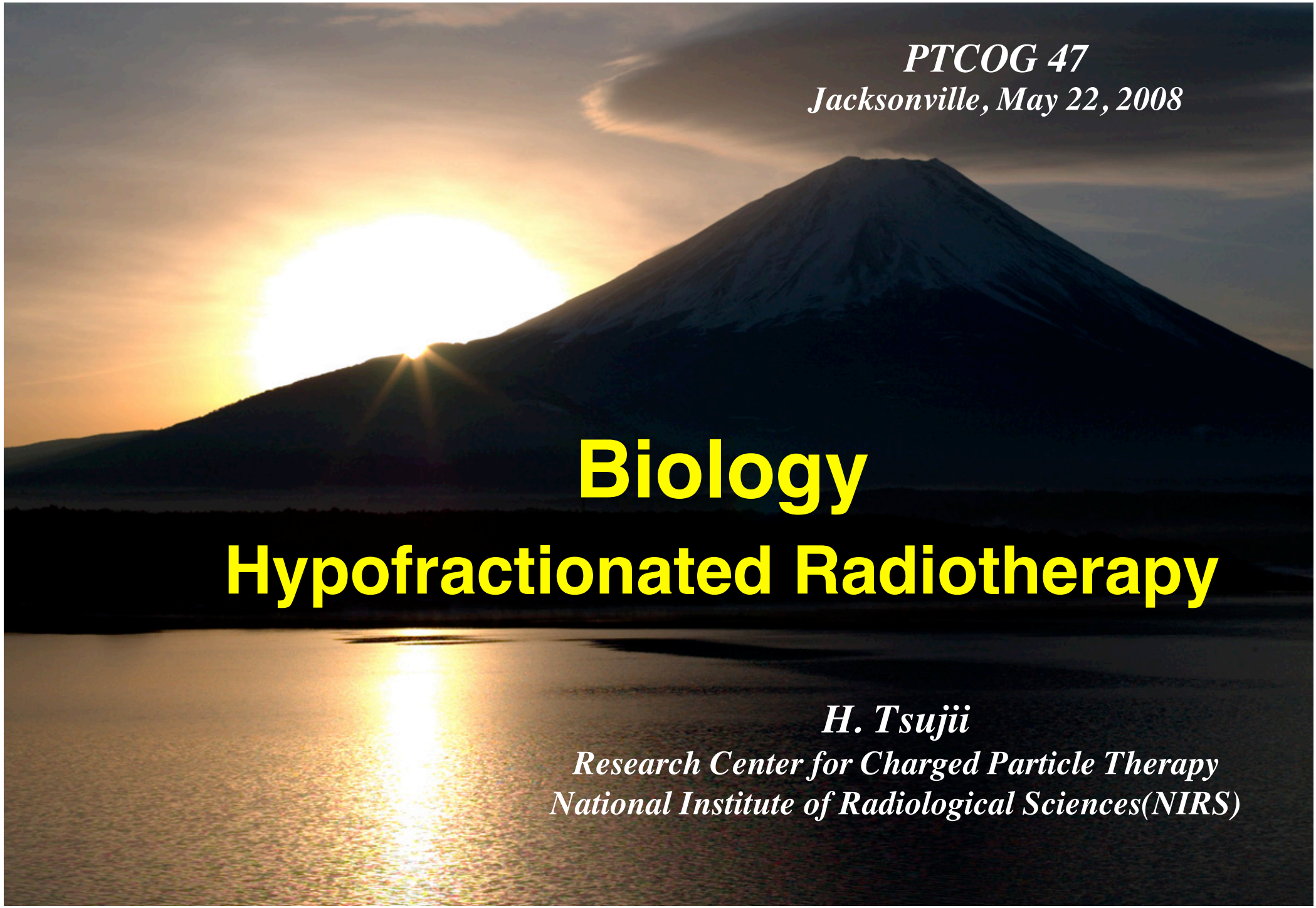

PTCOG 47
Jacksonville, May 22, 2008

Biology
Hypofractionated Radiotherapy

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Hypofractionated Radiotherapy

Very high radiation doses can be given to patients with tumors of the parallel organs using hypo-frationated radiotherapy with SBRT as well as charged particles without serious acute or long-term normal tissue morbidity.

Both lung and liver tumors have been successfully treated in this manner. Many other types of tumors like prostate cancer are also being challenged in C-ion RT using small number of fractions.

Hypofractionated Radiotherapy

In the case of charged particles, indications for hypofractionated radiotherapy can be also extended to many types of tumors, particularly in C-ion RT.

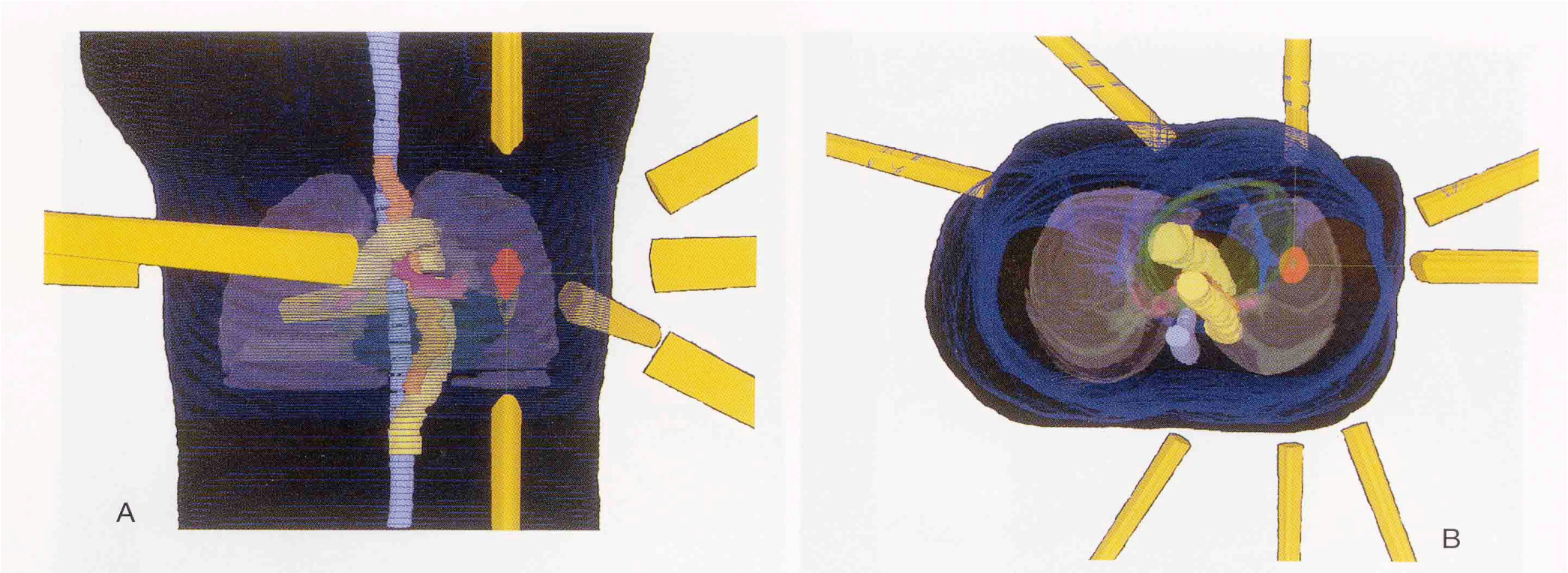
There are ample knowledge and experiences we can learn from high-tech photon therapy such as 3D-CRT, SRT and IMRT.

Factors to be considered for Hypofractionated Radiotherpy

- **Effect of proliferation**
- **Effect of reoxygenation**
- **Effect of volume**
- **Dose homogeneity and minimum dose**
- **Duration of single fraction delivery**
- **Tolerance dose of target organ:**

  Parallel vs Serial organ
- **High-LET effects**
- **Release of cytokines after high dose irrad**

SBRT in NSCLC



Three-dimensional representation of a typical beam arrangement for stereotactic body Radiation therary to a left-sided, early-stage lung cancer. **A:** The beams looking From a View directly in front of the patient. **B:** A view from the patient's feet. Contoured normal Structures are shown as well as the tumor's planning target volume(red).

Papiez L, Moskvin V, Timmerman RD: **SBRT,**
ed Kavanagh B, Timmerman R. Lippincott 2005

Comparison of BED (α/ß=10) of representative dose regimens used in SBRT vs. conventional RT for early-stage NSCLC.

Author	*Dose*	*Biologic Equivalent Dose*
Standard radiotherapy	2 Gy × 30–33 fx	72–79 Gy
Hara (58)	30 Gy × 1 fx	120 Gy
Nagata (50)	12 Gy × 4 fx	105 Gy
Timmerman (51)	20 Gy × 3 fx	180 Gy

Normal Tissue Dose Tolerance for SBRT delivered in 3 Fractions

Organ	*Volume*	*Dose (Gy)*
Spinal cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral brachial plexus	Any point	24 Gy (8 Gy per fraction)
Heart	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral bronchus	Any point	30 Gy (10 Gy per fraction)
Whole lung (right and left)	***Tolerance dose depends on PTV***	

Assumption in NSCLC

The total duration of SBRT is shorter than the starting time (T_k) of accelerated repopulation in tumors, believed to be 3 to 5 weeks in tumors with the same rate of repopulation.

For analysis, a T_k of 28 days was assumed with a repopulation doubling time (T_p) of 3 days.

It can be also assumed that no tumor cell repopulation occurs in the hypofractionated RT.

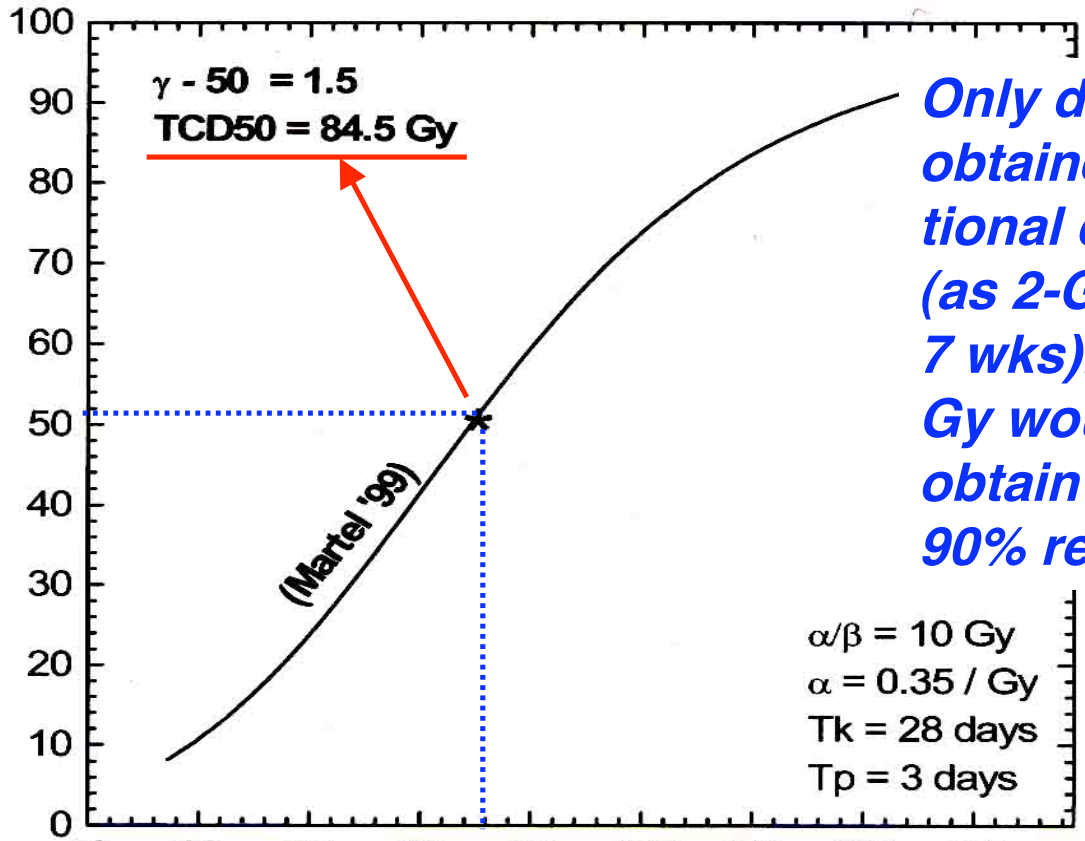
Martel MK, et al : Lung Cancer 1999; 24: 31-37 (Unv.Michigan)

Martel MK, et al : Lung Cancer 1999; 24: 31-37 (Unv.Michigan)

Dose was escalated to 103 Gy in 2-Gy fr given at 5 fr per wk.

Recurrence-Free Survival in NSCLC

Response-dose curve calc. from clinical parameters analysed by Martel et al. Lung Cancer, 24: 31-37, 1999.

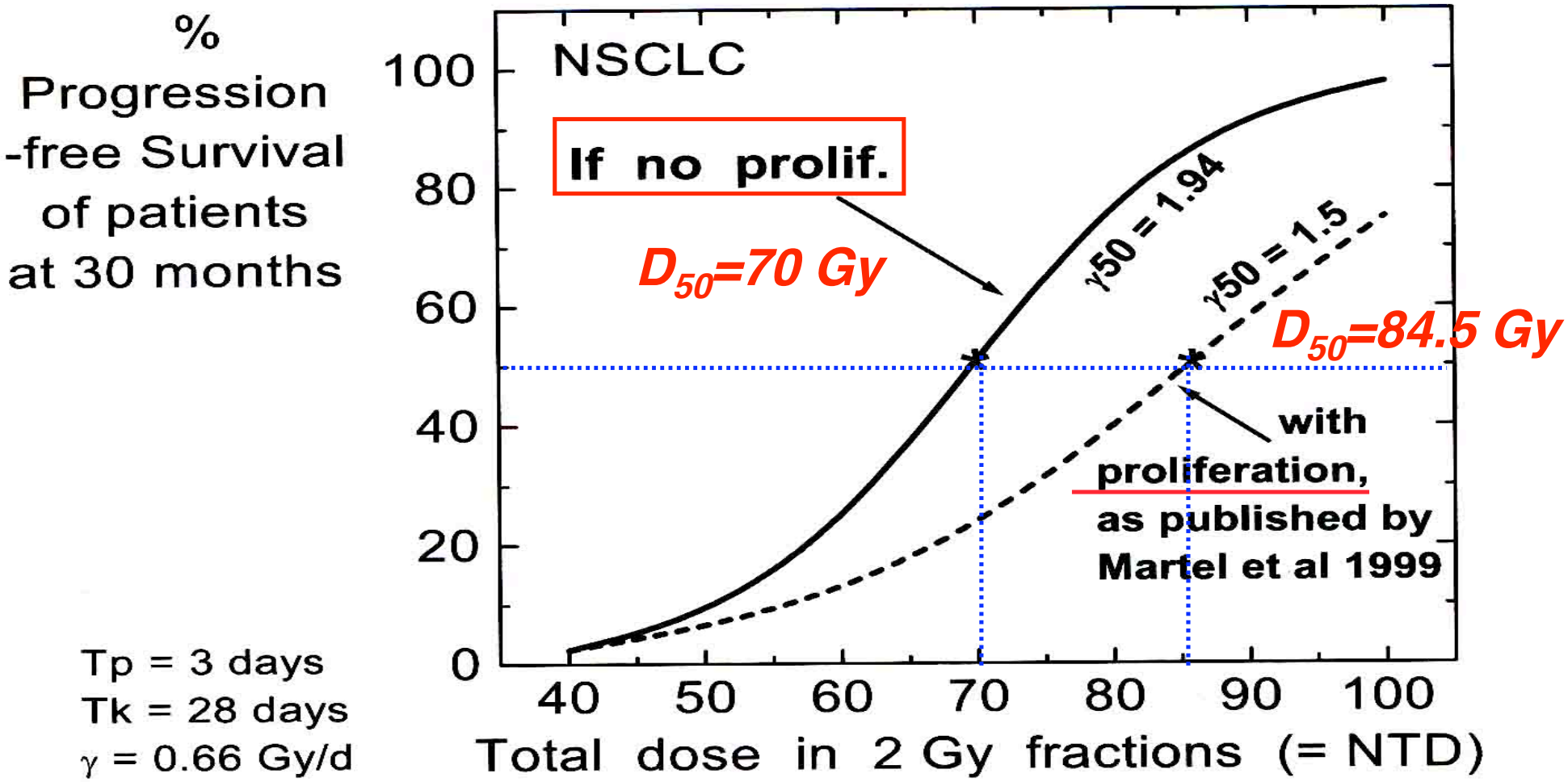


Total Dose @ 2 Gy/fr (Gy)	50	60	70	80	90	100	110	120	130	Gy
Overall Time (days)	32	39	46	53	60	67	74	81	88	days
BED no prolif (Gy-10)	60	72	84	96	108	120	132	144	156	Gy-10
BED Tp=3d & Tk=28d	57.4	64.7	72.1	79.5	86.9	94.3	102	109	116	Gy-10

Only dismal results are obtained with conventional doses of 60-70 Gy (as 2-Gy fractions in 6 or 7 wks). Doses up to 100 Gy would be required to obtain success in the 90% region.

Modeling Results from SBRT
- Effect of Proliferation -

It can be assumed that no tumor cell repopulation occurs in the hypofractionated RT



Martel MK, et al: Lung Cancer 1999; 24: 31-37

Repopulation during a course of RT

RTOG Study (1993)

Cox JD et al: IJROBP 1993;27, 493-498

397 pats treated with 69Gy of multi-fractionated RT

3-yr Survival	**17% without delay of treatment**
	1% with gaps exceeding 5 days
	(p=0.0001)

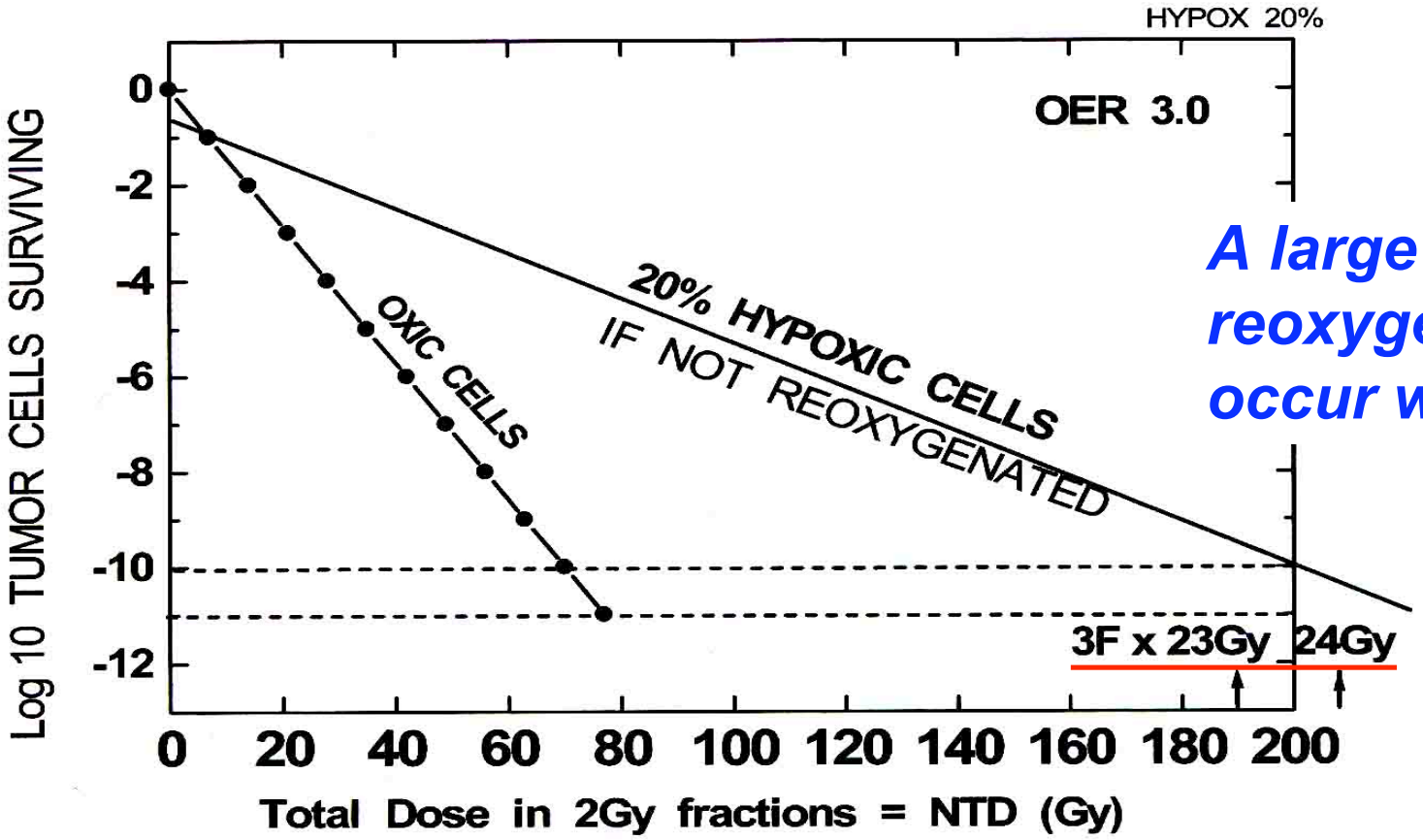
Effect of Reoxygenation

If radioresistant hypoxic cells were present in the tumors, or cells in a resistant phase of the cell cycles, the dose required would be 2.5 to 3 times greater than they were not.

If reoxygenation is incomplete so that only 1% of the tumor cells remain hypoxic, then many orders of magnitude (7 or 8) of resistant cells remain.

Therefore, total doses 2 to 3 times greater than 60 or 70 Gy would be required to obtain a finite chance of eliminating malignant cells from the target.

Why do we need high doses to sterilize tumors?



A large amount of reoxygention can occur within 24 hrs.

FIGURE 1.3. Schematic diagram of cell survival curves for well-oxygenated cells (*full line with filled circles*), with a line of less slope representing 20% hypoxic cells remaining hypoxic throughout radiotherapy with 2-Gy fractions. The oxygen enhancement ratio is assumed to be 3. To reduce the proportion of surviving cells to 10^{-11} would require three fractions of more than 24 Gy.

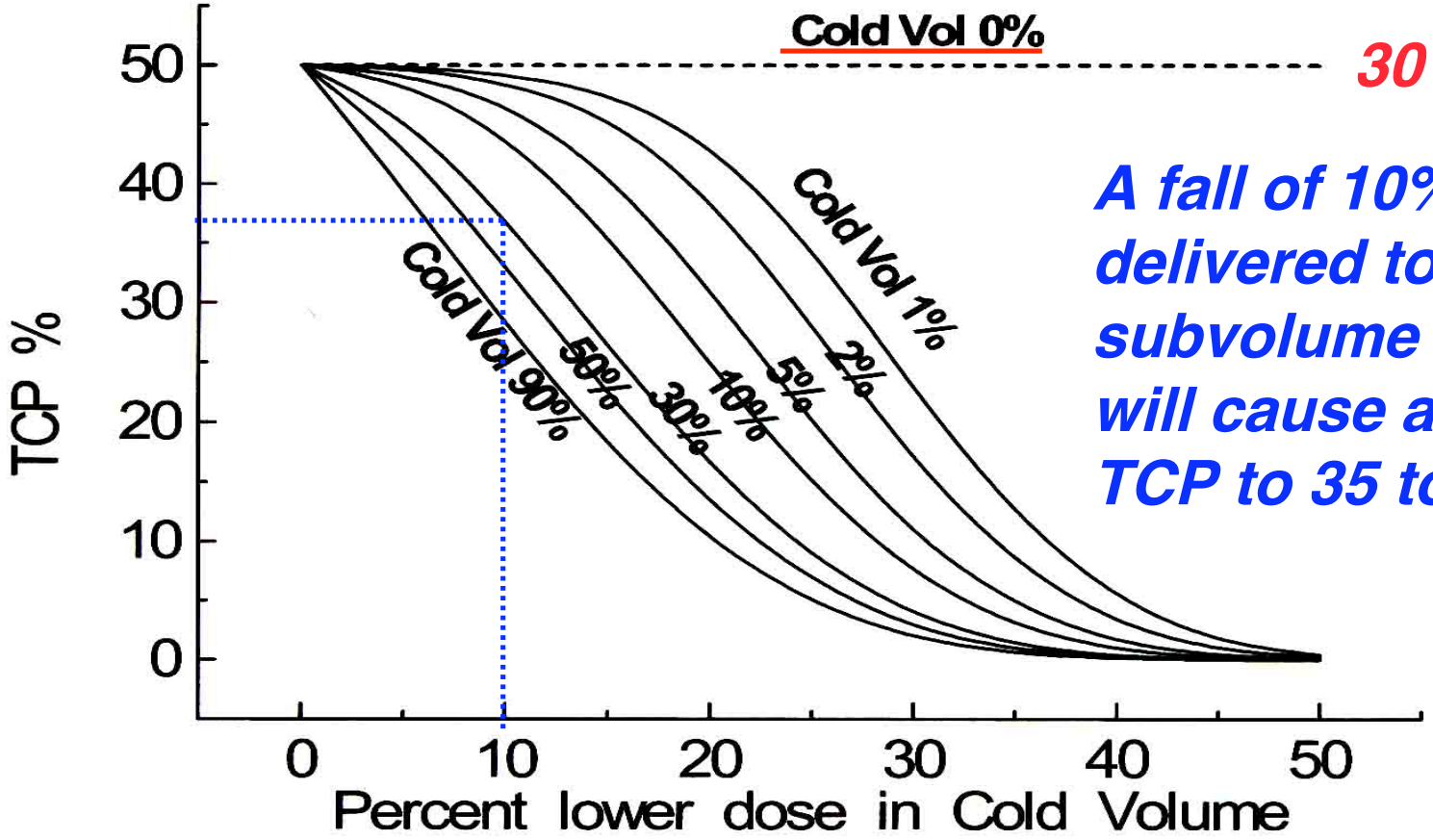
Fowler JF, Tome WA, and *Welsh JS: SBRT, ed Kavanagh B, Timmerman R. Lippincott 2005

Dose inhomogeneity and intra-fraction radiation repair

In IMRT, an apparently small-volume tail but of surprisingly low dose can appear on the DVH, unless a minimum tumor dose is specified.

This problem can be avoided if the effective uniform dose (EUD) is calculated from the DVH of the target, and is not allowed to be less than the prescribed dose.

Volume Effect : Cold Spots in the Isodose Distribution



30 x 2 Gy = 60 Gy

A fall of 10% in dose delivered to a 30% cold subvolume in the tumor will cause a modest fall of TCP to 35 to 40 % TCP.

FIGURE 1.4. The decrease in TCP (tumor control probability), plotted against percent reduction in dose in each subvolume. Each curve is for a different tumor subvolume. It is assumed that a homogeneous treatment of 30×2 Gy = 60 Gy would yield TCP = 50%.

Towe WA, Fowler JF,: 2002

A fall of 25% in tumor dose delivered to a 20% subvolume of tumor lead to unacceptably low TCPs of 10%.

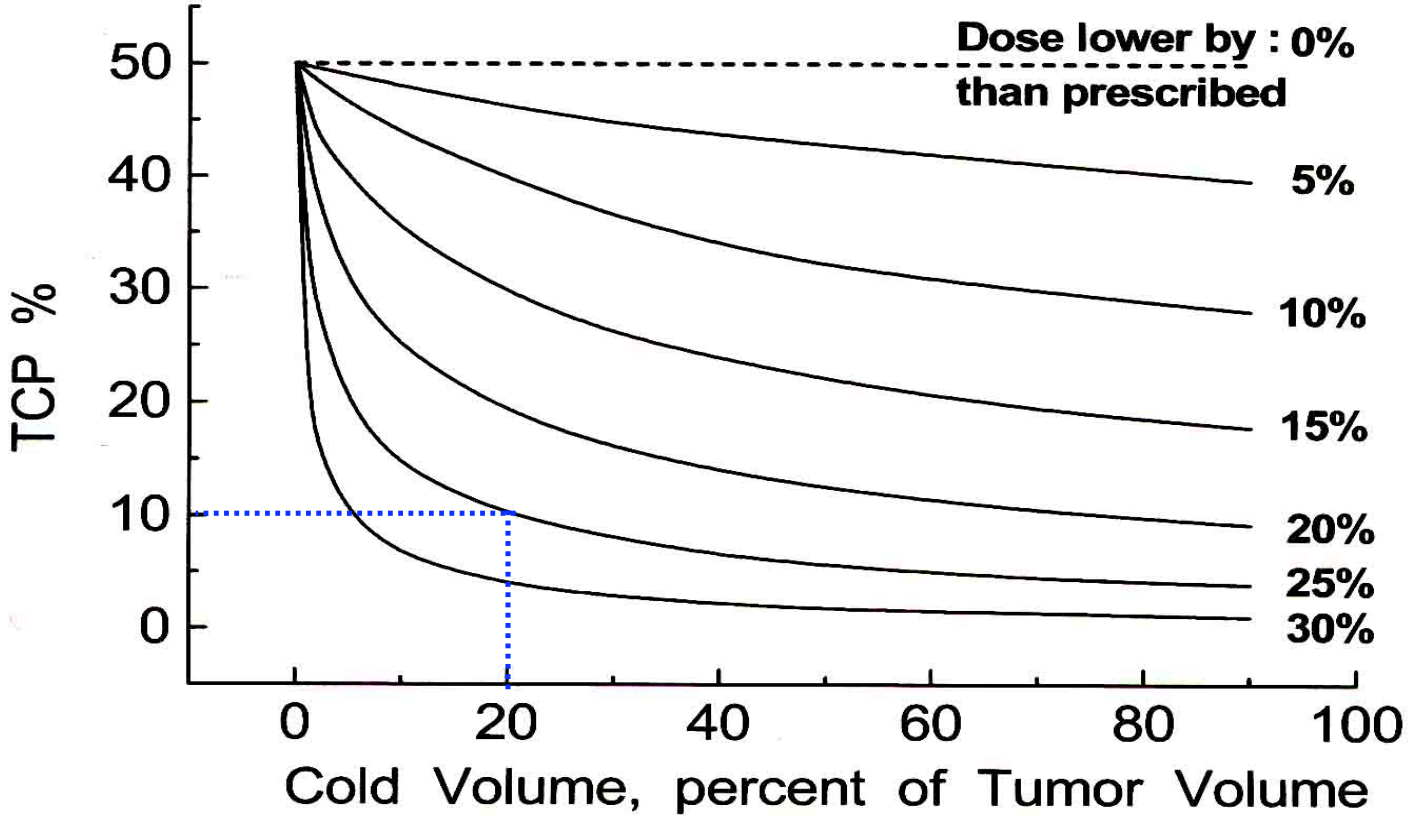


FIGURE 1.5. The same data as in Fig. 1.4 but plotted against percentage of tumor volume, each curve being for a different dose reduction. A 30% dose reduction in a 10% volume (*lowest curve*) gives a much lower tumor control probability (TCP) (8%) than a 10% dose reduction (*second curve down*) in 30% of the tu-

Towe WA, Fowler JF,: 2002

Estimated loss of biologic efficiency (BED) with prolonged fraction delivery

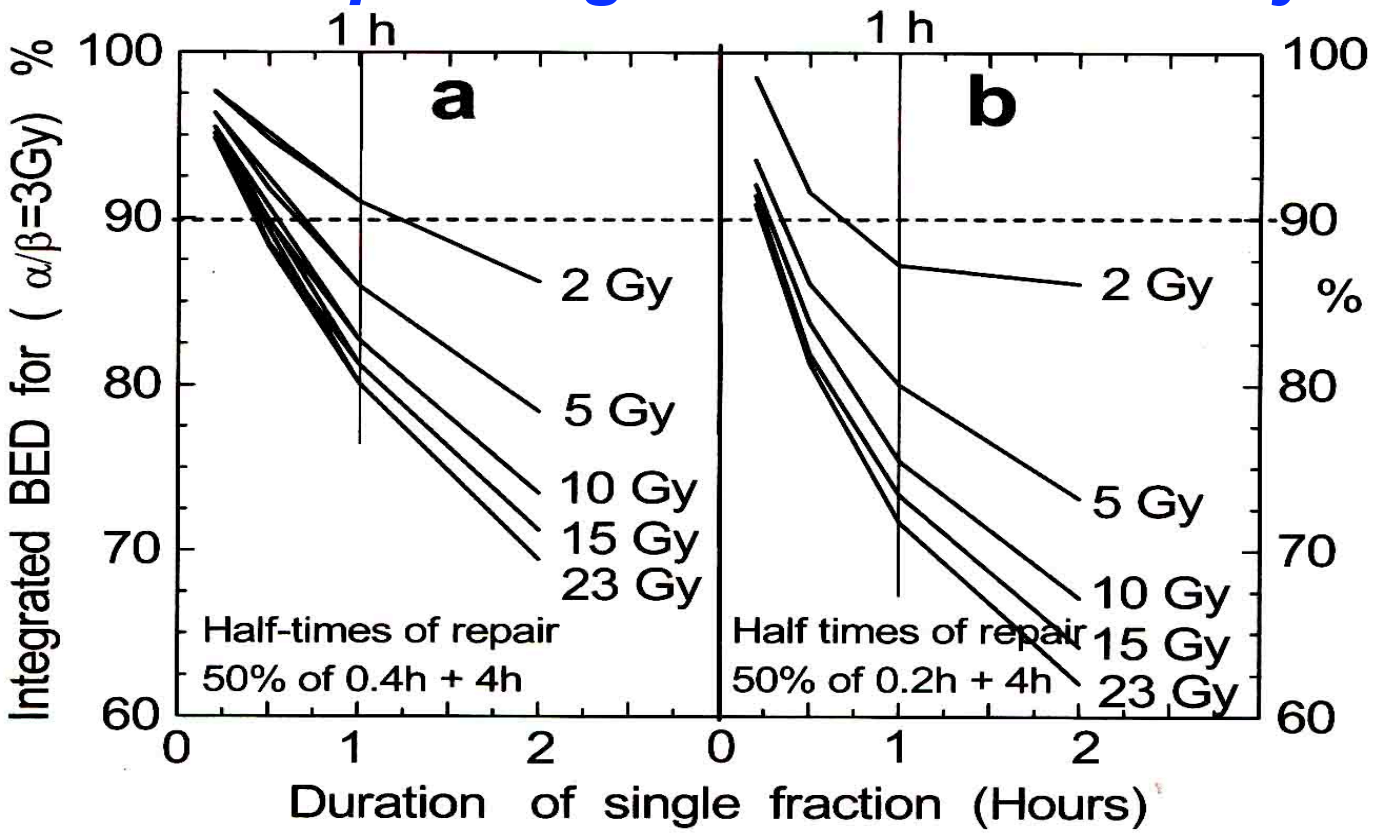


FIGURE 1.6. Estimated losses of biologically effective dose (BED) (for late effects, $\alpha\beta = 3Gy$) as a function of prolonged delivery times for fraction sizes of 2 to 23 Gy. Two monoexponential repair rates are assumed (30), with two equally weighted half-times of 0.4 hour +4.0 hours **(A)** and 0.2 hours +4.0 hours **(B).** The effect of faction size is illustrated. The longer half-life has a small effect up to 1 hour's duration. The loss of BED is ap-

Radiation damage repair is not monophasic but consists of at least two components with different half time.

Duration of Rx delivery should be recorded.

Fowler JF, :2005

Normal tissue considerations

An ablation with enormous increases in dose may be feasible if the organ is a good approximation to a "parallel organ" so that the loss of such small volume of functioning tissue is tolerated, and if it contains no particularly sensitive structures.

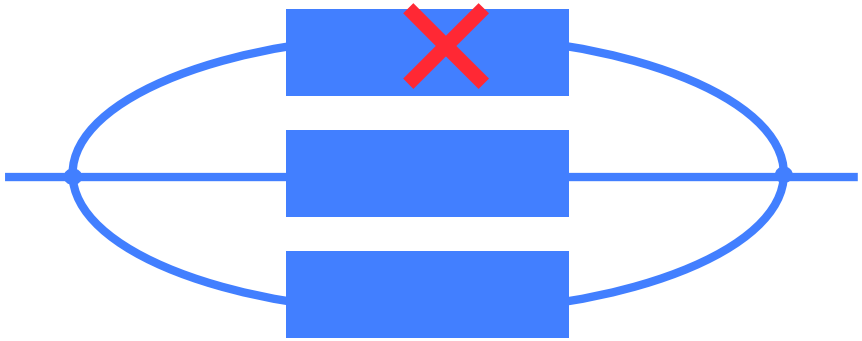
→ Lung, Liver, etc

Tolerance of target organ

Serial organ

Spinal cord, GI tract, etc

Parallel organ



Lung, Liver, Bone, etc

Mixed

Treatment of prostate

Volume effect and Hypoxia

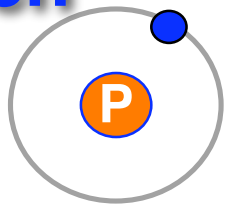
Diameter Of Sphere	Volume (cm^3)	Dose that can be given
5cm ϕ	66	1.0
4cm	34	2.0
3cm	9.5	5.0 - 7.0

Theoretically, the use of a single fraction is probably the worst radiobiologic alternative, because it gives no chance of reoxygenation or any shift out of a resistant phase of cell cycles or nutritional deprivation. It would be expected to require a considerably larger total dose to be effective on tumors than even a small number of dose fractions.

Characteristics of Ion Beams

1. Advanced dose distribution（Protons、C-ions）
2. Greater RBE and lower OER（C-ions）

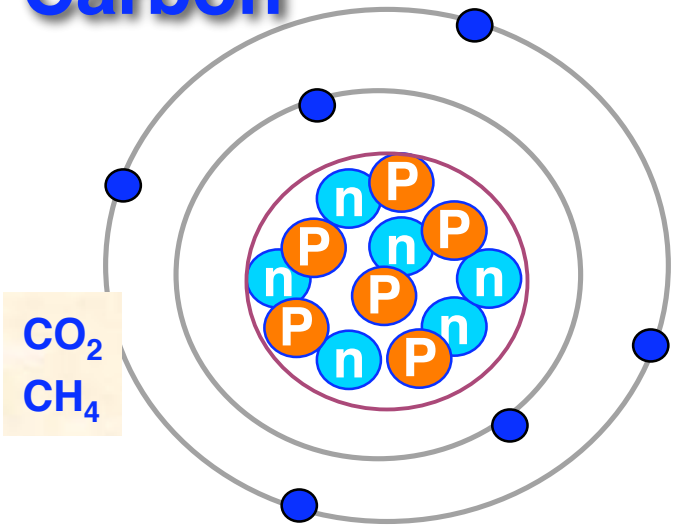
Hydrogen



Proton（1＋）

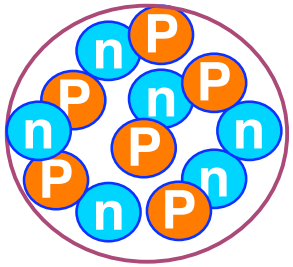
P + e^-

Carbon



CO_2
CH_4

Carbon ion（6+）



+ $6e^-$

Hypofractionated Particle Beam Therapy

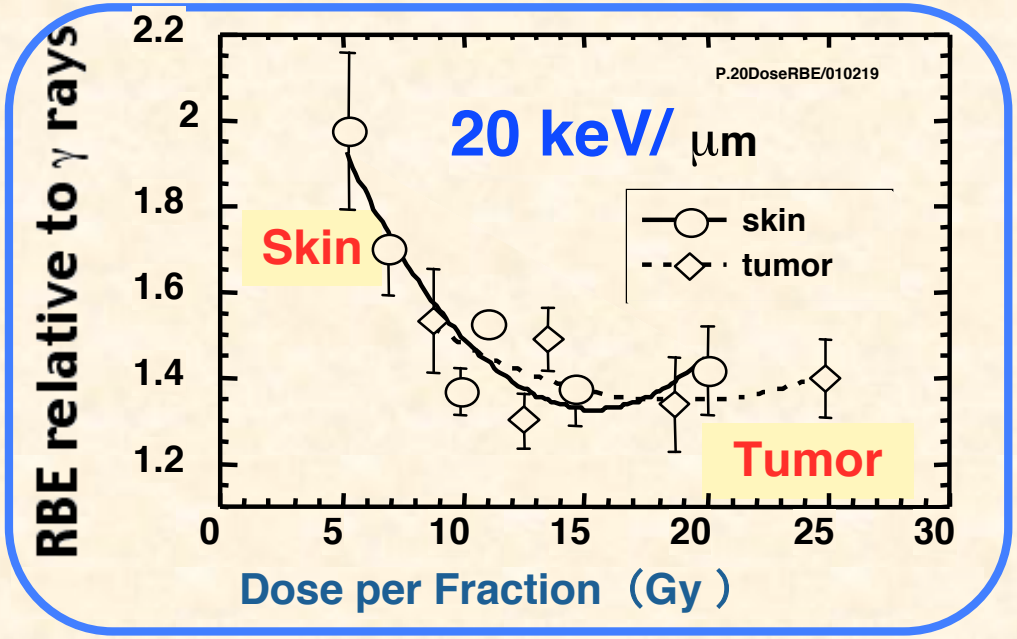
One of the most successful RT is the hypofractionated proton therapy for ocular melanoma.

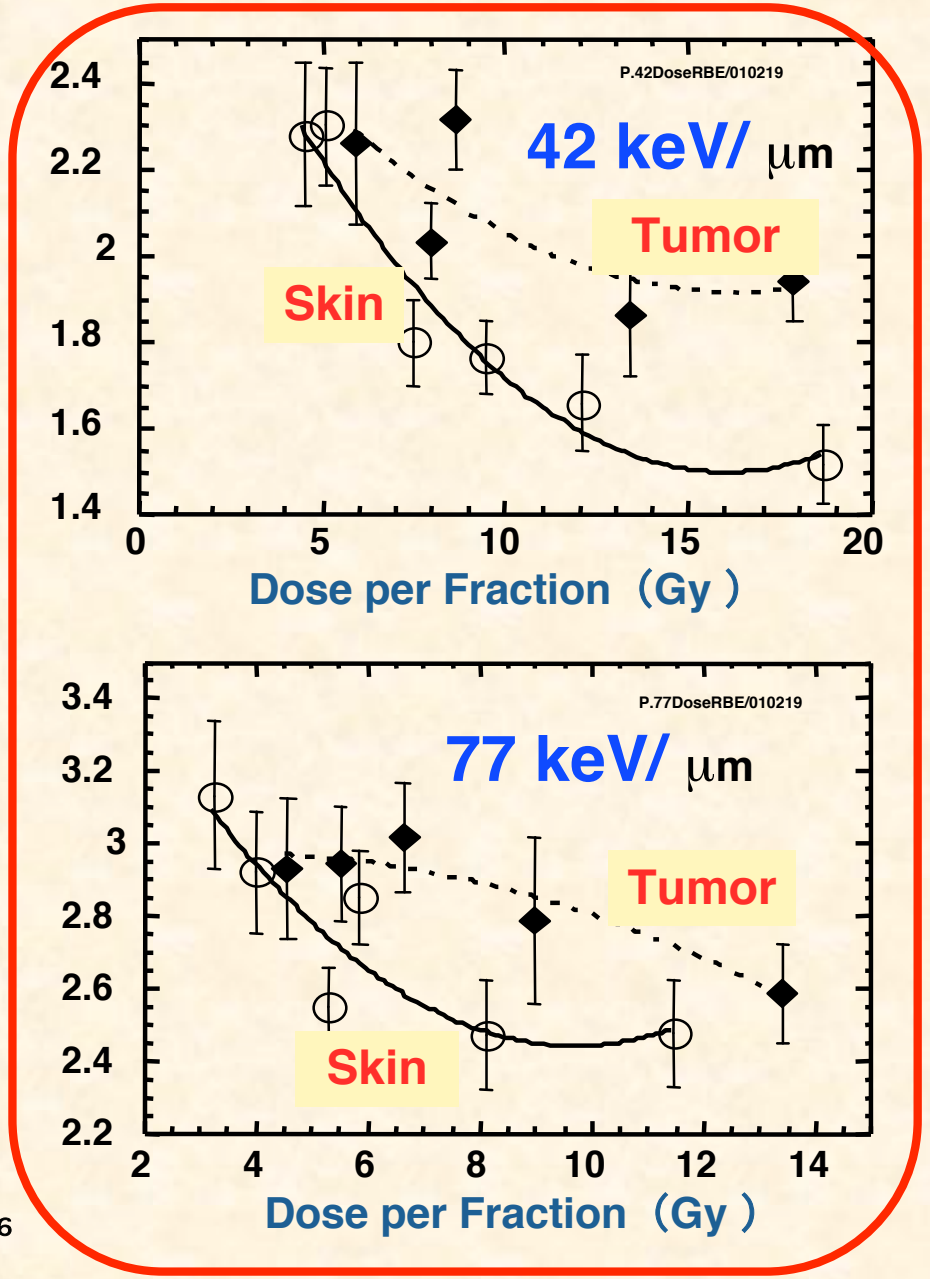
Biological Background for Hypo-fractionated radiotherapy with Carbon Ion beams

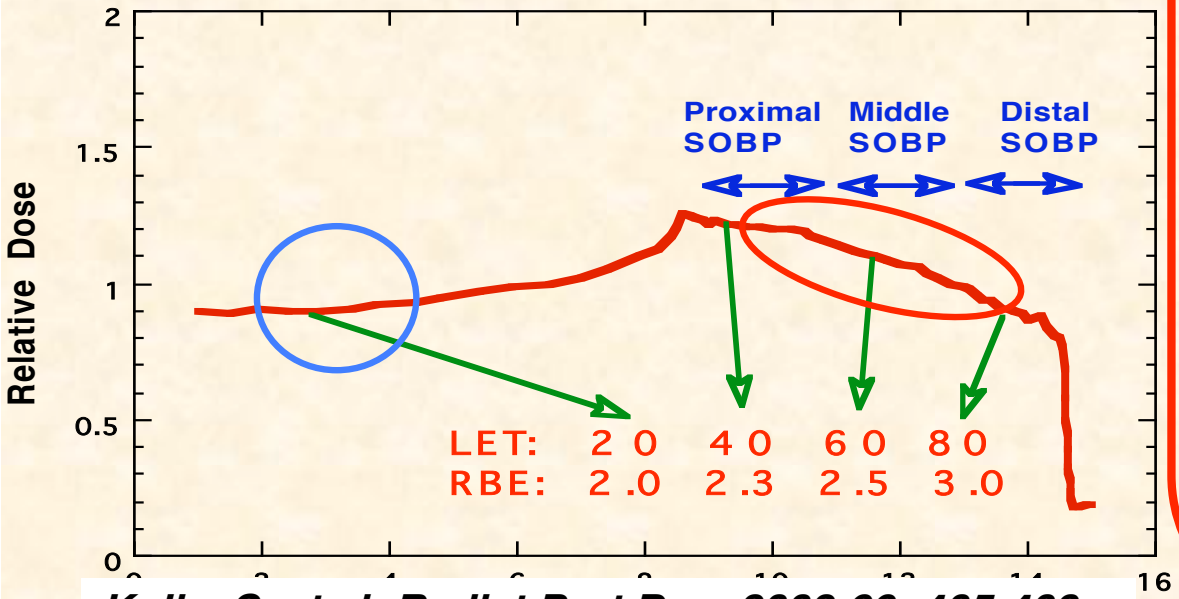
Koike S, et al: Radiat Prot Dos. 2002;99: 405-408.
Ando et al. : J.Radiat.Res.,46:51-57, 2005.
Denekamp J: Int J Radiat Biol. 71: 681-694, 1997.

- **Experiments with carbon ions and fast neutrons demonstrated that increasing their fraction dose tended to lower the RBE for both the tumor and normal tissues, but the RBE for the tumor did not decrease as rapidly as the RBE for the normal tissues.**
- **These results substantiate that the therapeutic ratio increases rather than decreases even though the fraction dose is increased.**
- **The experiments have also provided the biological evidence for the validity of a short-course hypo-fractionated regimen in carbon ion RT.**

RBE vs. Fraction Size in Carbon Beam Irradiation

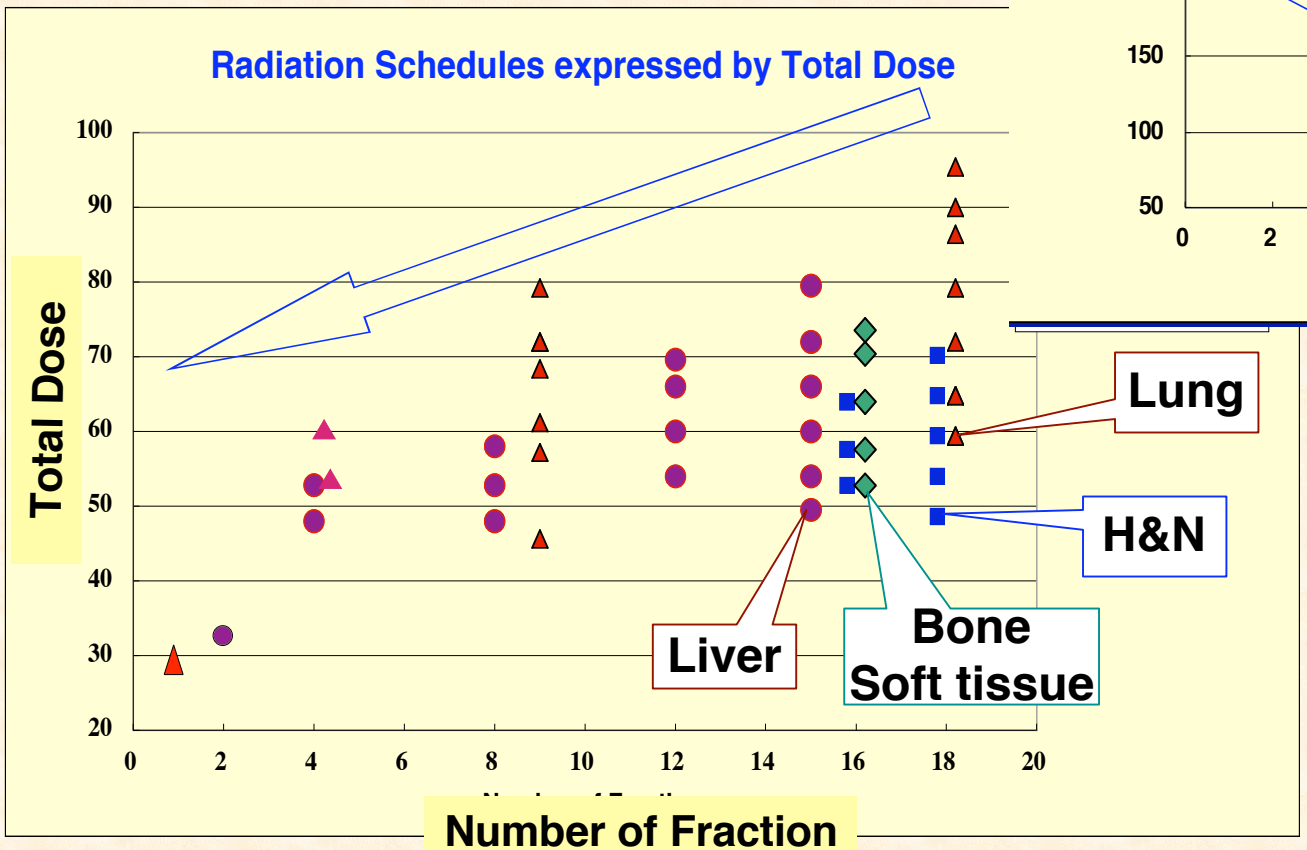


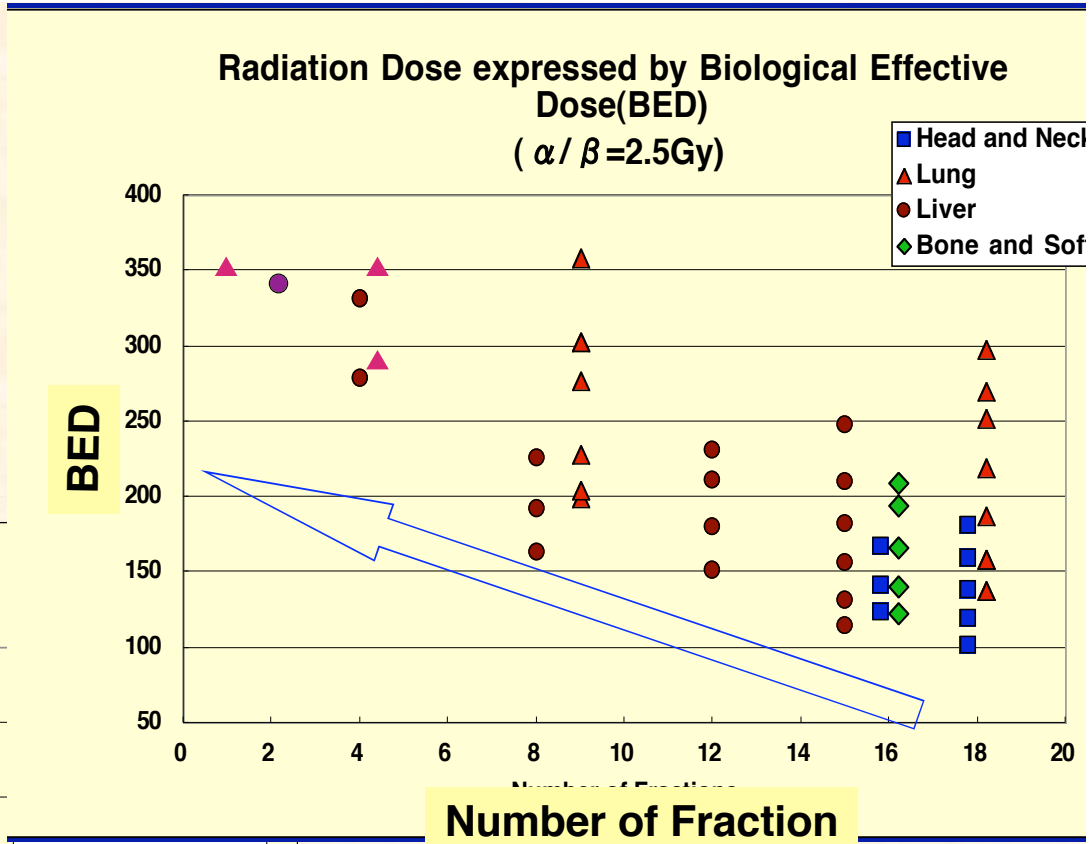




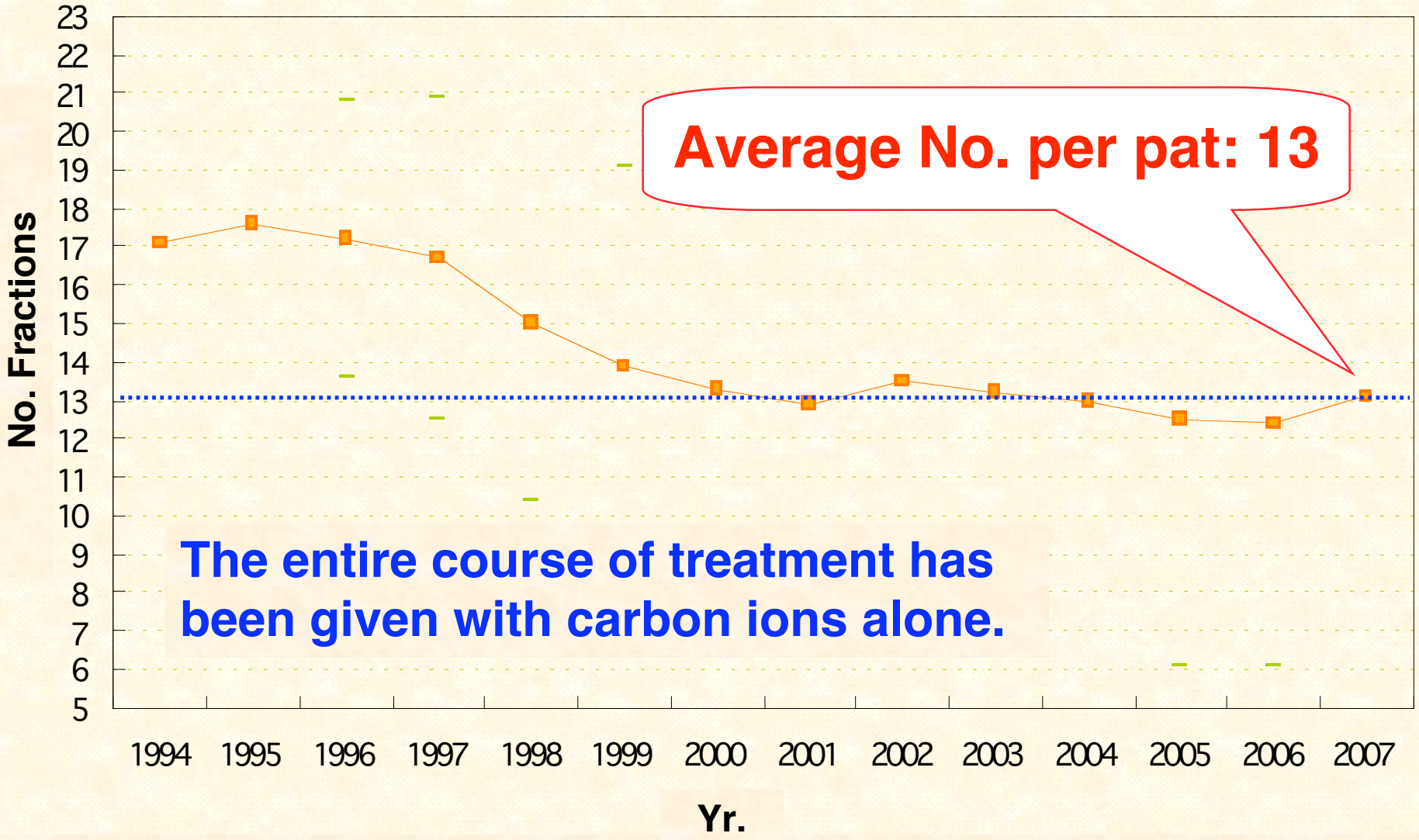
Koike S, et al: Radiat Prot Dos. 2002;99: 405-408.
Ando et al. : J.Radiat.Res.,46:51-57, 2005

Dose Escalation Study in Carbon Ion Therapy at NIRS





Hypofractionated Radiotherapy has been performed in Carbon Ion RT



Optimal dose-fractionations determined in dose escalation studies for carbon ion radiotherapy at NIRS

Tumor Sites		Dose-Fractionation (GyE/fr/week)	Gy /fr	BED (α/β=10)	BED (α/β=2.5)
Skull Base		60.8 / 16 / 4	3.8	83.9	153.2
H & N:	ACC,MM etc	57.6 / 16 / 4	3.6	78.3	140.5
		64.0 / 16 / 4	4.0	89.6	166.4
	Sarcoma	70.4 / 16 / 4	4.4	101.4	194.3
NSCLC: (Stage I)	Peripheral type	90.0 / 18 / 5	5.0	135.0	270.0
		72.0 / 9 / 3	8.0	129.6	302.4
		52.8 / 4 / 1 (T1)	13.2	122.5	331.6
		60.0 / 4 / 1 (T2)	15.0	150.0	420.0
		40.0 or 44.0 / 1 / 1day	40.0 or 44.0	-	-
	Hilar type	68.4 / 12 / 3	5.7	107.4	224.4
Liver:	HCC	79.5 / 15 / 5	5.3	121.6	248.0
		69.6 / 12 / 3	5.8	110.0	231.1
		58.0 / 8 / 2	7.2	100.1	226.2
		52.8 / 4 / 2	13.2	122.5	331.6
		38.8 / 2 / 2 days	19.4	114.1	339.9
Prostate		66.0 / 20 / 5	3.3	87.8	153.1
		63.0 / 20 / 5	3.2	82.8	142.4
		57.6 / 16 / 4	3.6	78.3	140.5
Bone / Soft tissue		70.4 / 16 / 4 (Pelvis)	4.4	101.4	194.3
		64.0 / 16 / 4 (paraspinal)	4.0	89.6	166.4
Rectum (Post-ope recurrence)		73.6 / 16 / 4	4.6	107.5	209.0
Uterine Cervix (Adenocarcinoma)		74.4 / 20 / 5	3.7	102.1	185.1

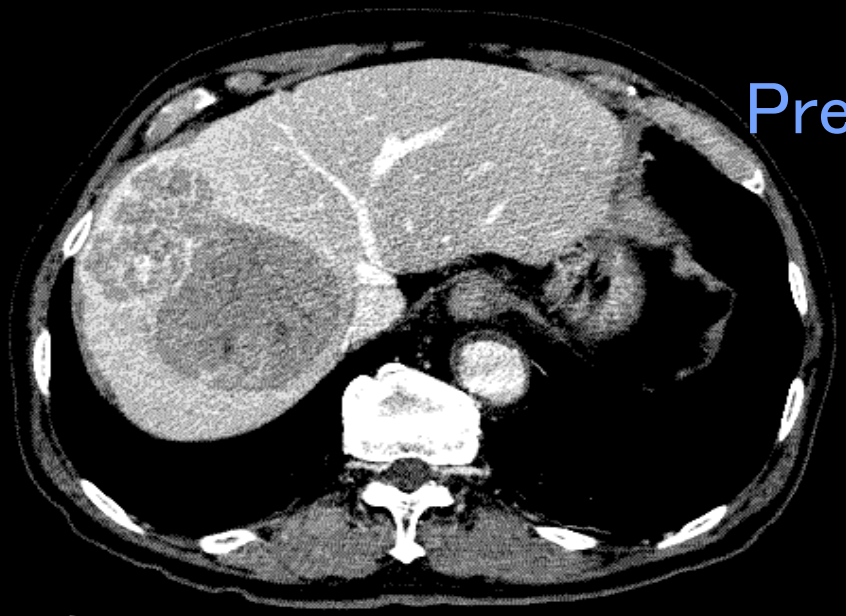
Local control and morbidity of carbon ion RT in hepatocellular carcinoma.

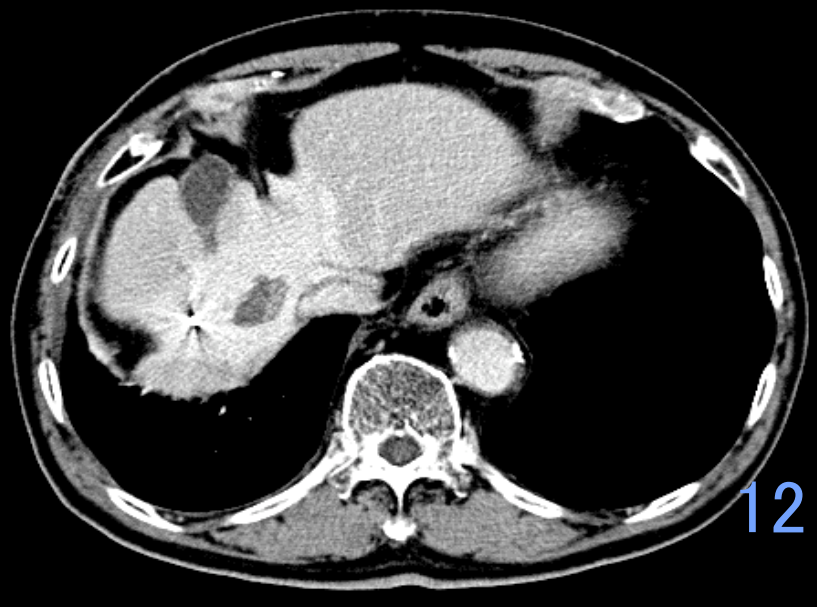
Fractionation		Local Control		Morbidity (3~12 mo)					
			3-yr		Grade (CTC modified)				
TD	/ Fx / Wk	No.	LC	No.	0	1	2	3	4
49.5～79.5/	15fx /5wk	24	81%	20	10	4	5	1(5%)	0
54.0～69.6/	12fx /3wk	34	86%	24	16	2	6	0(0%)	0
48.0～58.0/	8fx /2wk	24	86%	16	10	5	0	1(6%)	0
48.0～52.8/	4fx /1wk	75	90%	54	40	6	6	2(4%)	0
32.0~38.8 /	2fx /2day	36	90%	13	9	2	2	0(0%)	0
Total		181	-	127	85	19	19	4(3%)*	0

* All recovered to pre-treatment function.

S8/5, 7.7×7.0 cm

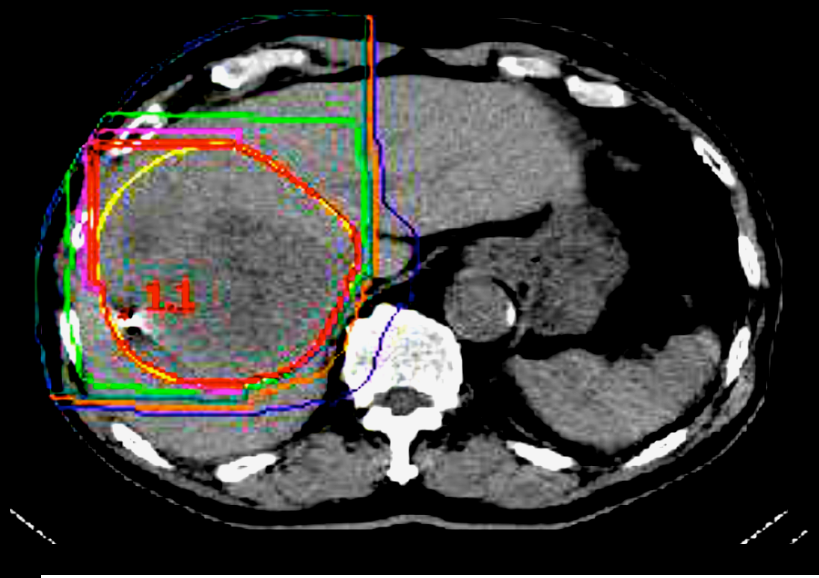
Pre-RT



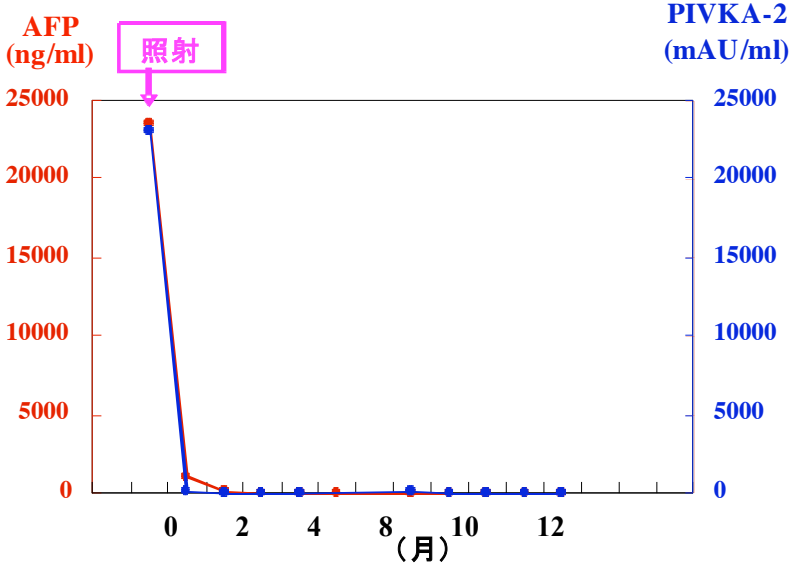


12 mo.

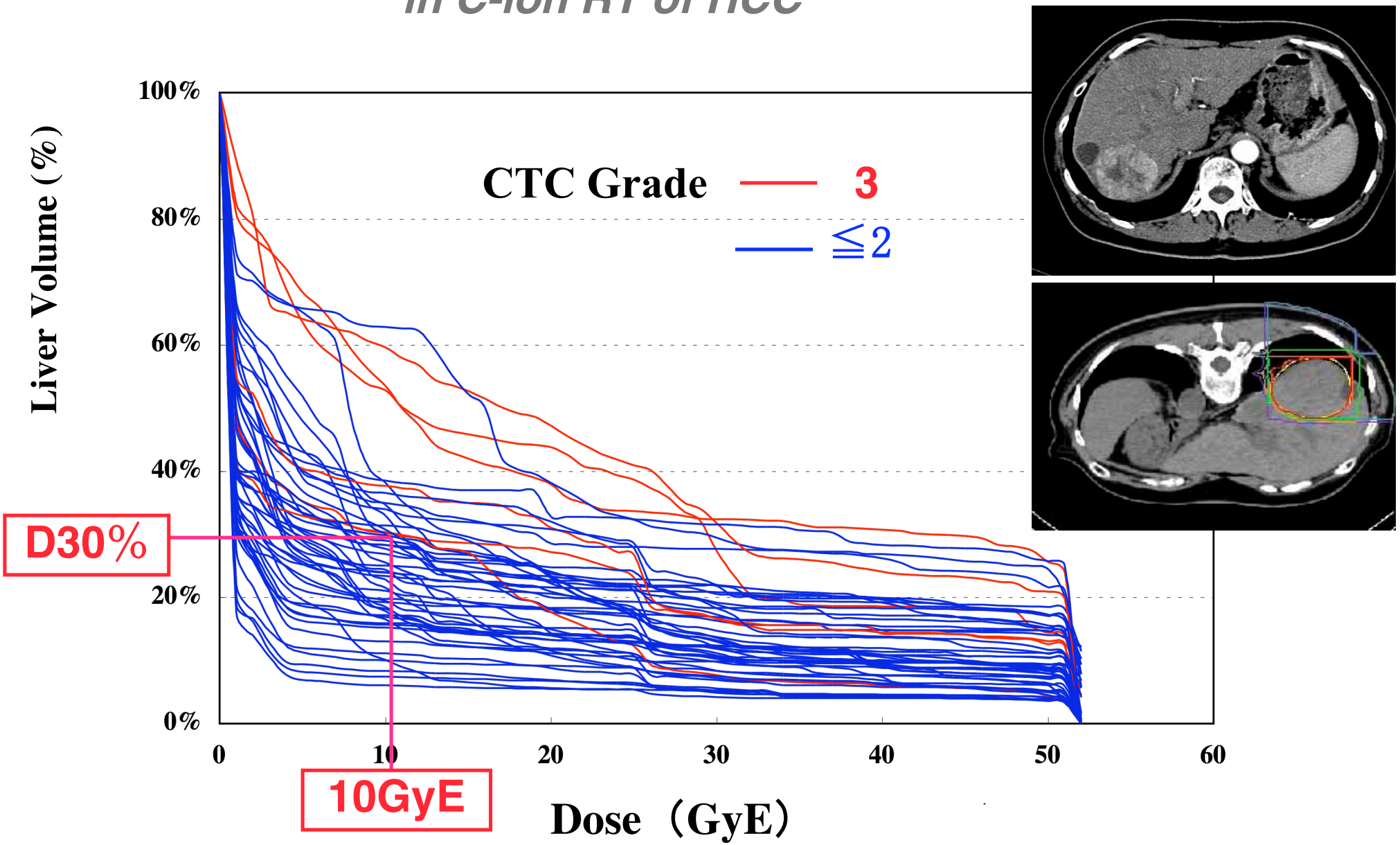
38.8GyE/2fr



Tumor marker



DVH of the Liver for Early Change of GOT in C-ion RT of HCC



Clinical Study on Carbon Beam Therapy for Stage I Non-Small Cell Lung Cancer

9303	9701	9802	0001	0201
Phase I/III (1994)	Phase I/II (1997)	Phase Ⅱ (4/99 - 11/00)	Phase I/II (12/00 - 11/03)	Phase I/II (12/03 ~)
18 fr / 6 wks 47 pats	9 fr / 3 wks 34 pts	9 fr / 3 wks 50 pats	4 fr / 1 wk 79 pats	Single-dose 84 pats

Dose-escalation

59.4GyE	68.4GyE	28GyE
64.8	72.0	30
72.0	75.6	34
79.2	79.2	36
86.4		38
90.0		40
95.4		42
		44

Total 129 pats

72GyE

52.8GyE for stage IA

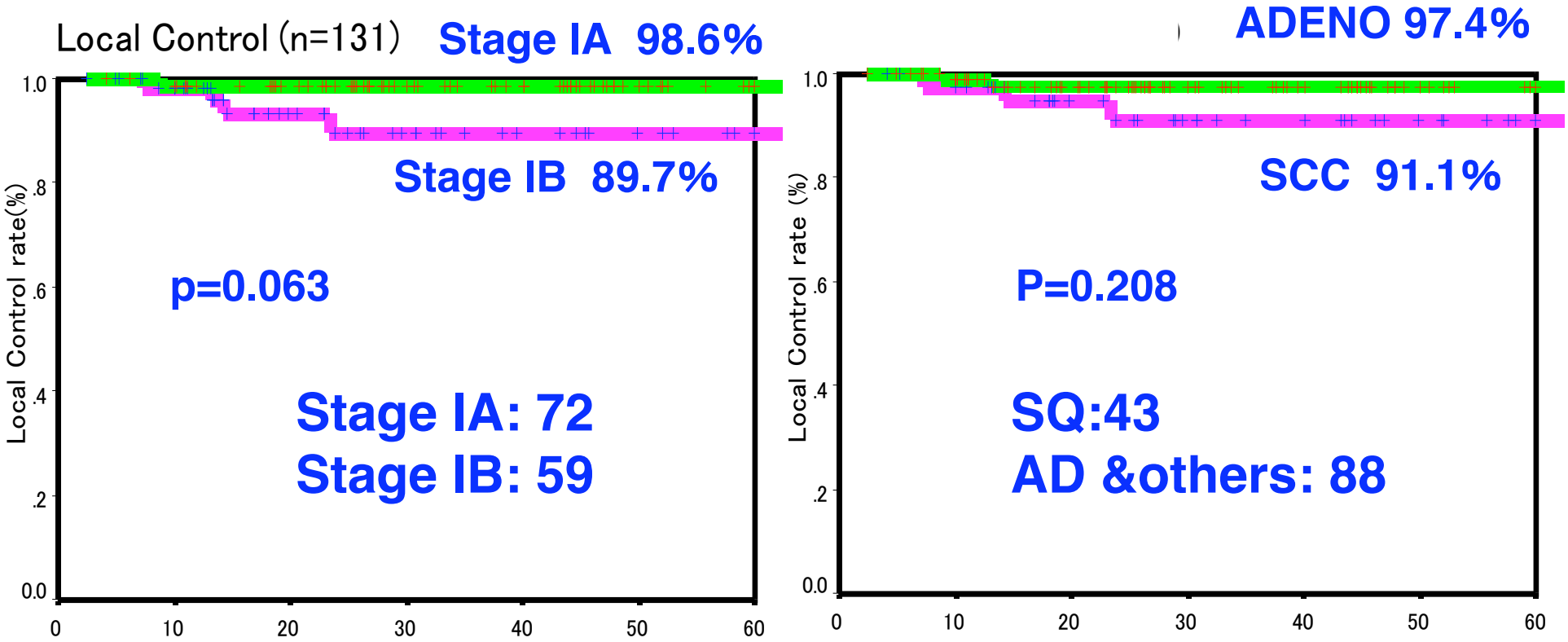
60.0GyE for stage IB

Dose recommended

90GyE 72 GyE

Local Control by Size and Histology

4 and 9 fractions

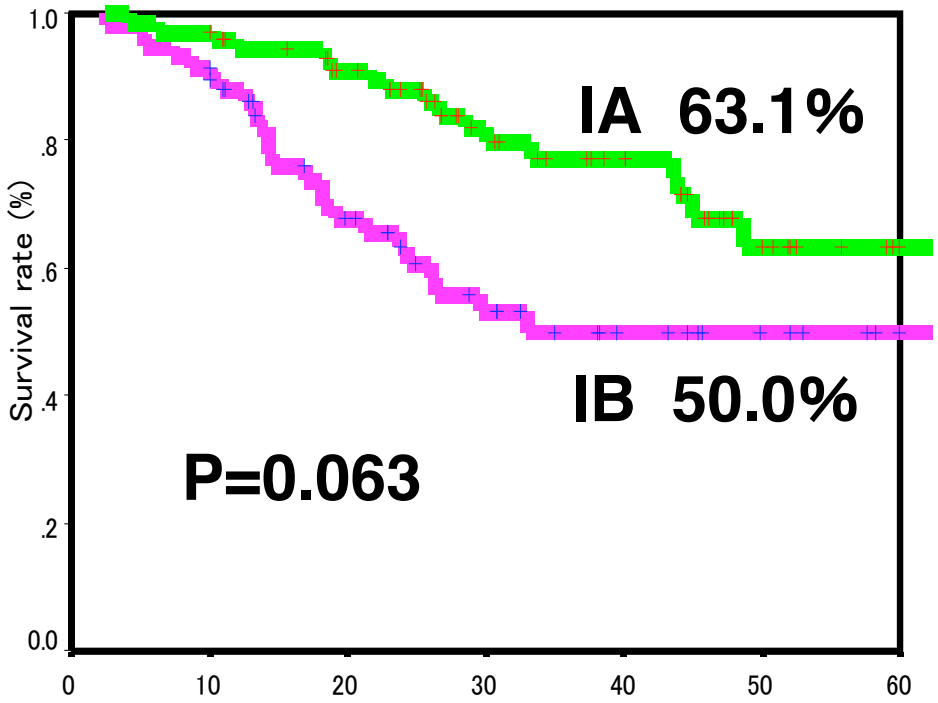


Survival in Stage I Lung Ca

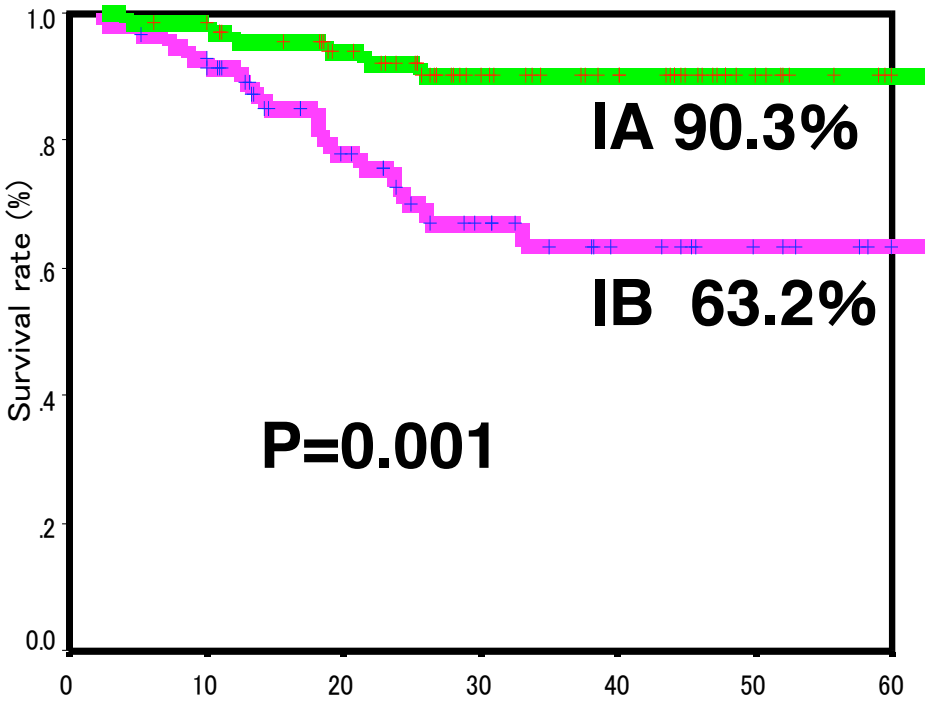
4 and 9 fractions

Stage IA: 71
Stage IB: 58

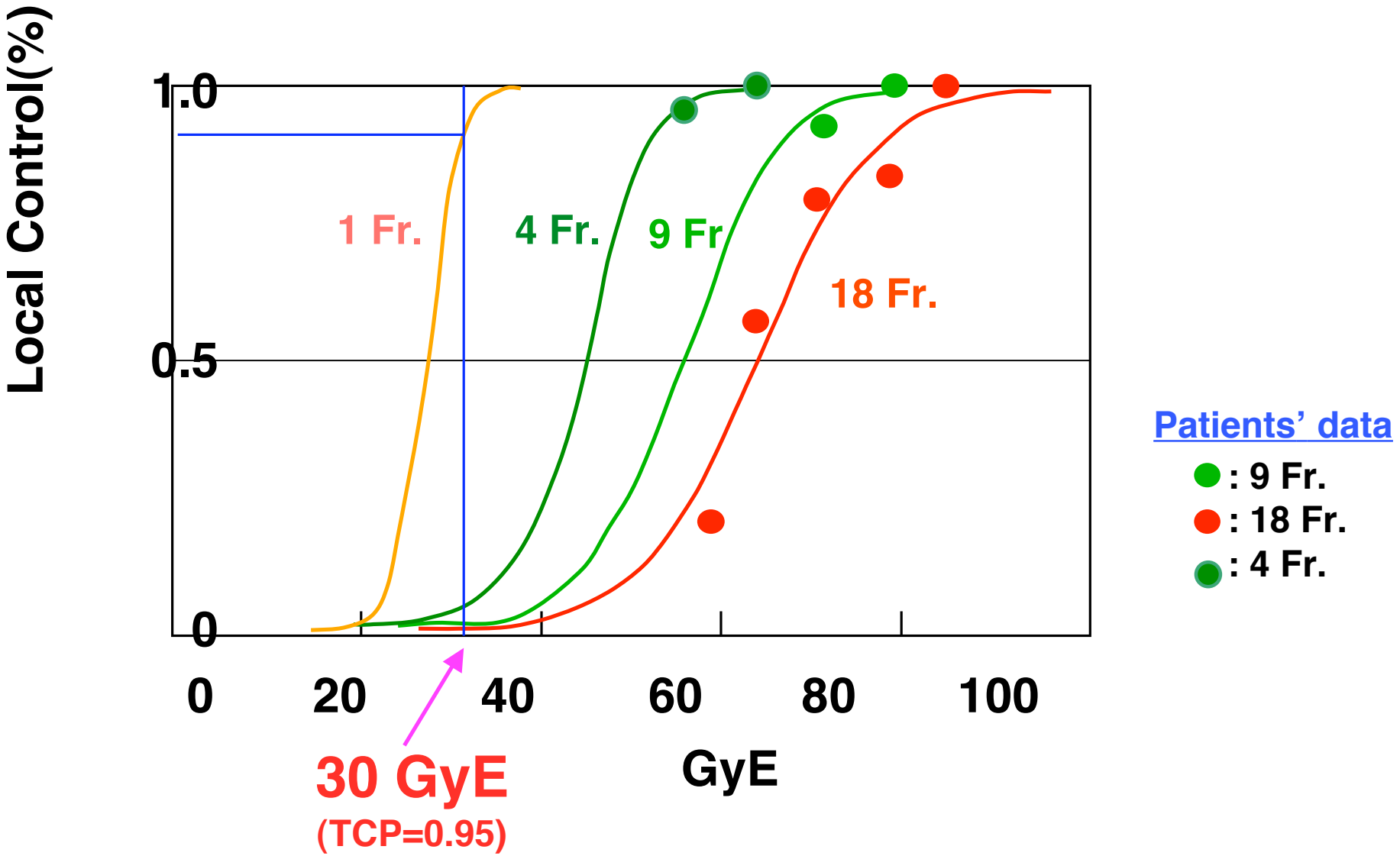
Overall



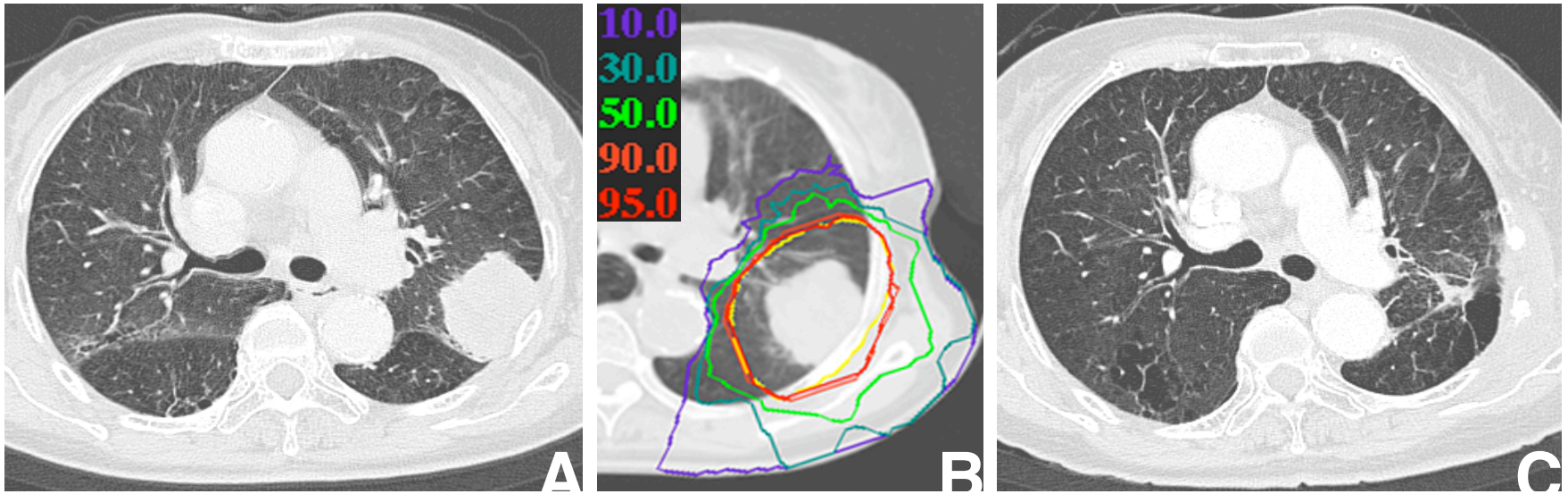
Cause-specific



Local Control vs. Carbon Ion Dose for Different Fractionations in NSCLC



71y/o F（Sq Cell Ca, cT2N0M0）



Single fraction (40.0GyE)

After 18 mo,

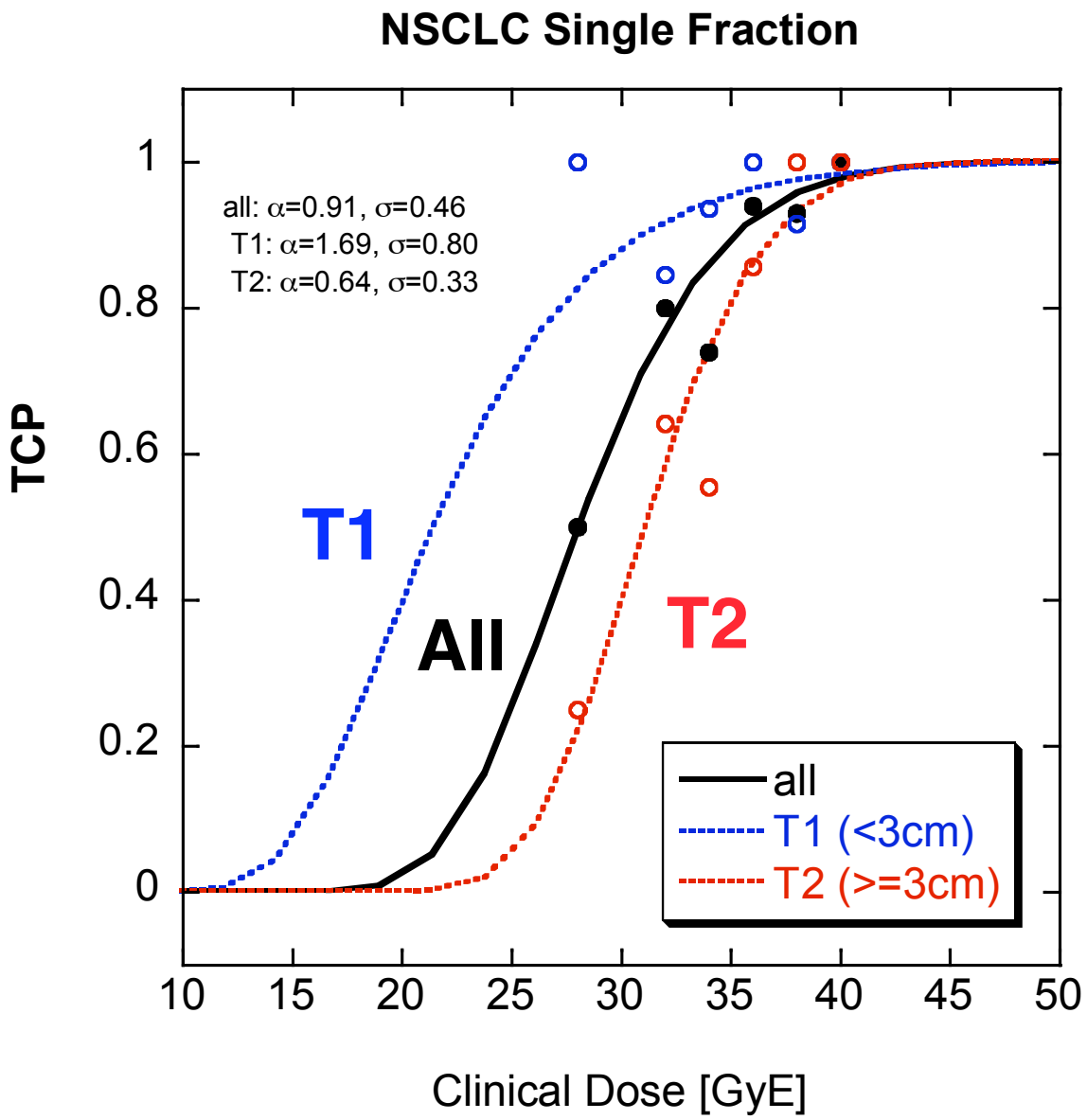
Local Control in Single Fraction

(Baba, 2008)

N=152

Total Dose GyE	T1 (≤3cm)		T2 (>3cm)	
	12 mo.	24 mo.	12 mo.	24 mo.
28.0 (n=6)	100.0	100.0	50.0	25.0
32.0 (n=27)	69.2	69.2	75.0	88.8
34.0 (n=34)	93.8	81.8	64.7	57.1
36.0 (n=18)	100.0	100.0	85.7	85.7
38.0 (n=14)	90.0	90.0	100.0	100.0
40.0 (n=15)	100.0	100.0	66.7	66.7
42.0 (n=15)	90.0	-	75.0	-
44.0 (n=23)	85.7	-	100.0	-

Tumor Control Probability in Stage I NSCLC



Hypofrationated RT for Prostate Ca

- **Recent reports of a low α/ß ratio for prostate cancer lead to the background that prostate cancer can be safely and effectively treated with a very short course of external beam RT**

  (Fowler; 2001, Brenner; 1999, Buchesne; 1999)

- **A shortened course of radiotherapy is very attractive option for men who might not be candidates for brachytherapy or who find a 7-week to 8-week course of daily treatment prohibitive because of logistics or cost.**

Clinical Trials in Prostate Canceer at NIRS

Total enrolled: 663 pts. Period:95.Jun. ~ 07.Aug.

562 treated with 20fr / 5wks,

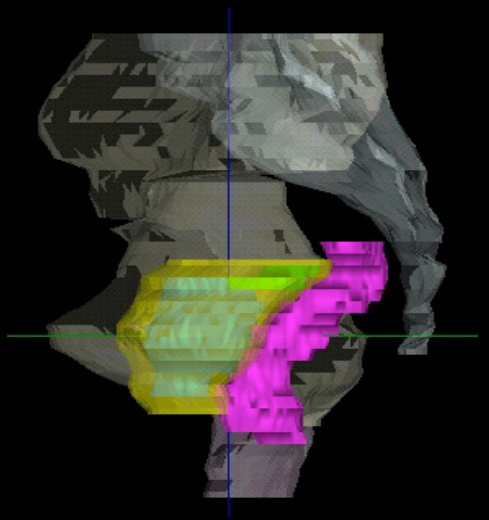
97 treated with 16f / 4wks

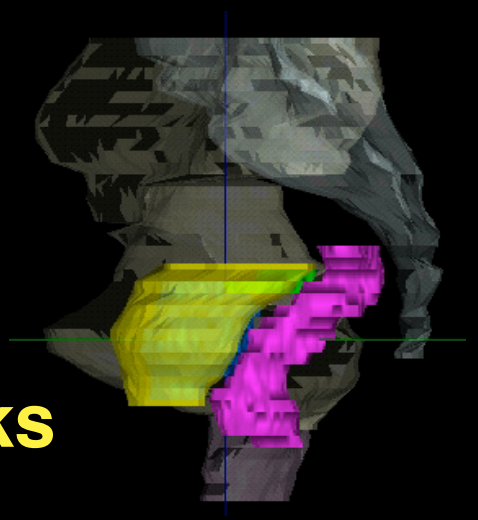
Protocol	Period	Dose Fractionation	No.pts
Dose Escalation	95.6~00.2	54~72GyE / 20fr/ 5wks	96
Phase II	00.4~07.8	63 or 66GyE / 20fr / 5wks	466
Current Fract.	03.12~07.8	57.6GyE / 16fr / 4 wks	97
Total	95.6~07.8		659

Carbon Ion Therapy of Prostate Ca

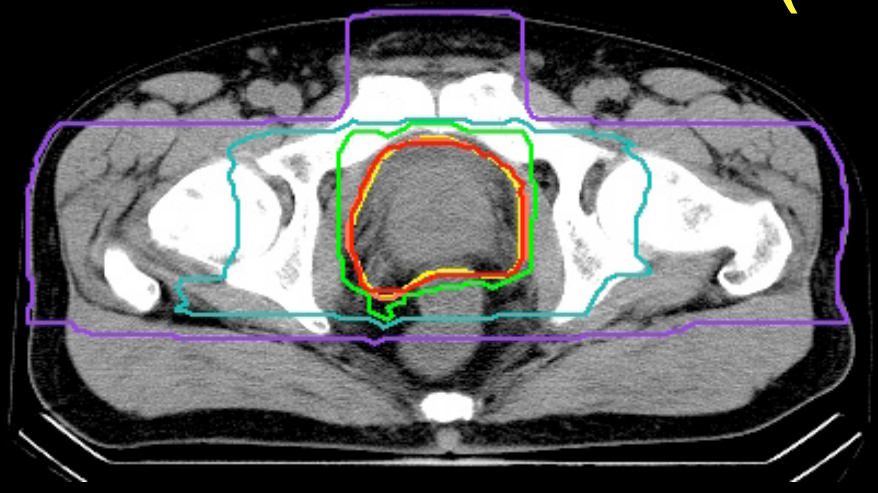
3 fields

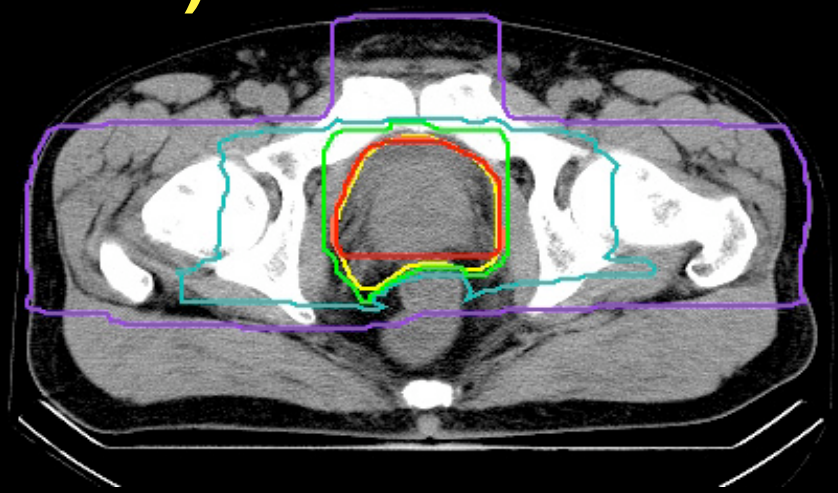
5 fields



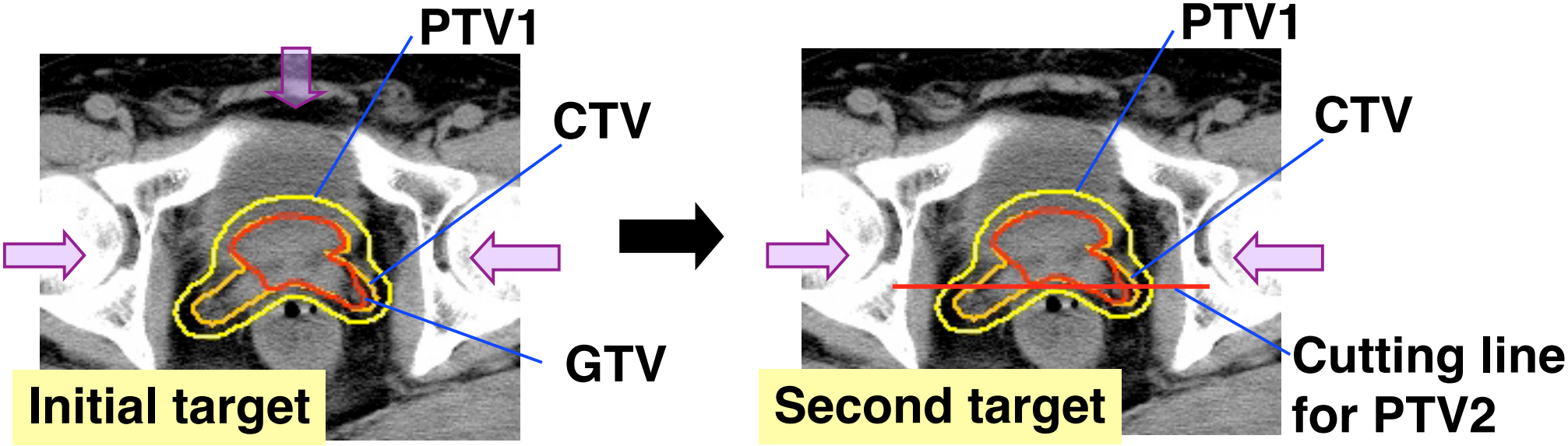


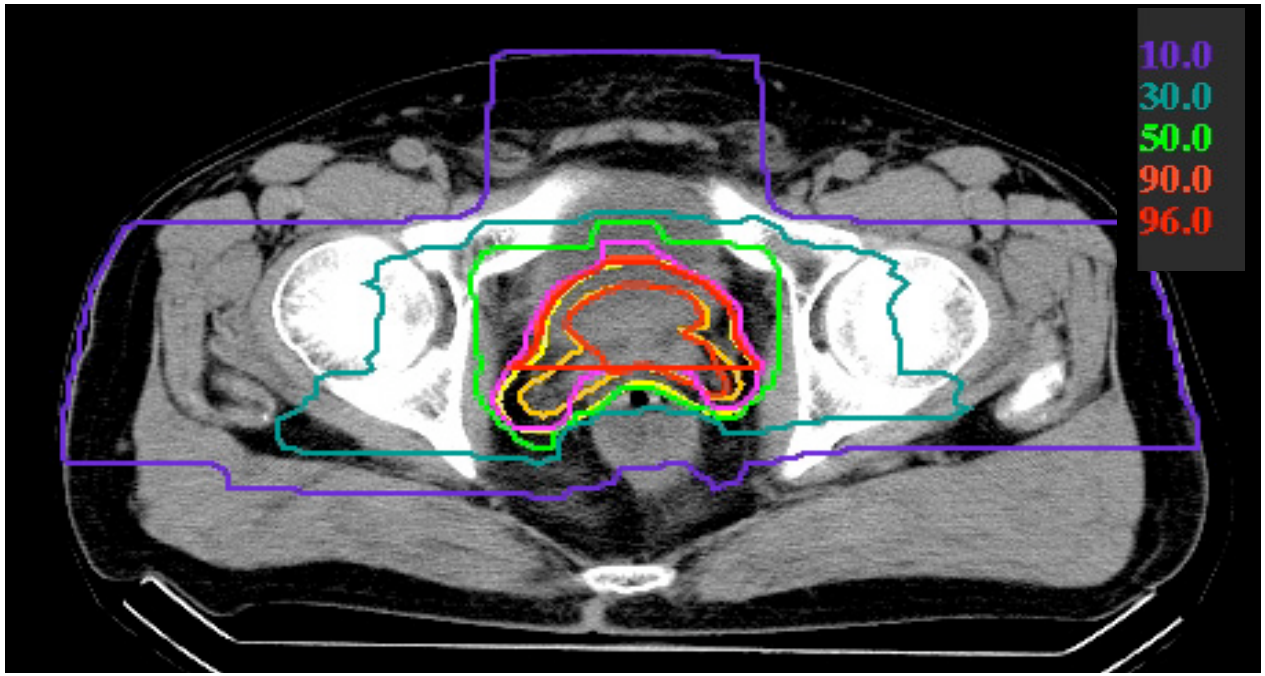
66Gy/16fr/5wks
(3.3GyEx16)

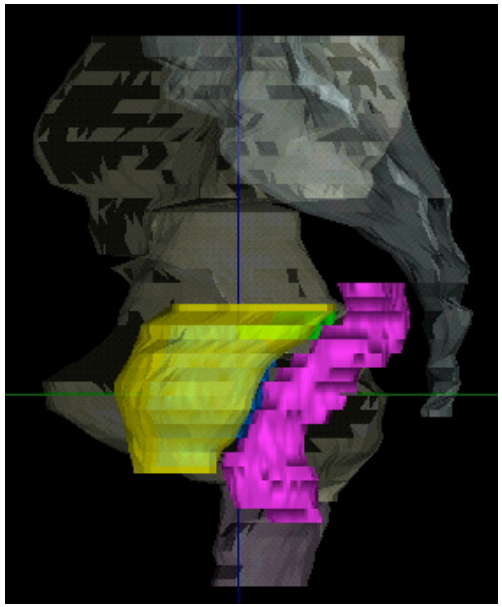




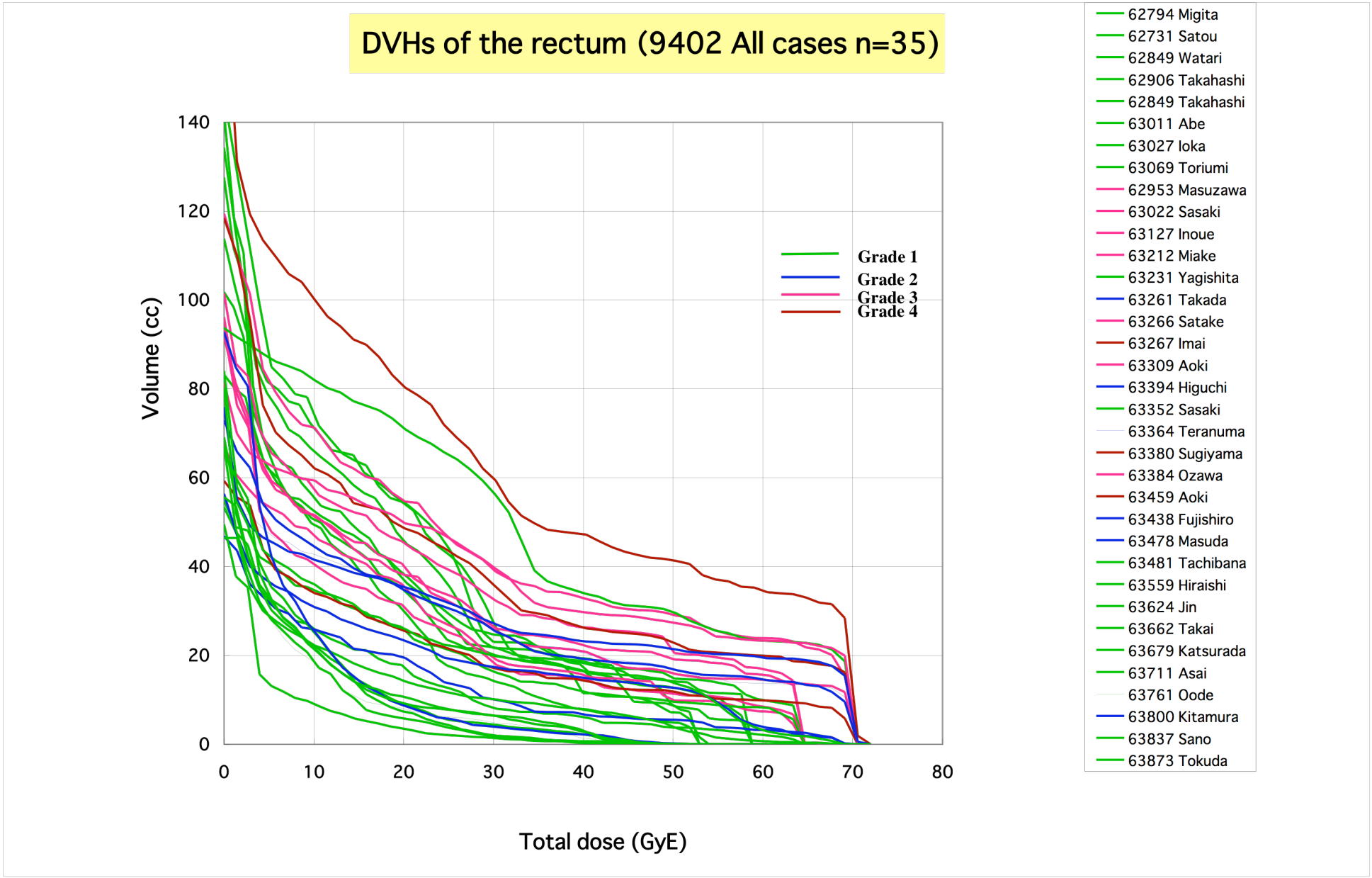
T3bN0M0


PTV1
CTV
GTV
Initial target
PTV1
CTV
Cutting line
for PTV2
Second target

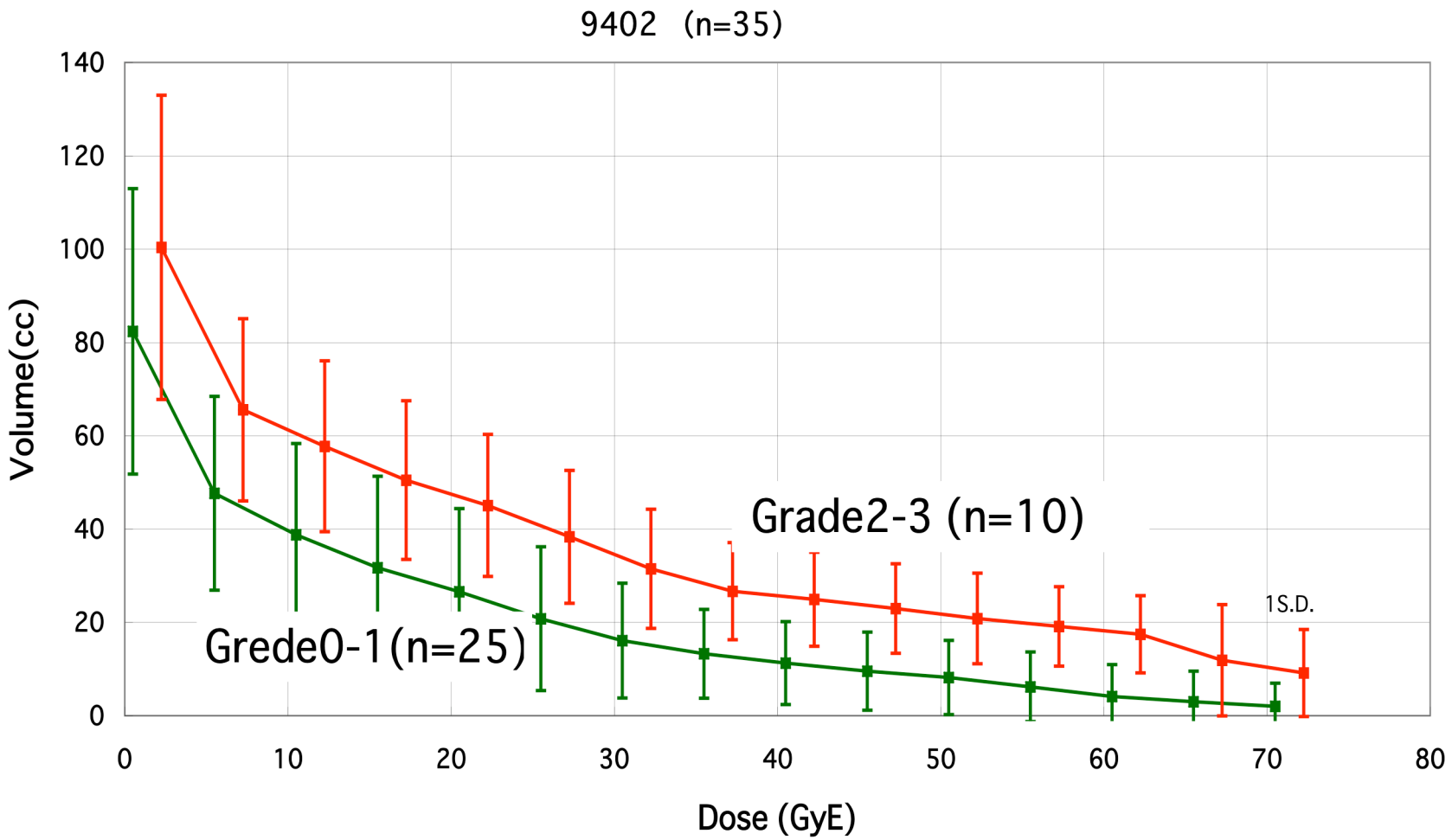

10.0
30.0
50.0
90.0
96.0



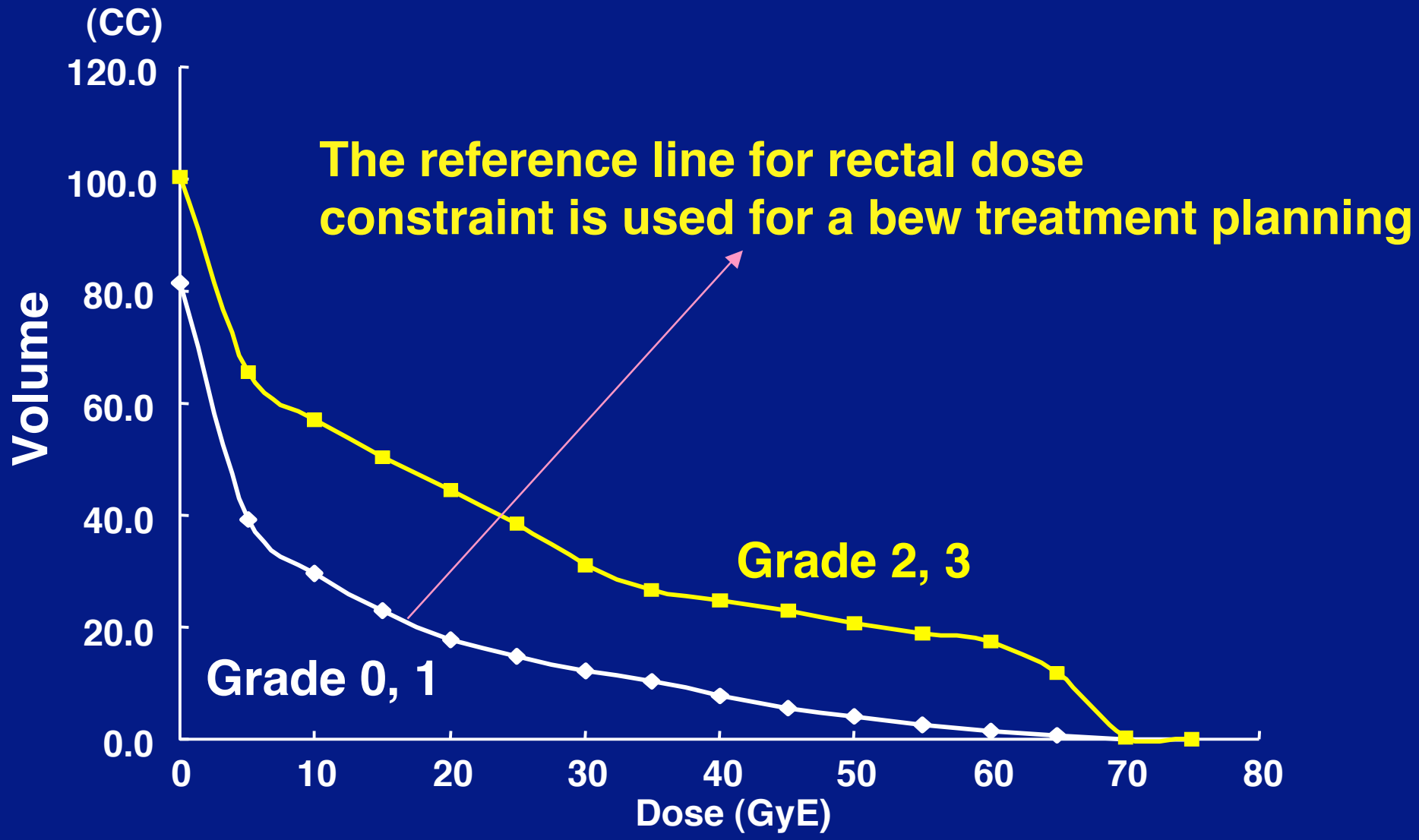
DVHs of the Rectum in Carbon Ion Therapy for Prostate ca



DVHs of the Rectum in Carbon Ion Therapy for Prostate ca



Average DVHs of the Rectum
(according to Late Rectal Morbidity at 1st phase I/II study)

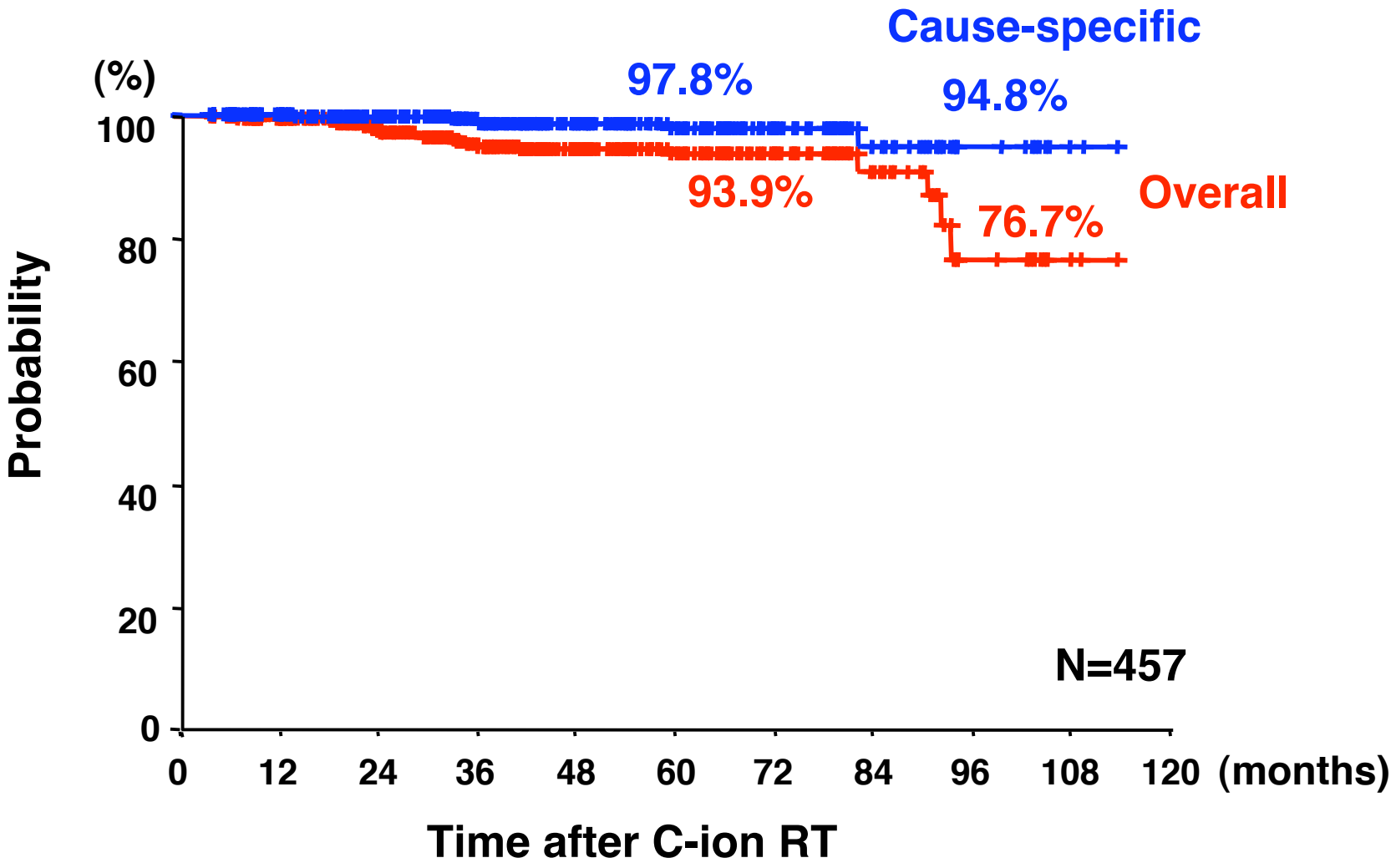


Comparison of Late Toxicities

Institutes	RTx	Dose/fr.	No. of pts.	Morbidity ≥ G2 Rectum	Morbidity ≥ G2 GU
Maximum Reaction					
MDAnderson CC.[1)]	3DCRT	78Gy/39f	151	26.0%	13.0%
Cleveland CF.[2)]	IMRT	70Gy/28f	770	4.4%	5.2%
Loma Linda U.[3)]	Proton	75CGE/40f	901	3.5%	5.4%
NIRS[5)]	Carbon	63-66GyE/20f	288	1.8%	5.9%
At Last Follow-up					
Fox Chase CC.[4)]	3DCRT	≥76Gy/38f	232	11.0%	7.0%
NIRS[5)]	Carbon	63-66GyE/20f	288	0.9%	2.4%

1) DA Kuban et al.IJROBP 70; 2008
2) PA Kupelian et al. IJROBP 68; 2007
3) RW Schulte et al. Strahlenther Oncol 176; 2000
4) GE Hanks et al. IJROBP 46; 2000
5) H.Tsuji, et al. IJROBP 63; 2005

Survivals



H.Tsuji. ECCO at Barcelona 2007, IJROBP 63 2005, H.Ishikawa Radiother. Oncol 2006

Comparison with other RTx
(5-year bNED, iPSA>20)

Institutes	RTx	Dose	No. of pts.	5-yr Biochemical NED (iPSA>20)
MDAnderson CC.[1)]	3DCRT	78Gy/39f	53 (PSA>10)	39%(8y-rate)
Fox Chase CC.[2)]	3DCRT	≥76Gy/38f	232	26-63%
Cleveland CF.[3)]	IMRT	70Gy/28f	770	72%
Loma Linda U.[4)]	Proton	75CGE/45f	901	45%
NIRS [5)]	Carbon	66.0GyE/20f	186	80% 72%(8y)

1) DA Kuban et al.IJROBP 70; 2008

2) GE Hanks et al. IJROBP 46; 2000

3) PA Kupelian et al. IJROBP 63; 2005

4) JD Slater et al. IJROBP 59; 2004

5) H.Tsuji, et al. IJROBP 63; 2005

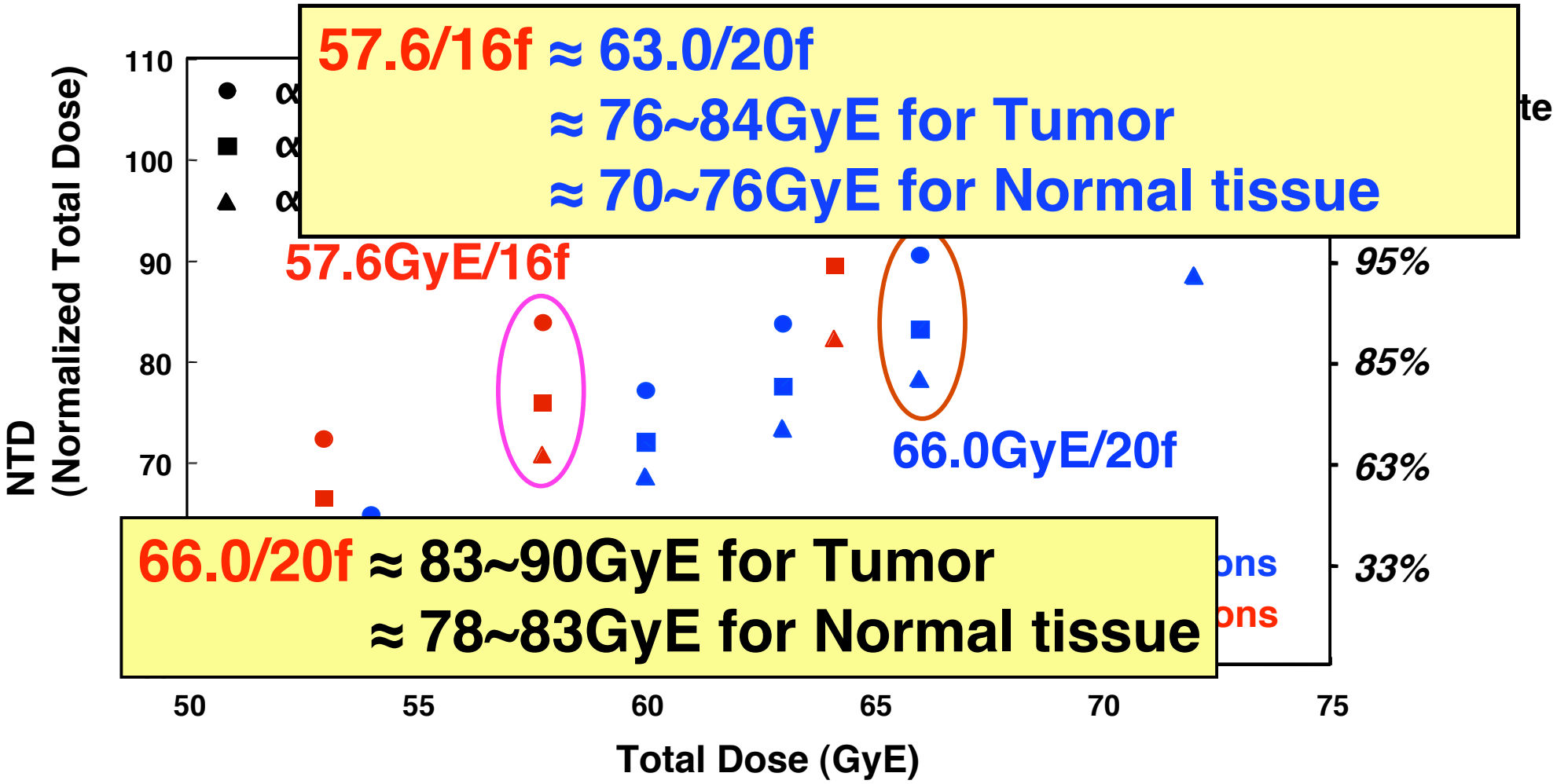
Comparison of Survivals

Treatment	Dose (Gy/f)	OS* in each Risk Group**					
		Group 2		Group 3		Group 4	
		No.pts	5-y OS	No.pts	5-y OS	No.pts	5-y OS
RTOG Meta analysis#							
RT alone	(65-70GyE/35f)	443	82%	338	68%	324	52%
RT+ Hormone		114	76%	138	79%	103	63%
Carbon							
RT+ Hormone	(66.0GyE/20f)	118	95%	125	92%	56	89%

*Overall Survival Rate **Risk Group: Group 2; GS2-6, T3 or GS7, T1-2
Group 3; GS7, T3 or GS8-10, T1-2
Group 4; GS8-10, T3

#RTOG: Radiation Therapy Oncology Group
Mack Roach III et al IJROBP; 47(3): 617-627, 2000

Hypofractionated schedule in C-ion RT for prostate cancer



Stereotactic hypofractionated radiotherapy of the prostate, 33.5Gy in five fractions for localized disease: first clinical trial results (Madsen et al: IJROBP 67; 1099-1105, 2007)

- **Phase I/II trial: 40 pats (2000-2004)**
  - Low-risk disease; GS≤6, PSA≤10ng/mL, ≤T2aNxMx
  - Prostate volume; median 56.4cc (13.7 - 134.5 cc)
  - Total dose; 33.5 Gy (6.7 Gy x 5 fr)

	Acute		Late	
Grade	GU	GI	GU	GI
0	49%	61%	55%	63%
1	28%	26%	25%	30%
2	21%	13%	20%	8%
≥3	0%	0%	0%	0%

Toxicity
(Scoring with RTOG-LENT)

Dose	No.	Rectum				Bladder/urethra			
GyE/f.	pts	G0	G1	G2	G3	G0	G1	G2	G3
Maximum									
66.0/20f	288	81.3	17.0	1.7	0	35.1	58.3	6.6	0
63.0/20f	169	91.1	7.1	1.8	0	76.3	23.1	0.6	0
57.6/16f	87	89.7	10.3	0	0	74.7	25.3	0	0
Last F/U									
66.0/20f	288	93.1	6.6	0.3	0	80.9	16.0	3.1	0
63.0/20f	169	94.7	4.7	0.6	0	94.7	5.3	0	0
57.6/16f	87	94.3	5.7	0	0	95.4	4.6	0	0

Median follow-up period:
66.0/20f;49.2m, 63.0/20f;15.1m, 57.6/16f;21.4m

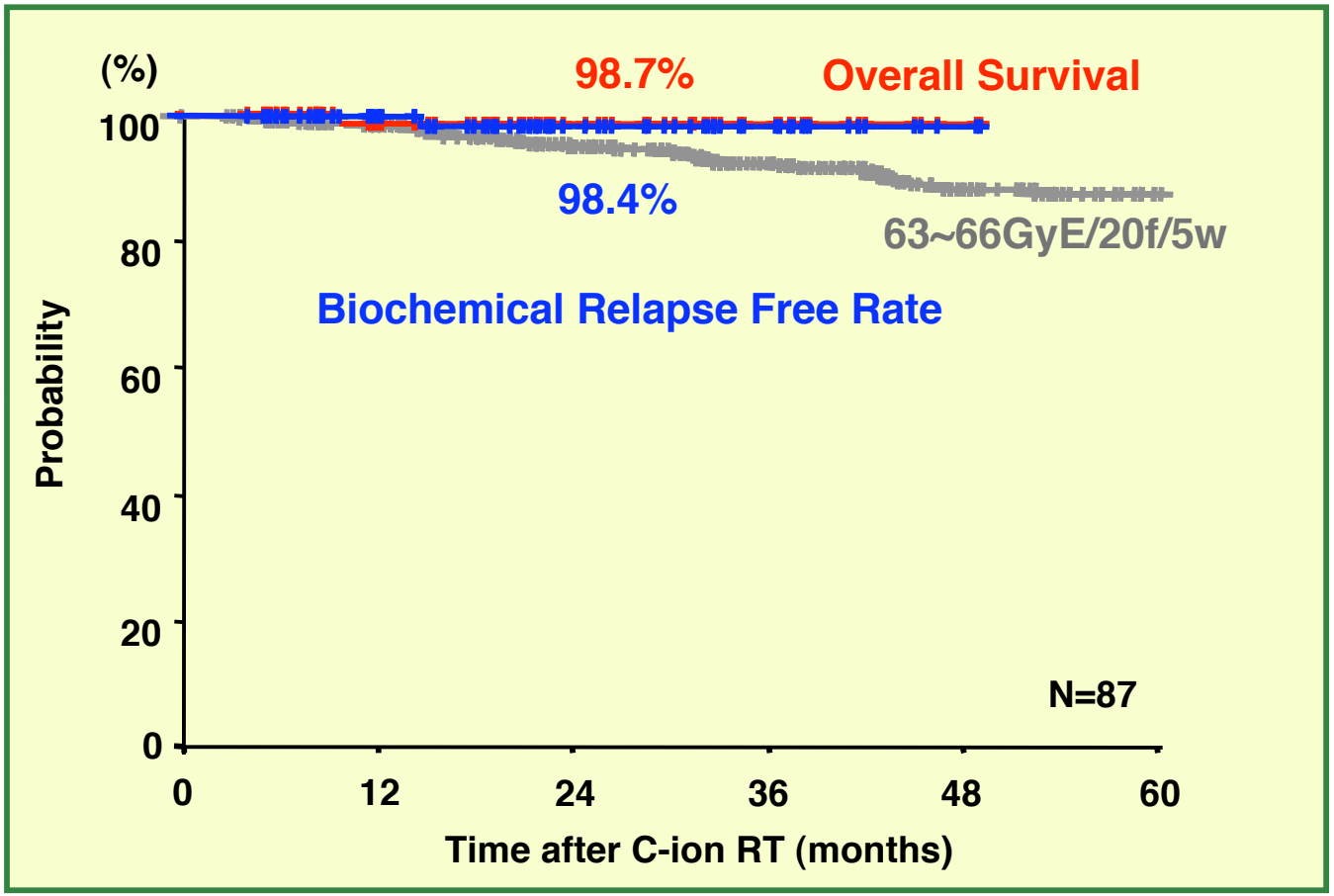
A Shorter Fractionation:57.6GyE / 16f

87 patients (out of 97 pts)

Average age; 69.5 y.o. (51~80)

Follow-up; Median 21.4 months (6~49 m)

Risk Group	No.pts.
Low	17(20.7%)
Interm.	19(21.8%)
High	49(57.5%)



Summary

- **There is a significant advantage in shortening the overall time and fractions of radiotherapy at least to 3 - 4 weeks or even shorter, which has been done effectively in radiotherapy with C-ion RT.**

- **This means that the facility can be operated more efficiently, offering treatment for a larger number of patients than is possible with other modalities over the same period of time.**