LA TOMOTERAPIA IN ITALIA: ESPERIENZE A CONFRONTO

BARD 20 NOVEMBRE 2010

DI MUZIO NADIA
H. S. RAFFAELE – MILANO

PHASE I-II STUDY OF HYPOFRACTIONATED SIMULTANEOUS INTEGRATED BOOST WITH TOMOTHERAPY FOR PROSTATE CANCER (ACUTE AND LATE TOXICITY)

PHASE I-II STUDY OF HIPOFRACTIONATED (58 GY /20 FR) ADJUVANT TOMOTHERAPY FOLLOWING PR+PL (ACUTE AND LATE TOXICITY)

TARGET DOSE

Volumes	Low risk NCCN		Intermediate risk NCCN Roach formula <15%		High risk NCCN Roach formula ≥ 15%	
	D/fr	Dtot	D/fr	Dtot	D/fr	Dtot
PTV1 (LN+P+VSI)*			1.85	51.8	1.85	51.8
PTV2(P+VSI)	2	56	2.2	61.6	2.34	65.5
PTV3(P+ $VS_{1/3}$)	2.2	61.6	2.34	65.5	2.65	74.2
P TV4 (P)	2.55	71.4	2.65	74.2	2.65	74.2
P OVERLAP	2.34	65.5	2.34	65.5	2.34	65.5

HYPOFRACTIONATION

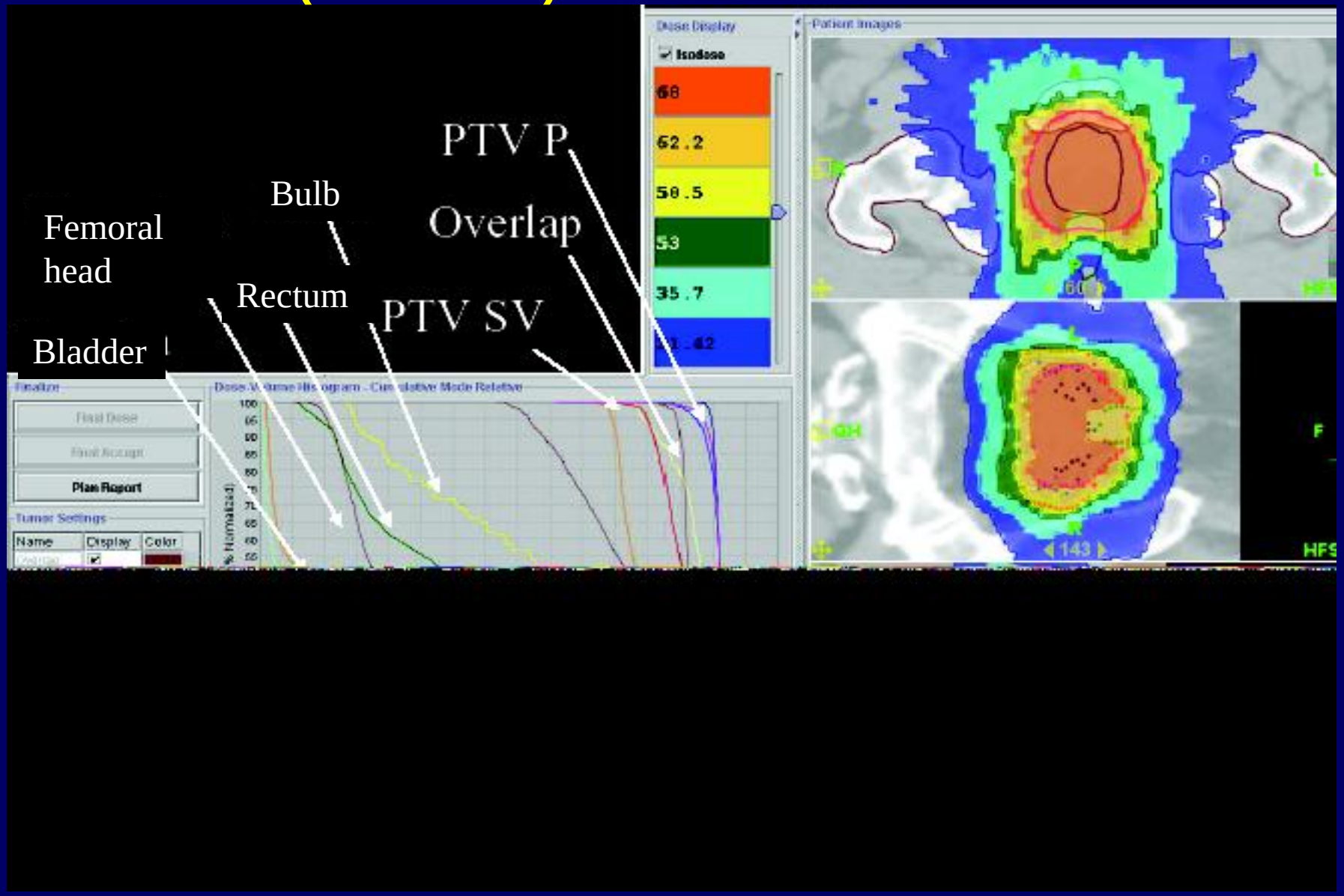
- **Considering → α/β = 3**
- **EQD2 for α/β ranging from 1.5 to 15.5**

VOLUME	**D/fr**	**Nominal D**	EQD2α/β**1.5**	EQD2α/β **3**	EQD2α/β**10**	EQD2α/β**15.5**
PELVIS	1.85	51.8	49.6	50.2	51.1	51.4
VS	2	56	56	56	56	56
	2.2	61.6	65.1	64.1	62.6	62.3
VS/P OVERLAP	2.34	65.5	71.9	70	67.4	66.8
P/VS 1/3 PROX	2.55	71.4	82.6	79.3	74.7	73.6
	2.65	74.2	88	83.8	78.2	77

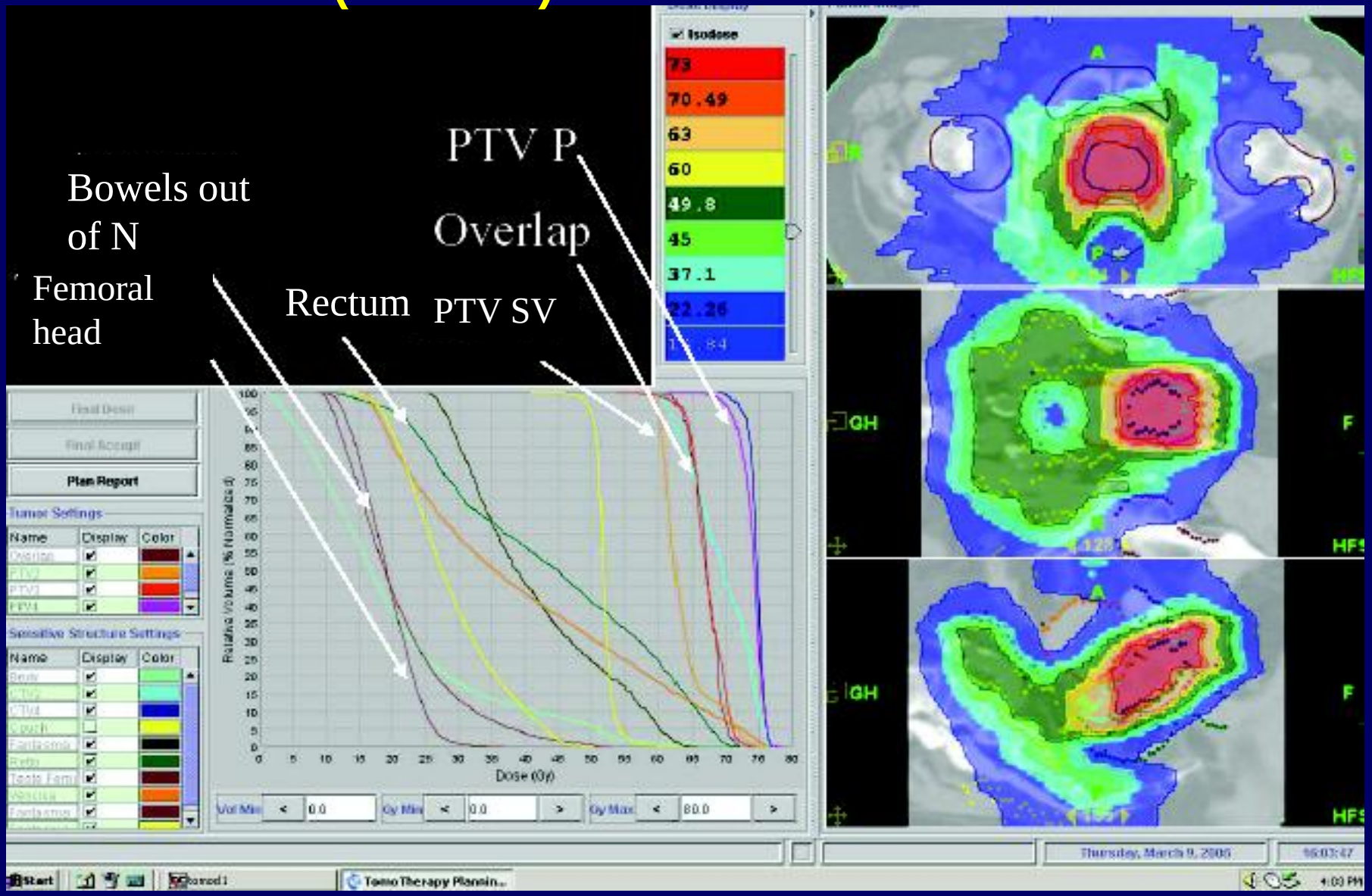
TREATMENT PLANNING

Target-OAR	Dose- Costraints
PTV1-3	V95% > 98 %; Dmax < 105 %
PTV4 (not including rectum overlap)	V95% > 98 %; Dmax < 105 %
Rectum Overlap	V65.5 Gy > 99 %; V72 < 5 %
Rectum	: V50Gy < 35 %; V60Gy < 25 %; V65Gy < 15 %
Bladder	: V60Gy < 35 %
Femoral head	: Dmax < 35 Gy
Bowel	Minimizing volume of bowel receiving 20Gy maintaining good coverage of PTV
Cauda equina sacrum (considering in case of pelvic limphnodal irradiation)	Dmax < 45 Gy

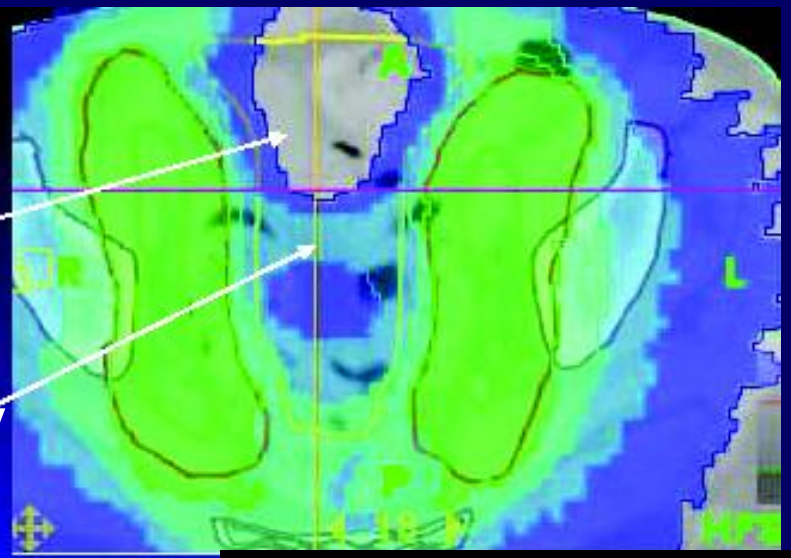
TOMOSIB (NO LNFs)

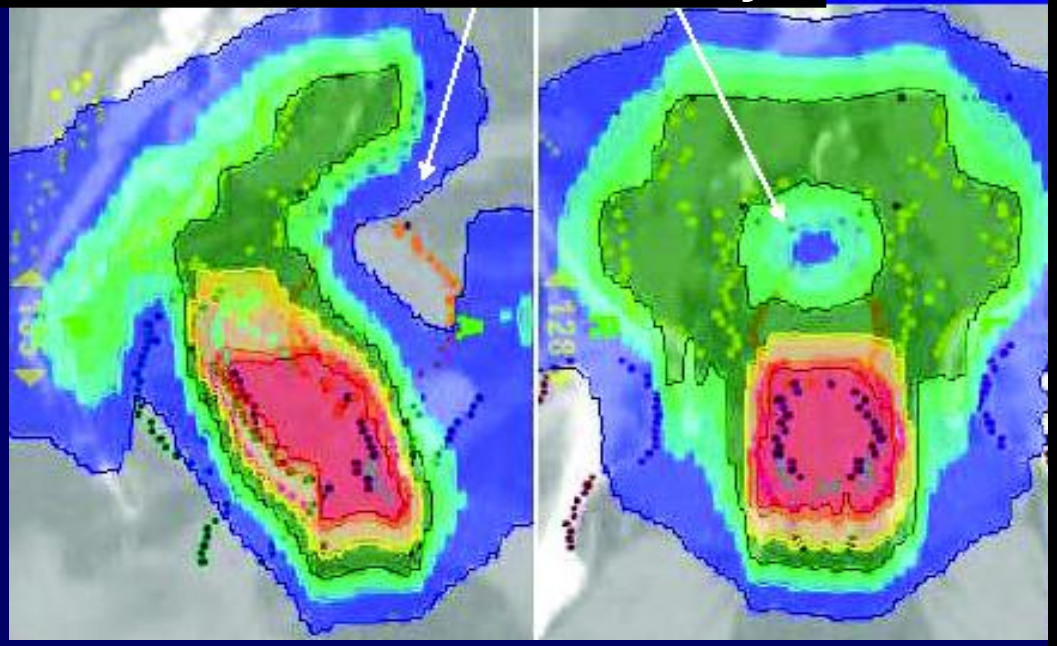


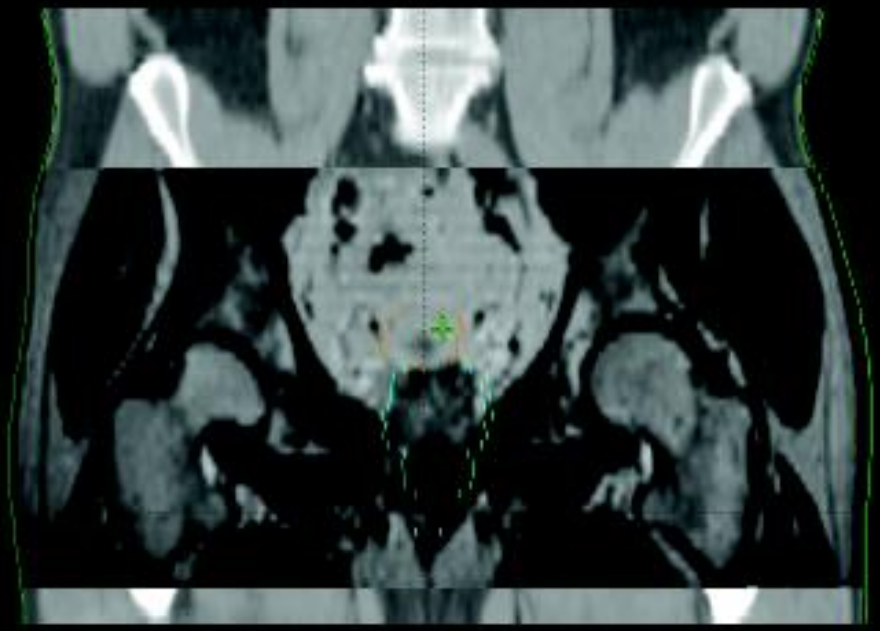
TOMOSIB (+ LNFs)

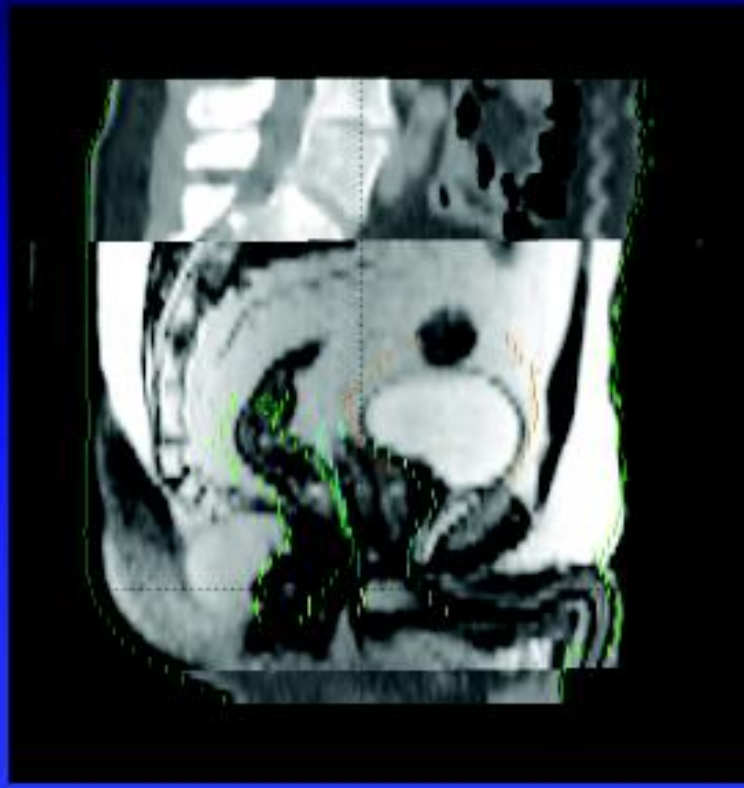


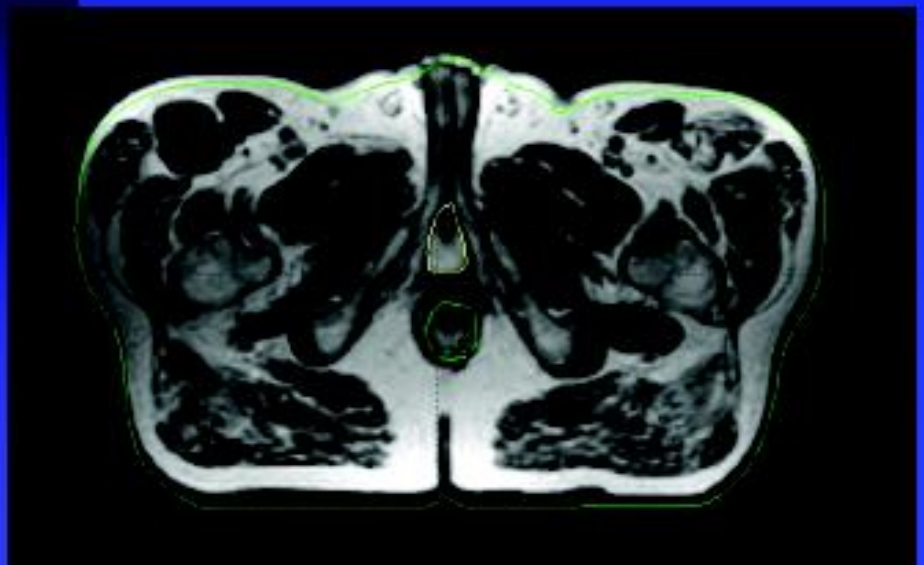
TOMOSIB (+ LNFs)

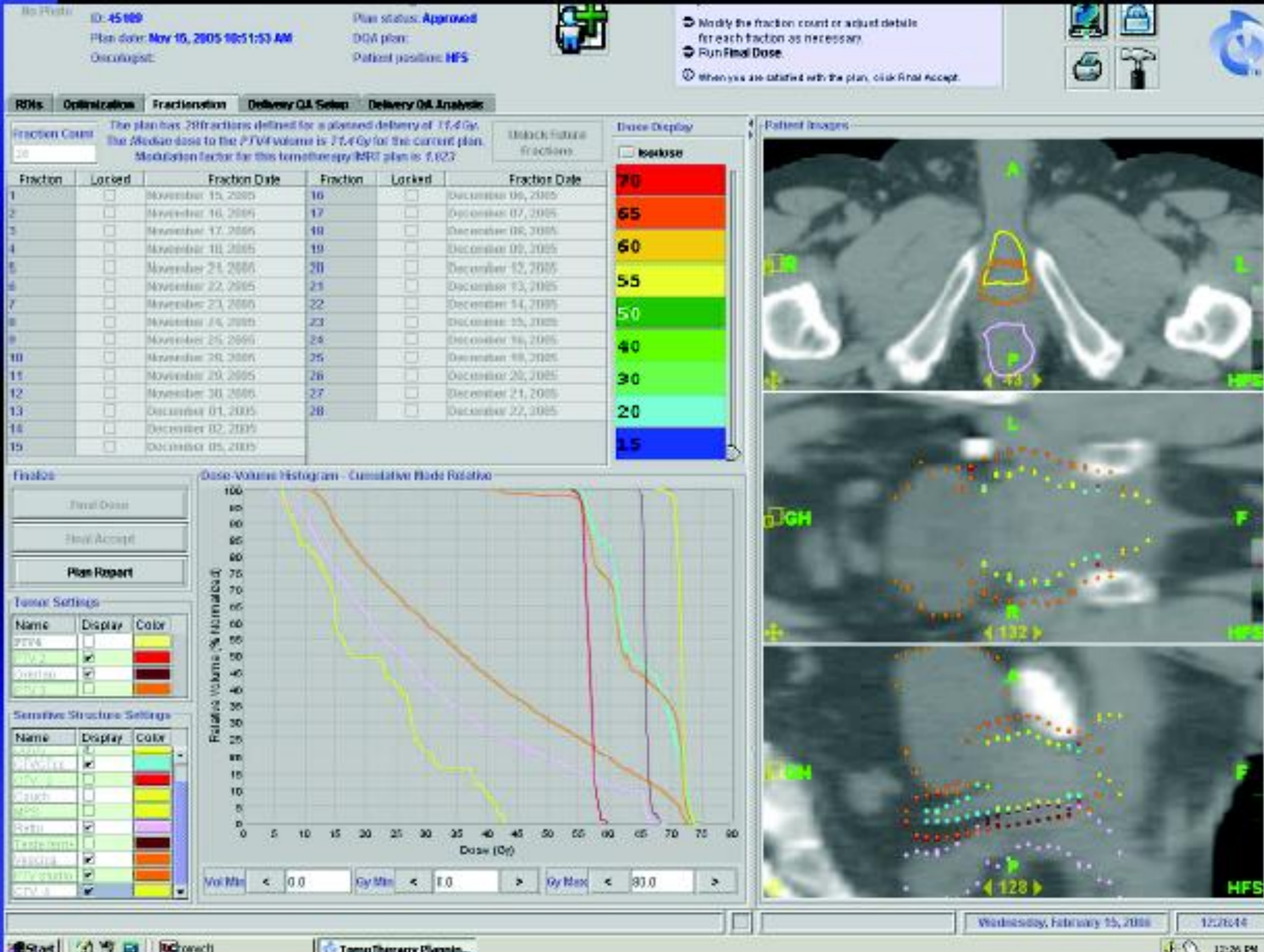






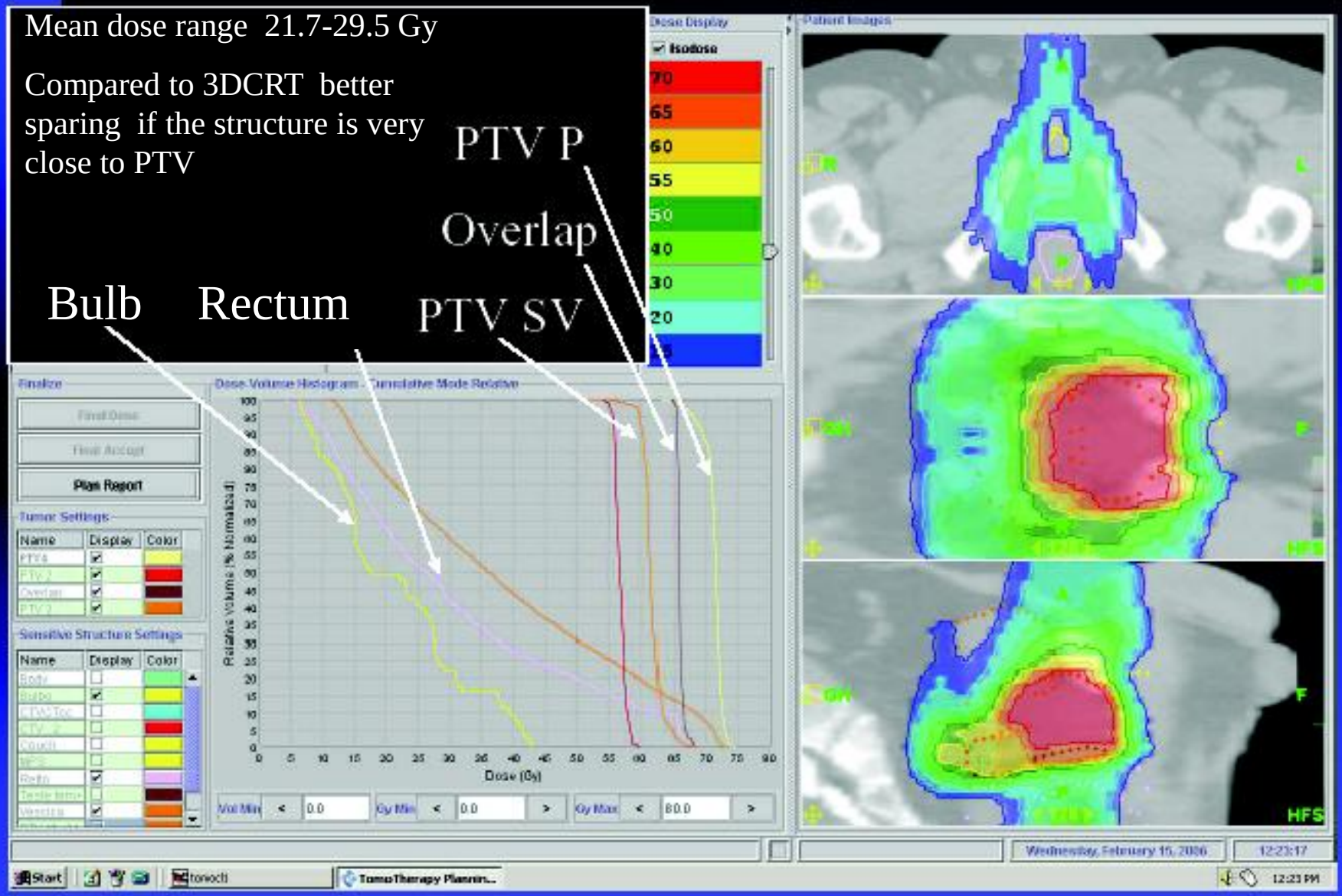




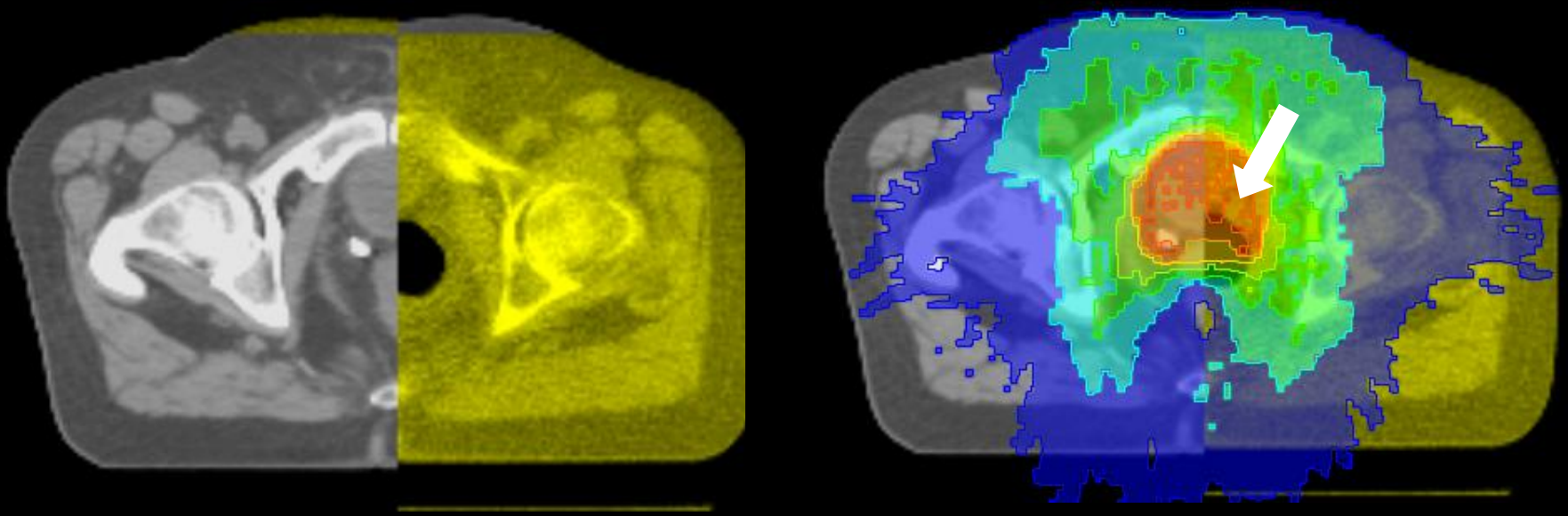


ID: 45109
Plan date: Nov 15, 2005 10:51:53 AM
Oncologist:
Plan status: Approved
DQA plan:
Patient position: HFS
Modify the fraction count or adjust details for each fraction as necessary.
Run Final Dose.
When you are satisfied with the plan, click Final Accept.
ROIs
Optimization
Fractionation
Delivery QA Setup
Delivery QA Analysis
Fraction Count
Unlock Future Fractions
Fraction
Locked
Fraction Date
Dose Display
Isodose
70
65
60
55
50
40
30
20
15
Patient Images
Finalize
Final Dose
Final Accept
Plan Report
Tumor Settings
Name
Display
Color
Sensitive Structure Settings
Dose-Volume Histogram - Cumulative Mode Relative
Relative Volume (% Normalized)
Dose (Gy)
Vol Min
Gy Min
Gy Max
HFS
Start
TomoTherapy Plannin...

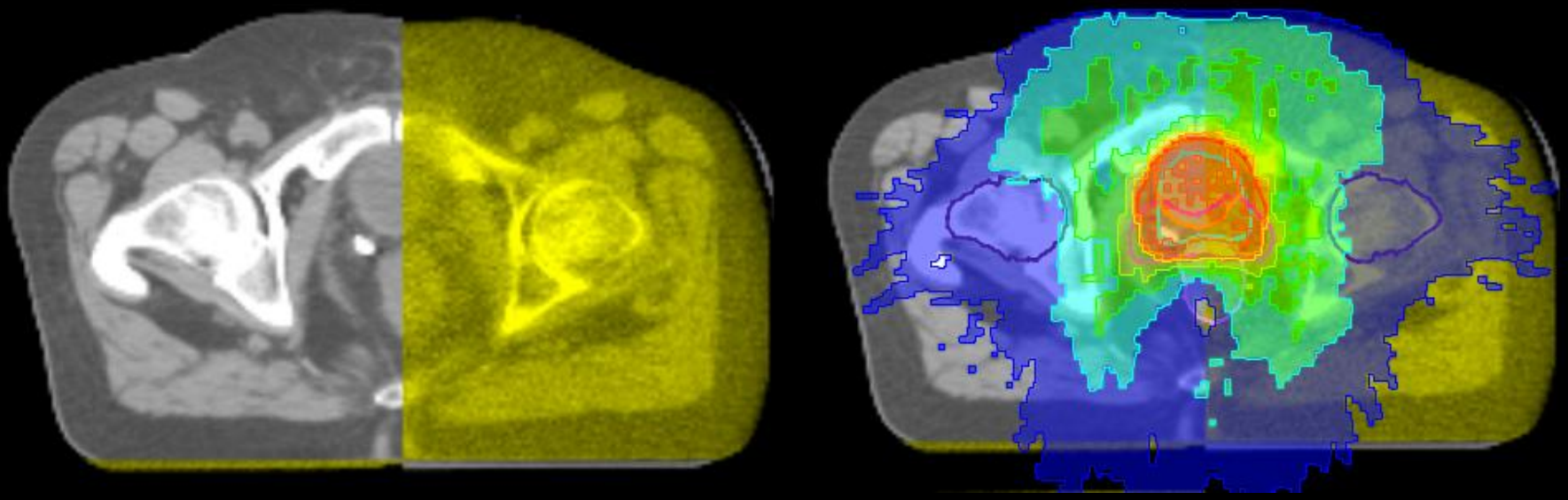
TomoSIB BULB-SPARING



MV-CT : RECTAL DISTENSION



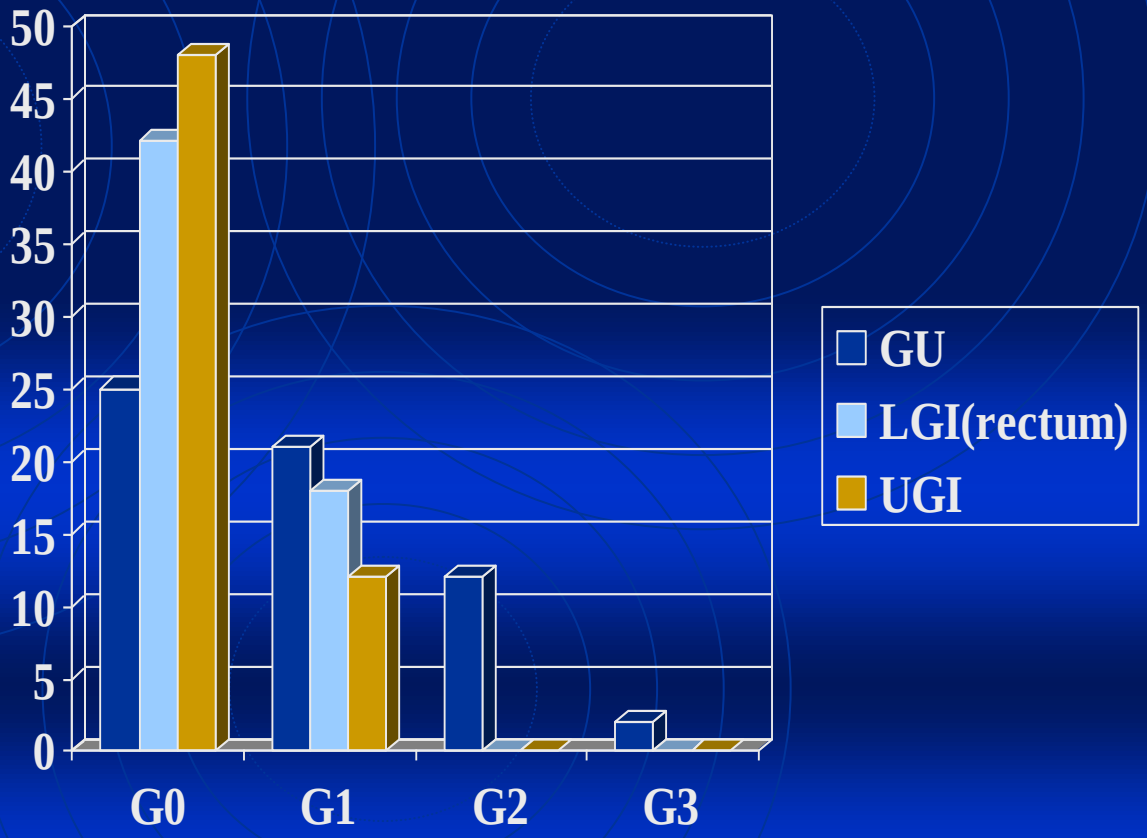
MV-CT : RECTAL EVACUATION



60 pts median follow up : 38.7 months (24.2- 50.1 m)

ACUTE TOXICITY RESULTS

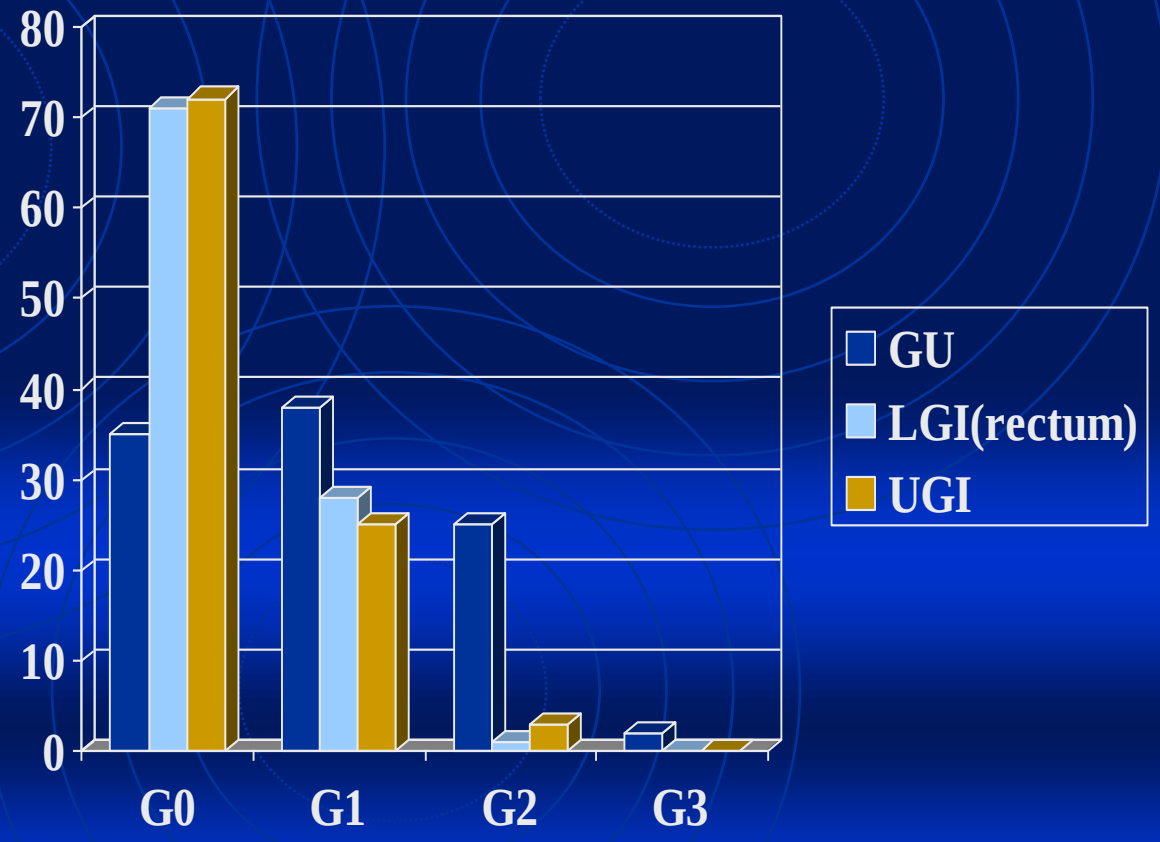
RTOG	GU	LGI	UGI 29/60
G0	25	42	48
G1	21	18	12(5)
G2	12	0	0
G3	2	0	0



100 pts median follow up : 32.2 months (8.4-47m)

ACUTE TOXICITY RESULTS

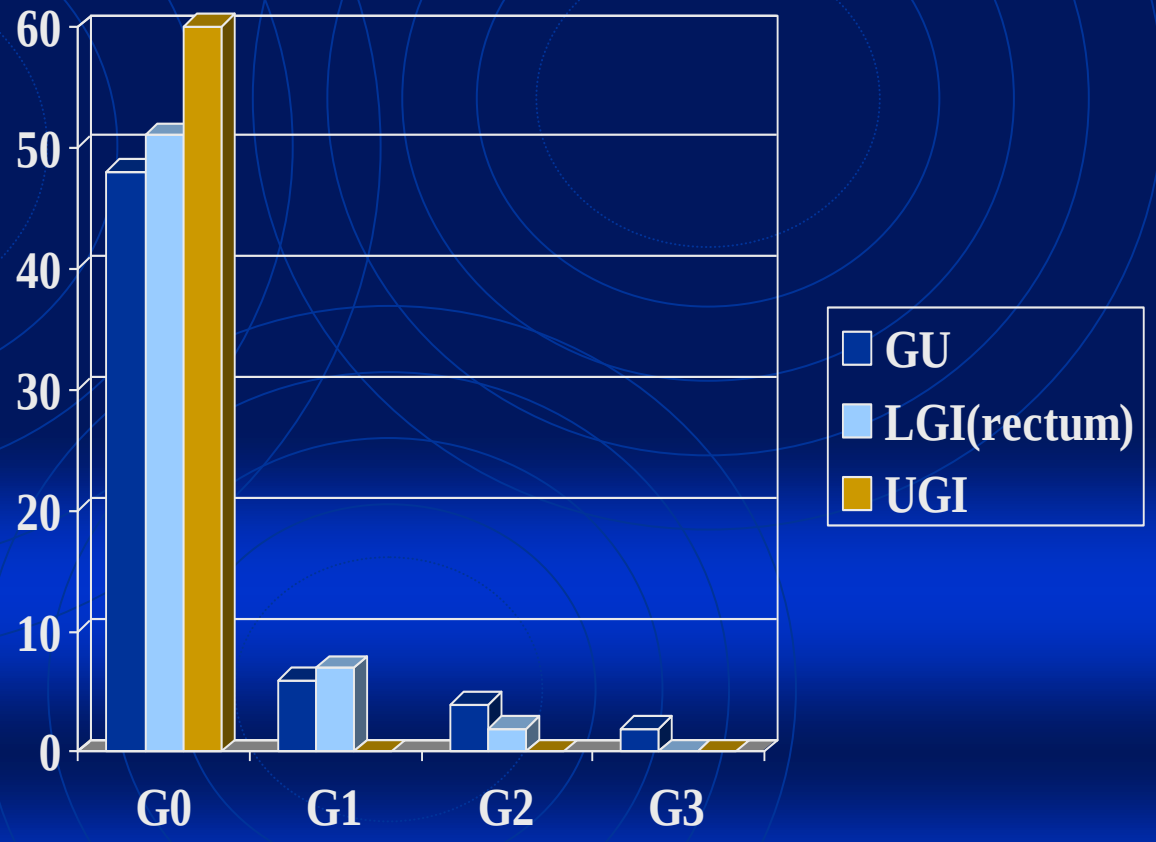
RTOG	GU	LGI	UGI
G0	35	71	72
G1	38	28	25
G2	25	1	3
G3	2	0	0



60 pts median follow up : 38.7 months (24.2- 50.1 m)

LATE TOXICITY RESULTS

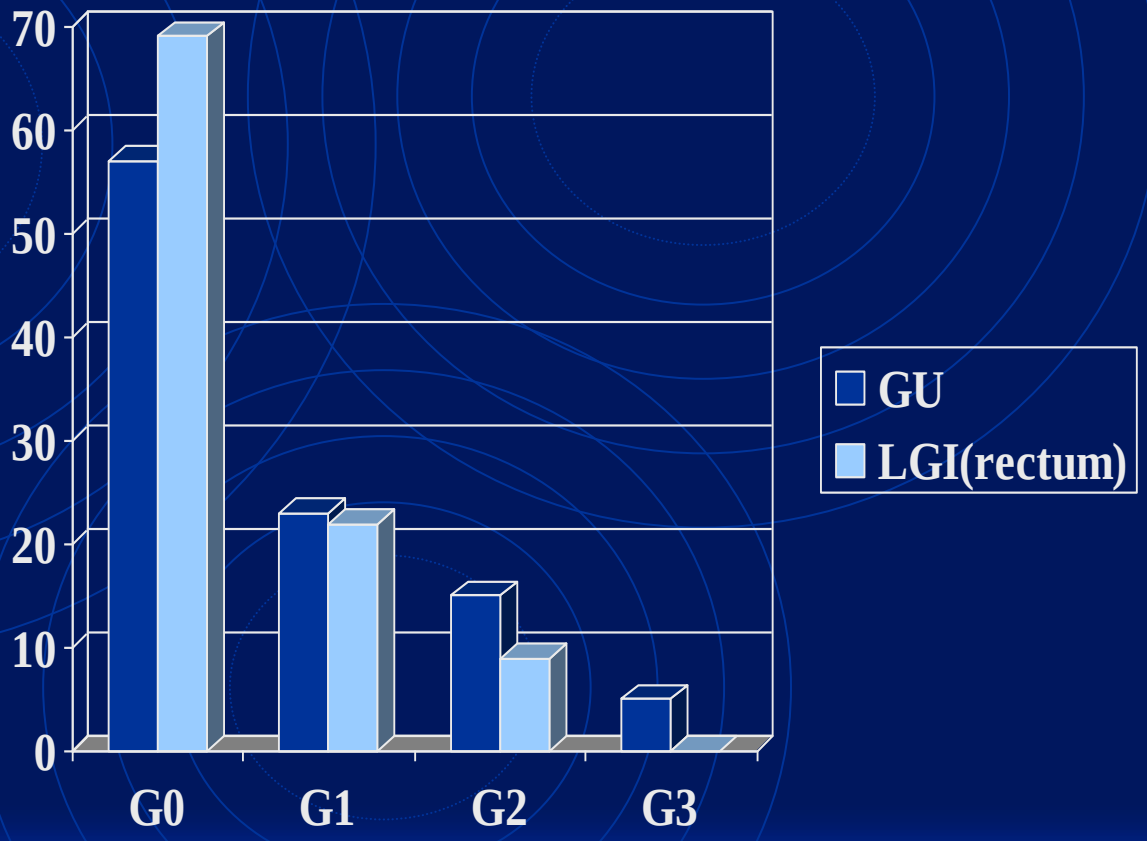
RTOG	GU	LGI	UGI 29/60
G0	48	51	60
G1	6	7	0
G2	4	2	0
G3	2	0	0



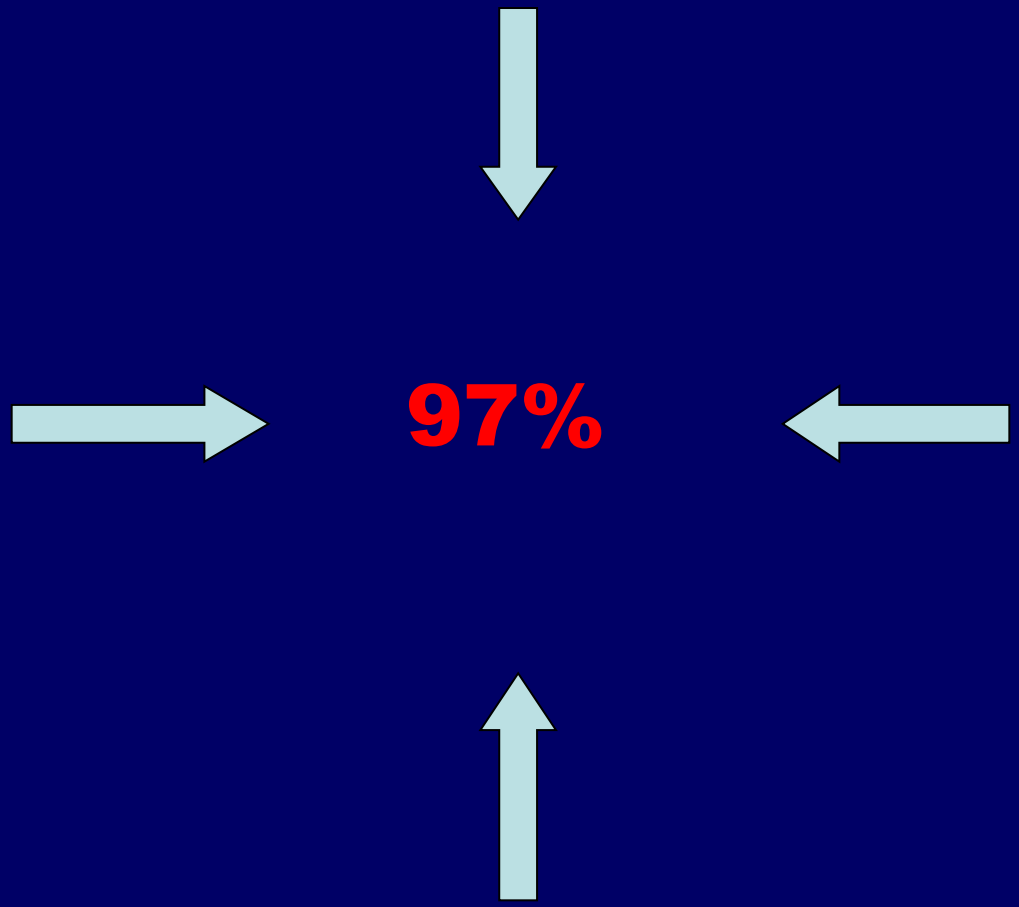
100 pts median follow up : 37.2 months (8.4- 47m)

LATE TOXICITY RESULTS

RTOG	GU	LGI
G0	57	69
G1	23	22
G2	15	9
G3	5	0



bDFS median follow up 3y (7-47 months)



Updated results

(median follow-up <u>57 months</u>)

of a Phase I-II study

of hypofractionated (58 Gy/20 fr)

adjuvant Tomotherapy following PL+RP

Jan 2005 → March 2006

50 node-negative, HR (ECE/R1) patients

- 12 pT2 R1

- 32 pT3a (11 R1)

- 3 pT3b (1 R1)

Volumes and doses

- **CTV 1 : prostatic bed + vesicles bed (for pT3b only)**
- **CTV 2 : prostatic bed**

Prescription and 2-Gy equivalent doses

Volume	Fractionation Gy/fr	# fractions	Nominal dose	EQD2
CTV1/PTV1	2.65	20	53	**60***
CTV2/PTV2	2.90	20	58	**68-70***

*** EQD2 per $\alpha/\beta = 3$**

→ Corresponding EQD2 for α/β ranging from 1.5 to 10

Volume	If $\alpha/\beta = 1.5$	If $\alpha/\beta = 3$ *(sperimental hypothesis)*	If $\alpha/\beta = 10$
CTV2/PTV2	73 Gy	**68 Gy**	62 Gy

Radiother & Oncol 2008

ORIGINAL CONTRIBUTION

Adjuvant Radiotherapy for Pathologically Advanced Prostate Cancer

A Randomized Clinical Trial

Design, Setting, and Patients Randomized, prospective, multi-institutional, US clinical trial with enrollment between August 15, 1988, and January 1, 1997 (with database frozen for statistical analysis on September 21, 2005). Patients were 425 men with pathologically advanced prostate cancer who had undergone radical prostatectomy.

Intervention Men were randomly assigned to receive 60 to 64 Gy of external beam radiotherapy delivered to the prostatic fossa (n=214) or usual care plus observation (n=211).

Conclusions In men who had undergone radical prostatectomy for pathologically advanced prostate cancer, adjuvant radiotherapy resulted in significantly reduced risk of PSA relapse and disease recurrence, although the improvements in metastasis-free survival and overall survival were not statistically significant.

Thompson et al., JAMA 296 : 2329-2335, 2006

Hypofractionated TOMO vs conventionally fractionated (1.8 Gy/fr), high-dose (68-72Gy) 3DCRT. Patient characteristics

*pT2R1 and pT3a only

	3DCRT n=175*	TOMO n=50	p
Median FU	94 months	57 months	< 0.0001
Median iPSA	9 ng/mL	7 ng/mL	0.12
pT2 / pT3	26%/74%	32%/68%	0.40
Positive SM	67%	48%	0.01
Gleason score 8-10	18%	22%	0.52
Adjuvant HORM	18% (median 12 mos)	14% (median 20 mos)	0.50

hfTOMO vs cf3DCRT (68-72Gy): TOX and clinical outcome

	3DCRT n=175	TOMO n=50	p
Median FU	73 months	57 months	< 0.0001
Late proctitis≥ 2	5%	2%	0.35
Late TOX GU ≥ 2	20%	26%	0.36
Late TOX GU 3	6.5%	10%	0.41
5-years bRFS	84%	96%	0.05

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Predominant Treatment Failure in Postprostatectomy Patients Is Local: Analysis of Patterns of Treatment Failure in SWOG 8794

Gregory P. Swanson, Michael A. Hussey, Catherine M. Tangen, Joseph Chin, Edward Messing, Edith Canby-Hagino, Jeffrey D. Forman, Ian M. Thompson, and E. David Crawford

Conclusion

The pattern of treatment failure in high-risk patients is predominantly local with a surprisingly low incidence of metastatic failure. Adjuvant radiation to the prostate bed reduces the risk of metastatic disease and biochemical failure at all postsurgical PSA levels. Further improvement in reducing local treatment failure is likely to have the greatest impact on outcome in high-risk patients after prostatectomy.

J Clin Oncol 25:2225-2229.

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 2, pp. 346–350, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.10.008

CLINICAL INVESTIGATION **Prostate**

RADIOTHERAPY AFTER PROSTATECTOMY: IS THE EVIDENCE FOR DOSE ESCALATION OUT THERE?

CHRISTOPHER R. KING, PH.D., M.D., AND DANIEL S. KAPP, PH.D., M.D.

Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA

With an expected proportional gain in the bRFS rate of ~3% per incremental Gray, a randomized trial testing a SRT dose of 64 vs. 70 Gy or an adjuvant trial testing 60 vs. 66 Gy would require a total of approximately 250 patients and would be expected to detect a ~20% difference in the 5-year bRFS rate between the two treatment arms (assuming

Table 1. Patient characteristics

Characteristic	All (n = 334)	RT dose ≥70 Gy (n = 181)	RT dose <70 Gy (n = 153)	p
Follow-up (mo)	108	88	128	<0.0001
Age (y) (range, 45–78)	66	66	66	ns
Initial PSA (ng/mL) (range, 1.2–93)	12	12	12	ns
Neoadjuvant androgen deprivation	151 (45)	64 (35)	87 (57)	0.0001
Postoperative PSA (ng/mL)	0.02	0.02	0.01	ns
Pathologic stage				
pT2	59 (18)	38 (21)	21 (14)	ns
pT3a	135 (40)	73 (40)	61 (40)	ns
pT3b	114 (34)	59 (33)	55 (36)	ns
pT4	26 (8)	10 (6)	16 (10)	ns
Positive surgical margins	221 (66)	126 (70)	95 (62)	ns
Gleason score				
Mean	7	6.8	6.2	ns
Median	7	7	7	ns
2–6	124	44 (24)	80 (52)	<0.0001
7	142	95 (52)	47 (31)	0.001
8–10	54	31 (17)	23 (15)	ns
Not available	14	11	3	
No. of pelvic lymph nodes removed (range, 2–42)	13	12	14	ns
Time to EART (mo) (range, 1.1–7.4)	3.1	3.6	2.6	0.0006
RT dose (Gy)				<0.0001
Mean	68.2	70.8	65.1	
Median	70.2	70.2	66.6	
Adjuvant androgen deprivation	78 (23)	51 (28)	27 (18)	0.03
Median duration (mo)	13.5	13	18.5	0.03

Abbreviations: RT = radiotherapy; PSA = prostate-specific antigen; EART = early adjuvant RT. Values are median or number (percentage), unless otherwise noted.

IJROBP, 2009

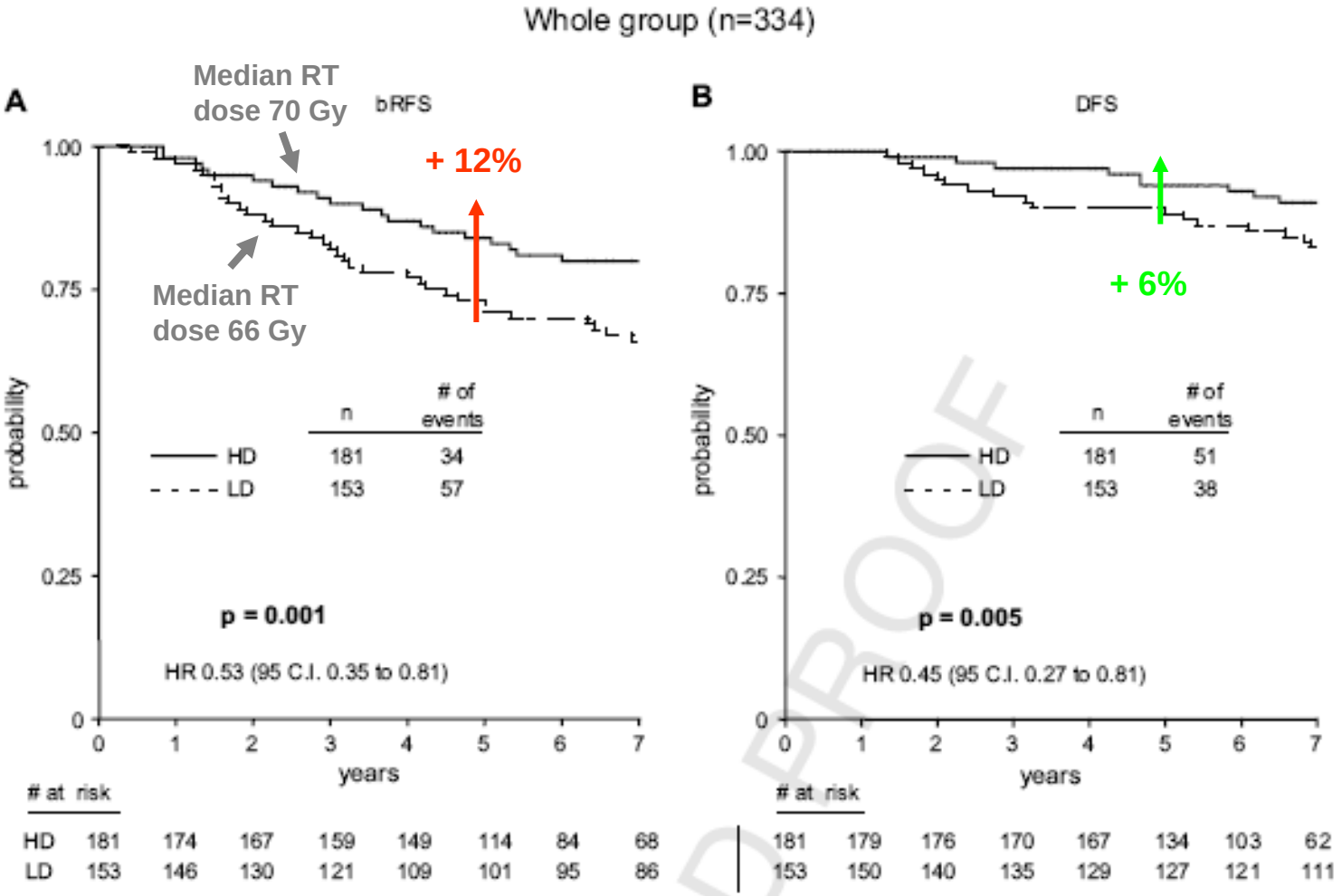

Fig. 1. (A) Biochemical relapse-free survival (bRFS) and (B) disease-free survival (DFS) by early adjuvant radiotherapy dose (n = 334). HD = high dose; LD = low dose; HR = hazard ratio; C.I. = confidence interval.

IJROBP, 2009

Table 5. bRFS in the whole group, AAD-naïve patients, and hormone-naïve patients, according to EART dose

Parameter	bRFS, % (*n*)		Gain (%)	*p*
	<70.2 Gy	≥70.2 Gy		
All (*n* = 334)	71 (153)	83 (181)	+12	0.001
Adjuvant AD-naïve only (*n* = 256)	73 (126)	85 (130)	+12	0.009
Hormone-naïve (*n* = 162)	81 (77)	93 (85)	+12	0.016

Abbreviations as in Tables 2 and 3.

IJROBP, in press

Volumes and doses

- **CTV 1 : prostatic bed + vesicles bed (for pT3b only)**
- **CTV 2 : prostatic bed**

Prescription and 2-Gy equivalent doses

Volume	Fractionation Gy/fr	# fractions	Nominal dose	EQD2
CTV1/PTV1	2.65	20	53	**60***
CTV2/PTV2	2.90	20	58	**68-70***

*** EQD2 per α/β = 3**

→ Corresponding EQD2 for α/β ranging from 1.5 to 10

Volume	If α/β = 1.5	If α/β = 3 (sperimental hypothesis)	If α/β = 10
CTV2/PTV2	73 Gy	**68 Gy**	~~62 Gy~~

Radiother & Oncol 2008

Next step

Phase III Trial
Postoperative hfTOMO vs cf 3DCRT
in high-risk node-negative CaP patients

Hypofractionated Tomotherapy

Volume	Fractionation Gy/fr	# fractions	Nominal dose	Corresponding EQD2
PTV1	2.9	20	58	>>68-70*

*** for a/b ratio < 3**

®

High-dose, conventionally fractionated RT

Volume	Fractionation Gy/fr	# fractions	Nominal dose	Corresponding EQD2
PTV1	1.8	40	72	68-70*

Endpoint
+8% 3- and 5-year bRFS
Sample size estimate

Power	α	From	To	N1	N2	@
80%	0.05	96%	88%	204	204	3 yr
80%	0.05	93%	85%	204	204	5 yr
90%	0.05	96%	88%	264	264	3 yr
90%	0.05	93%	85%	264	264	5 yr

Esperienza HSR TOMO ADV 65.8 Gy in 28 frazioni

- 111 pazienti trattati tra 5/2006 – 12/2008
- 76 pN0 / 35 pN+
- Follow-up mediano intera casistica : 35.7 mesi
- Dei 76 pN0 : 2/76 recidive LN, entrambe in LN LA

Esperienza HSR TOMO ADV 65.8 Gy in 28 frazioni Tossicità

		GU	GE	PROCT
ACUTA	Grado 2	6%	2%	-
	Grado 3	-	-	-
		GU	GE	PROCT
LATE	Grado 2	6%	2%	1%
	Grado 3	2%	-	-

Conclusions

- The treatment is well tolerated and convenient for the patient (significant reduction of treatment time and cost, both direct / indirect)

- GU Tox :

  Acute: results comparable to those reported in many conventional fractionation series and in other hypofractionated trials

  Late: Increase tox expected ,but at the moment acceptable

- GI TOX

  Acute rectal : excellent sparing of the rectum (only G1 acute toxicity)

  Late rectal : No G3, only few G2. Excellent late toxicity profile

  uGI acute: no patients reported acute toxicity greater than G1 thanks to the dramatic reduction of the fraction of the intestinal cavity receiving between 20 and 50 Gy

  Late: No G3, only few G2. Excellent late toxicity profile

- bDFS

  Promising data

Conclusions

- Moderately hypofractionated postoperative Helical Tomotherapy in high-risk, node negative, CaP patients is feasible and safe.
- The slightly increased risk of Grade ≥ 2 GU sequelae suggest the need to careful select patients candidates to hypofractionated regimens.
- The promising 5-year 98% bRFS is strongly suggestive of an a/b ratio for residual CaP after RP very close to 1 Gy.
- A Phase III trial comparing hypo- *vs* conventionally fractionated high-dose RT is warranted.