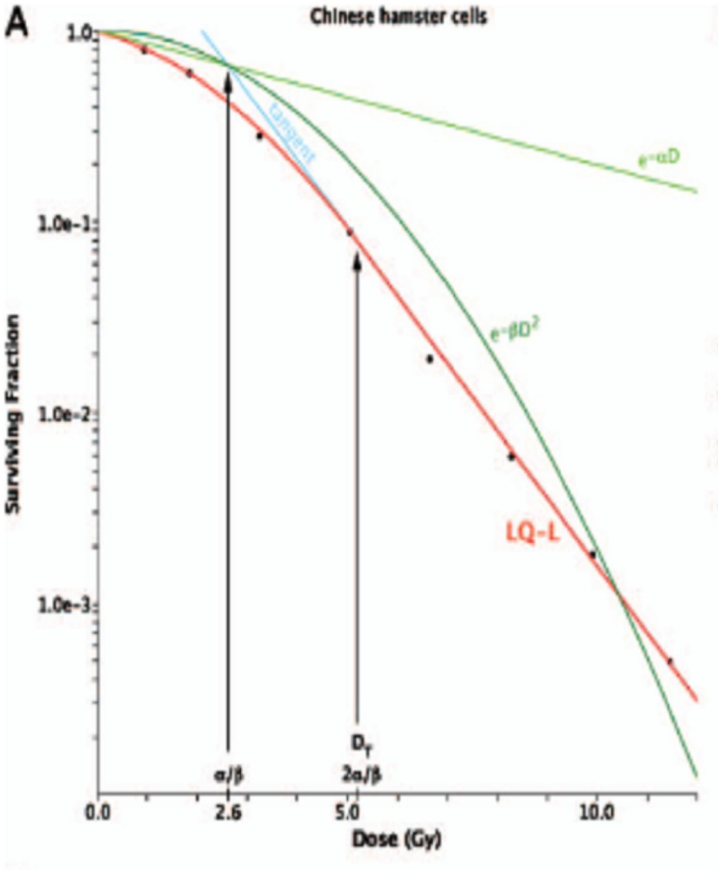
Algoritmus LQ-L modelu v BED

$$\mathrm{BED}_n = D + [D^2/(\alpha/\beta)] \quad \text{for } D < D_T$$

$$\mathrm{BED}_n = D_T + [D_T^2/(\alpha/\beta)] + [(\gamma/\alpha)(D - D_T)] \quad \text{for } D \geq D_T,$$

$$\gamma / \alpha = 1 + [2D_T / (\alpha / \beta)] \qquad D_T = 2(\alpha / \beta)$$

Zhoda LQ-L modelu s experimentom



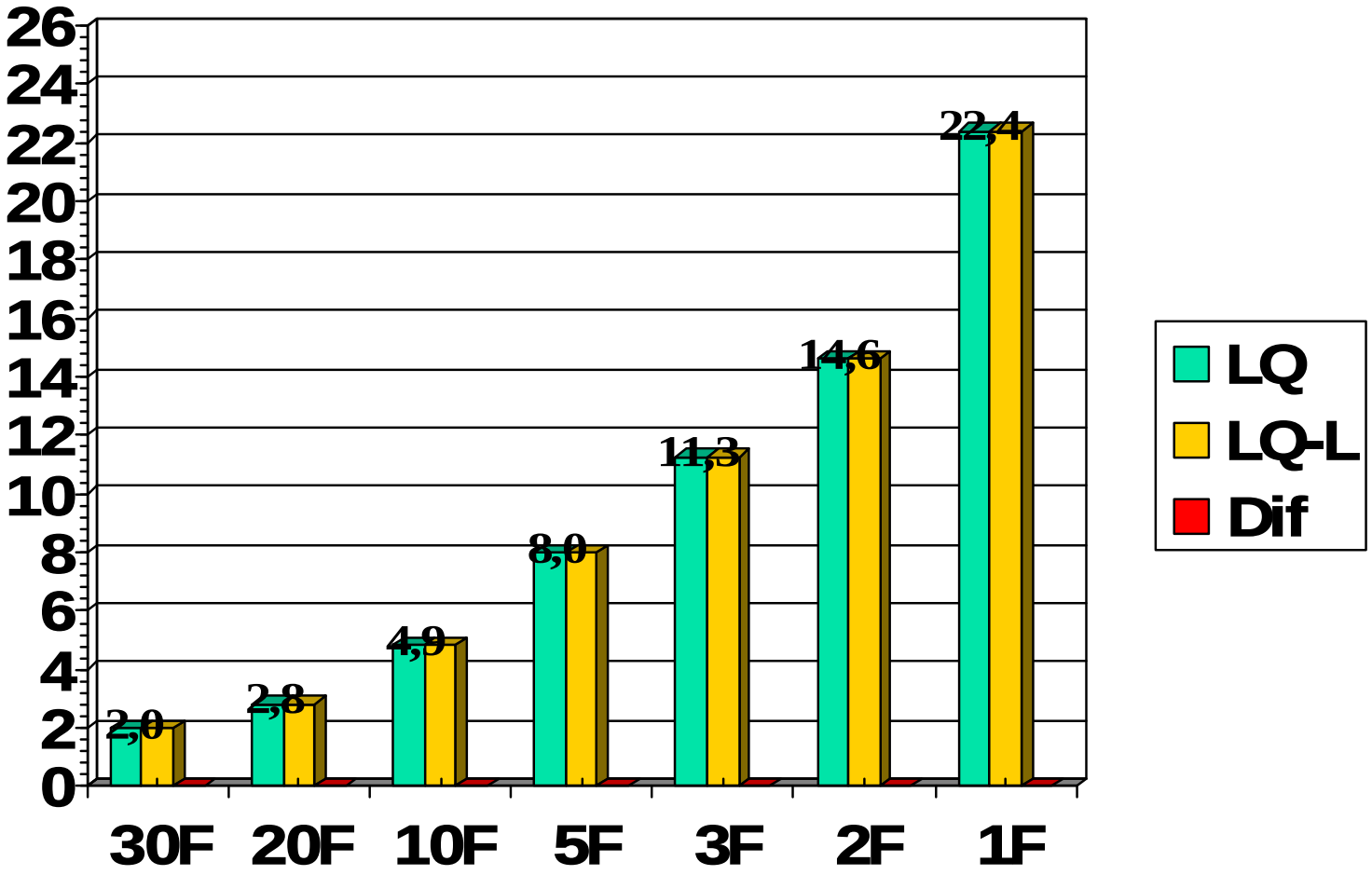
Chinese Hamster cells

Experimentálne výsledky tesne fitujú krivku SF

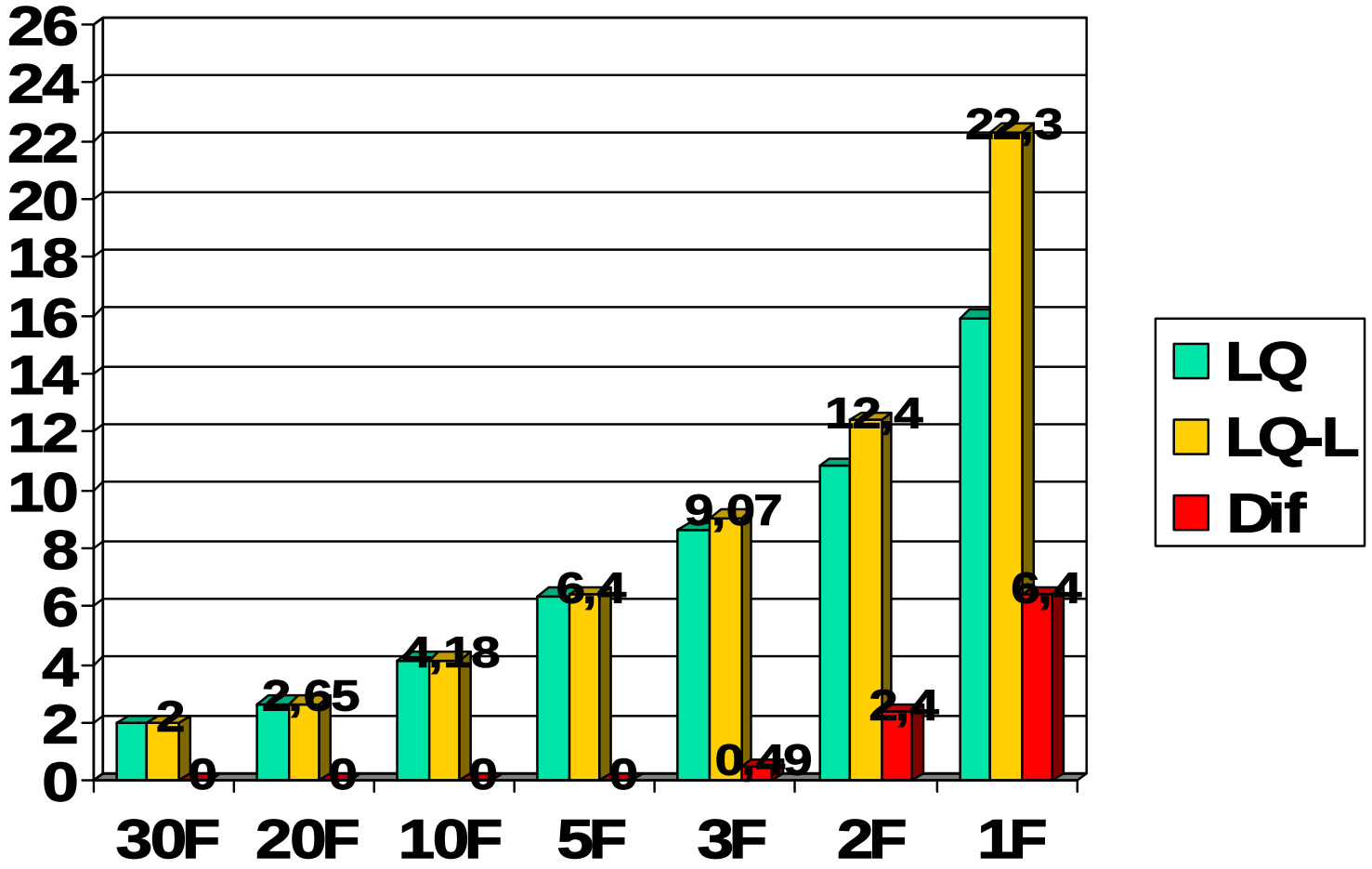
do 6 Gy

potom (3. komponenta) fituje krivku do linearity

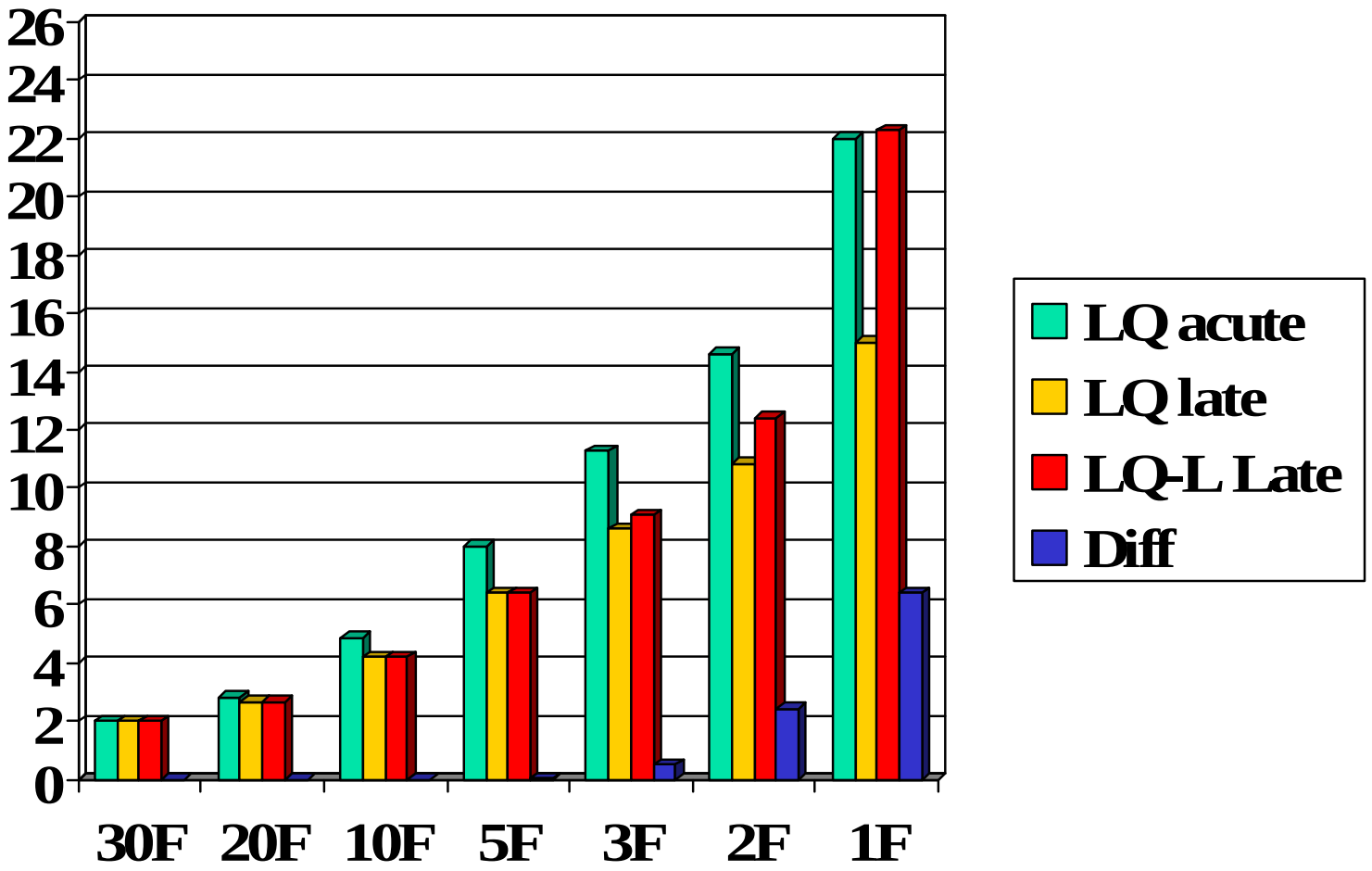
Dávka/frakciu /Gy/ pre konštantnú BED_{10Gy} =72Gy ⇒ LQD_2=60Gy



Dávka /frakciu pre neskoré účinky NT pri konštantnej BED_{10Gy} =72 Gy => LQD_2=60Gy

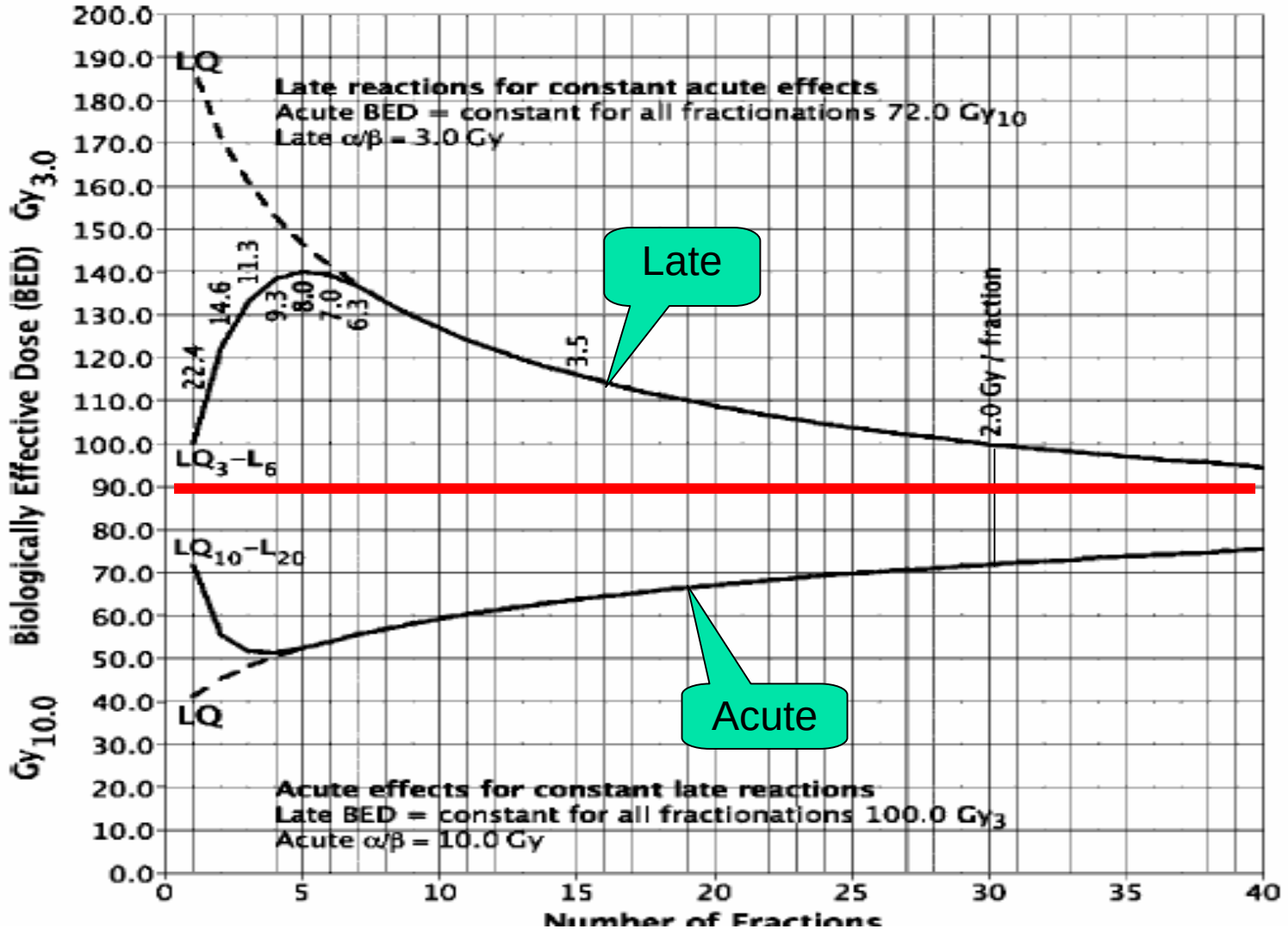


Porovnanie d/f pri skorých a neskorých



Grafická interpretacia BED=F($N_{frakcii}$)

(acute vs late reactions)



Testovanie modelu LQ-L

Algoritmy modifikovaného modelu boli testované na odporúčaných limitoch

- z práce : R.Timmerman:

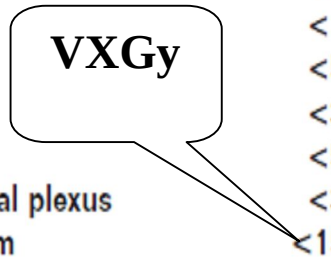
Seminars in radiation Oncology Oct. 2008

- Report AAMP

Int.J.Rad.Onc.Biol.Phys. 2010

Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
THREE-FRACTION TREATMENT				
Optic pathway	<0.2	15 (5 Gy/fx)	19.5 (6.5 Gy/fx)	Neuritis
Cochlea			20 (6.67 Gy/fx)	Hearing loss
Brainstem	<1	18 (6 Gy/fx)	23 (7.67 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25	18 (6 Gy/fx)	22 (7.33 Gy/fx)	Myelitis
	<1.2	11.1 (3.7 Gy/fx)		
Cauda equina	<5	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	Neuritis
Sacral plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Esophagus*	<5	21 (7 Gy/fx)	27 (9 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Heart/pericardium	<15	24 (8 Gy/fx)	30 (10 Gy/fx)	Pericarditis
Great vessels	<10	39 (13 Gy/fx)	45 (15 Gy/fx)	Aneurysm
Trachea and ipsilateral bronchus*	<4	15 (5 Gy/fx)	30 (10 Gy/fx)	Stenosis/fistula
Skin	<10	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Stomach	<10	21 (7 Gy/fx)	24 (8 Gy/fx)	Ulceration/fistula
Duodenum*	<5	15 (5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Jejunum/ileum*	<5	16.2 (5.4 Gy/fx)	27 (9 Gy/fx)	Enteritis/obstruction
Colon*	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Colitis/fistula
Rectum*	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Proctitis/fistula
Bladder wall	<15	15 (5 Gy/fx)	30 (10 Gy/fx)	Cystitis/fistula
Penile bulb	<3	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	Impotence
Femoral heads (right and left)	<10	21.9 (7.3 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	18.6 (6.2 Gy/fx)		Malignant hypertension

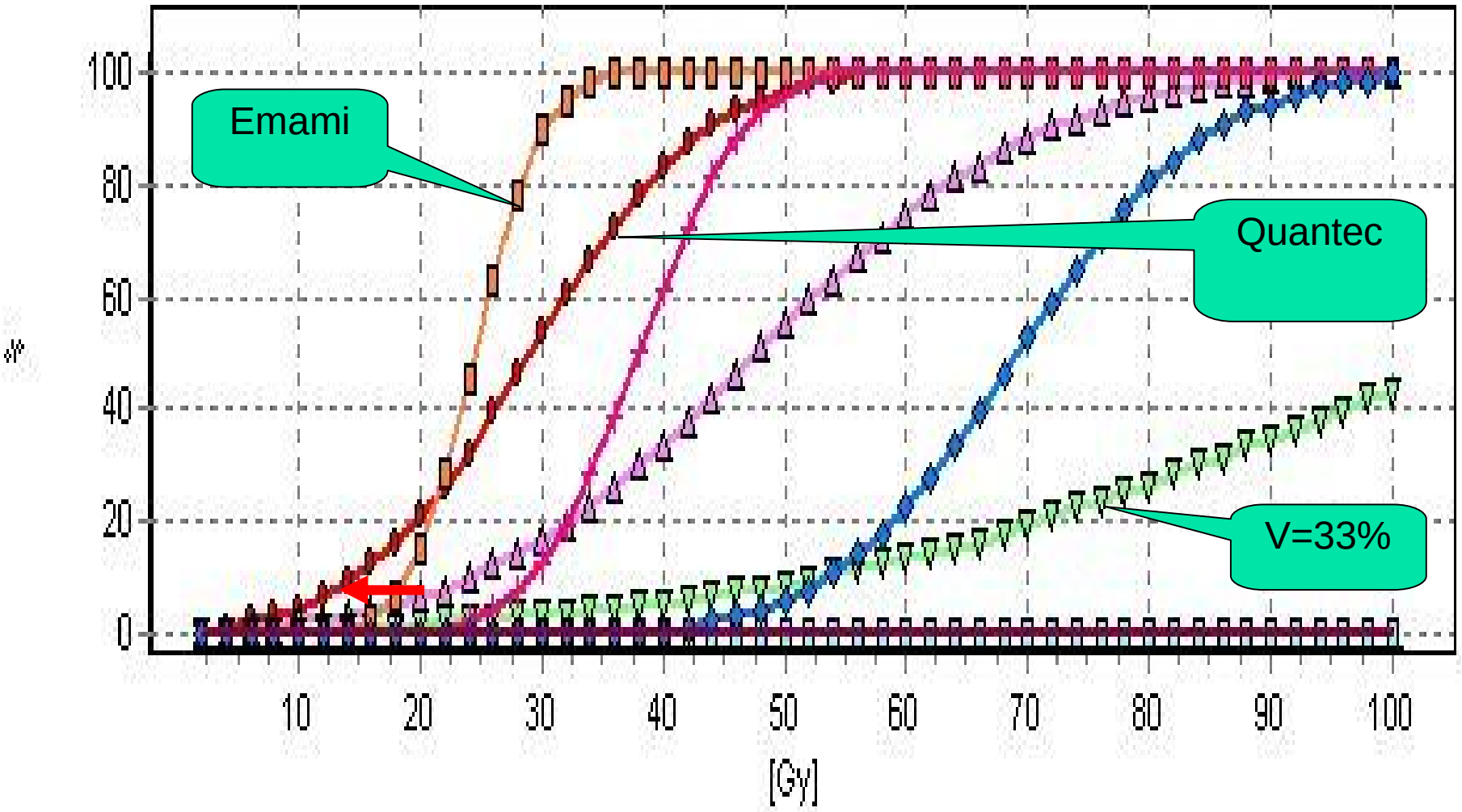
Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	10.5 (3.5 Gy/fx)	Basic lung function
Lung (right and left)	1,000	11.4 (3.8 Gy/fx)	Pneumonitis
Liver	700	17.1 (5.7 Gy/fx)	Basic liver function
Renal cortex (right and left)	200	14.4 (4.8 Gy/fx)	Basic renal function



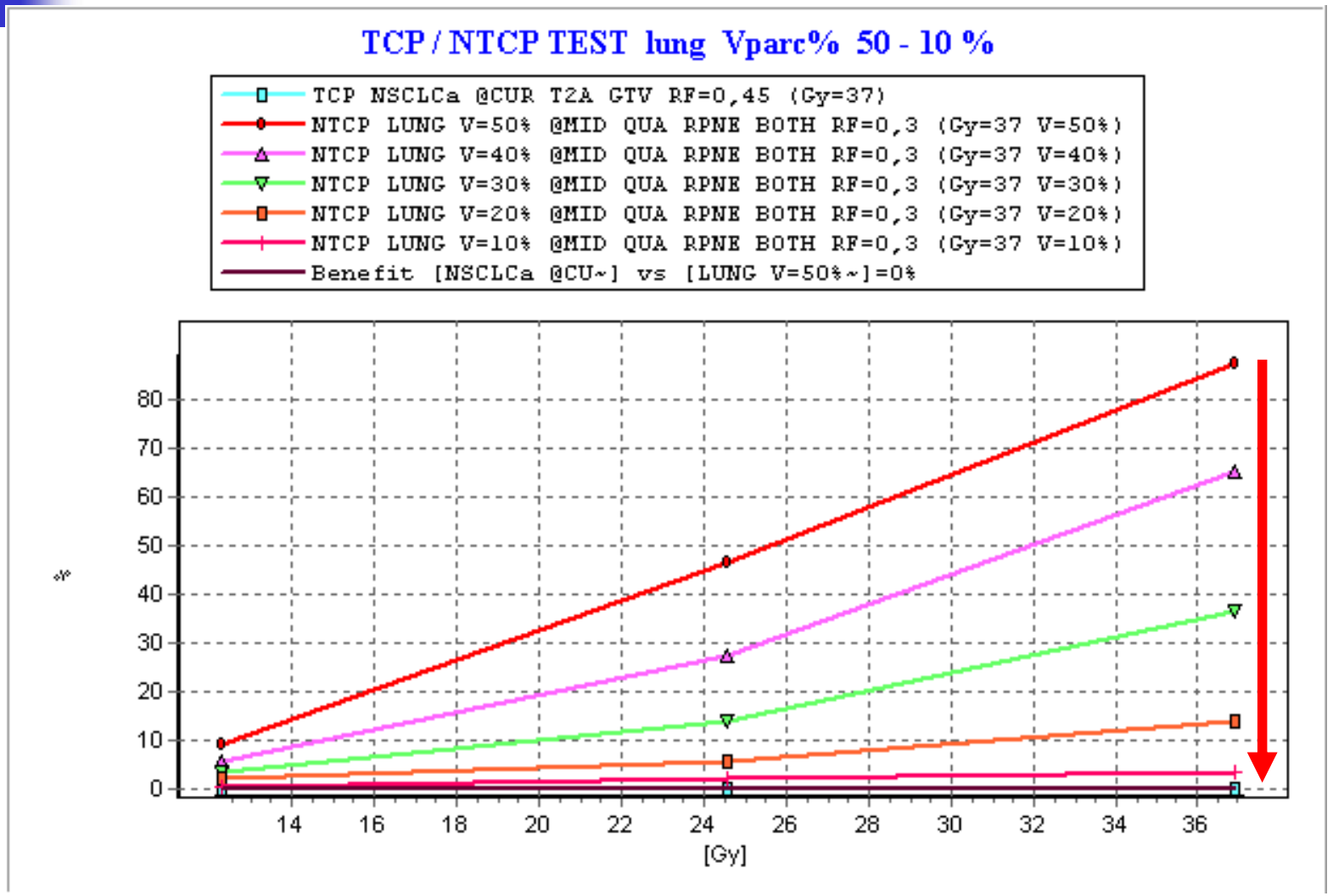
Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
FIVE-FRACTION TREATMENT				
Optic pathway	<0.2	20 (4 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			27.5 (5.5 Gy/fx)	Hearing loss
Brainstem	<1	26 (5.2 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25	22.5 (4.5 Gy/fx)	30 (6 Gy/fx)	Myelitis
	<1.2	13.5 (2.7 Gy/fx)		
Cauda equina	<5	30 (6 Gy/fx)	34 (6.4 Gy/fx)	Neuritis
Sacral plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus*	<5	27.5 (5.5 Gy/fx)	35 (7 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Heart/pericardium	<15	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10	47 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and ipsilateral bronchus*	<4	18 (3.6 Gy/fx)	38 (7.6 Gy/fx)	Stenosis/fistula
Skin	<10	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Stomach	<10	28 (5.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula
Duodenum*	<5	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Jejunum/ileum*	<5	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	enteritis/obstruction
Colon*	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	colitis/fistula
Rectum*	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	proctitis/fistula
Bladder wall	<15	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	cystitis/fistula
Penile bulb	<3	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10	30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	23 (4.6 Gy/fx)		Malignant hypertension

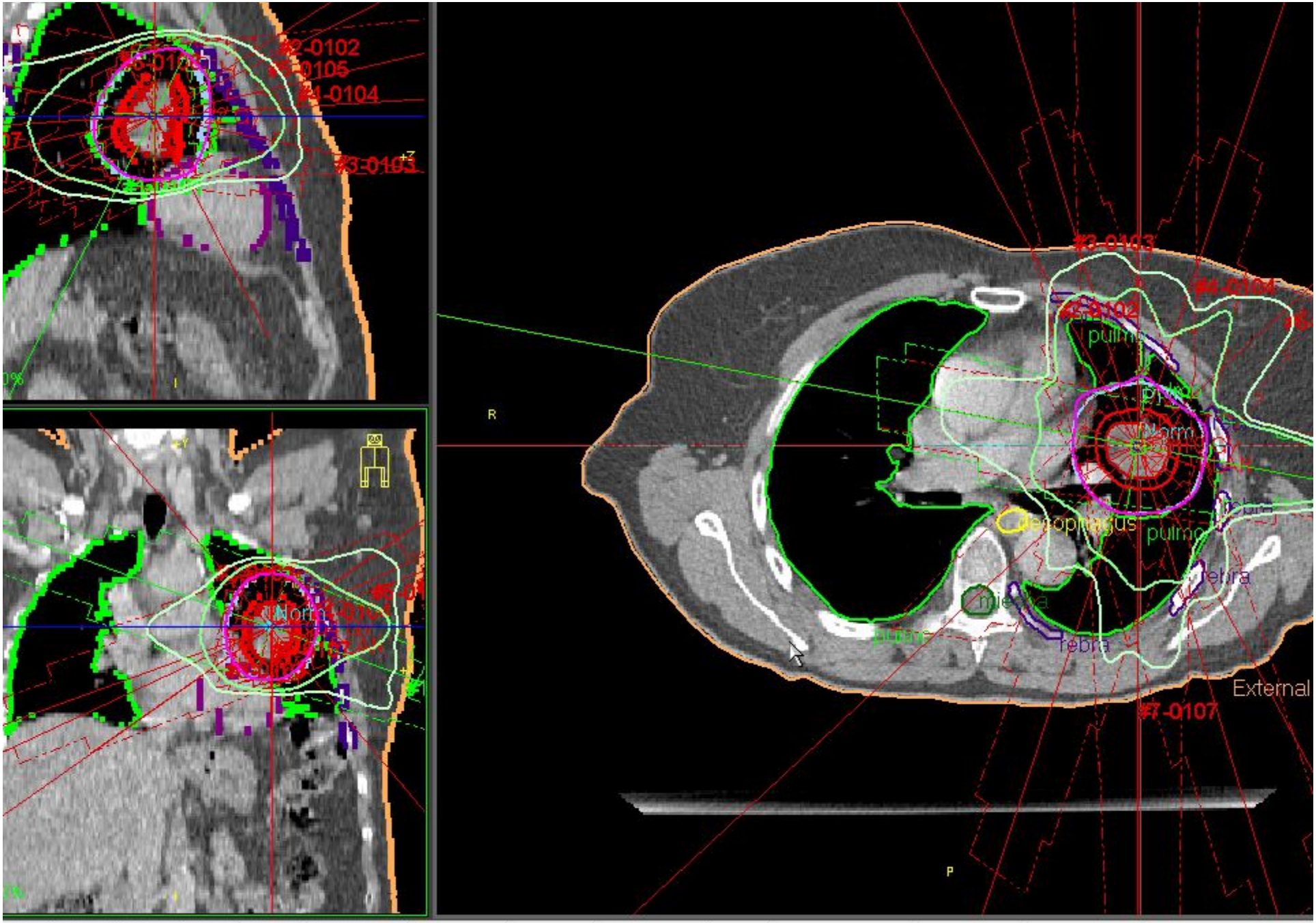
Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	12.5 (2.5 Gy/fx)	Basic lung function
Lung (right and left)	1000	13.5 (2.7 Gy/fx)	Pneumonitis
Liver	700	21 (4.2 Gy/fx)	Basic liver function
Renal cortex (right and left)	200	17.5 (3.5 Gy/fx)	Basic renal function

NTCP $_{Lung}$ (Emami vs QUANTEC)



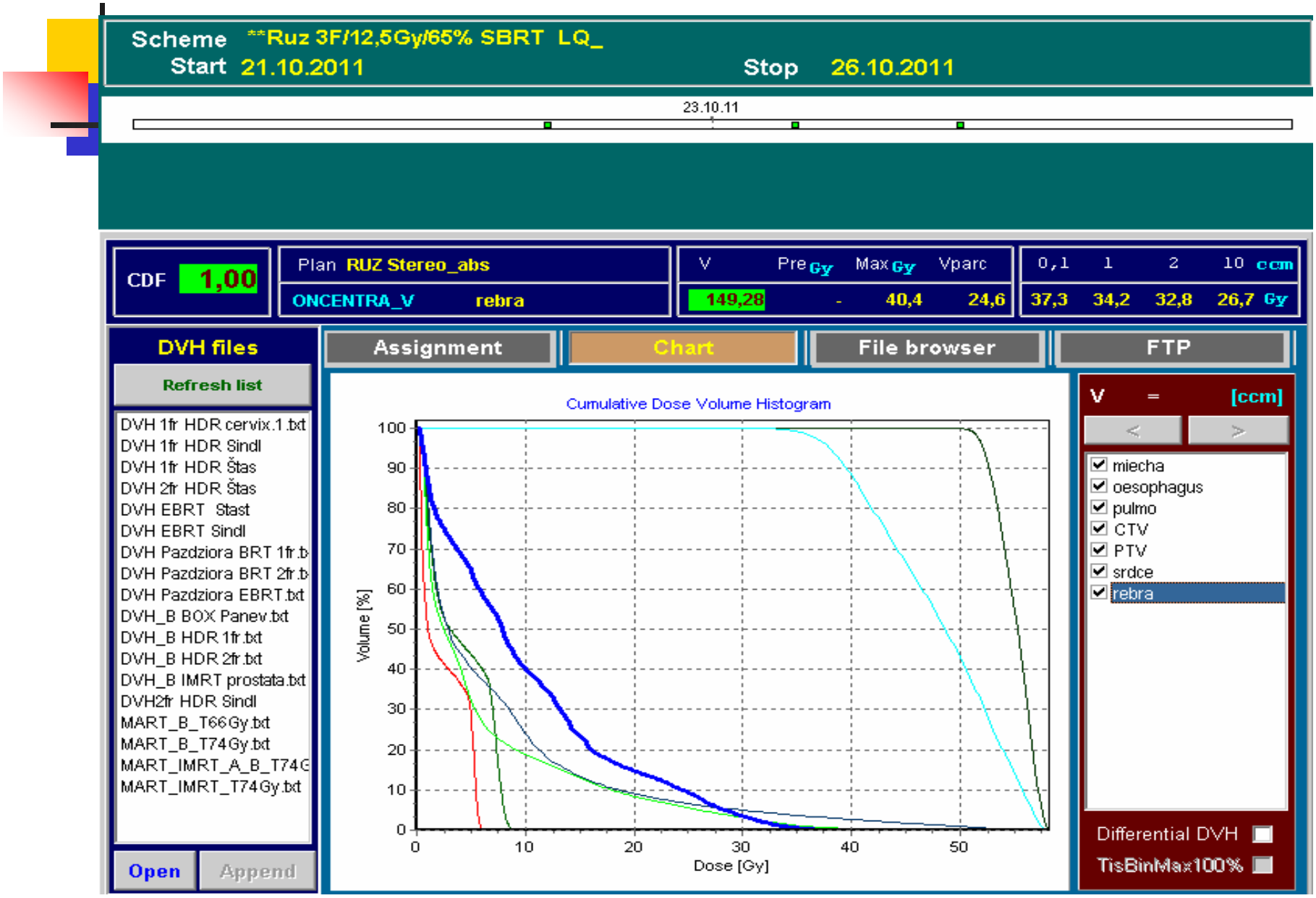
Významný vply ožiareného objemu plúc !
Simulácia V_{parc} = 50 % do 10 %



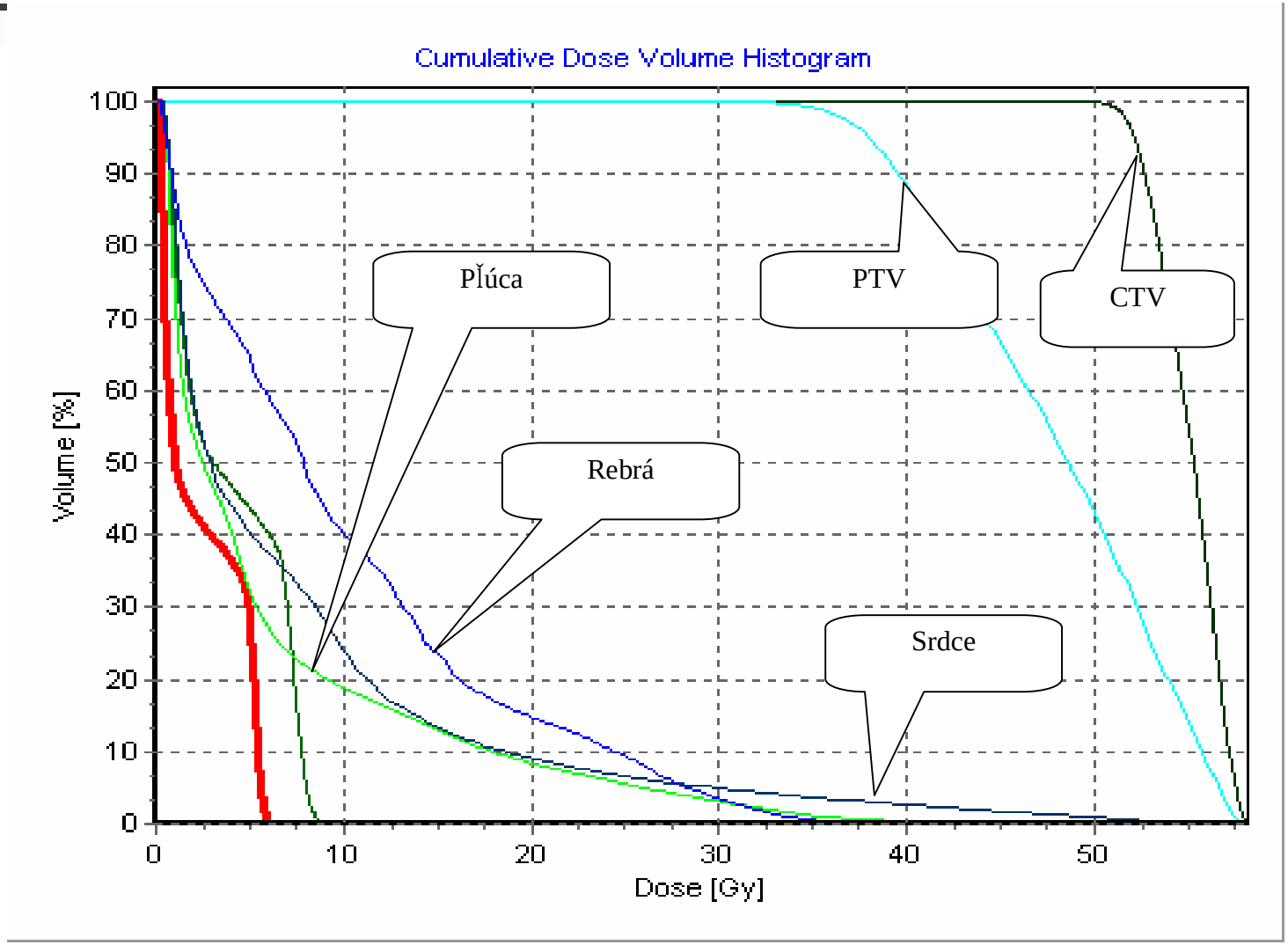


(cm)	Y2 (cm)	X (cm)	Y (cm)	Z (cm)	Y Offset (cm)	Depth (cm)	SSD (cm)	Gantry (deg)	Arc Dir	Collimator (deg)	Couch (deg)	Wedge Label	Wedge Angle (deg)
3.90	3.90	-0.00	0.00	0.00	0.00	10.38	89.62	100.00	N/A	0.00	20.00	N/A	N/A

Nadstavba údajov z DVH v BioGray

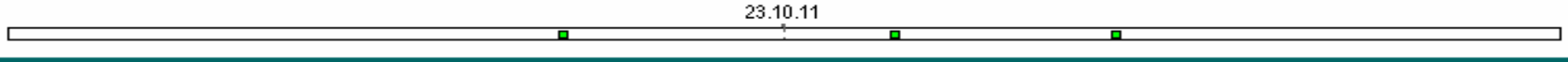


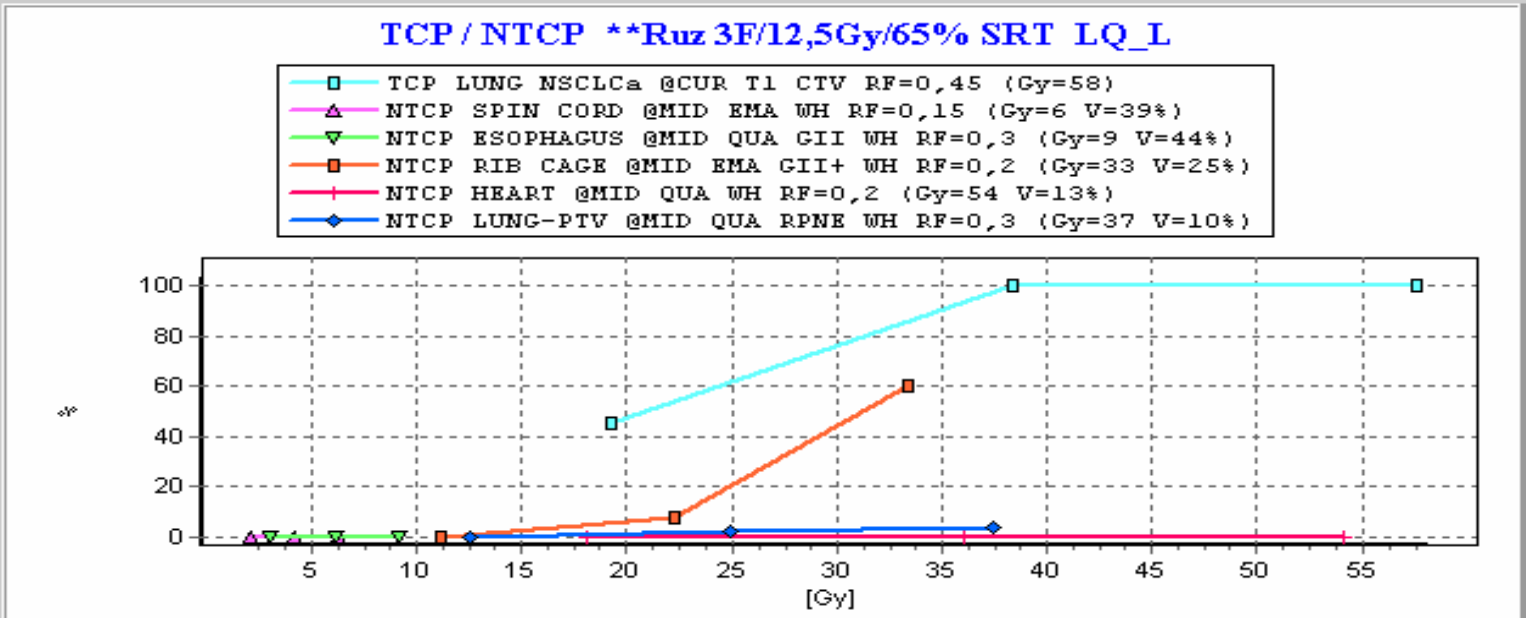
CDVH pre SBRT 3F/ 12,5 Gy/65% PTV (=57,7Gy v izocentre) NSCLC I.



Scheme **Ruz 3F/12,5Gy/65% SRT LQ_L

Start 21.10.2011 Stop 26.10.2011





BED | TCP / NTCP

Gy | Date

TCP / NTCP opt.

- [x] Show benefit factor
- [ ] Show all tumour
- [x] End - point values

Vparc [%] 95

Save Vparc

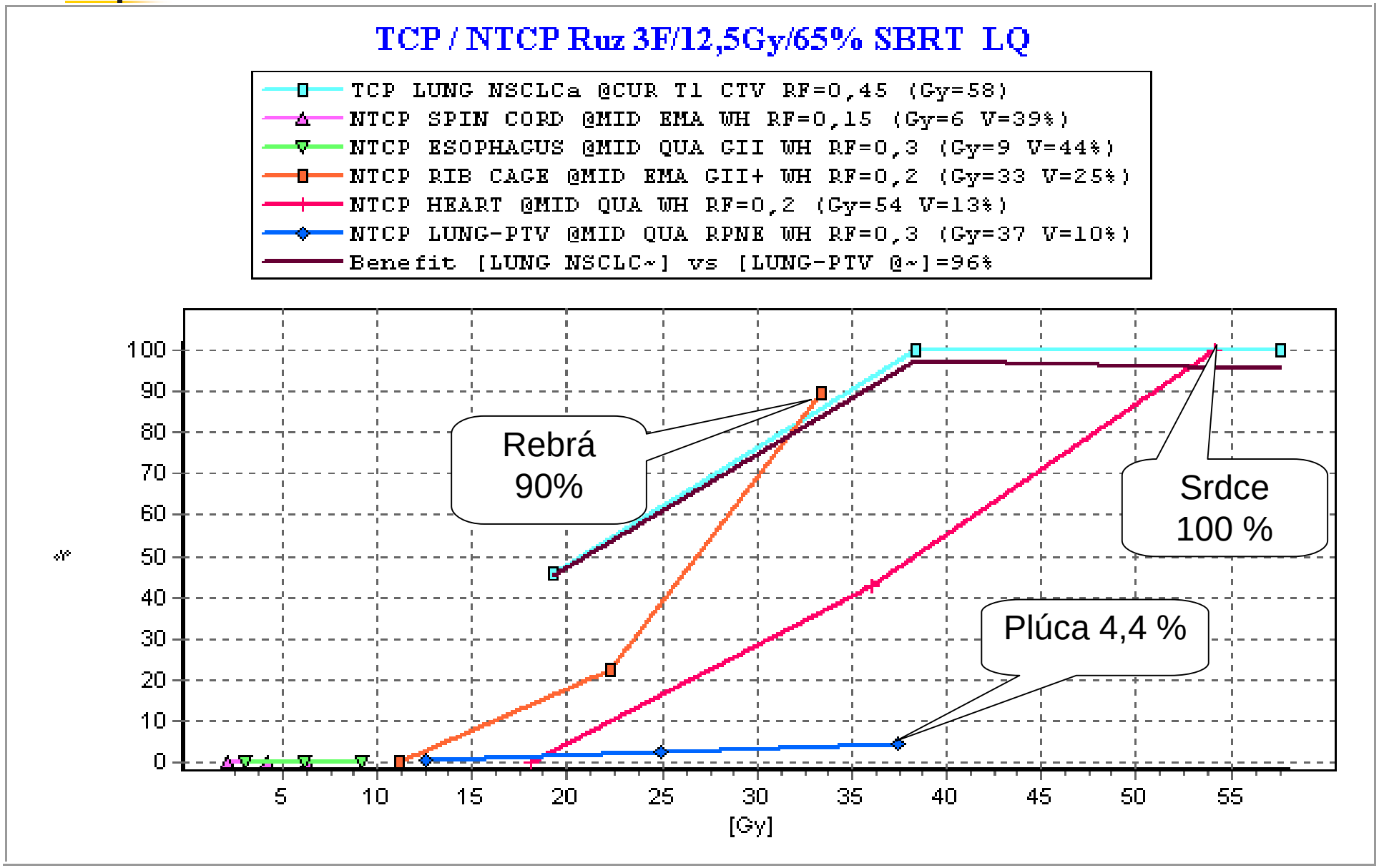
LKB | LQL | Kew

CB V1 | Export chart

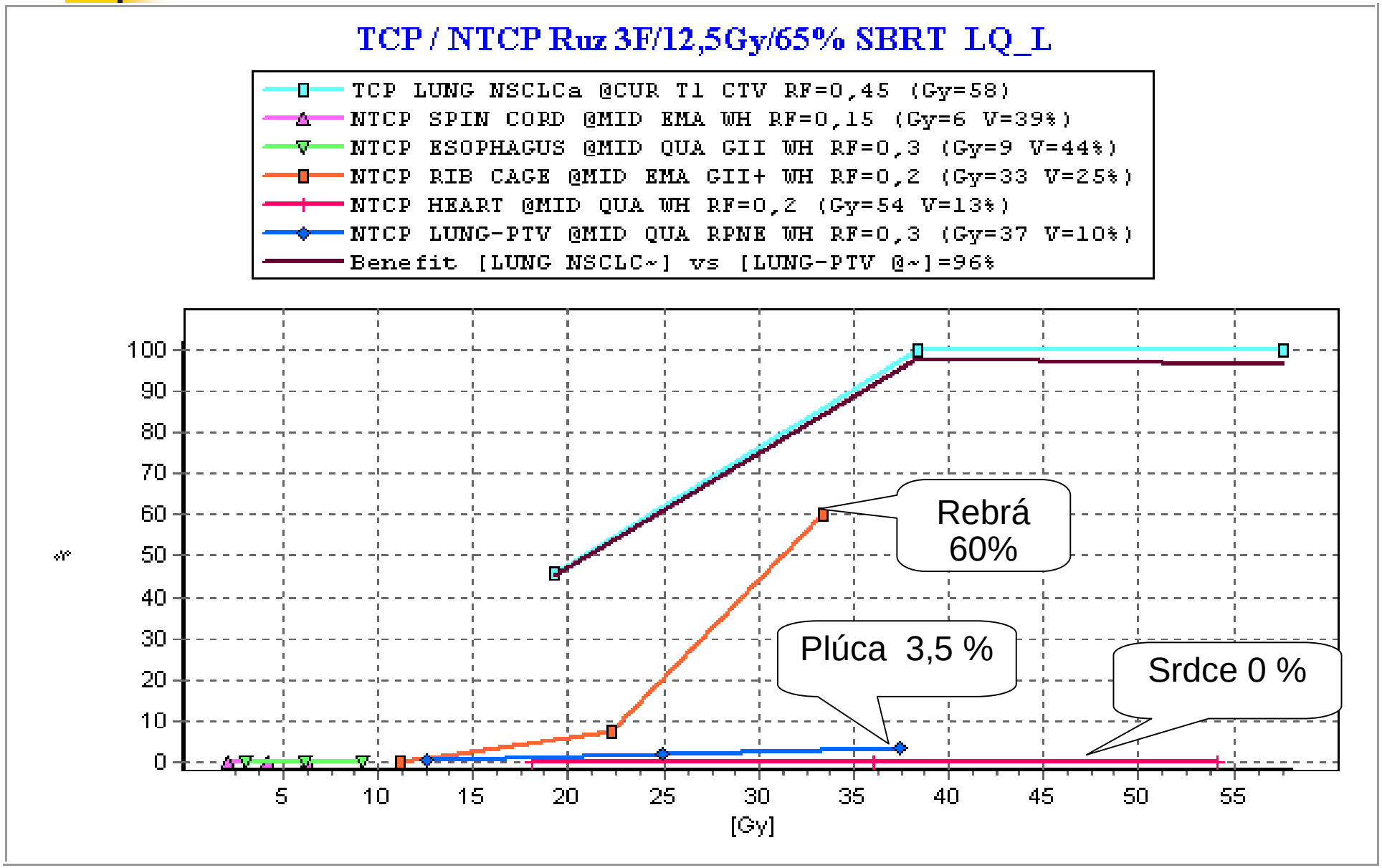
		Std. scheme				Current scheme						TPS: DVH						
!	Tissue	Fr	Ds	Gy	BED	Fr	Ds	Gy	BED	DEq	Vpa	N/TCP	Vpc	Vef	Dmax	Dmed	EUD	N(E)
T	LUNG NSCLCa @CUR T1 CTV RF	30	40	60	61,4	3	6	58	168	140	95	100,0	95	92	58,2	55,1	55,1	0,0
T	LUNG NSCLCa @CUR T1 PTV RF	30	40	60	61,4	3	6	58	168	140	81	100,0	83	75	58,1	48,0	47,8	0,0
L	SPIN CORD @MID EMA WH RF=0	25	33	44	88,0	3	6	6	13	7	39	0,0	40	93	6,1	2,4	5,1	0,0
L	ESOPHAGUS @MID QUA GII WH	27	37	54	90,0	3	6	9	19	11	44	0,0	45	58	9,0	4,0	4,8	31,9
L	RIB CAGE @MID EMA GII+ WH	25	33	50	83,3	3	6	33	131	79	25	60,2	25	83	40,4	9,9	24,4	0,4
L	HEART @MID QUA WH RF=0,2	20	29	40	80,0	3	6	54	247	123	13	0,0	13	23	56,1	7,2	10,1	57,3

Scheme | Courses | DVH | Diagrams | Protocol

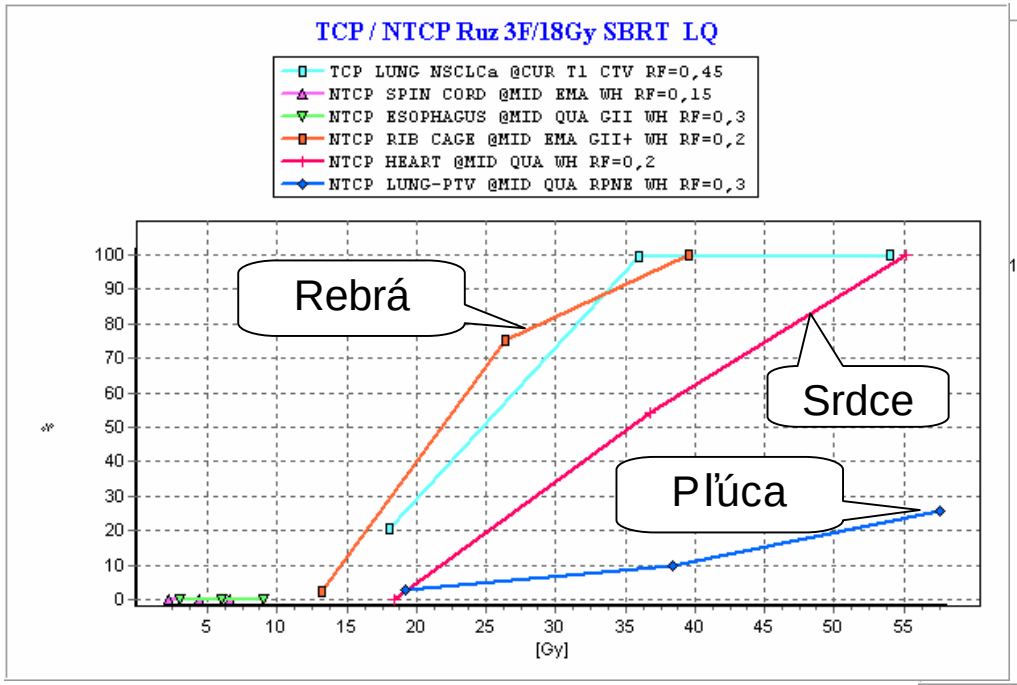
Podl'a LQ modelu :

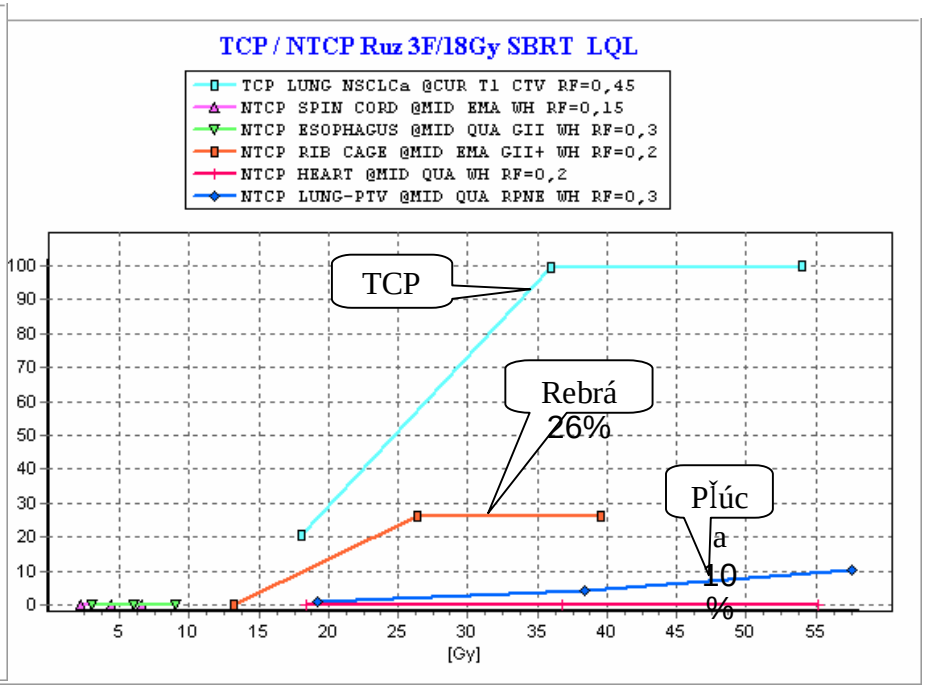


Podl'a LQ-L modelu:

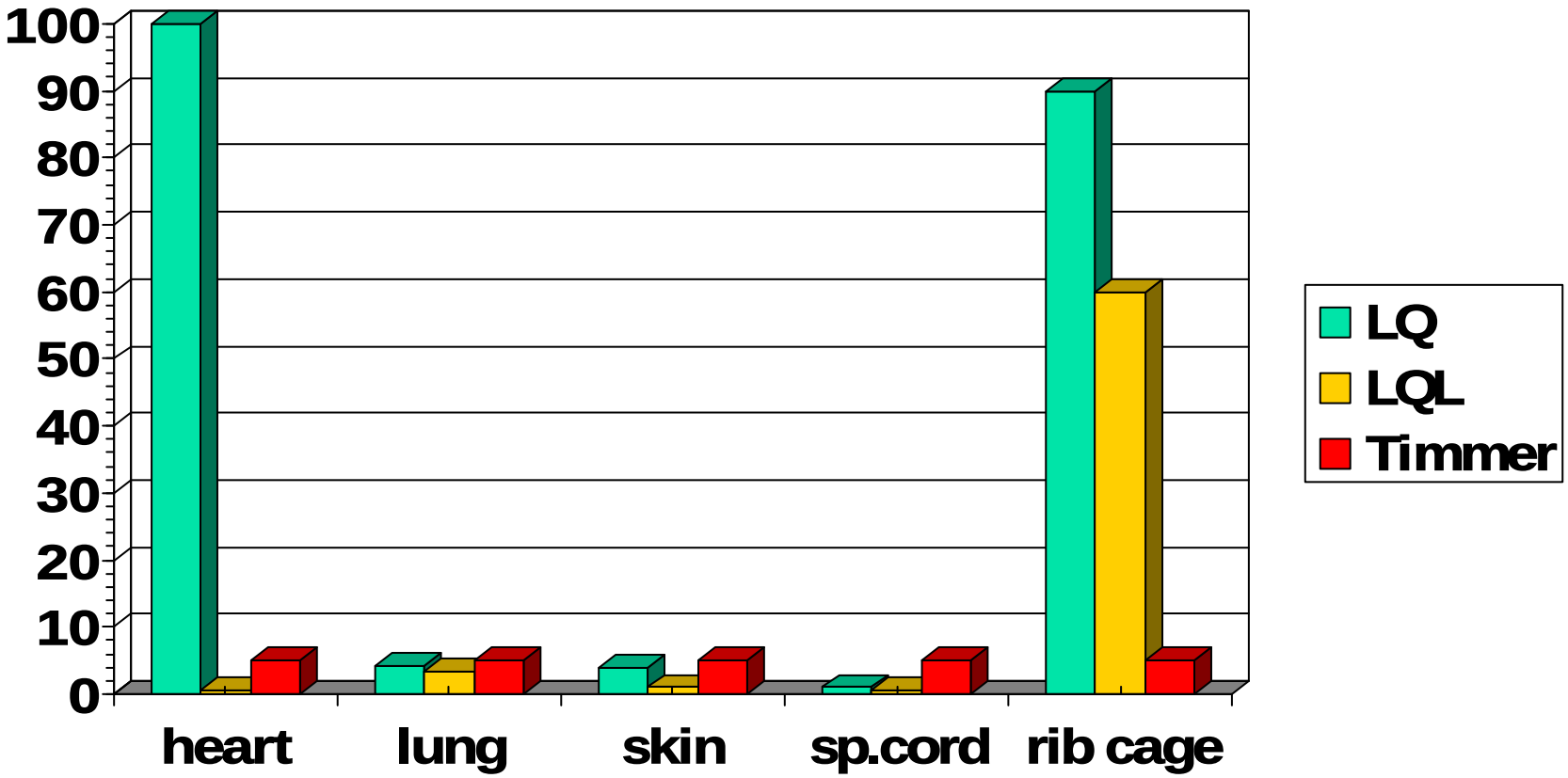


LQ –model LQ-L model

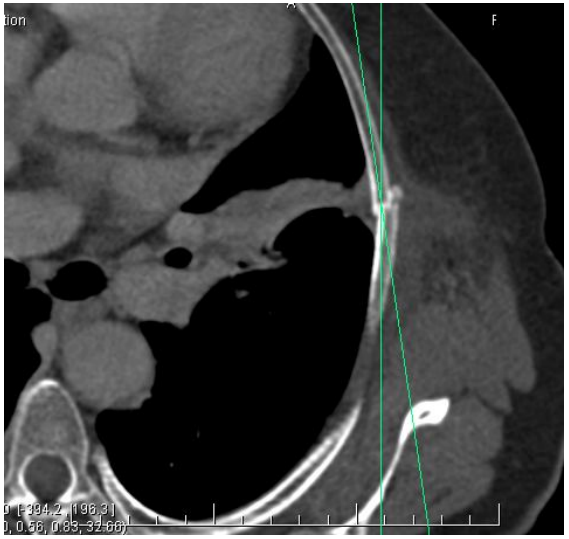


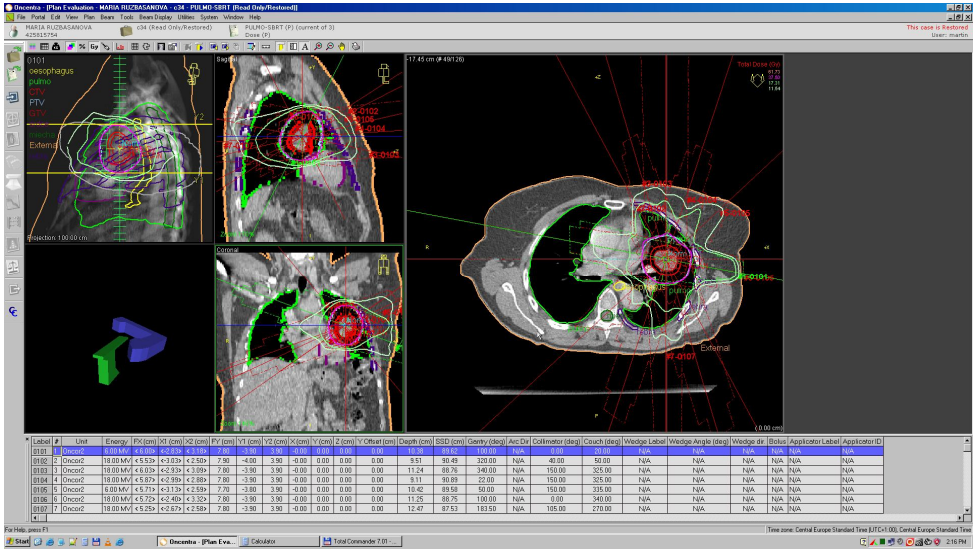


Porovnanie NTCP s limitmi pre toxicitu Gr.III. v 3F režime SBRT



Zlomenina rebra predikovaná z retrospektívneho modelovania NTCP





Dáta z BioGray : TD_{max} = 40Gy , $LQD_{2\text{-}(LQ\_L=}$ 79 Gy_3 !!!

NTCP (LQ) = 90 % !!! NTCP(LQ_L) = 60 % !!!

Aký je dopad v gyn.HDR brachyterapii ?

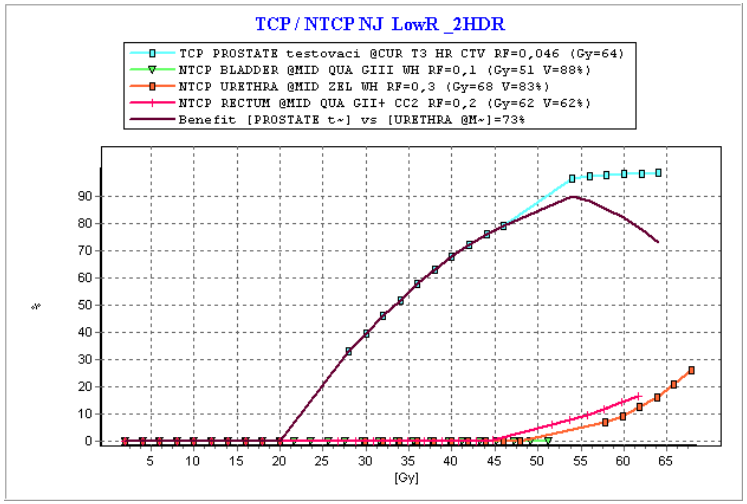
- Vplyv je zanedbateľný !

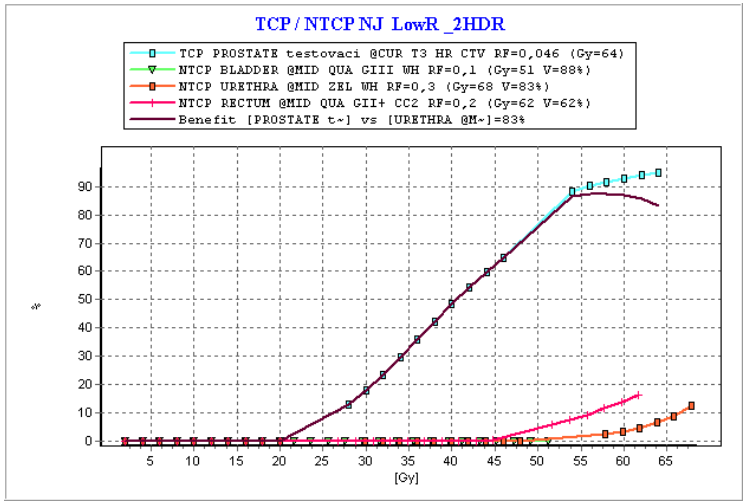
  dávky na kritické orgány pri HDR - frakcionácii 4 - 5 F/ 5 – 7Gy/ na A/CTV

  (= 60- 80 %)

- Významný dopad sa prejaví až pri dávkach 10Gy/frakciu

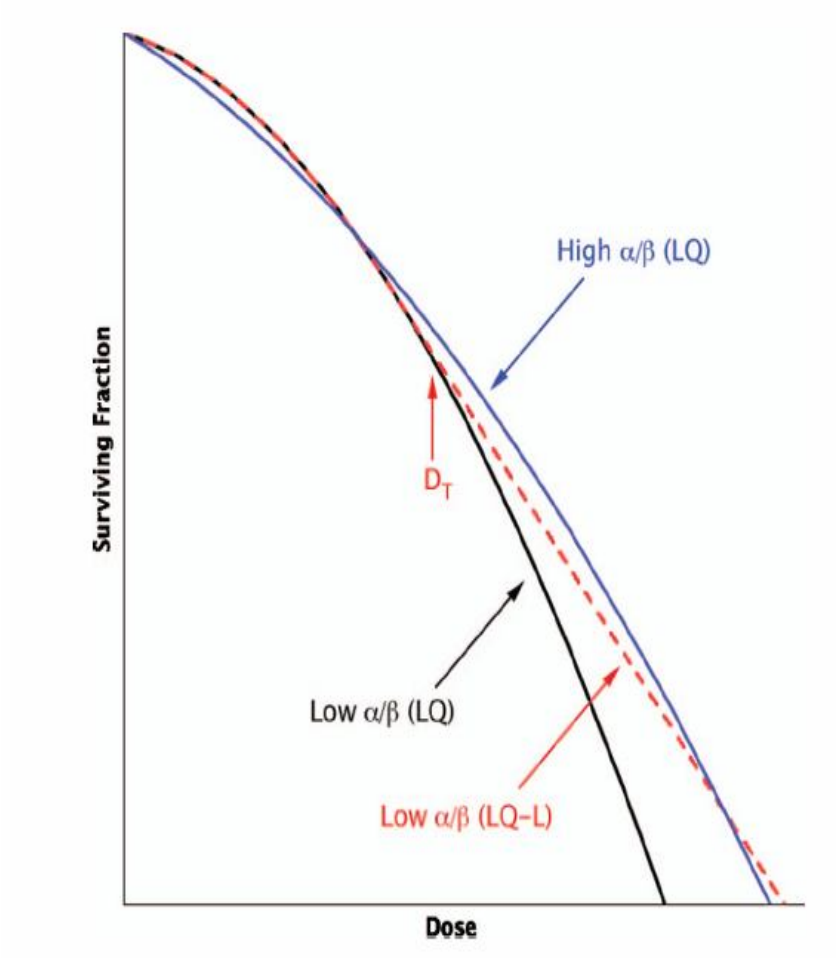
Aký dopad pri EBRT+HDR u Ca prostaty ?





	TCP/NTCP	TCP/NTCP	Pokles TCP / NTCP	
Ca prostaty	98,5 %	94,9	**o 4 %**	
Uretra	26,0 %	12,4 %		**o 54 %**

Ako sa LQ-L prejaví v klinike ?



U nízkych α/β

(napr. Ca prostaty α/β= 1,5 Gy

TCP o 4-5 % nižšie !)

Pri $\alpha/\beta >=$ (Lung Ca)

(α/β = 10 Gy)

TCP sa znižuje zanedbateľne

Late effects znižuje

α/β= 3 Gy

o 10 - 50 % bodov !

Diskusia

- FSRT sa úspešne využíva pri liečbe inoper. NSCLC I.a II.st. , HCC i iných lokalitách

  Pozorované late efekty III. gr. pod 3 %

  Lagerwaald et al. 219 pct. Červ.čas. 2008

- Radiobiol. simulácie BED/EQD_2 a NTCP umožňujú vylúčiť chyby pri využití dát DVH a zvolenej frakcionácie.

Závery z modelovania

1. **Rozšírenie algoritmu LQ-L pre hypoF v SBRT spresnilo výpočty BED a NTCP pri d/fr >= 6 Gy.**
2. **Dopad fenoménu na predikciu NTCP sa prejavuje**

   pri <= 3F významne !

   pri N >= 5F je nevýznamný.
3. **V gyn. HDR brachy pri N >= 4F sa neprejavuje**
4. **Pri 2F/8Gy HDR brachy u Ca prostaty model predikuje zníženie BED o 14 Gy a TCP o 3-4 %.**

Overall message

„In spite of advanced technology

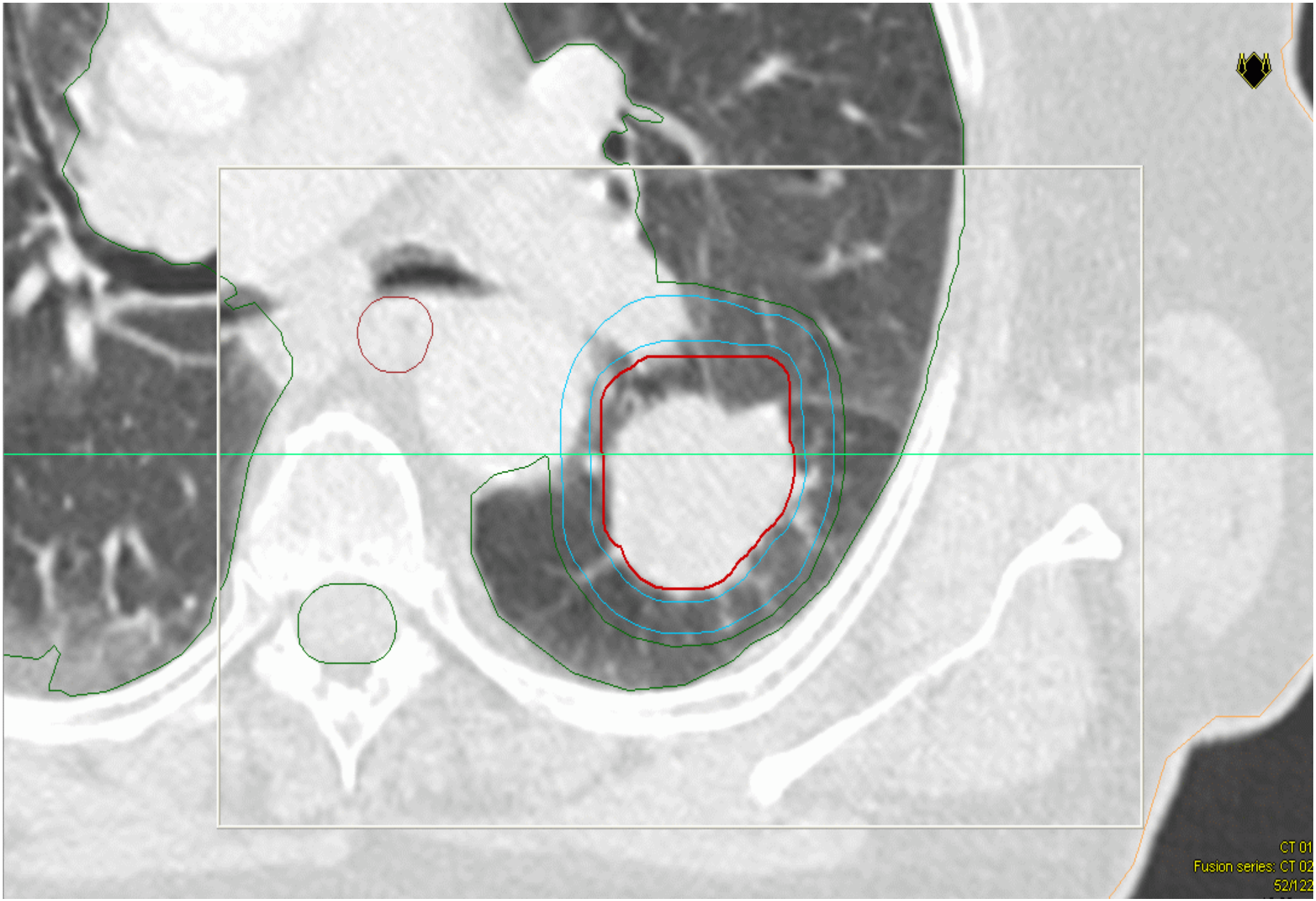
„golden tool" of good radiotherapy

still remains - radiobiology!

Prof. J. Overgaard

ESMO/ECCO/ESTRO Congress

Stockholm 2011


CT 01
Fusion series: CT 02
52/122

Ponuka

- **Rádiobiologické modelovanie účinkov RT sa stáva súčasťou procesu optimalizácie plánovania modalít RT a QA**
- **Na túto problematiku (vrátane SBRT) bude zameraný plánovaný workshop :**

  „Putovanie v „5. dimenzii rádioterapie“

  11.-12 .10.2012 v MOÚ Brno