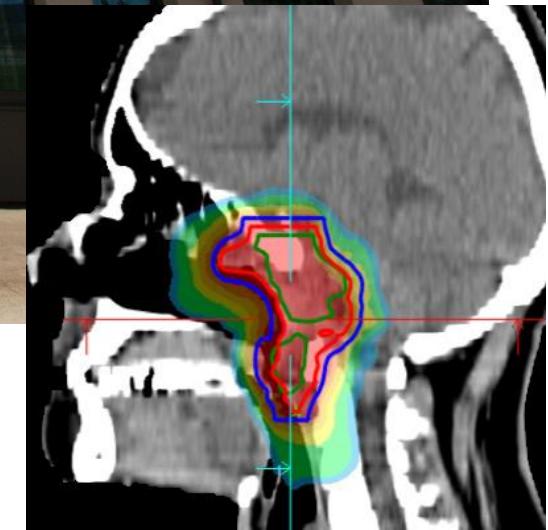


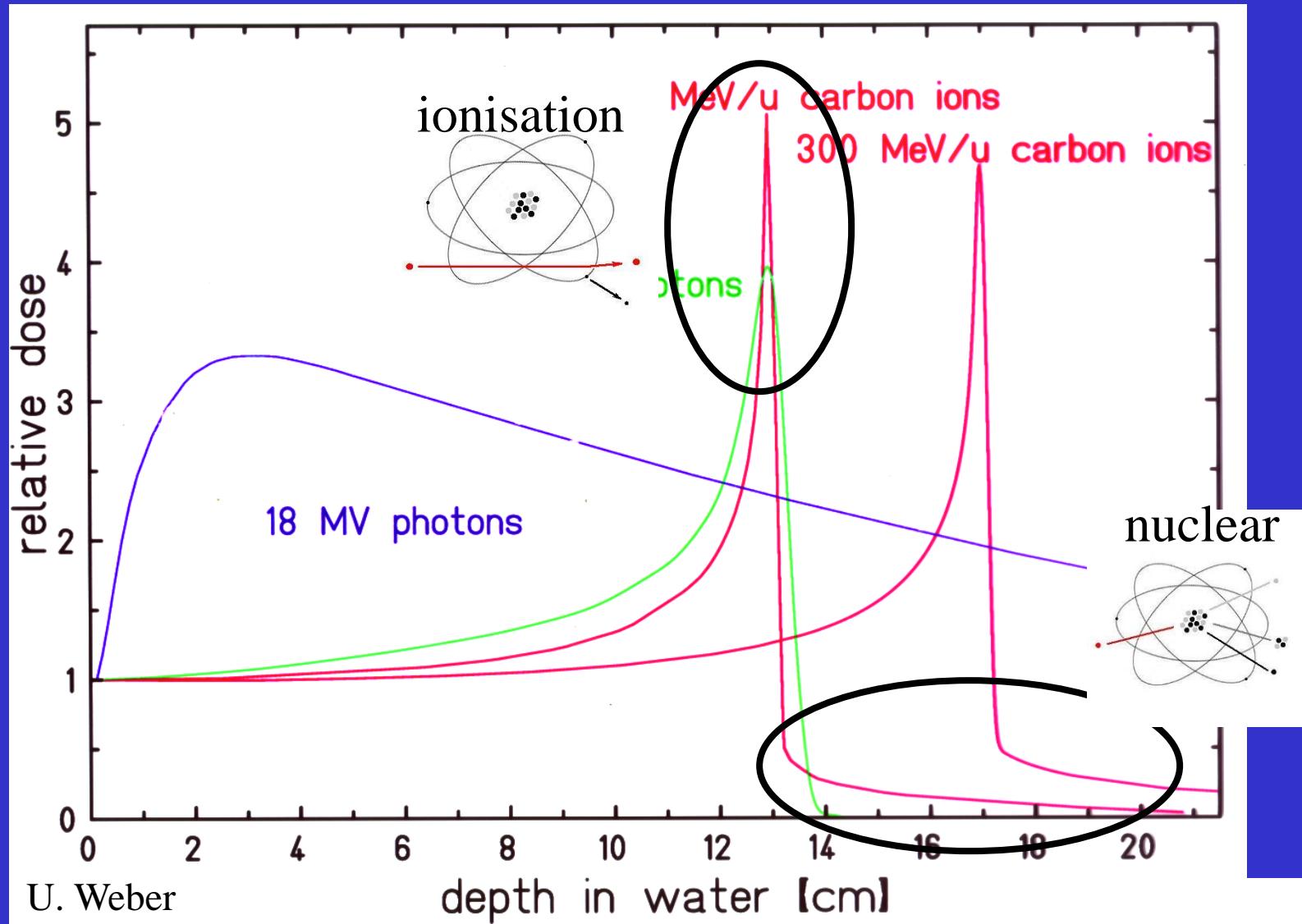
Radiobiology II (real patients)



Advanced School on Medical Accelerators and
Particle Therapy



Depth dose distribution of various radiation modalities



What happens as carbon ion penetrates and slow down ?

- They deposit more and more energy
- Bragg peak
- The mean distance between two ionization events becomes smaller and smaller
- High LET

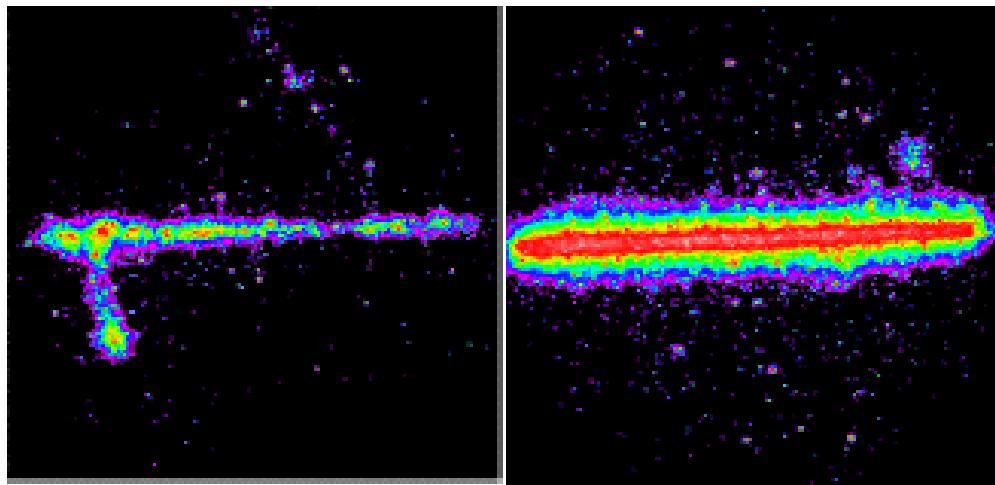
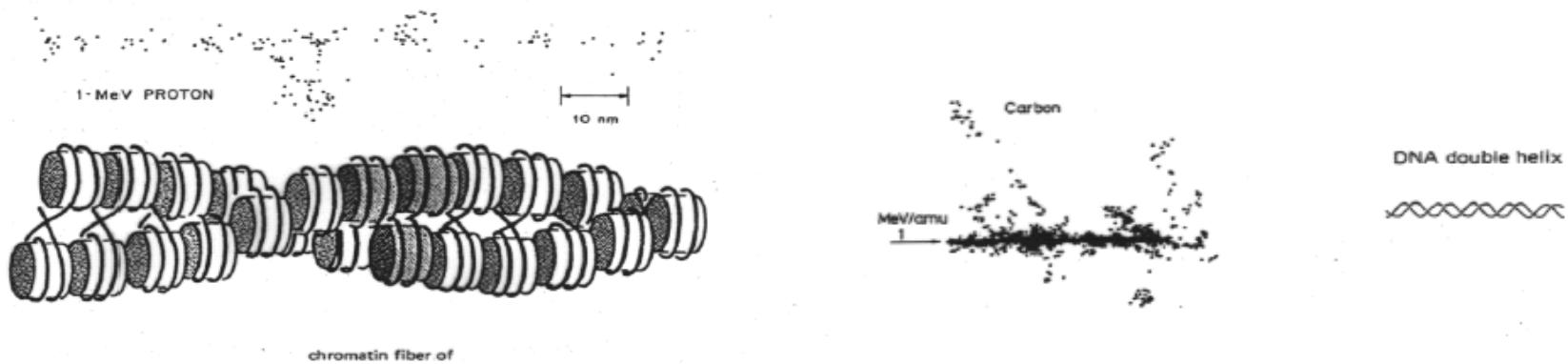


Fig.1: Carbon ion tracks in 10 hPa TEA gas, tracked by OPAC
(a): 400 MeV/u C ion *(b): energy close to 0,7 MeV/u*



SS
BBBBBBBBBBBBBBBBBBBBB BBBBBBBBBBBBBBBBBBBBBB
BBB BBBBBBBBBBBBBB
SS

-  Sugar Damage
-  Base Damage
-  Double Strand Br

1000 MeV/n He

SSSSSSS SSS S S SSS S S S S S S S S S S S S S
B
B
S S

A A A A A A A A A A A A A A A A A A A A

10 MeV/n Fe

A. Chatterjee, LBNL

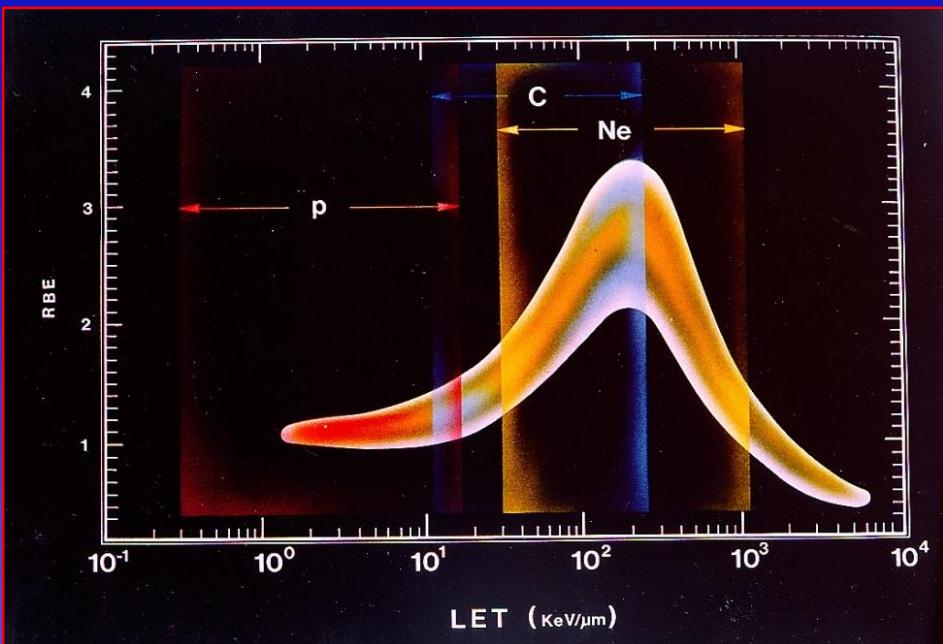
-10.0 sec

Jakob et al. Proc. Natl. Acad. Sci. USA 2009

Courtesy of M. Durante

© GSI

LET

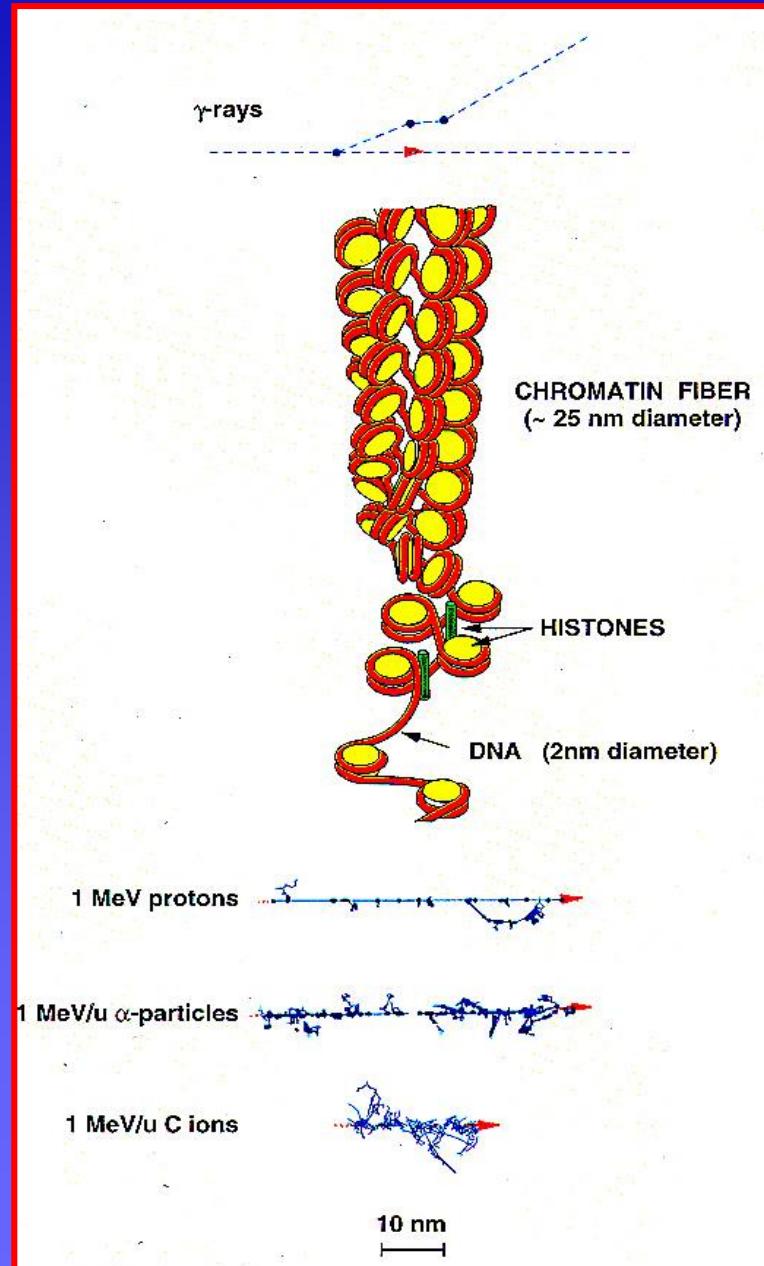


low LET

1-----1-----1-----1-----
(<20 KeV/micron)

high LET

1---1---1---1---1---1---1---1---1---1---

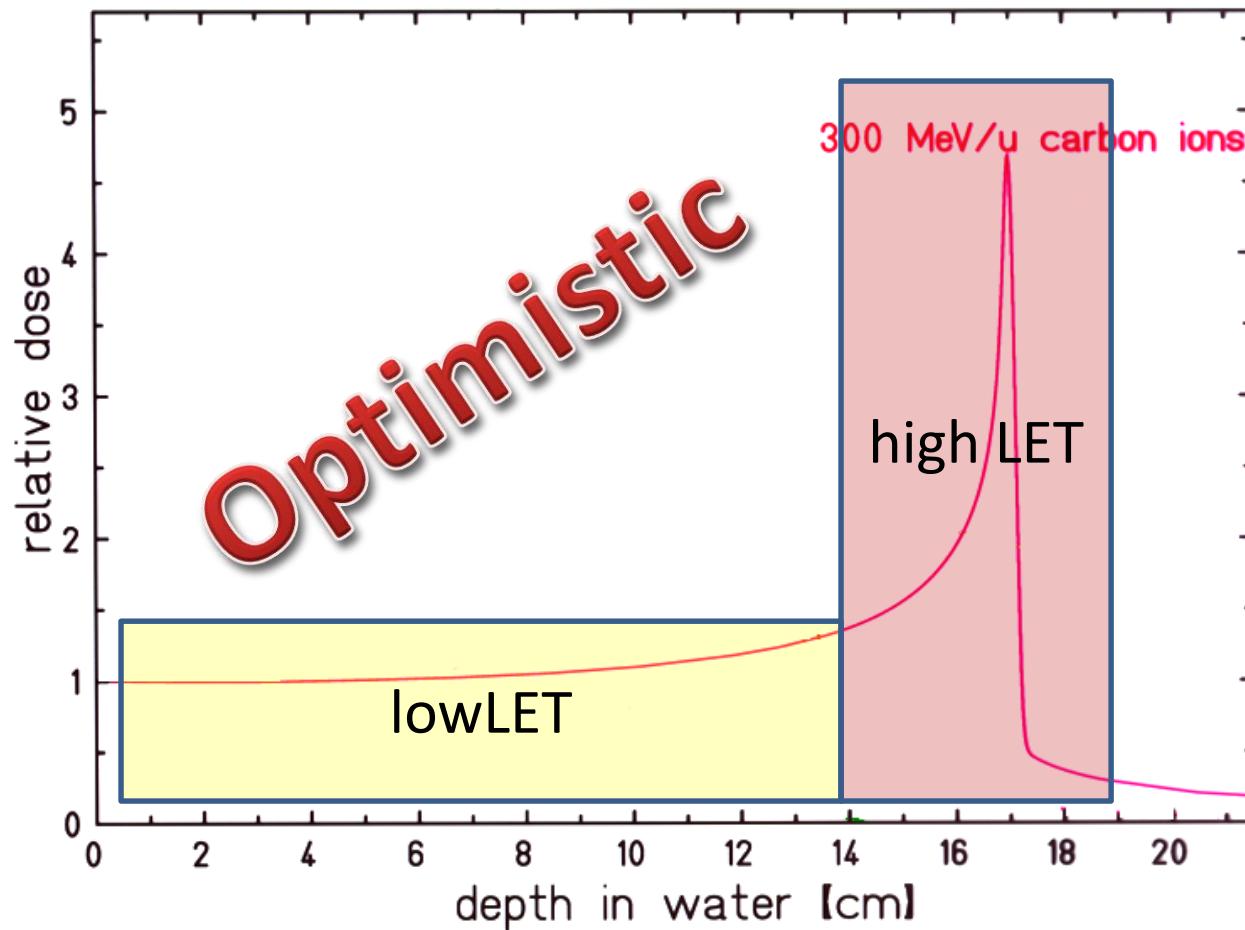


So why carbon ions ?

- Good dose distribution
- High LET only in the last part of the path

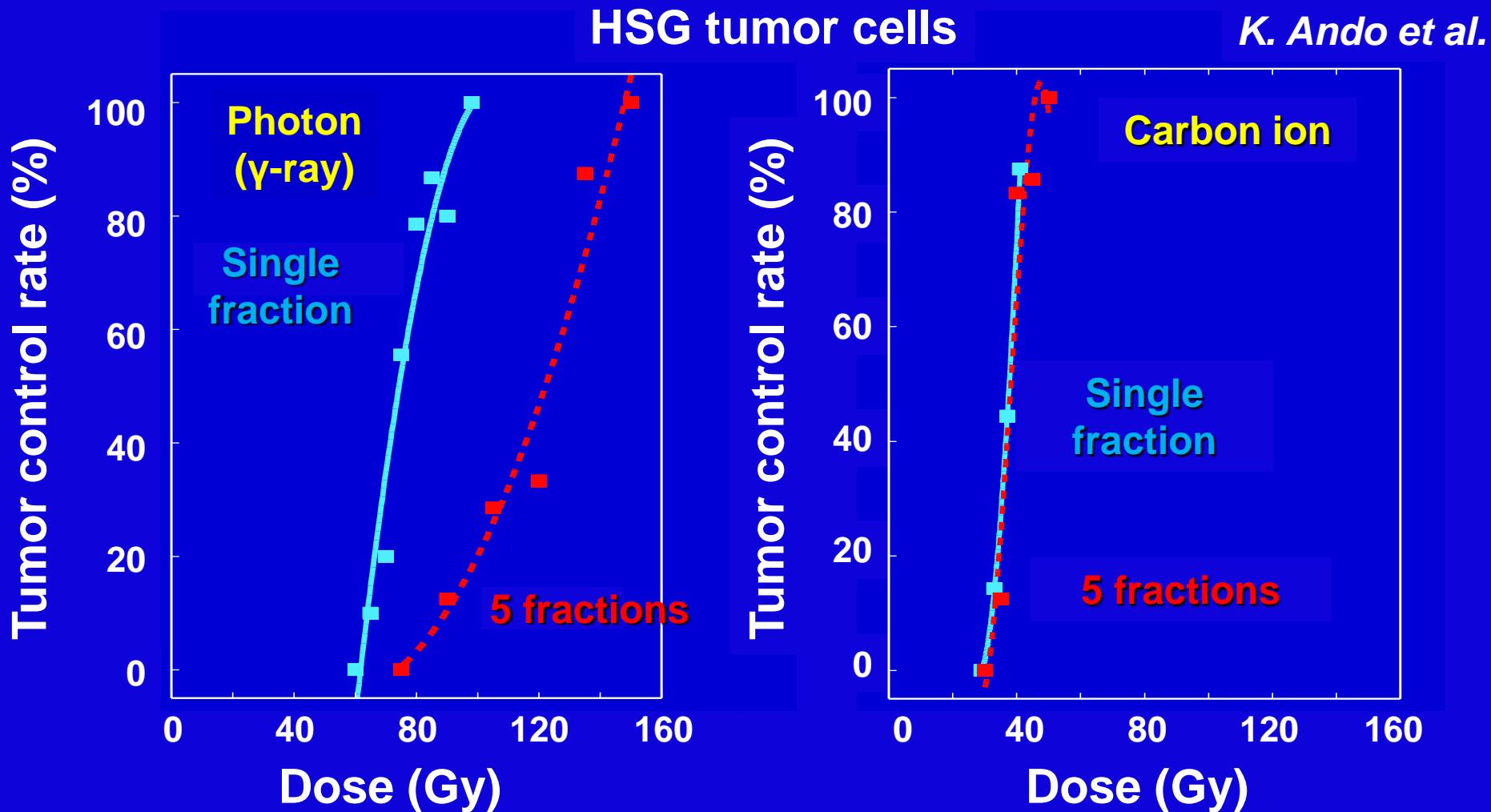
Carbon ions

High LET RT ?(only where you need it)



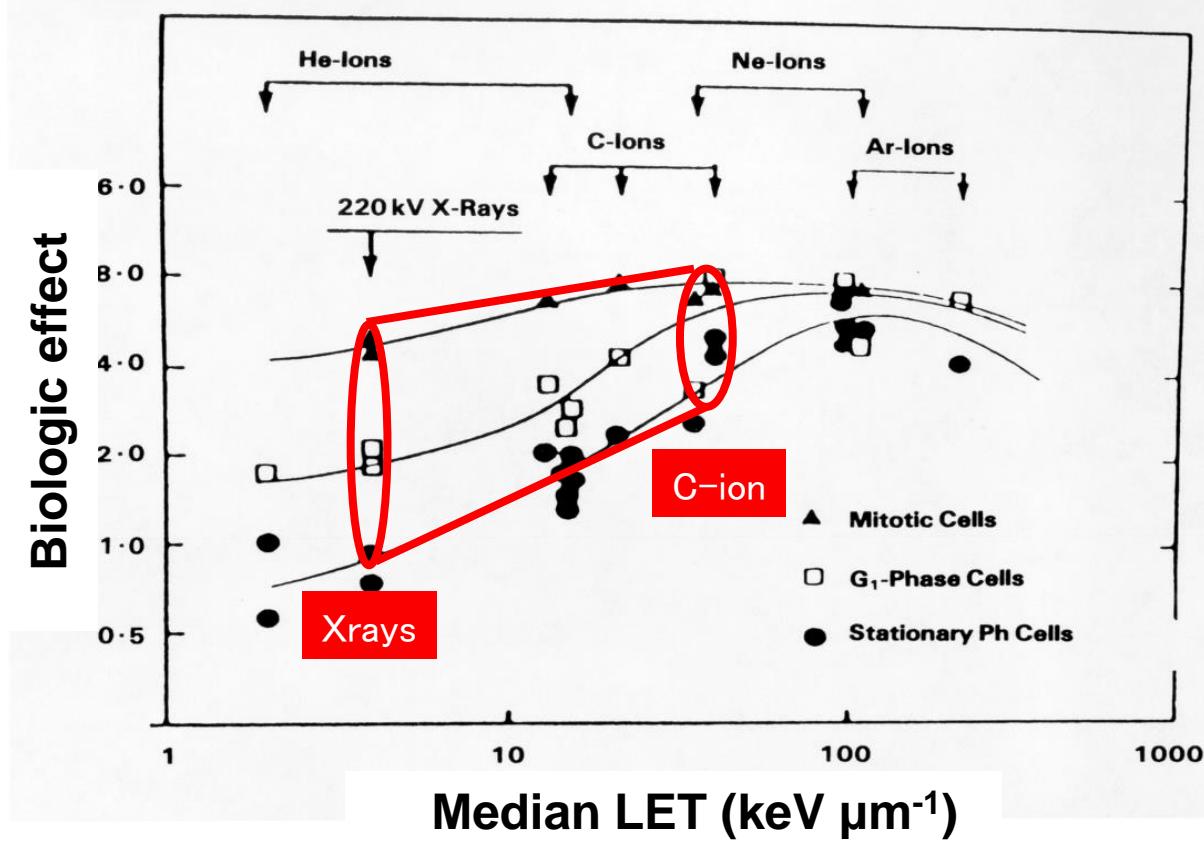
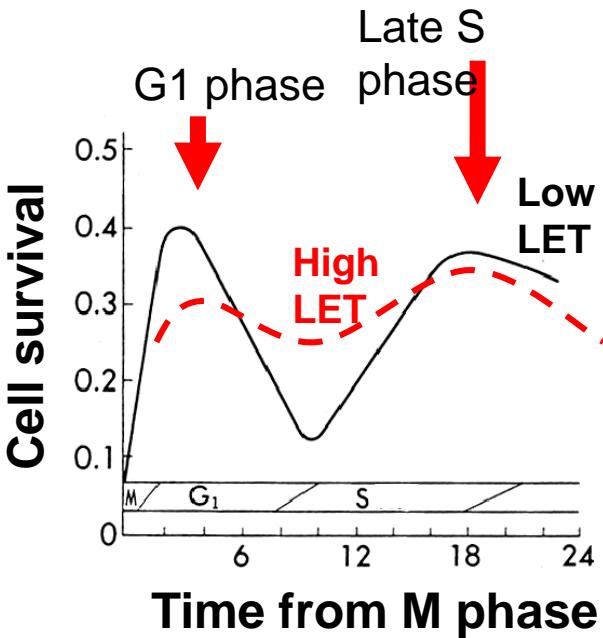
Fractionation effects

Carbon ion beam has minimal fractionation because of less repair capability



Radiation Sensitivity by Cell Cycle

Carbon ion beam have less difference of radiation sensitivity by cell cycle



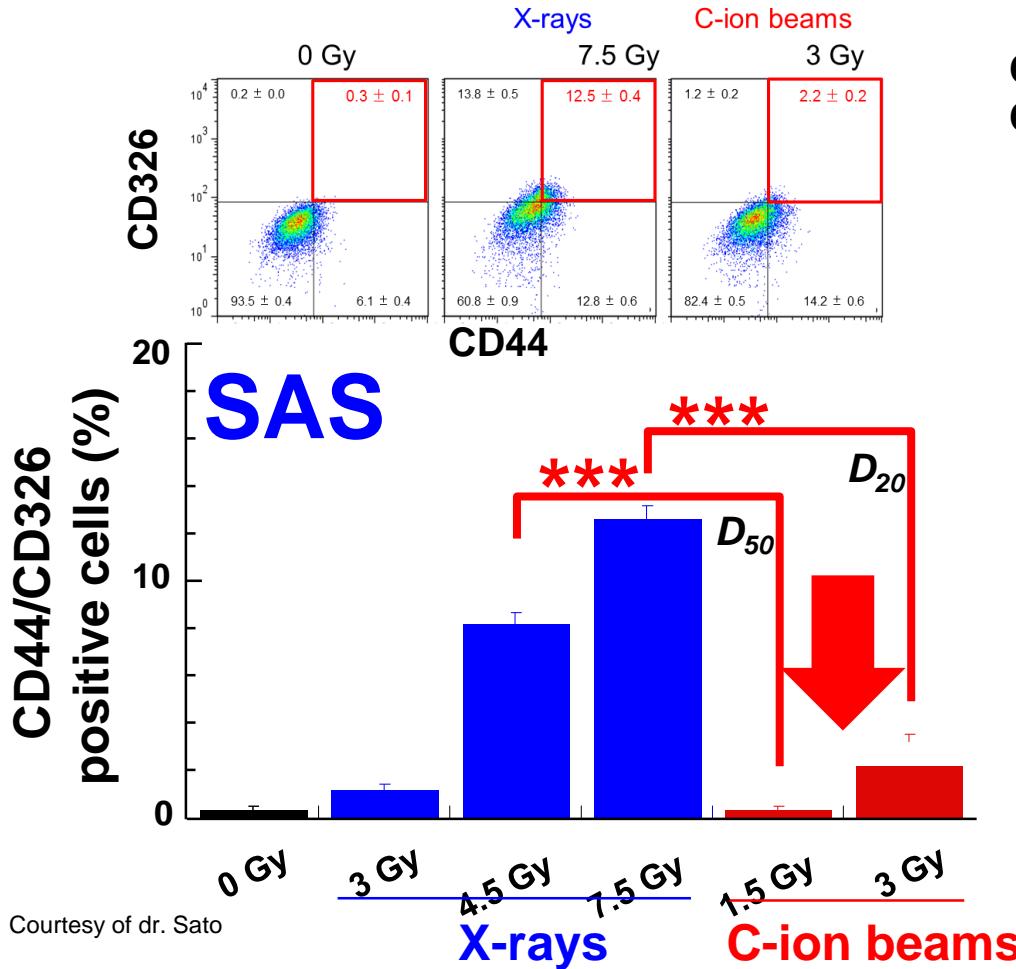
Courtesy of dr. Sato

J.D.Chapman, *Radiation. Biology in cancer research*

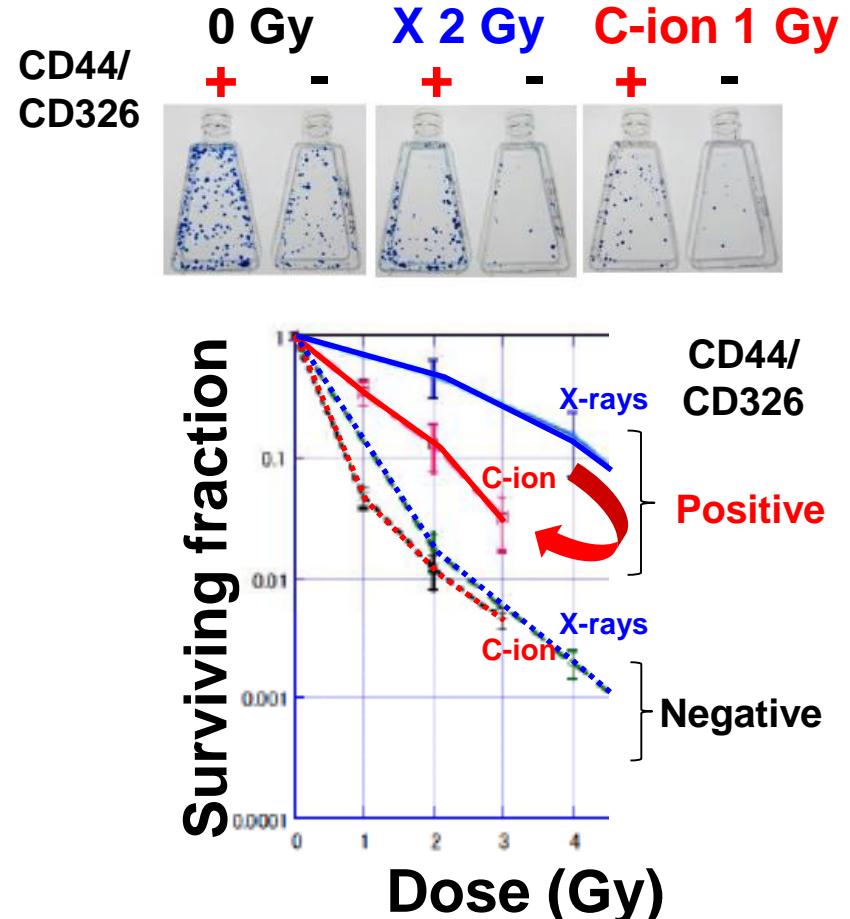
C-ion overcomes cancer stem cells radioresistance

CD44 and CD326: marker of cancer stem like cell

SAS cells: human tongue cancer cells

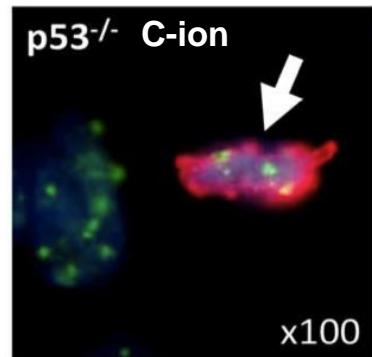
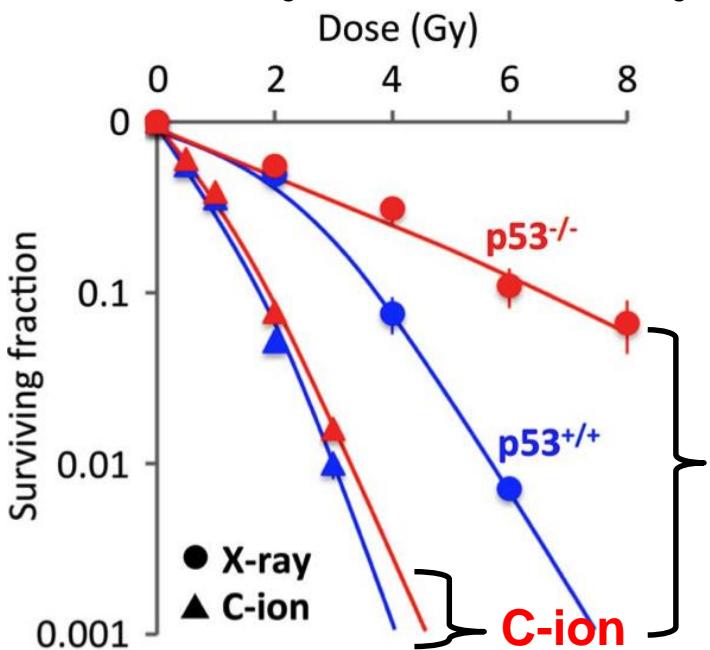


HCT114 cells: human colon cancer cells

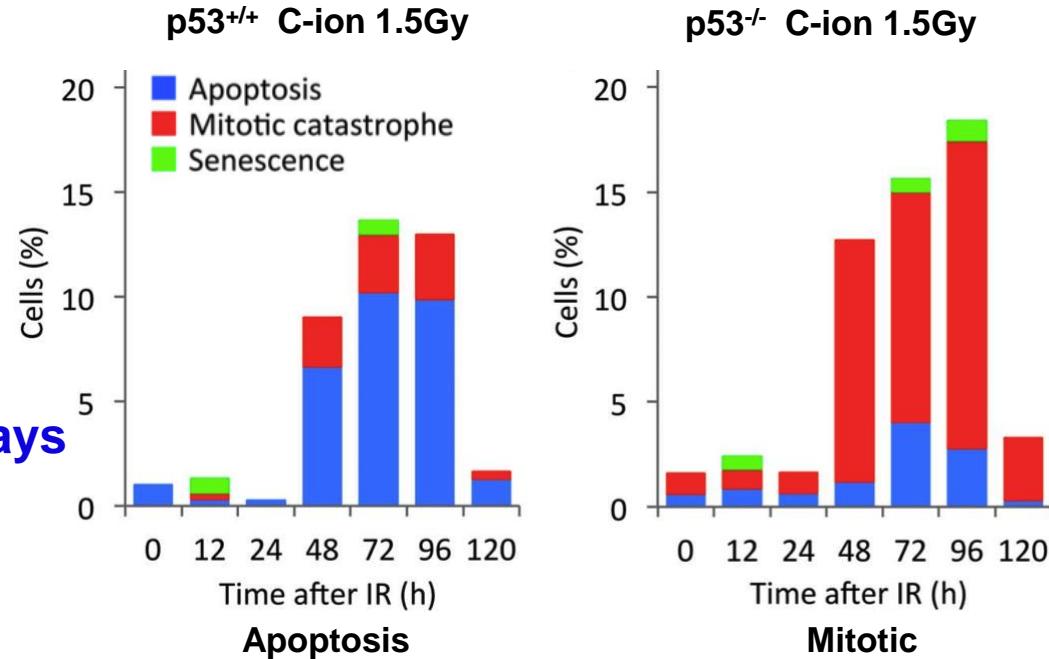


C-ion efficiently induce mitotic catastrophe in apoptosis-resistant p53 mutant cancer cells

Colony formation assay

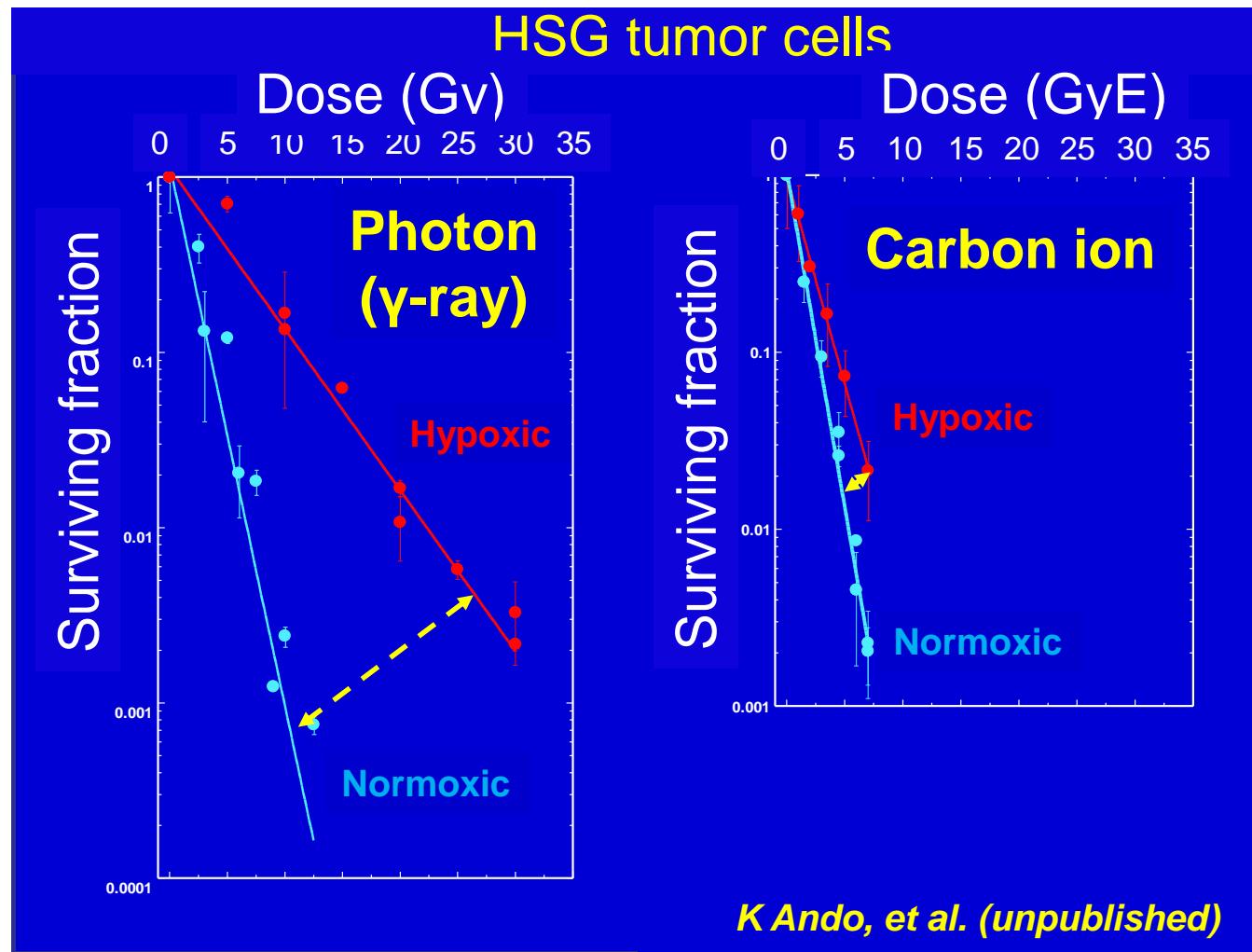
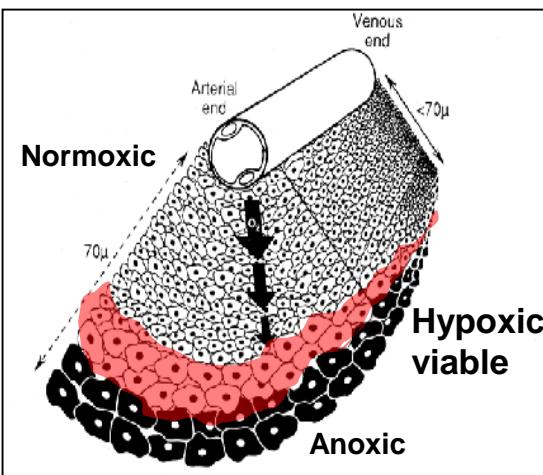


Cell death evaluation by DAPI staining



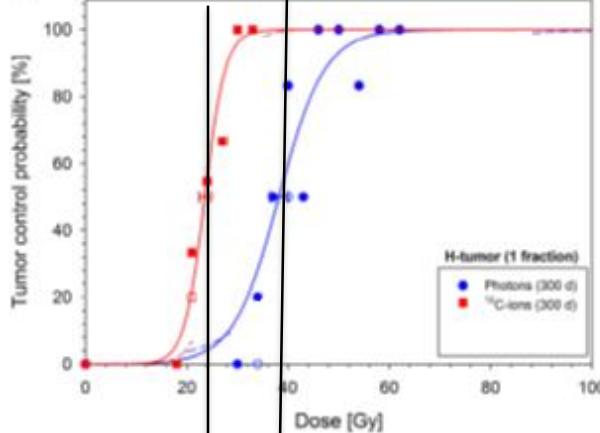
Radiation Sensitivity by Hypoxia

Carbon ion beam have significantly smaller OER than photons

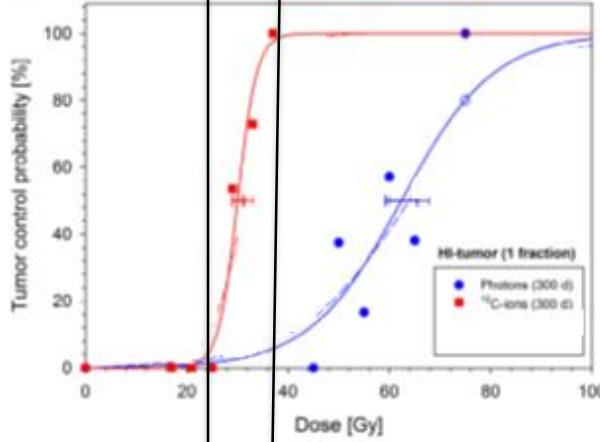


Courtesy of dr. Sato

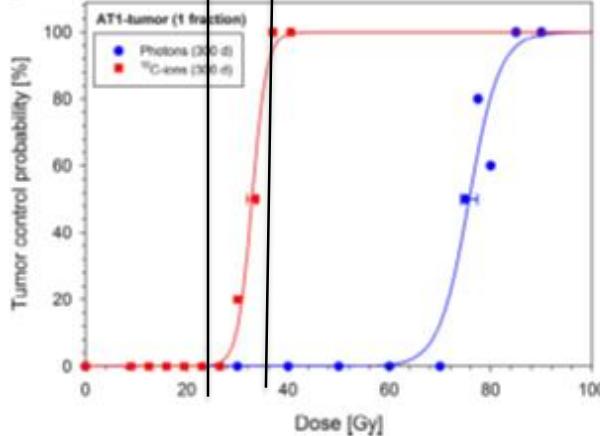
K Ando, et al. (unpublished)

A

Well
differentiated
prostate cancer

B

Moderately
differentiated
prostate cancer

C

poorly
differentiated
prostate cancer

Modified from C. Glowka et al. / Cancer Letters 378 (2016) 97–103

The Domain of Carbon Ion Therapy at NIRS

Tumors ; biological view points for high LET beam

- with large proportion of hypoxic cells
- do not well re-oxygenate
- with broad-shouldered dose survival curves by low LET radiation (**small α/β ratio**)
- slowly proliferating

Tumors ; clinical context (practical) mainly conformality

- empirically radio-resistant, such as sarcomas, melanoma, RCC, thyroid ca, and re-irradiation
- located close to radiosensitive organs ; para-spinal
- Not candidate to other therapies such as second surgery, limb amputation, concurrent chemo-radiation etc.
- unresectable or medically inoperable
- Better LC can translate into better outcome !!!

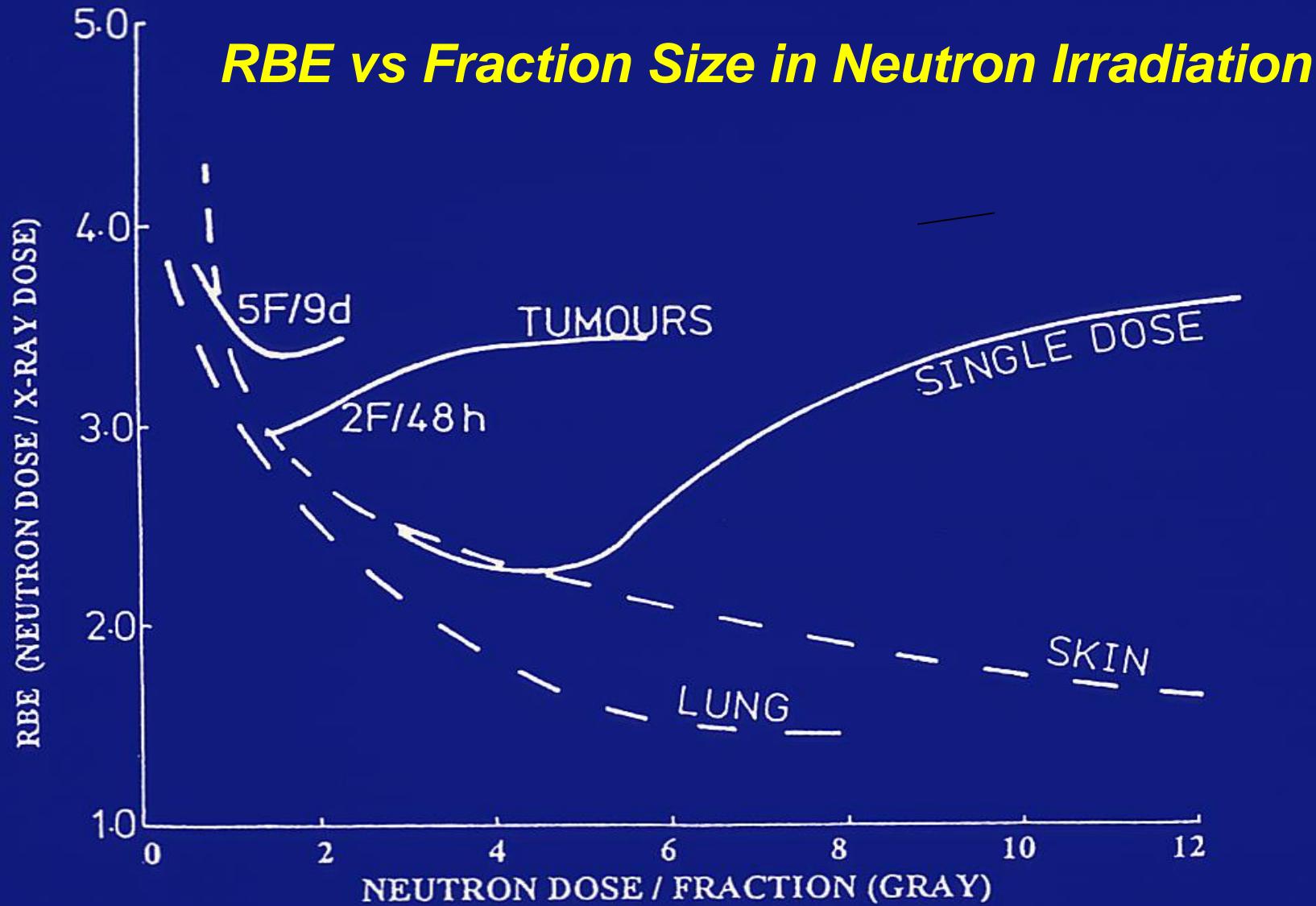
Biological Background for Hypo-fractionated radiotherapy with Carbon Ion beams

Koike S, et al: *Radiat Prot Dos.* 2002;99: 405-408.

Ando et al. : *J.Radiat.Res.*, 46:51-57, 2005.

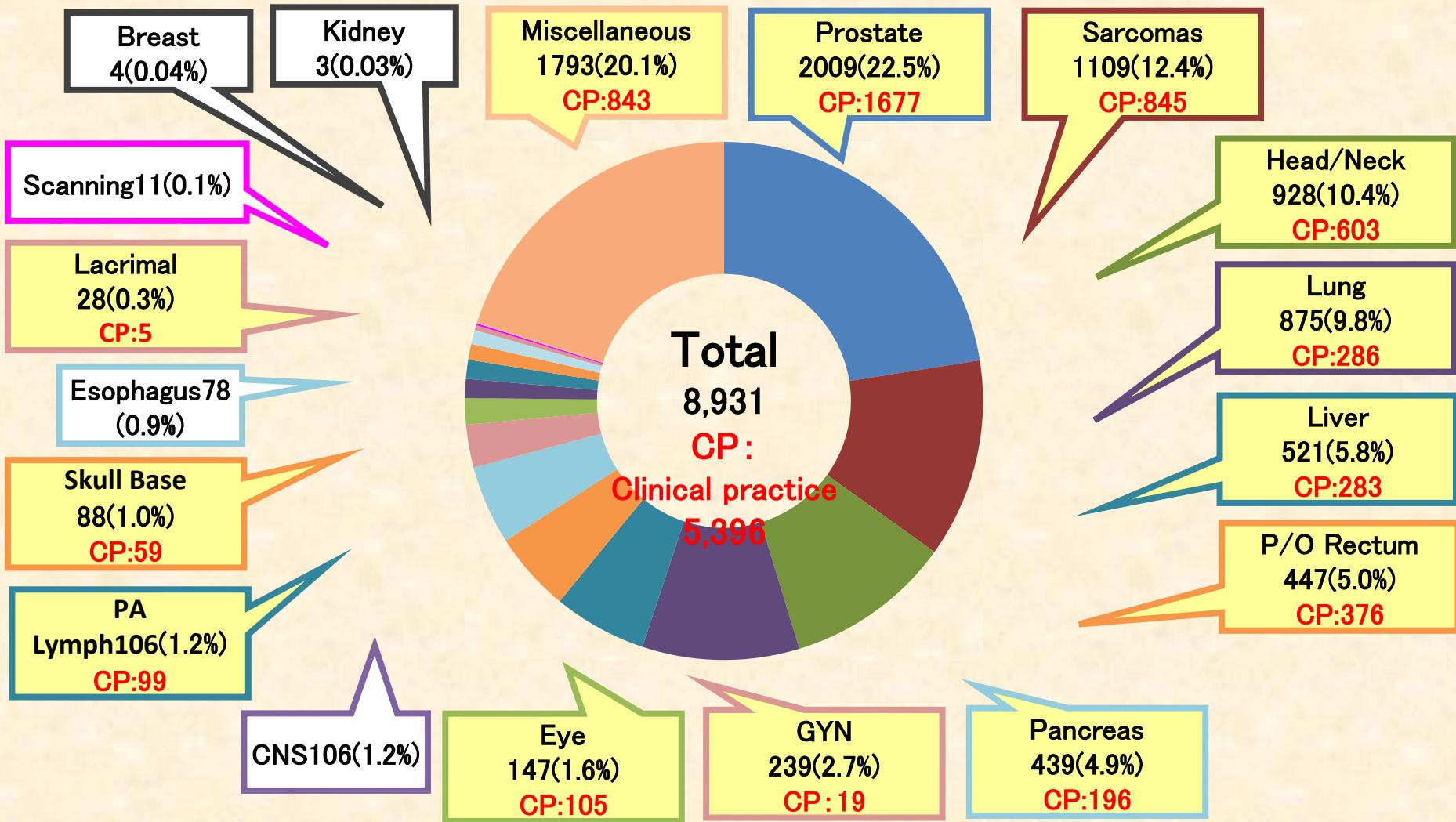
Denekamp J: *Int J Radiat Biol.* 71: 681-694, 1997.

- ◆ Experiments with carbon ions and fast neutrons demonstrated that increasing the 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.

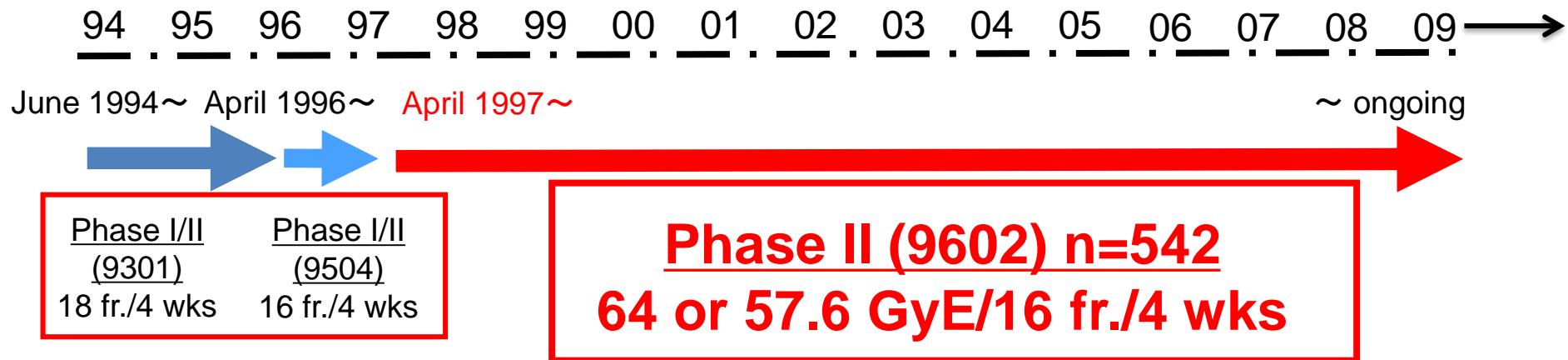


J.Denekamp, et al., Radiation Research 68, 93-103.1976.

Patient Distribution Enrolled in Carbon Therapy at NIRS (Treatment: June 1994~March 2014)



Carbon Ion Radiotherapy for Head-and-Neck Tumors



Rec. after surgery & Chemo

Rec. after chemotherapy

Rec. after surgery

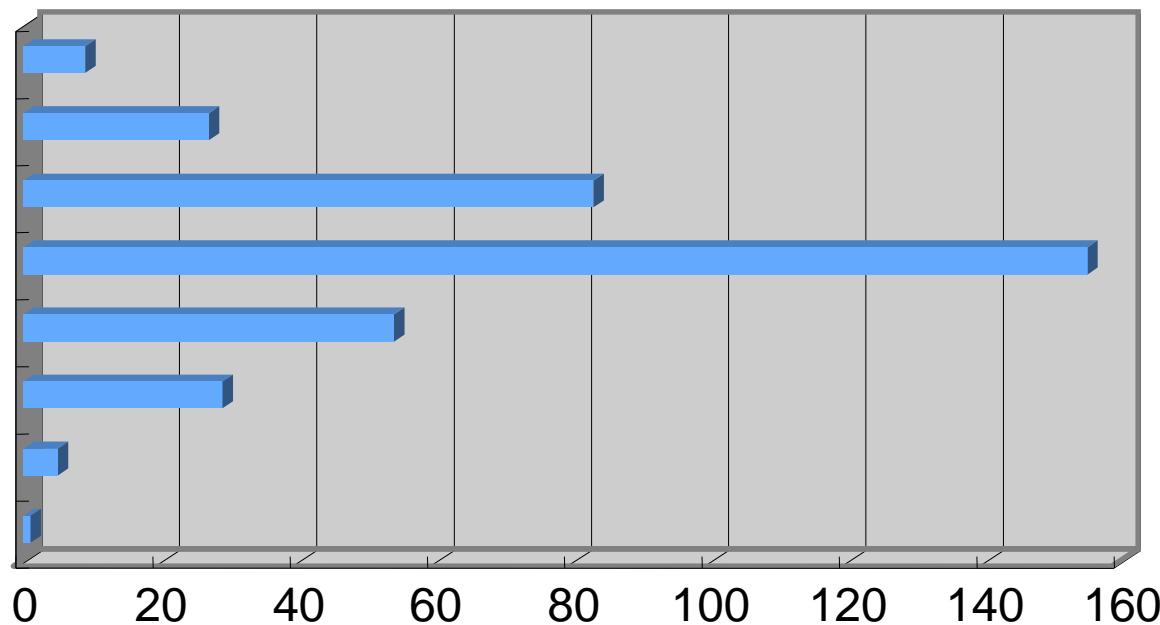
T4

T3

T2

T1

Tx



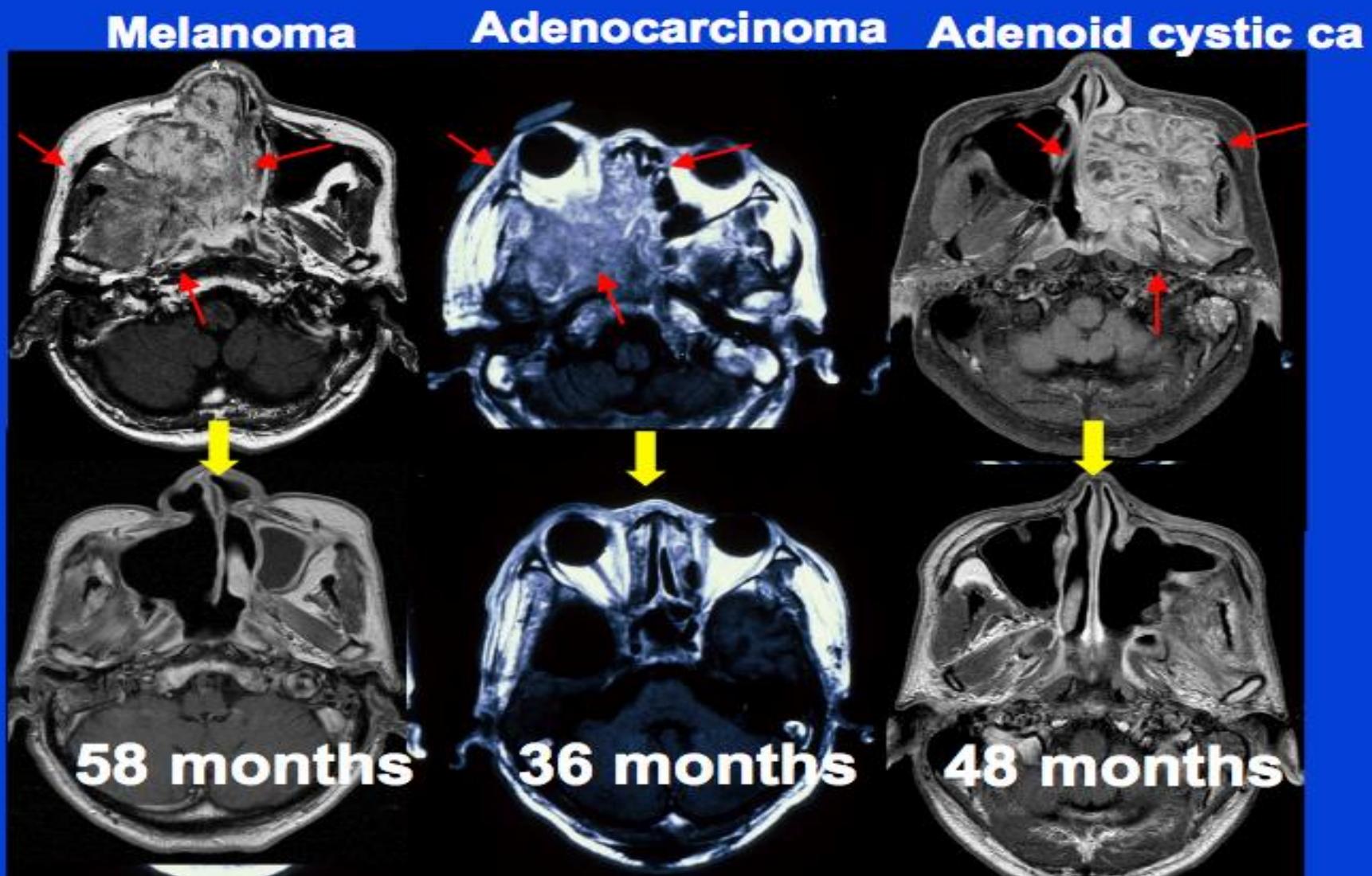
Mizoe et al. Int J Radiat Oncol Biol Phys. 2004;60:358-364

Hasegawa et al. Int J Radiat Oncol Biol Phys. 2006;64:396-401

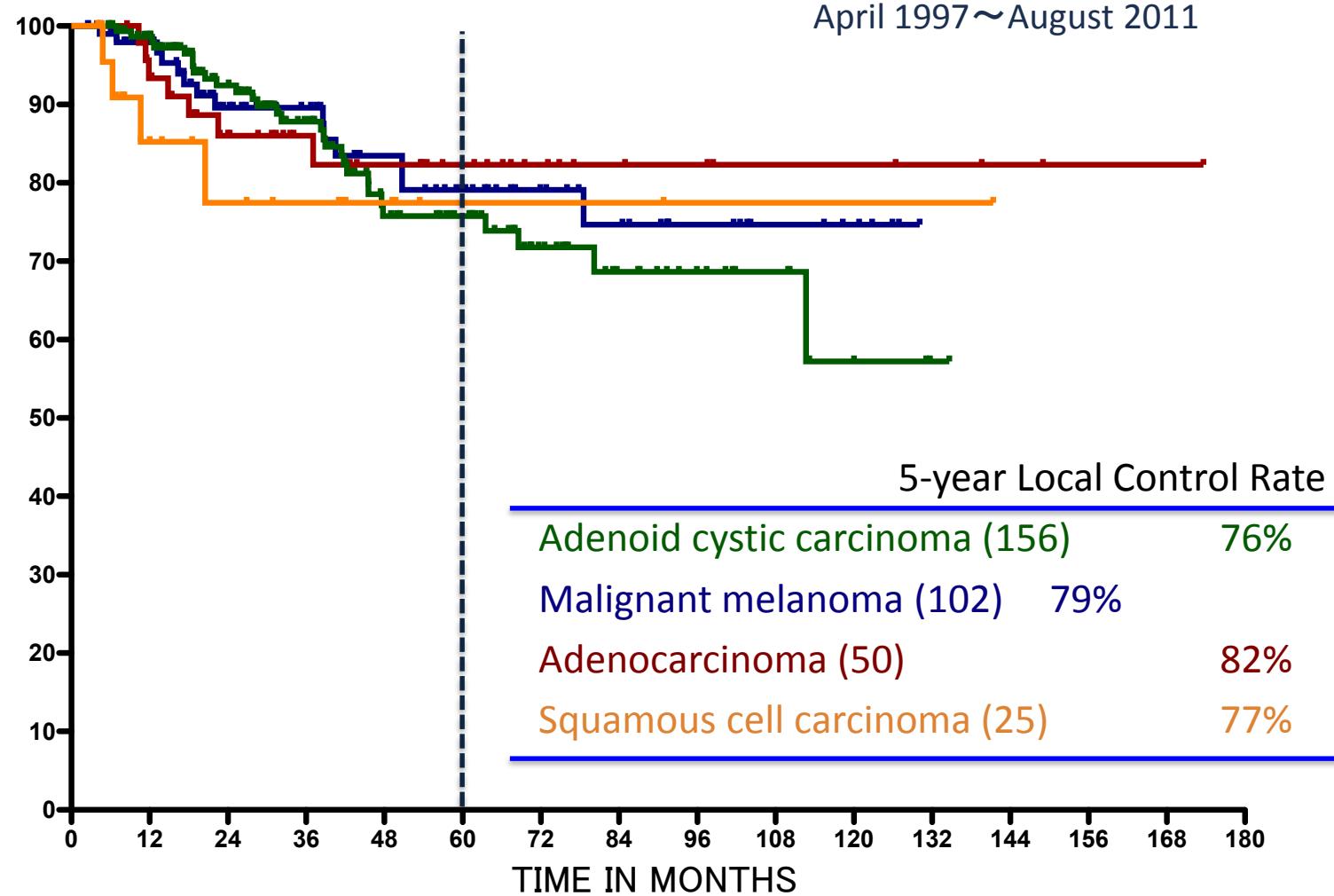
Yanagi et al. Int J Radiat Oncol Biol Phys. 2009;74:15-20

Mizoe et al. Radiother Oncol. 2012 Apr;103(1):32-7.

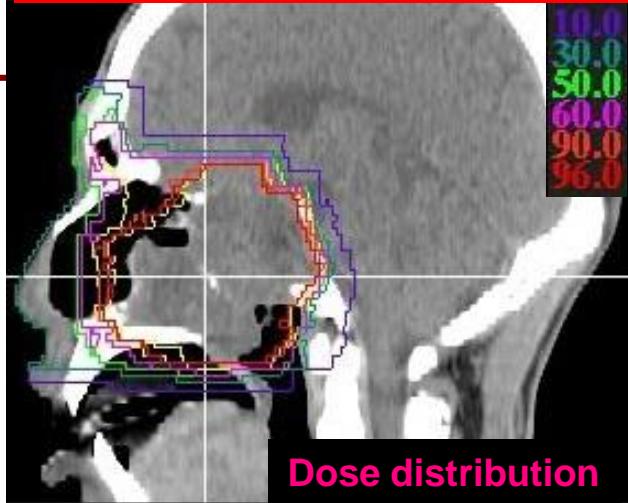
Head-and-Neck Cancers



Local Control according to Histological Types

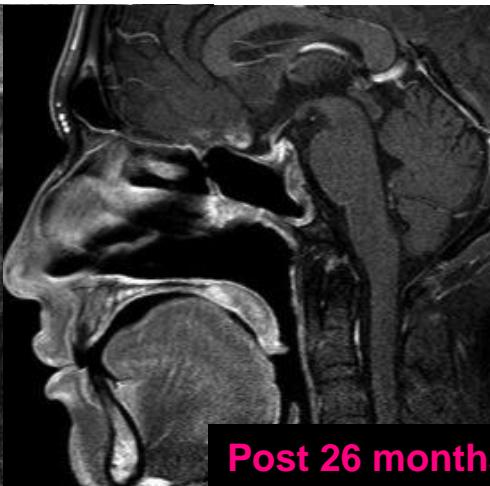
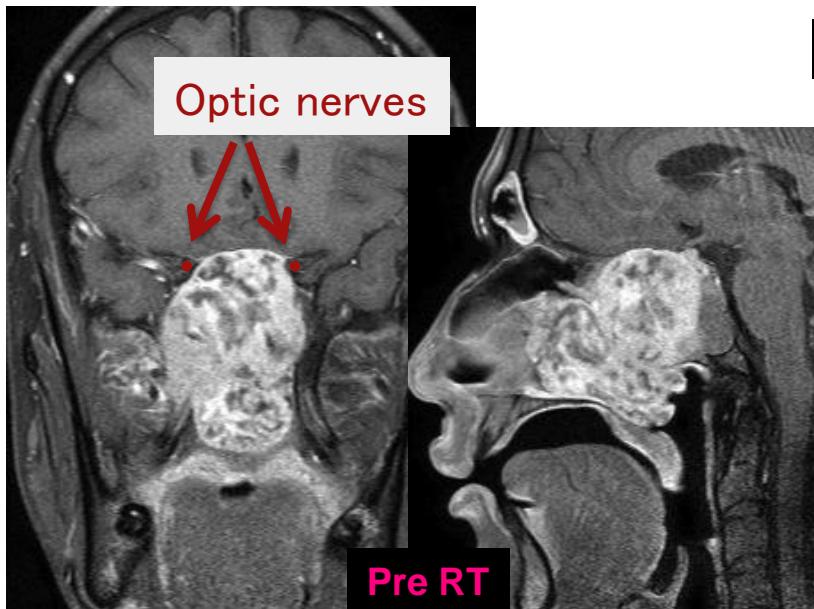
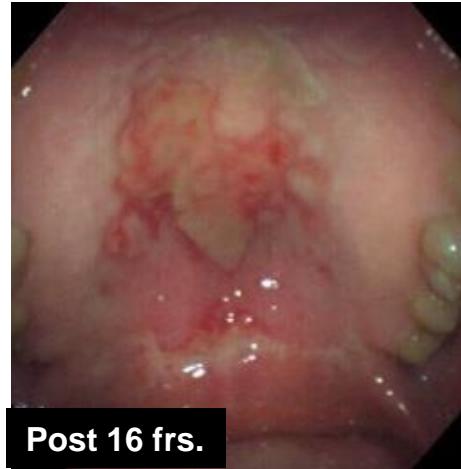


Paranasal Cavity Cancer (Target volume = 262 ml)



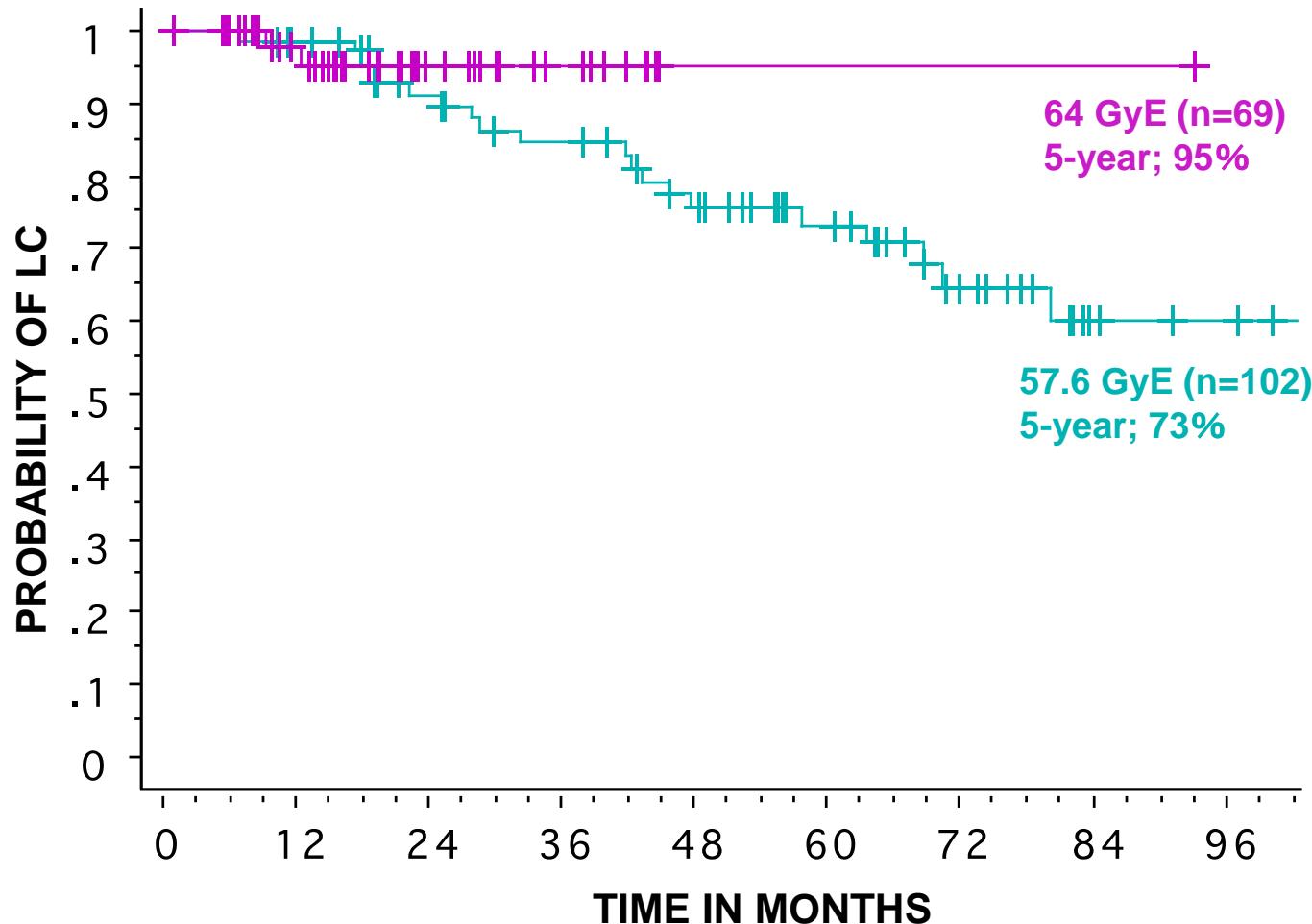
57.6 GyE/16 frs.

Acute Mucosal Reaction : Grade 2 or 3 (RTOG)



Phase II (9602) for Malignant Head-and-Neck Tumors

Local Control of ACC (n=171) according to Carbon ion Dose

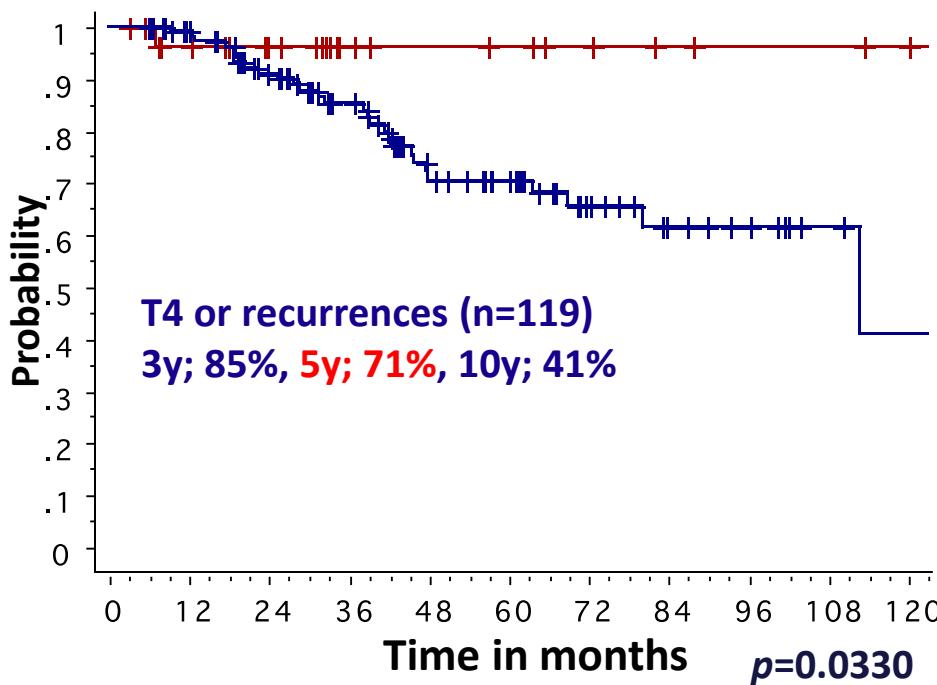


Carbon Ion Radiotherapy for Adenoid Cystic Carcinomas

Carbon ion dose: 64 or 57.6 GyE/16 frs.

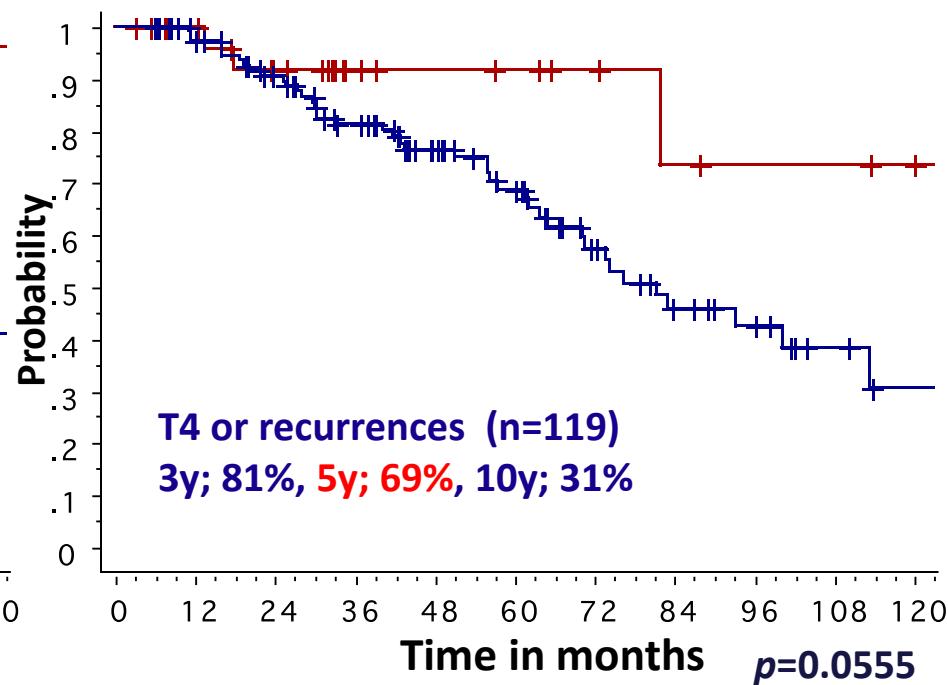
Local Control

T1 to T3 (n=32)
3-10y; 96%

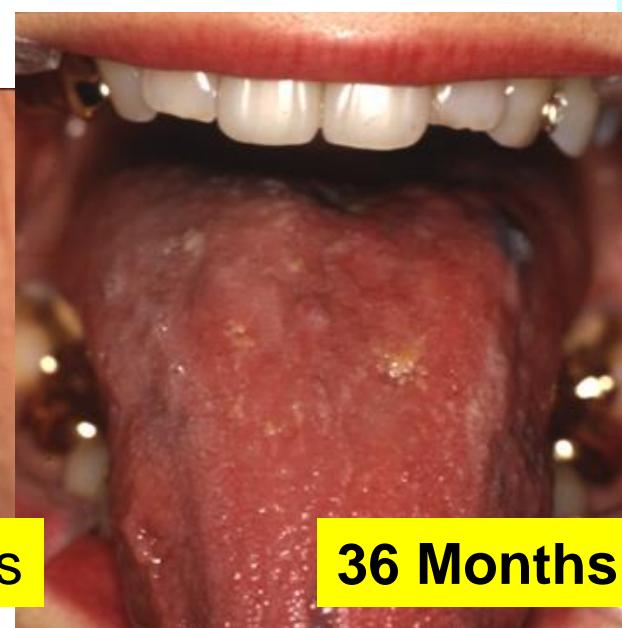
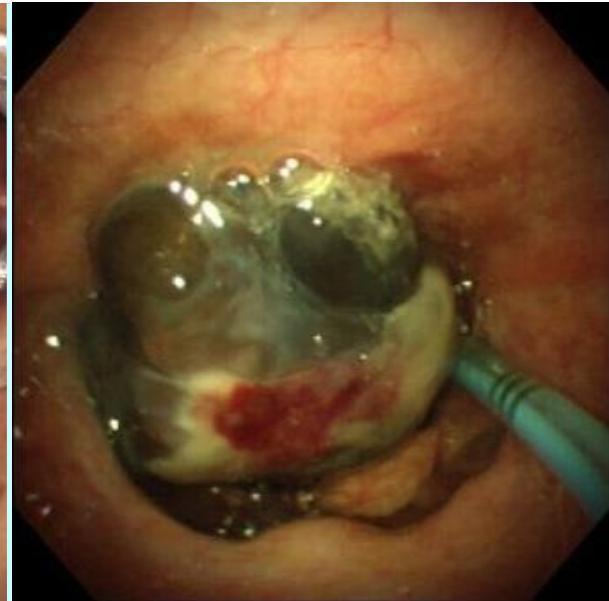


Overall Survival

T1 to T3 (n=32)
3-5y; 92%, 10y; 74%



MELANOMA at NIRS



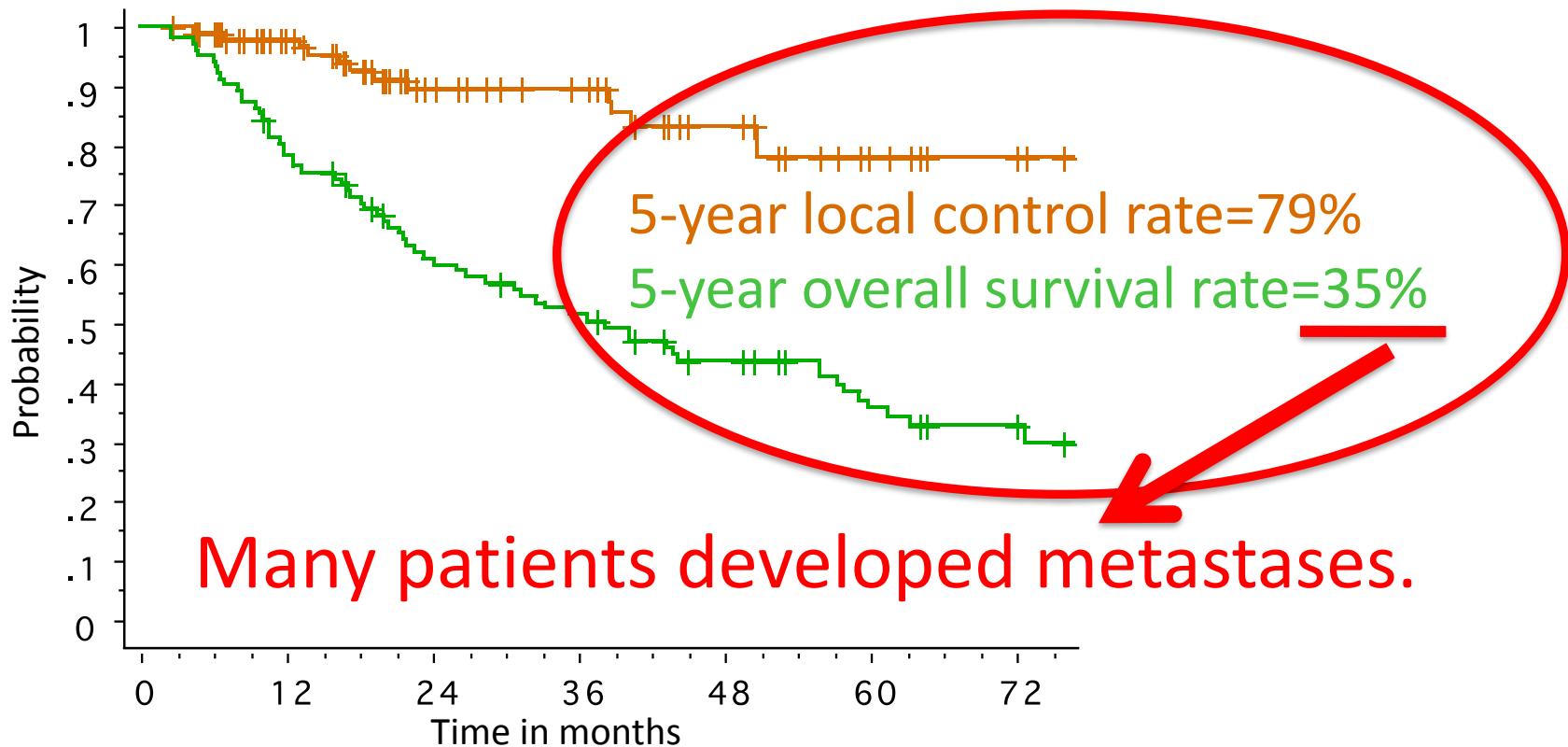
60 Months

36 Months

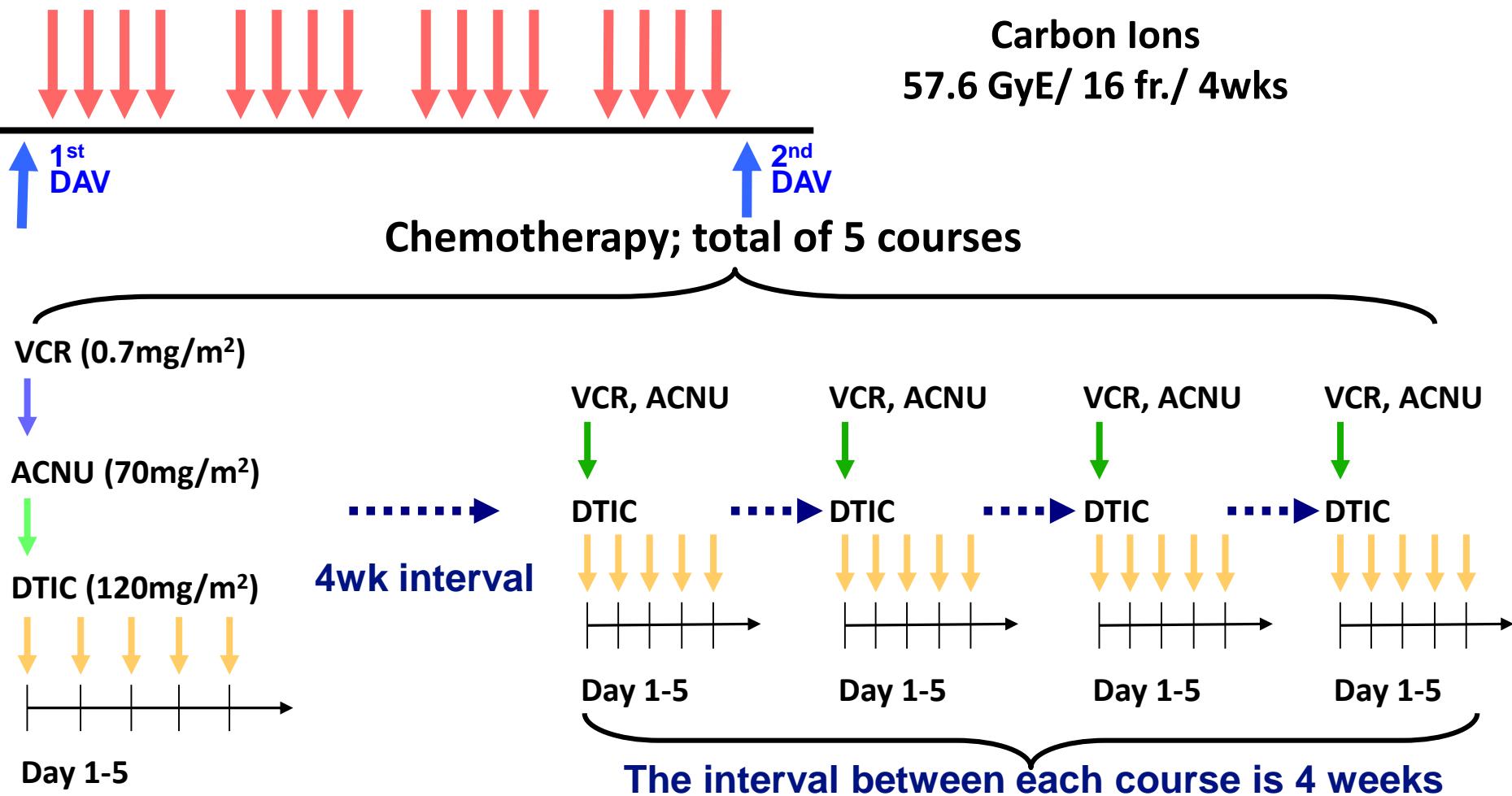
100 Months

Mucosal Malignant Melanoma(n=102)

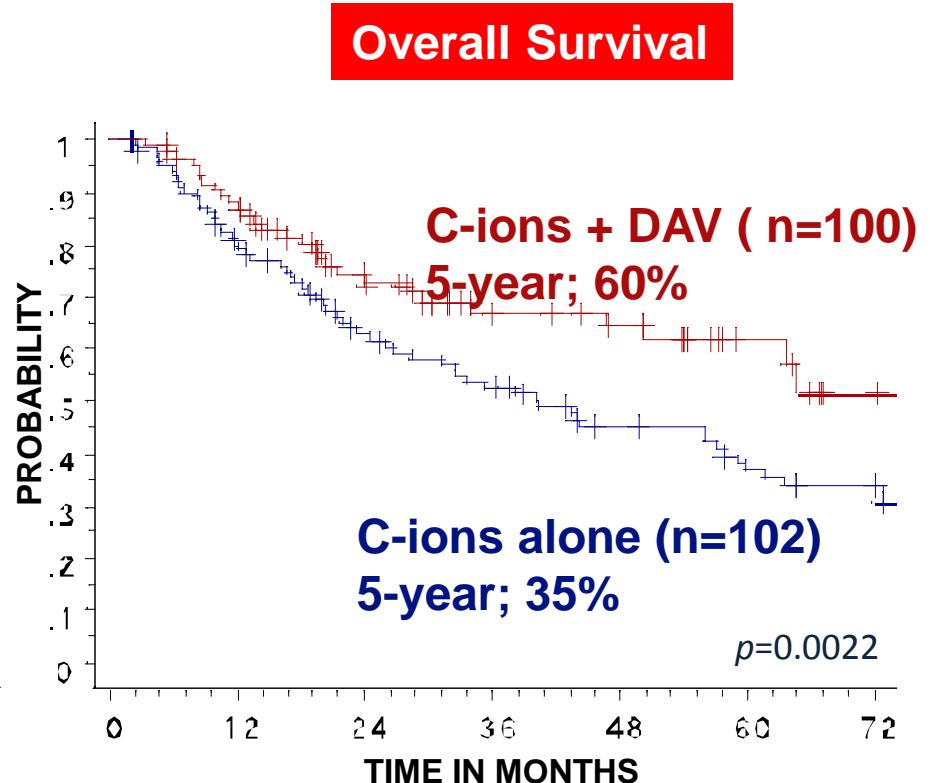
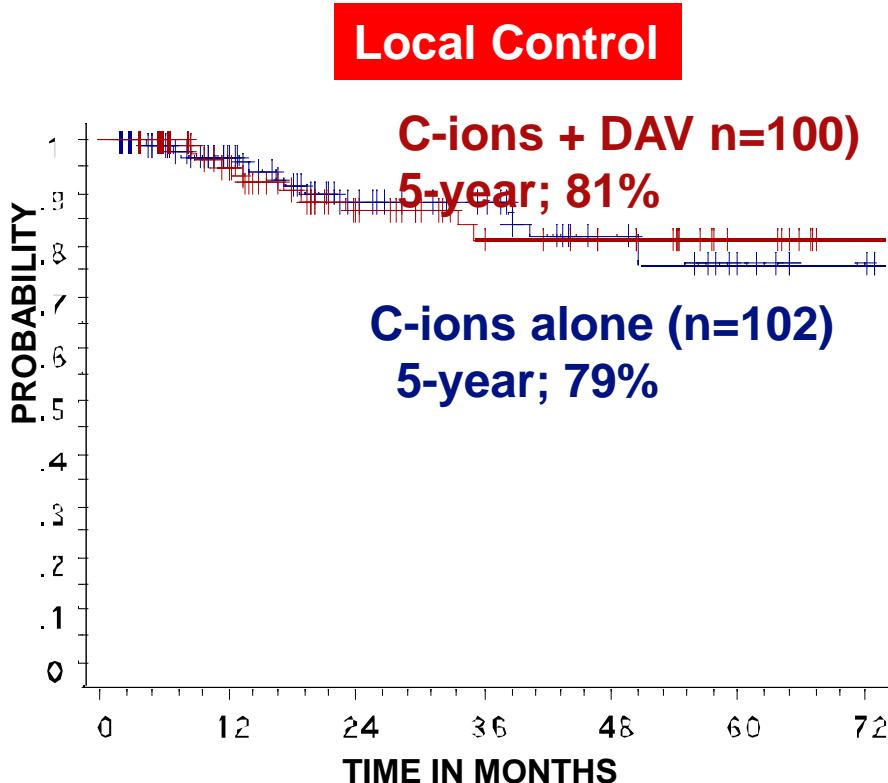
Carbon ion radiotherapy alone: 57.6 GyE/ 16 fr.



Combined Chemotherapy and C-ion RT for Mucosal Malignant Melanomas



Combined Chemotherapy and C-ion RT for MMM



Local Control and Overall Survival of Mucosal Malignant Melanomas

Morbidities in Carbon Ion Radiotherapy for Mucosal Malignant Melanomas with or without Chemo.

April 1997~February 2001: Carbon ions alone (102 cases)

April 2001~August 2011: Chemo-C-ions (107 cases)

Acute Radiation Morbidities		G0	G1	G2 (%)	G3 (%)
Skin	Carbon ions alone	10	55	28 (27)	9 (9)
	Chemo-C-ions	4	86	16 (15)	1 (1)
Mucosa	Carbon ions alone	11	46	36 (35)	9 (9)
	Chemo-C-ions	3	53	28 (26)	23 (21)

Late Radiation Morbidities		G0	G1	G2 (%)	G3 (%)
Skin	Carbon ions alone	54	43	1 (1)	0 (0)
	Chemo-C-ions	79	28	0 (0)	0 (0)
Mucosa	Carbon ions alone	64	27	3 (3)	0 (0)
	Chemo-C-ions	54	52	1 (1)	0 (0)

Clinical Experience at NIRS

Prostate

Nomiya et al. Br J Cancer. 2014;110(10):2389-95. Katoh et al. Int J Urol. 2014;21(4):370-5.
Nomiya et al. Cancer Treat Rev. 2013;39(8):872-8. Okada et al. Int J Radiat Oncol Biol Phys. 2012;84(4):968-72. Ishikawa et al. Int J Urol. 2012;19(4):296-305. Shimazaki et al. Anticancer Res. 2010 Dec;30(12):5105-11. Ishikawa et al. Radiother Oncol. 2006;81(1):57-64

More Hypofractionated Regimen

- 20fr. / 5wks** Dose-escalation study
 >>> Recommended dose; **63.0GyE**
- 16fr. / 4wks** Fixed dose; **57.6GyE**
 >>> Comparable Tumor Control
 with Lower Incidence of Toxicity
- 12fr. / 3wks** New Phase I/II Trial started in July 2010
 Fixed dose; **51.6GyE**

More Hypofractionation

Biologically Equivalent Dose

$$BED = TD \times (1 + D/\alpha/\beta)$$

Prostate Cancer

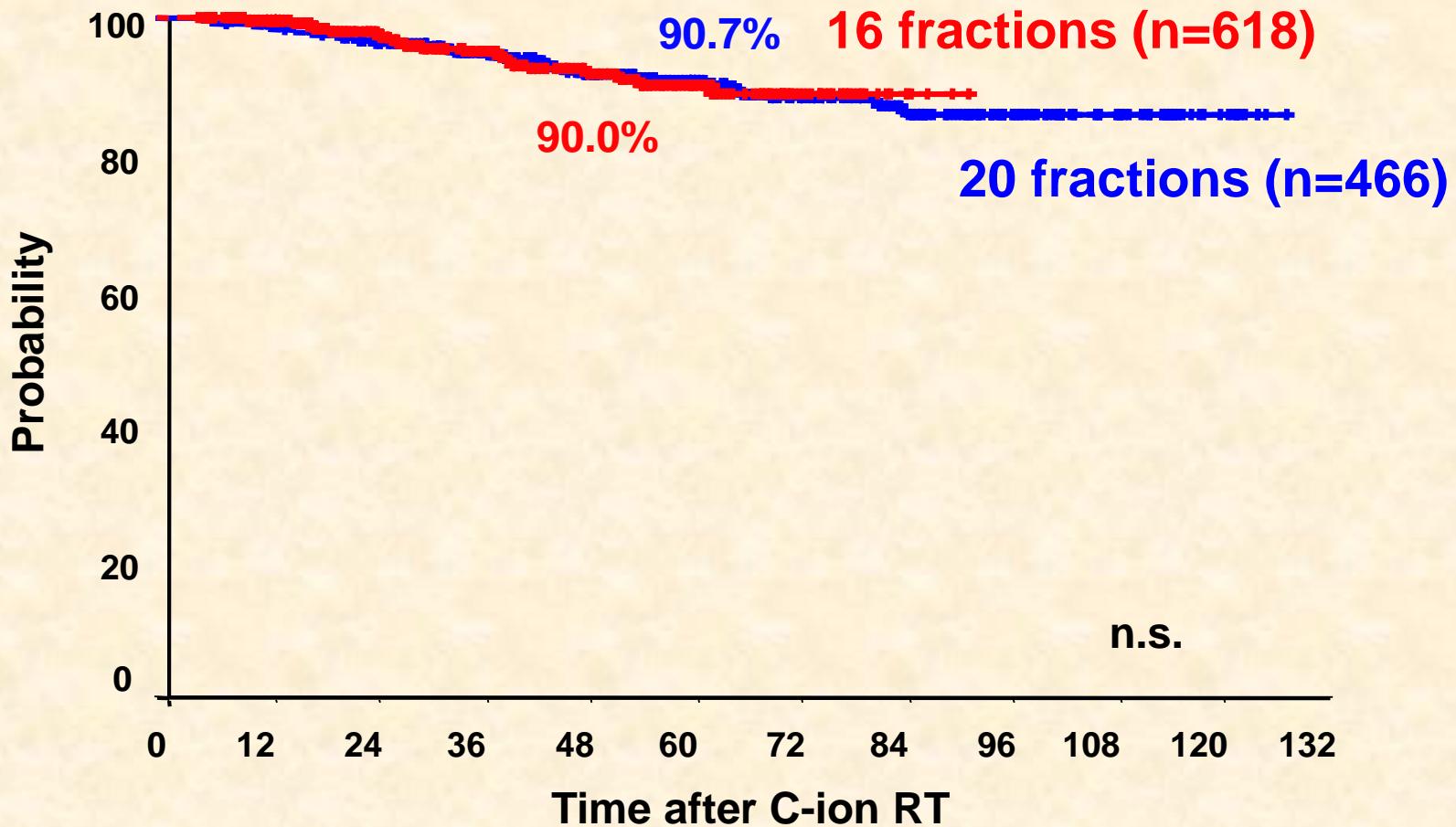
Total Dose (GyE / fr)	GyE per Fraction	α/β		
		1.5	3.0	5.0
66.0 / 20	3.30	211.2	138.6	109.5
63.0 / 20	3.15	195.3	129.1	102.7
57.6 / 16	3.60	195.8	126.7	99.1
51.6 / 12	4.30	199.5	125.5	96.0

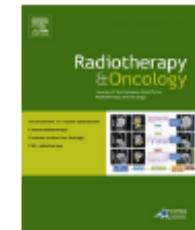
Late Toxicity (Rectum, GU)

Anti-tumor effect: $51.6/12f \geq 57.6/16f$ or $63.0/20f$

Toxicity: $51.6/12f \leq 57.6/16f$ or $63.0/20f$

Biochemical Relapse Free Rate by Fractionation





Prostate carbon ion therapy

A multi-institutional analysis of prospective studies of carbon ion radiotherapy for prostate cancer: A report from the Japan Carbon ion Radiation Oncology Study Group (J-CROS)



Takuma Nomiya ^{a,*}, Hiroshi Tsuji ^b, Hidemasa Kawamura ^c, Tatsuya Ohno ^c, Shingo Toyama ^d, Yoshiyuki Shioyama ^d, Yuko Nakayama ^a, Kenji Nemoto ^e, Hirohiko Tsujii ^b, Tadashi Kamada ^b

^aDepartment of Radiation Oncology, Kanagawa Cancer Center; ^bNational Institute of Radiological Sciences, Chiba; ^cGunma University Heavy Ion Medical Center; ^dIon Beam Therapy Center, SAGA-HIMAT Foundation; and ^eDepartment of Radiation Oncology, Yamagata University Hospital, Japan

Table 4

Toxicities by CTCAE ver 4.

		Grade			
		0-1	2	3	4
Acute (<i>n</i> = 2157)	GU*	2037 (94.4%)	119 (5.5%)	1 (0.0%)	0 (0%)
	GI*	2157 (100%)	0 (0%)	0 (0%)	0 (0%)
Late (<i>n</i> = 1929)	GU	1840 (95.5%)	88 (4.6%)	1 (0.0%)	0 (0%)
	GI	1921 (99.5%)	8 (0.4%)	0 (0%)	0 (0%)

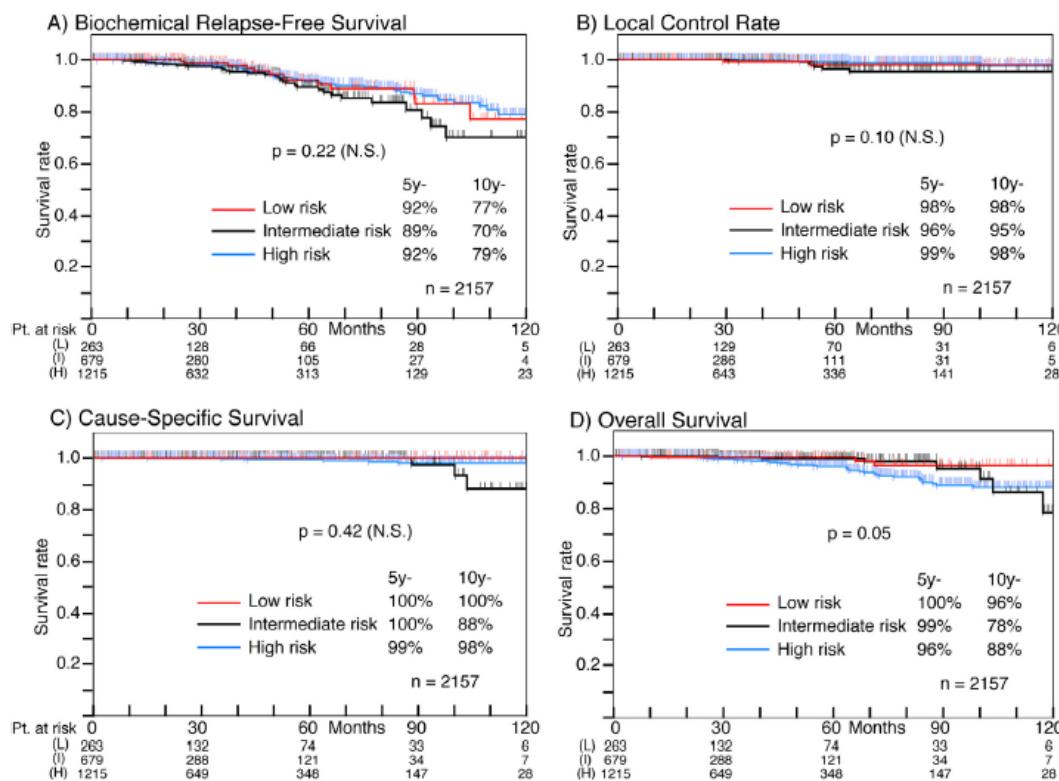


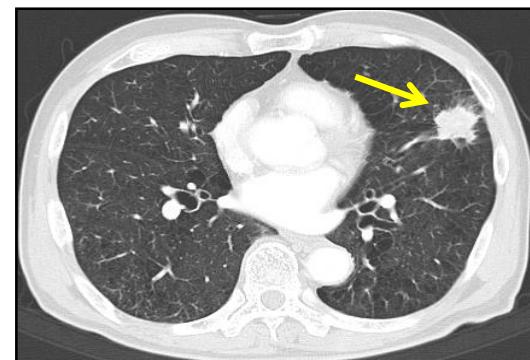
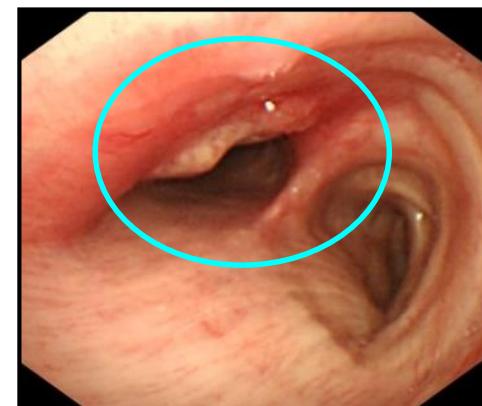
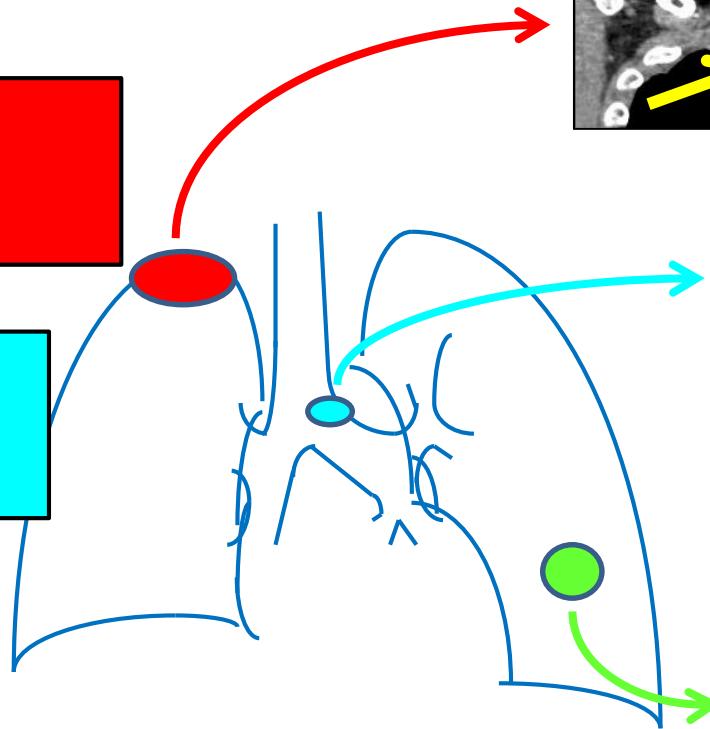
Fig. 1. Outcomes of CIRT for prostate cancer patients according to D'Amico risk group. (A) biochemical RFS. (B) local control rate. (C) cause-specific survival. (D) overall survival.

Carbon ion radiotherapy for non-small cell lung cancer

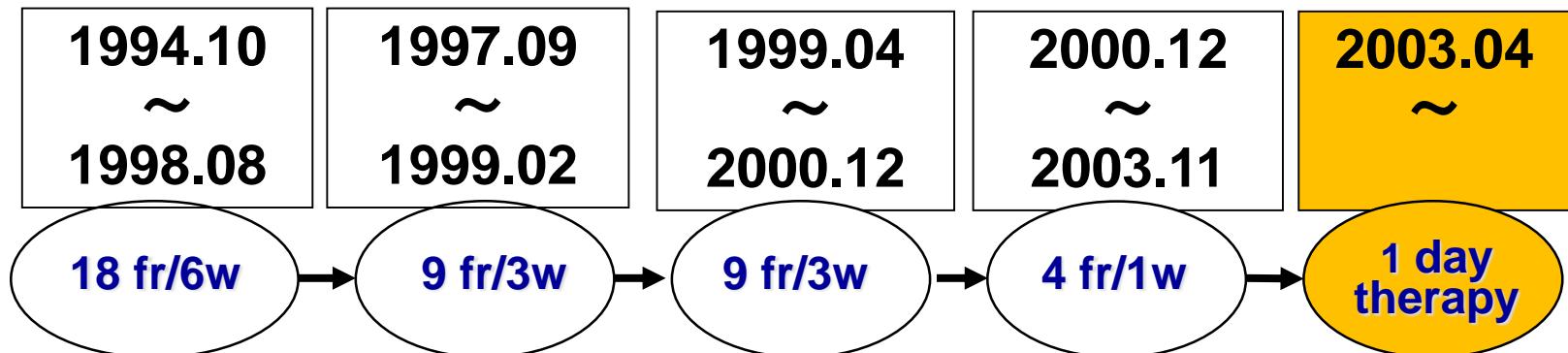
Chest wall invasion

Early cancer Central type

Peripheral Stage I



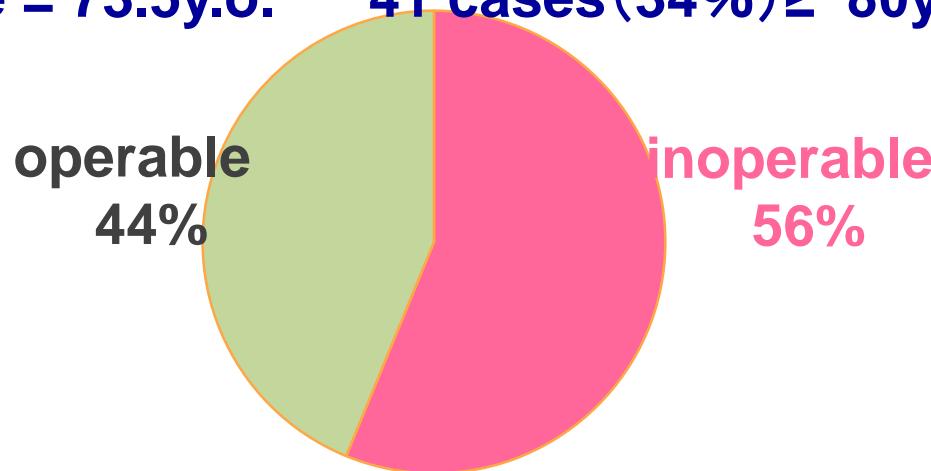
C-ion RT for Peripheral stage I NSCLC



n=198
(>36GyE:121)

Average age = 73.5y.o.

41 cases (34%) ≥ 80y.o.



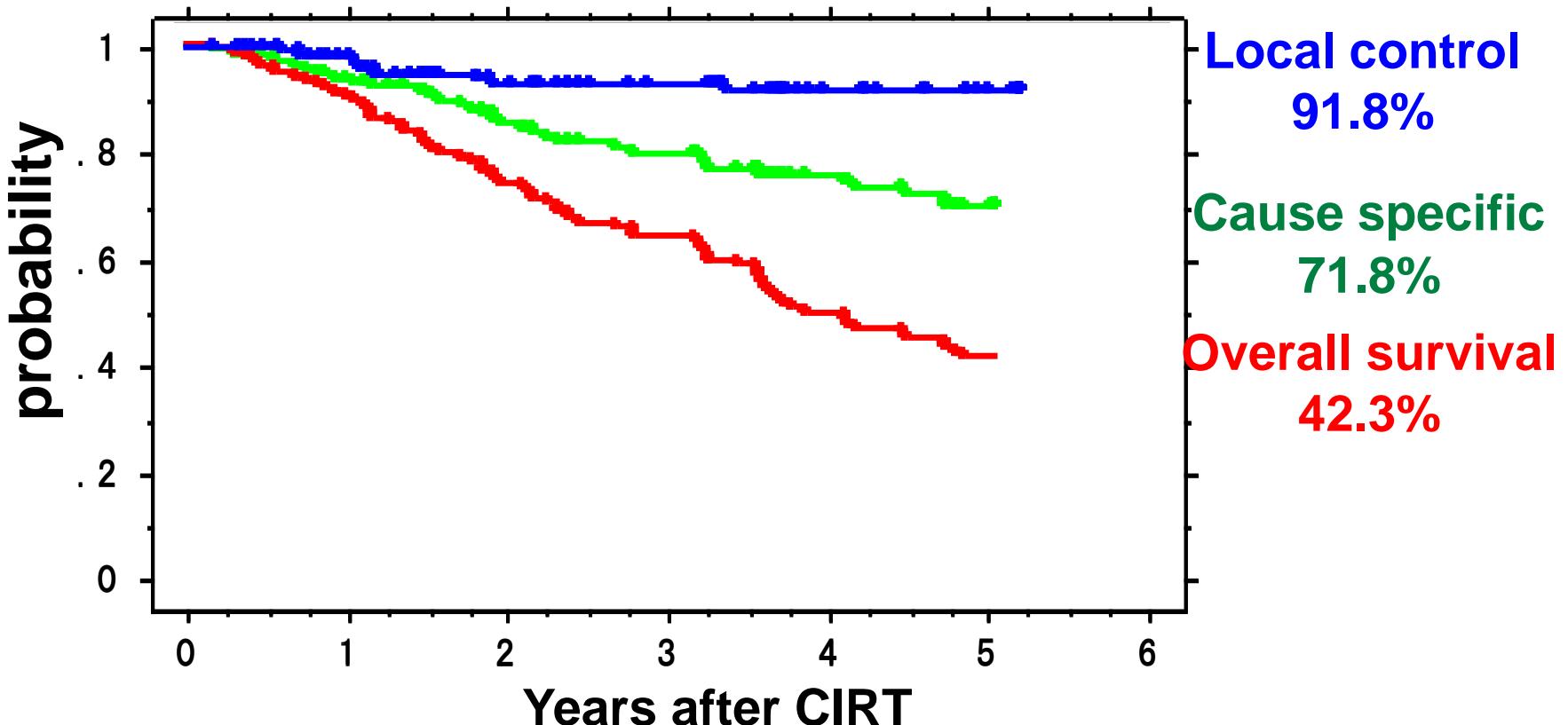
Adverse reaction in 4fr. and 9fr.

	Early(RTOG)					Late (RTOG/EORTC)						
	No.	Grade					No.	Grade				
		0	1	2	3	4≤		0	1	2	3	4≤
lung	131	129	0	2	0	0	127	0	121	6	0	0

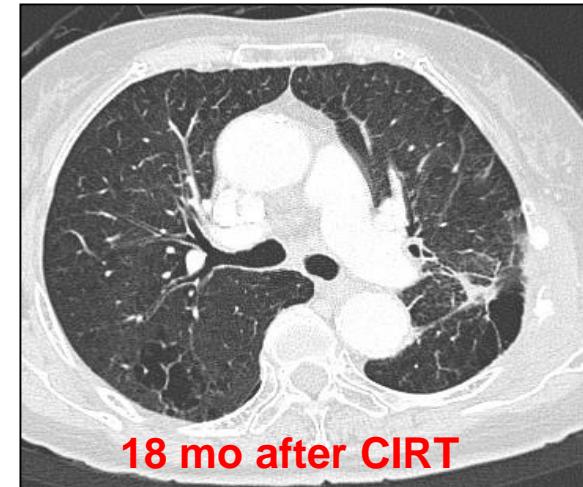
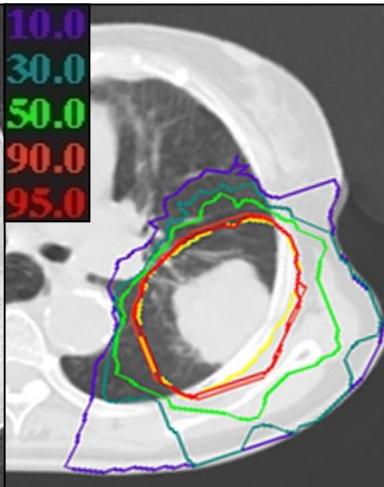
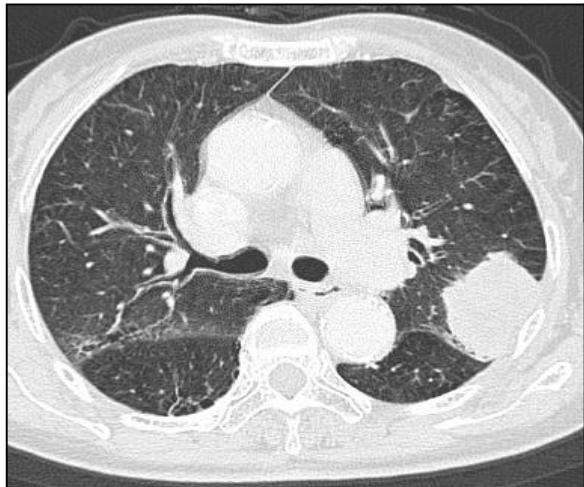
No toxic reactions greater than
grade 2 were observed.

Carbon ion radiotherapy for lung cancer in 4fr. and 9fr.

Local control and survivals for T1+T2
(n=131)



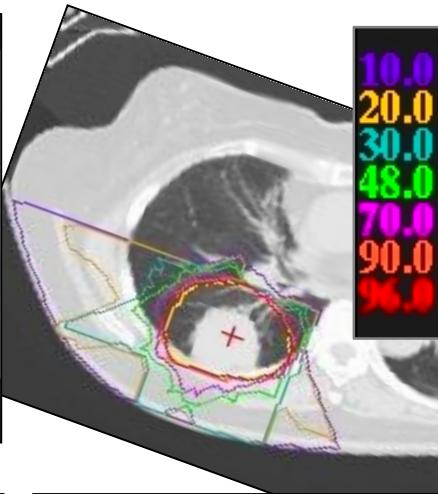
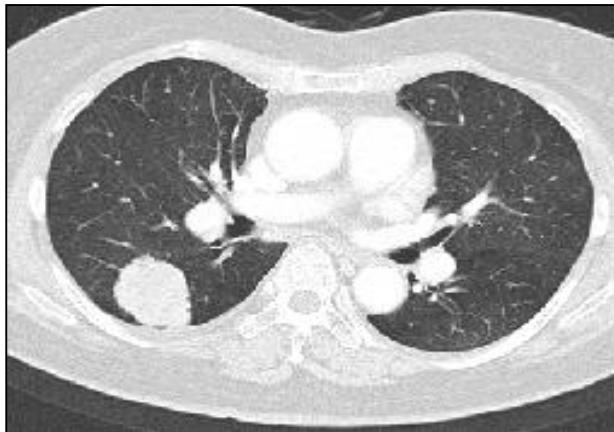
cT2N0M0 Squamous cell ca. 40.0GyE/single fraction



CIRT

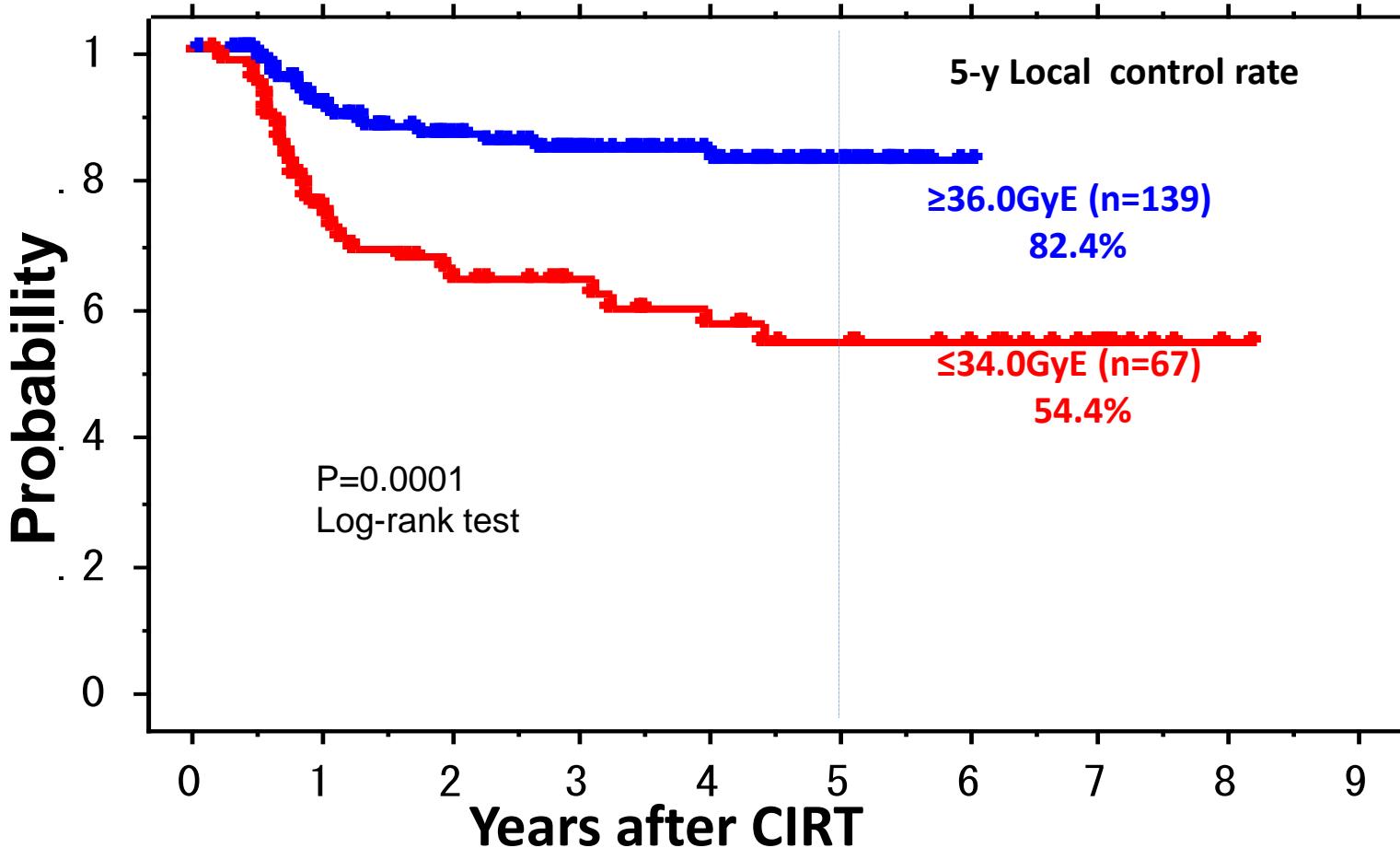
Grade 1
adverse
reaction

**cT2N0M0 Adenocarcinoma
48.0GyE/single fraction**



**Grade 1
adverse
reaction**

Local control and total dose (n=206) in $\leq 34.0\text{GyE}$ or $\geq 36.0\text{GyE}$



Liver Cancer

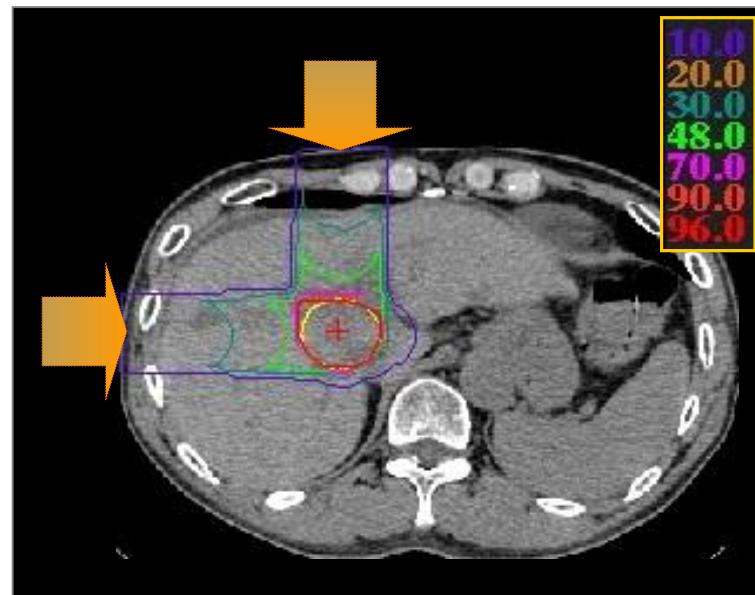
Hepatocellular cancer

Carbon Ion Radiotherapy for HCC

Apr. 1995 – Feb. 2011				Total n=274
Protocol	Category	Fractionation	Period	Number
9401	Phase I/II study	15f/5w	Apr. 1995 – Mar. 1997	24
		12f/3w		34
9603	Phase I/II study	8f/2w	Apr. 1997 – Mar. 2001	24
		4f/1w		28
0004	Phase II study	4f/1w	Apr. 2001 – Mar. 2003	47
0202	Phase I/II study	2f/2days	Apr. 2003 – Aug. 2005	36
0202(2)	Highly Advanced Medical Technology	2f/2days	Apr. 2006 –	81

Treatment data

Dose (GyE)	Number of patients
32.0 GyE/2 fr	6
33.6 GyE/2 fr	7
35.2 GyE/2 fr	5
37.0 GyE/2 fr	6
38.8 GyE/2 fr	44
40.8 GyE/2 fr	9
42.8 GyE/1 fr	11
45.0 GyE/1 fr	29



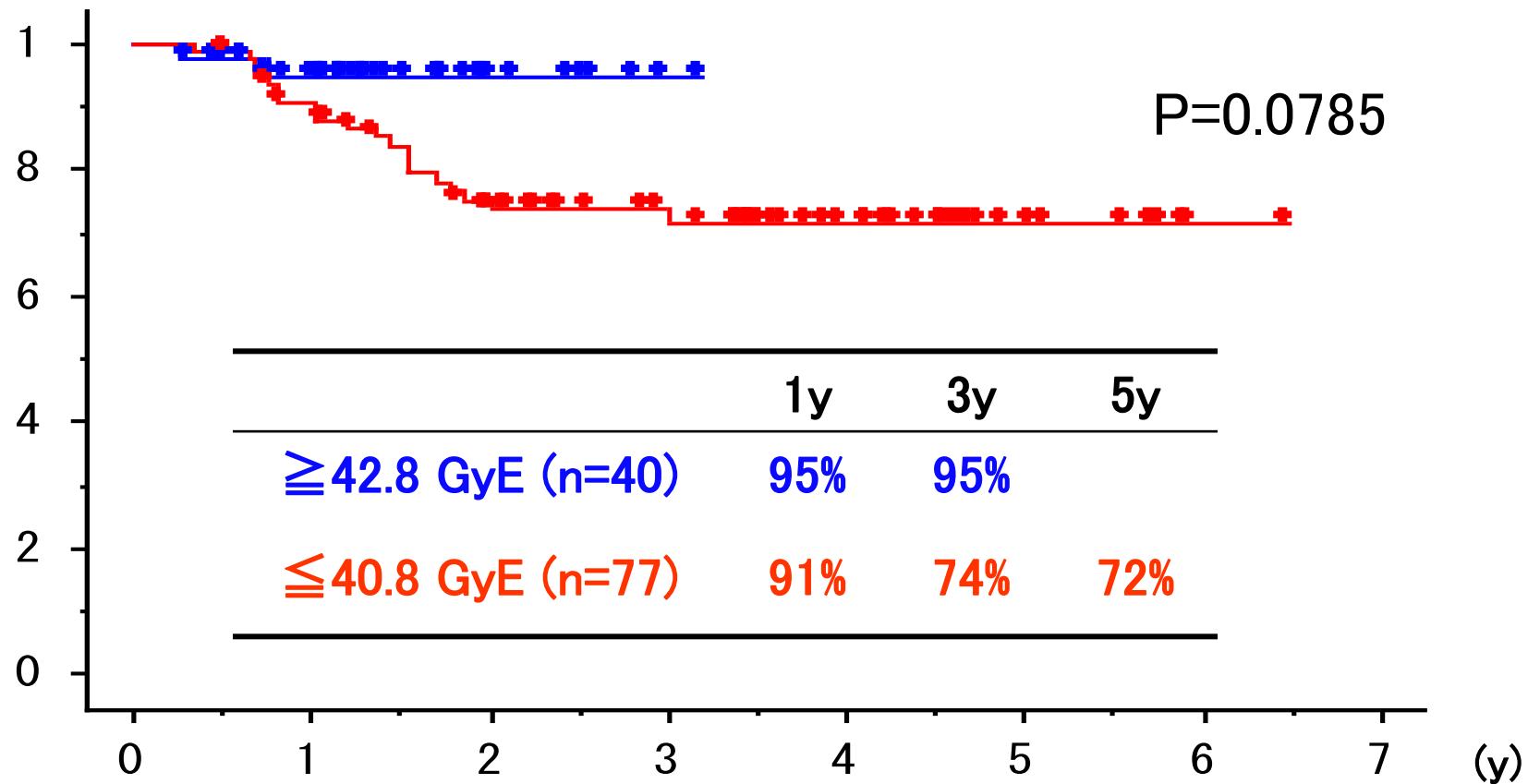
Early and Late toxicities

(Apr. 2003 – Feb. 2011)

	Early (NCI-CTC)					Late (RTOG/EORTC)					
	(n=117)	Gr0	Gr1	Gr2	Gr3	Gr4	(n=117)	Gr0	Gr1	Gr2	Gr3
Skin	1	115	1	0	0		4	113	0	0	0
Liver *	71	28	18	0	0		48	46	10	5	0
Lung	88	29	0	0	0		69	47	1	0	0

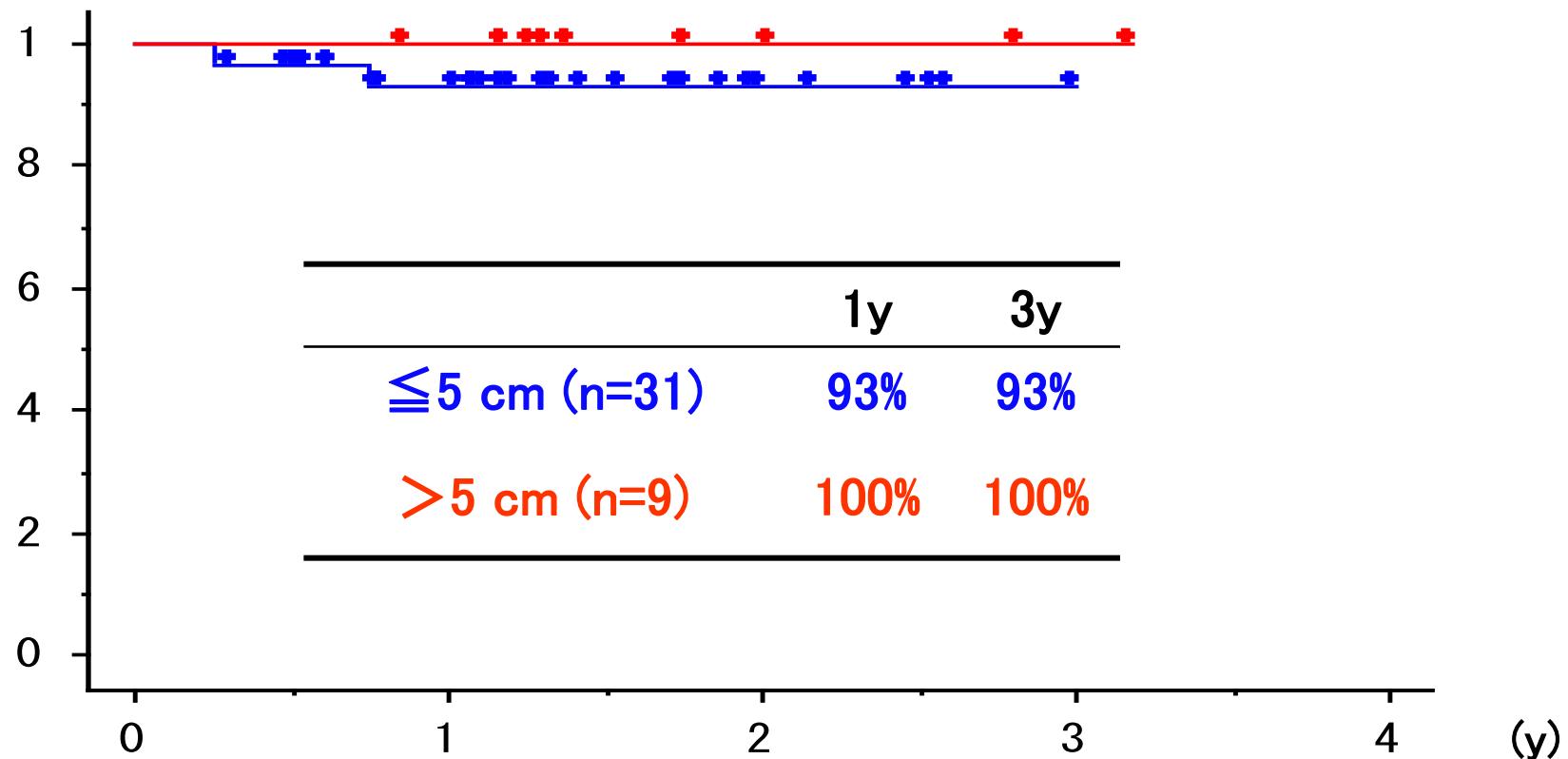
* 8 patients was excluded because they had additional treatment for hepatic lesion (local recurrence and/or recurrence in other loci) in late phase

Local control by total dose



Local control by tumor size

Patients treated with higher dose (≥ 42.8 GyE) (n=40)

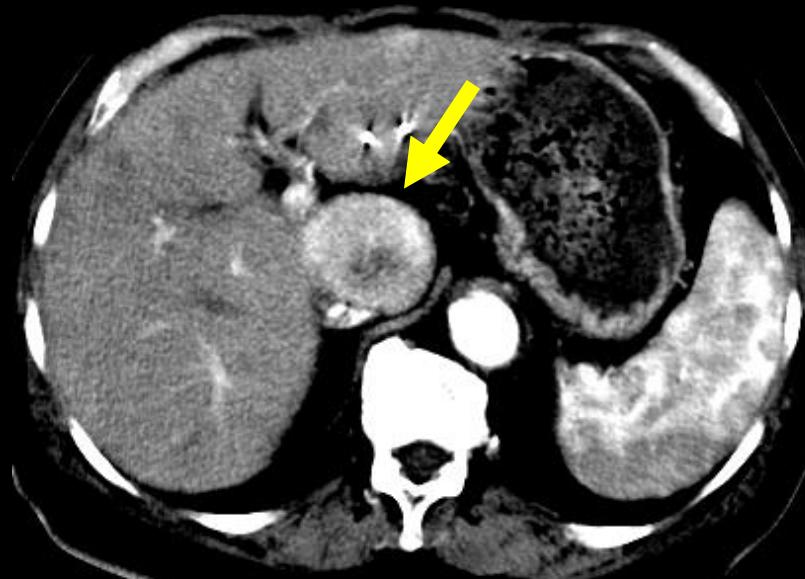


Case 1

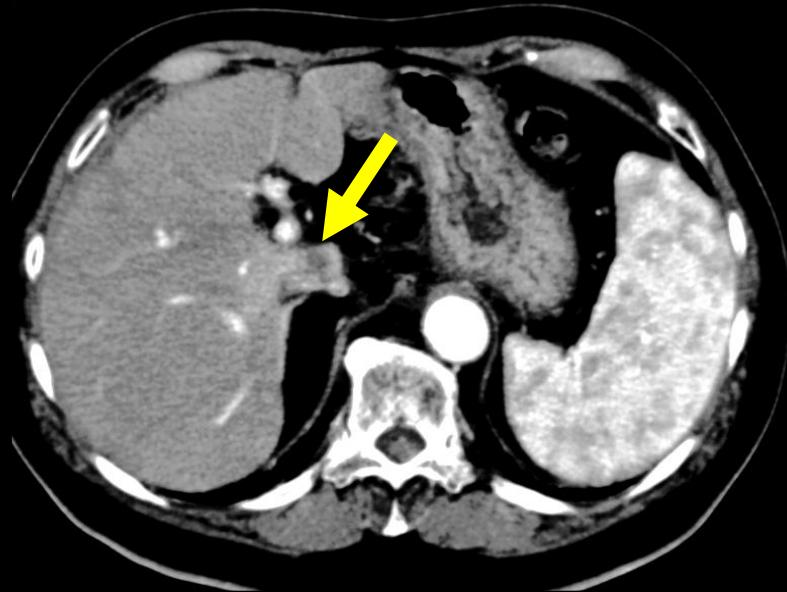
72y, male, 4.6 cm

52.8 GyE/4 fr

before



1 year after



Case 2

71y, male, 11.2 cm

52.8 GyE/4 fr

before



1 year after



Clinical Trials for Unresectable Bone and Soft Tissue Sarcomas

Phase I/II Dose Escalation Study
June 1996 – Feb 2000 n=59



J Clin oncol(20) 4466-4471.2002

Phase II Fixed Dose Study
April 2000 – Aug 2013 n=584



J Clin oncol(26)562s.2008

Palliative cases
April 2005-Aug 2013 n=336



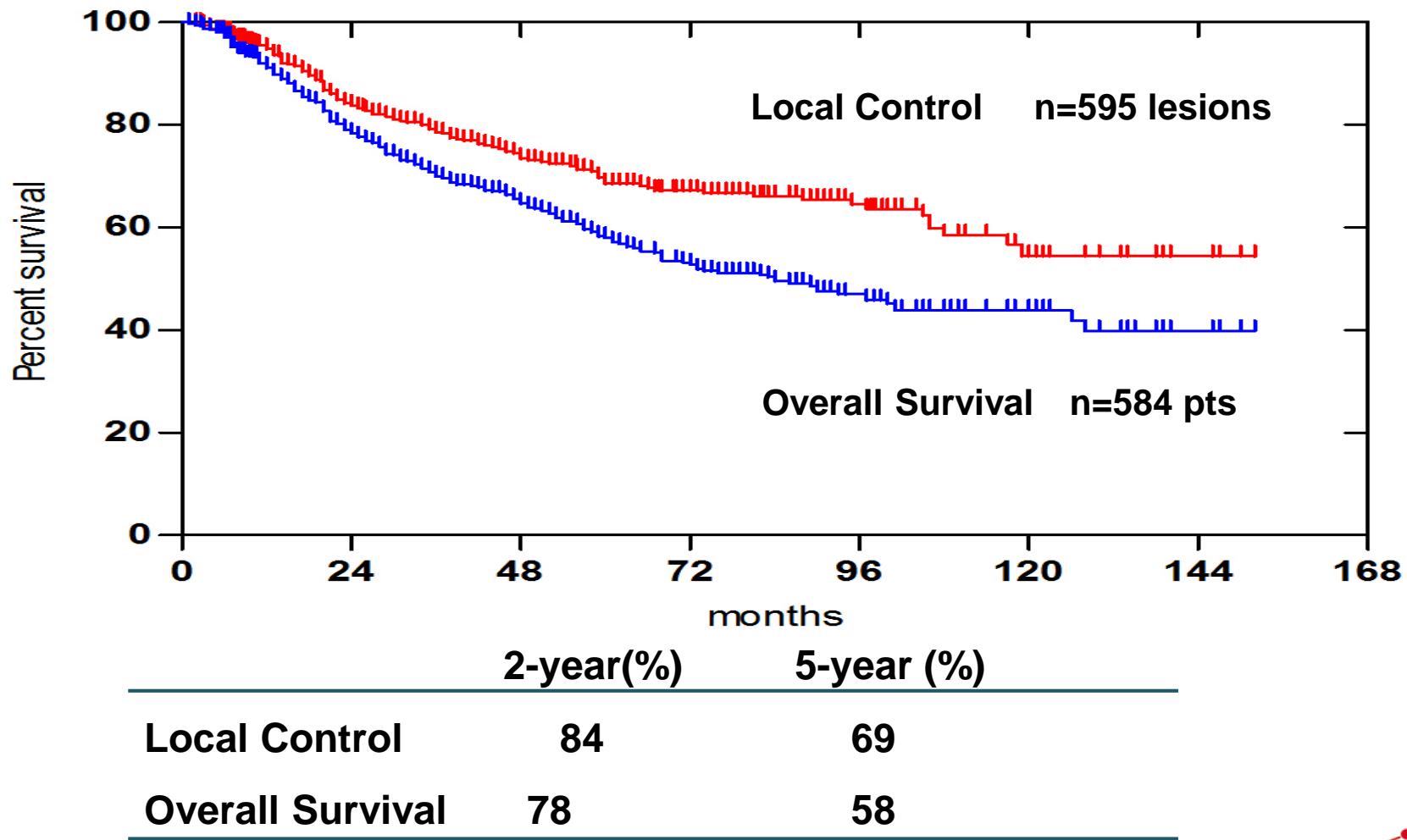
Short course regimen of 1,2, and 3 weeks

- Efficacy depended on total irradiated dose.(52.8GyE-73.6GyE/16Fr)
- G3 acute skin reactions were observed with the total dose of 73.6GyE/16Fr

- 70.4GyE/16Fr was basic workable dose.
- Better beam delivery to avoid severe skin reaction

Bone and Soft Tissue Sarcomas

Result of CIRT: Phase II Study n=584 patients



Bone and Soft Tissue Sarcomas

Late Morbidities after CIRT: Phase II Study

	Number	Grade					
		0	1	2	3	4	5
Skin/soft tissue	596	6	542	39	7	2	0
GI tract	494	488	2	0	0	3	0
Spinal cord	54	49	1	2	2	0	0
Edema	24	17	5	2	0	0	0

Impairment ADL (peripheral nerve dysfunction) : 27

Femoral neck fracture : 4 (all ilioacetabular sarcoma)

Late Soft Tissue/Skin Reaction in B & STSs

	No of Pts	Gr3-4 (%)
2000~2001	25	7 (28)
2002~2005 (Modified group)	151	2

Risk factor

Total Dose : 73.6
Two direction
Skin margin



Modifications

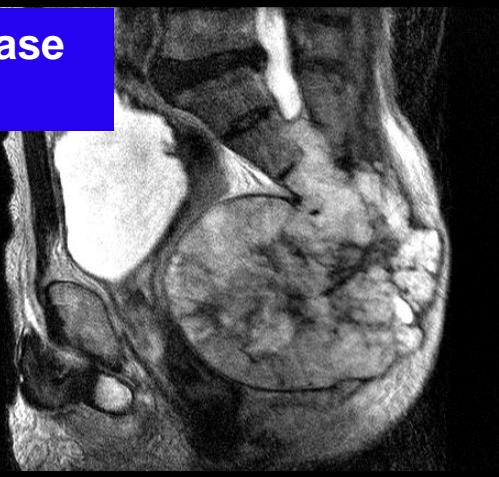
70.4 or less
Three direction or more
Reduced skin margin

Chordoma (of the sacrum)

Case
1



Case
2



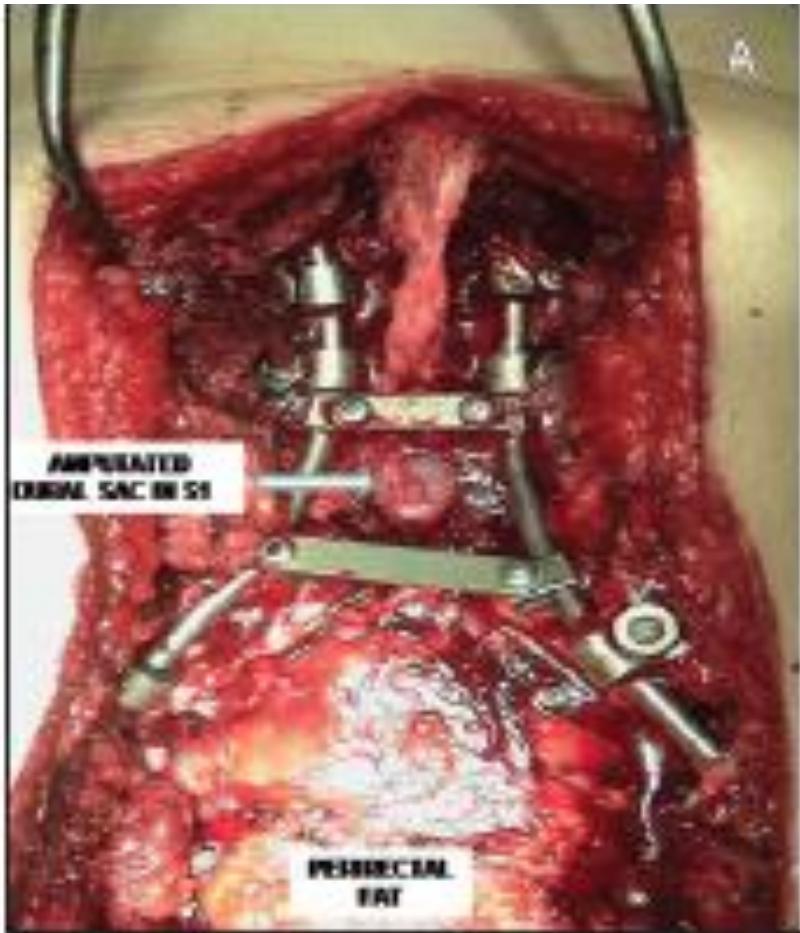
Case
3



- 3% of all primary bone sarcoma (50% from sacrum bone)
- Radio-chemo-resistant, and surgery is treatment of choice
- However, surgery is extremely difficult in many cases
- Slow growing, sometimes presenting huge tumor size

Imai R, Kamada T, Tsuji H, et al. Carbon Ion Radiotherapy for Unresectable Sacral Chordomas. Clinical Cancer Research. 2004;10:5741-5746.

TOTAL SACRECTOMY FOR SACRAL TUMOUR



The mean total operating time was 13.3 hrs (range: 8 – 20.1hrs); the mean total blood loss 14.1 ltrs (range: 4.2 – 33 ltrs). The mean length of hospital stay was 8.9mths (range: 2 – 36mths) in 9 cases received total en-bloc sacrectomy. (Molloy,2006)

Chordoma of the sacrum

Case
1



↓ 6 years

Case
2



↓ 5 years

Case
3



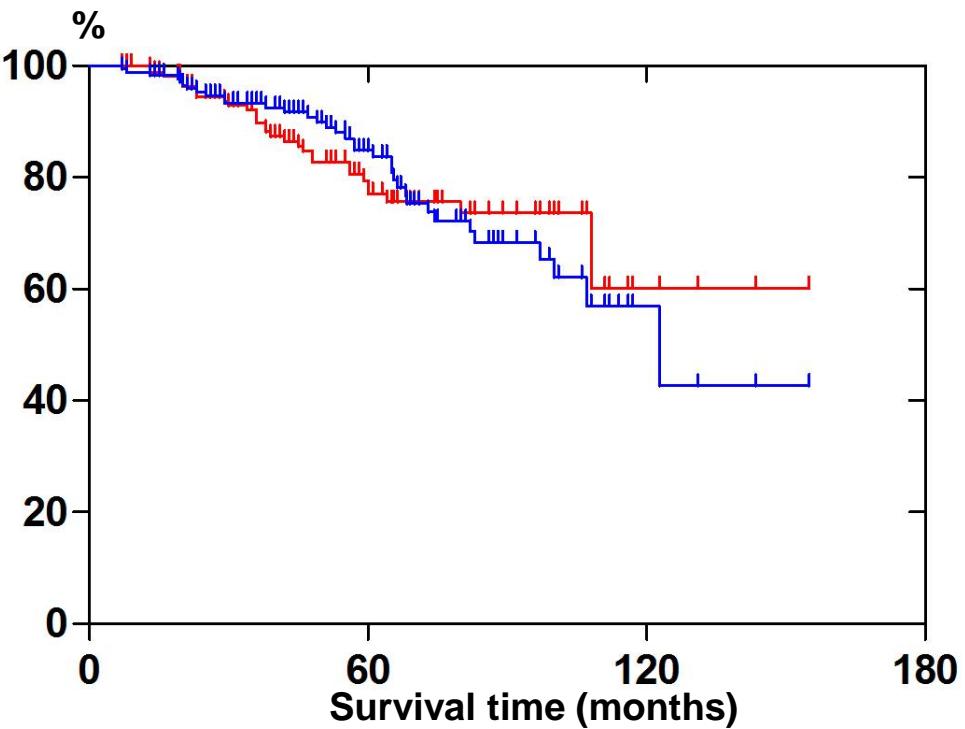
↓ 6 years



Chordoma of the Mobile Spine and Sacrum

1996.6-2011.2

n=183 pts (phase I/II and II study)



Median Follow-up : 68 months (7-155)

Median Age : 66 yo (26-87)

Median CTV : 330 cm³

(Sacral chordoma : Median 636 cm³)

Prescribed dose 64~73.4GyE/16Fx

Mobile spine :64GyE

Sacrum :67.2GyE

Patients remain ambulatory : 97%

Sciatic nerve dysfunction: 15pts

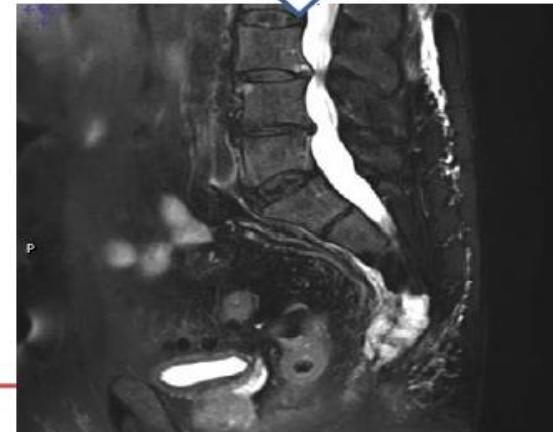
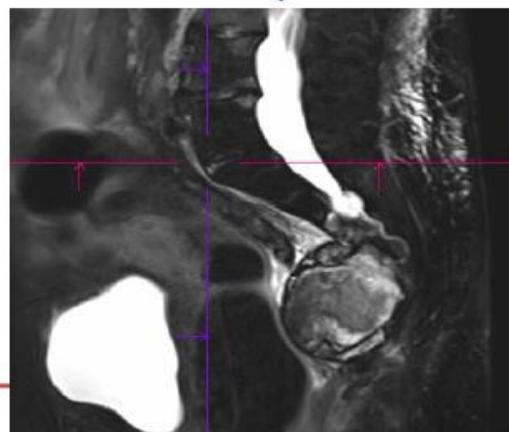
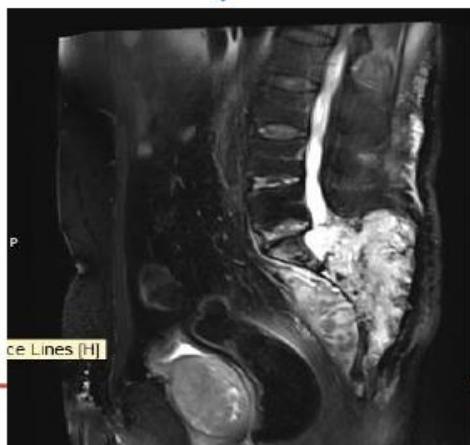
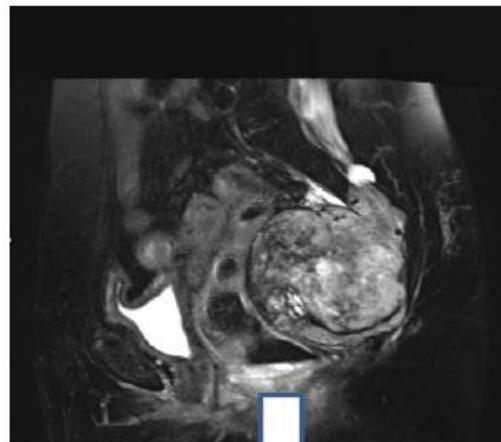
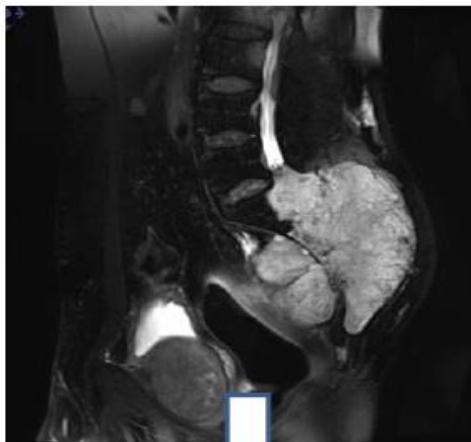
5-year(%)

Local Control

77

Overall Survival 85

CNAO experience after 1 year



Osteosarcoma of the Trunk

Matsunobu A, Imai R, Kamada T, et al.

Impact of Carbon Ion Radiotherapy for Unresectable Osteosarcoma of the Trunk.

Cancer 2012;118:4555-4563.

Case 1.



Case 2.



Case 3.



At 13 years

At 9 years

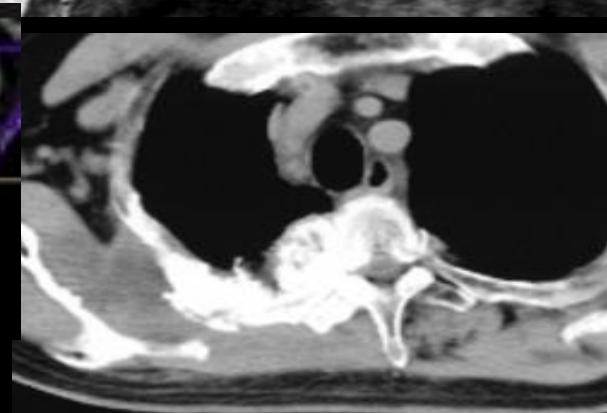
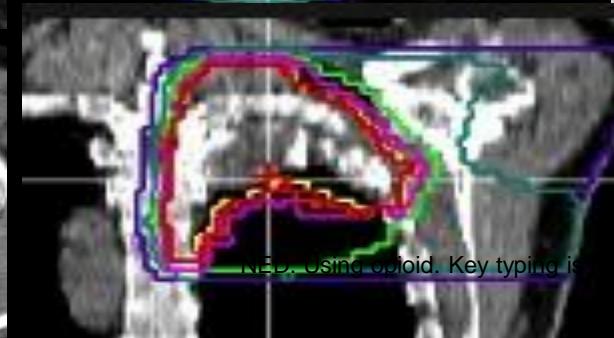
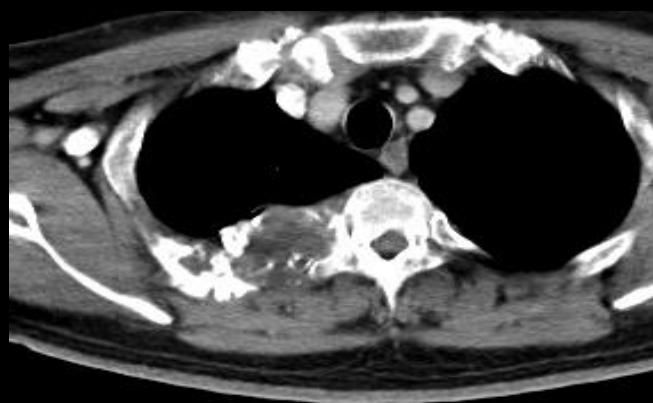
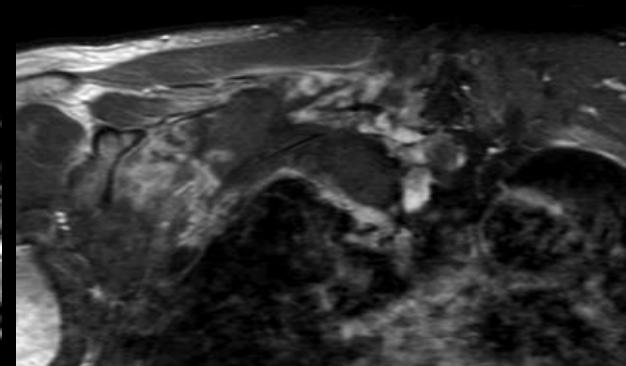
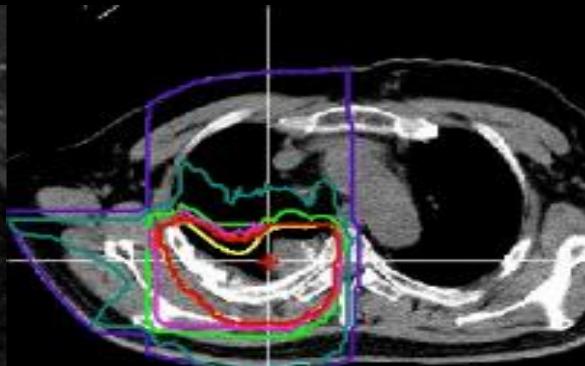
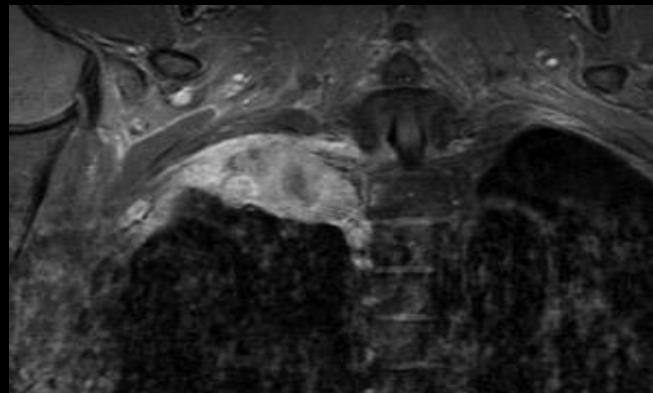
At 7 years

51M osteosarcoma of rt. rib

Before CIRT

70.4GyE/16Fr

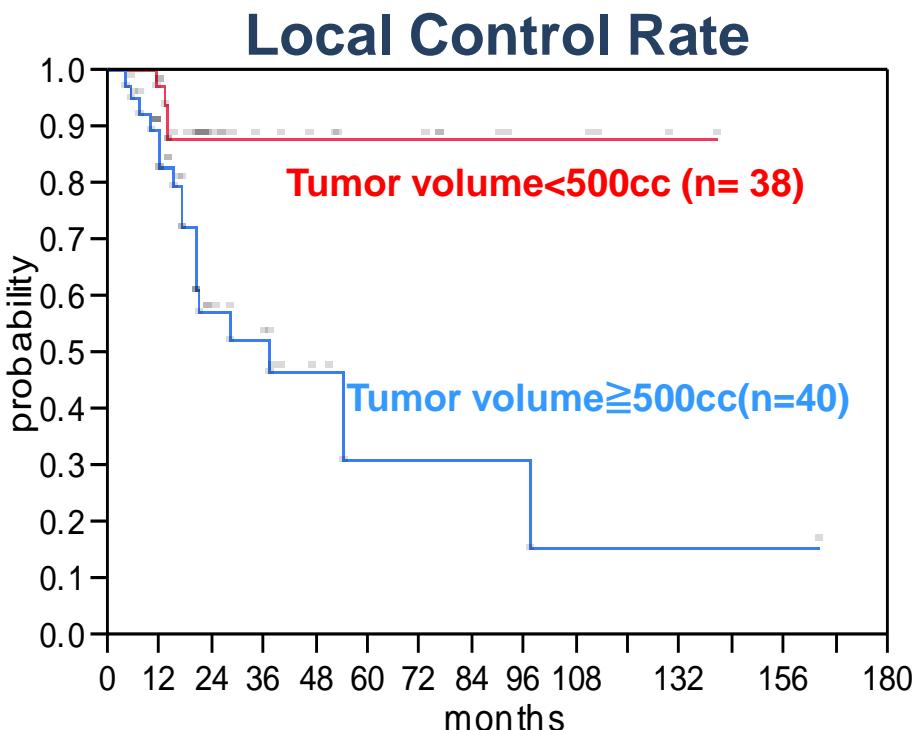
8 years after NED



Continue his job(management of construction company)

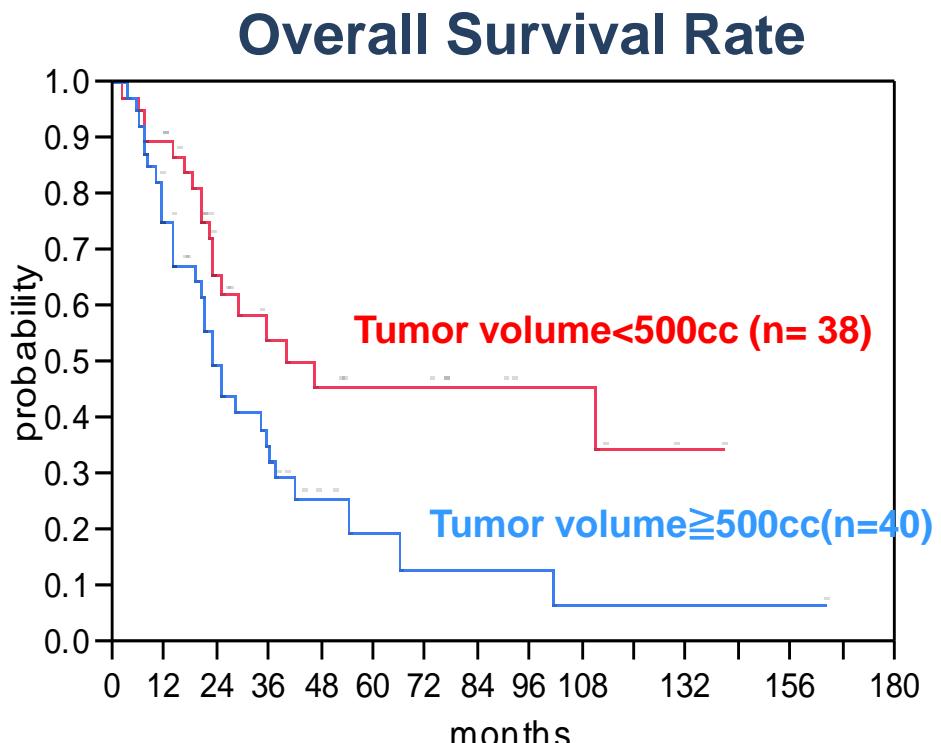
Osteosarcoma of the Trunk Result By Tumor Volume

A smaller tumor volume provides a better result.



	2y	5y
<500cc	87%	87%
≥ 500cc	57%	31%

Logrank p=0.0006



	2y	5y
< 500cc	65%	46%
≥ 500cc	19%	50%

Logrank p=0.015

Treatment of Locally Recurrent Rectal Carcinoma in Previously (Chemo)Irradiated Patients: A Review

Wout van der Meij, M.D.¹ • Anouk J. M. Rombouts, M.B.B.S.¹ • Heidi Rütten, M.D., Ph.D.²
 Andre J. A. Bremers, M.D., Ph.D.¹ • Johannes H. W. de Wilt, M.D., Ph.D.¹

¹ Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
² Department of Radiotherapy, Radboud University Medical Center, Nijmegen, The Netherlands

TABLE 3. Recurrent rectal carcinoma: outcome

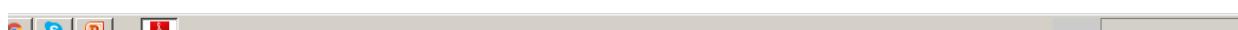
Reference	No. of patients ^a	Surgery, n (%)	R0/R1/R2, n (%)	Complications		Survival			
				EBRT toxicity, n (%)	Perioperative, n (%)	LC (%)	MFS (%)	DFS (%)	OS (%)
Alberda et al ²⁰	28	28 (100)	R0: 13 (46) R1: 12 (43) R2: 3 (11)	—	Mortality (1 mo): 2 (7) Morbidity: Surgical: 16 (57.0) Nonsurgical: 11 (39.0)	5 y 48.0%	5 y 66.0%	5 y 40.0%	3 y 56.0% 5 y 43.0%
Asoglu et al ¹⁷	36	36 (100)	R0: 24 (66.7) R1: 12 (33.3)	—	Mortality: 0 (0)				R0: 28 mo R1: 12 mo
Bosman et al ¹¹	135	135 (100)	R0: 75 (55.6) R1: 52 (38.5) R2: 8 (5.9)	Grade 3–4: 9 (7.0)	Mortality: 6 (4.4) Morbidity: Grade 3: 39 (28.8) Grade 4: 7 (5.2) Grade 5: 6 (4.4)	3 y 19.3% R0: 49.6% ^b R1: 14.4% ^b R2: 7.7% ^b	5 y 51.1% ^b	5 y 48.9% ^b	5 y 33.0% ^b
Dresen et al ¹⁵	78	78 (100)		—	—	3 y R1: 48.9%	3 y R1: 58.7%	—	3 y R1: 47.6%
Hesselmann et al ¹⁶	9	9 (100)	—	—	Mortality: 0 (0) Morbidity: 3 (33.0)	Median 33 mo	Median 33 mo	Median 33 mo	Median 33 mo
Kim et al ¹⁸	12	12 (100)	R0: 0 (0) R1: 9 (75) R2: 3 (25)	Acute: Grade 3: 0 (0) Grade 4: 0 (0) Late: Grade 3: 2 (16.7) Grade 4: 0 (0)	Mortality: 0 (0) Morbidity: 2 (16.7)	66% 3 y 54.6%	44% —	33% 3 y 31.3%	56% 3 y 50.9%
Park et al ¹⁹	23	23 (100)	R0: 23 (100)	—	Mortality: 0 (0)	—	—	—	5 y 35.1%
Rombouts et al ²¹	41	41 (100)	R0: 26 (63) R1/R2: 15 (36)	—	Mortality: 0 (0) Morbidity: 33 (80.5)	2 y 29.5%	2 y 43.3%	2 y 13.1%	2 y 72.0%
Valentini et al ¹³	59	39 (66)	R0: 21 (36) R1: 3 (5) R2: 15 (25) No Sx: 20 (34)	Acute: Grade 3: 3 (5.0) Grade 4: 0 (0) Late: Grade 3: 3 (5.0) Grade 4: 0 (0)	Mortality: 1 (2.6) Morbidity: 5 (12.8)	2 y R0: 69.0% R1–2/No Sx: 35.6%	2 y NS	2 y R0: 50.4%	2 y R0: 83.5%
						5 y 38.8%	5 y 42.0%	5 y 29.2%	5 y 39.3%

DFS = disease-free survival; EBRT = external beam radiotherapy; LC = local control; MFS = metastasis-free survival; NS = not significant; OS = overall survival; PRC = primary rectal carcinoma; R0 = no residual disease; R1 = microscopic residual disease; R2 = macroscopic residual disease; RI = reirradiation; RTx = radiotherapy; Sx = surgery.

^aData include patients with radiation therapy in PRC.

^bData include percentage for entire group (with/without RTx in PRC).

^cData include 24 patients, including 3 patients without EBRT in PRC.





Systematic Review

Reirradiation of locally recurrent rectal cancer: A systematic review

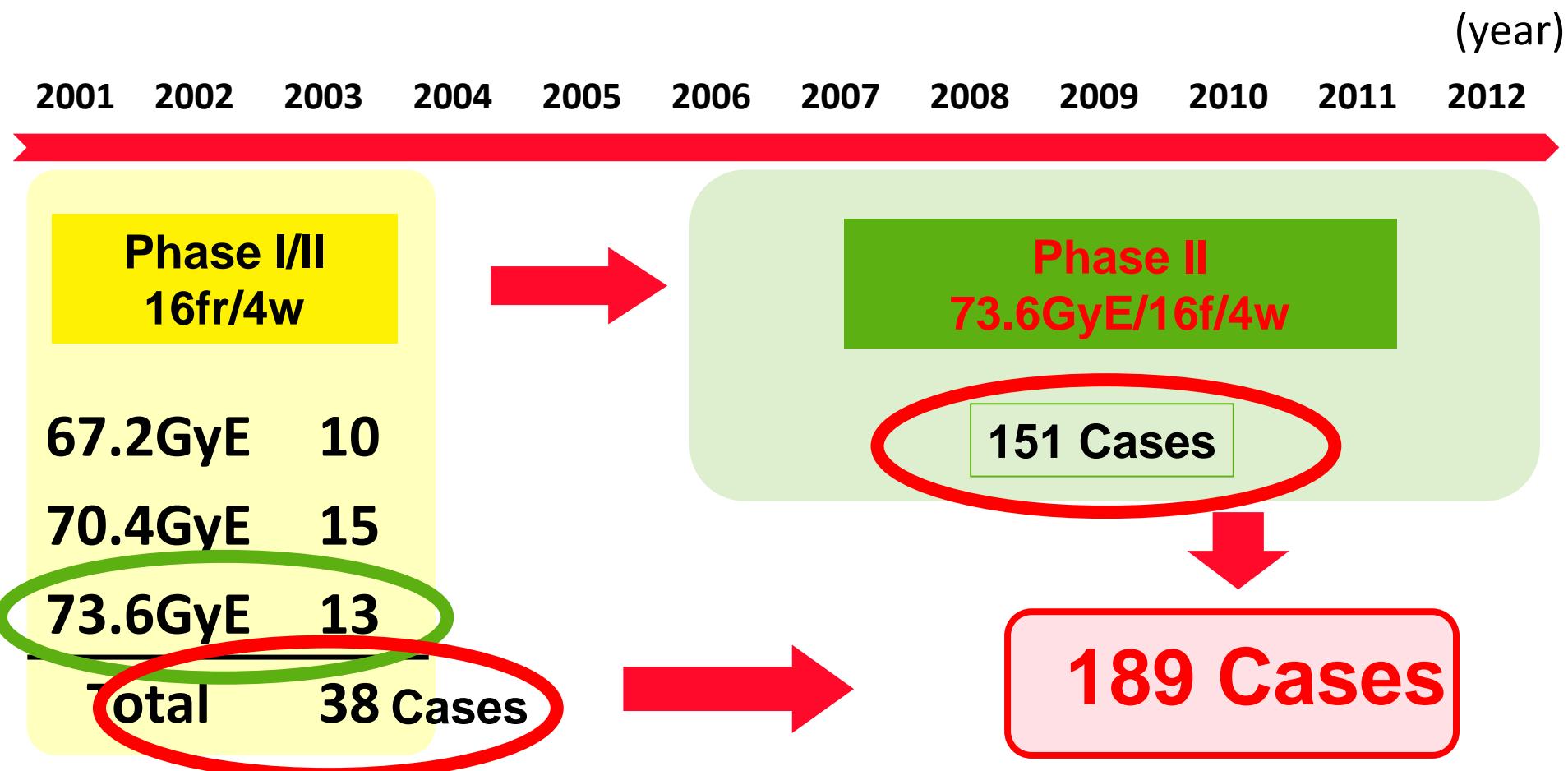


Marianne Grønlie Guren ^{a,b,*}, Christine Undseth ^a, Bernt Louni Rekstad ^c, Morten Brændengen ^a, Svein Dueland ^a, Karen-Lise Garm Spindler ^d, Rob Glynne-Jones ^e, Kjell Magne Tveit ^{a,b,f}

^aDepartment of Oncology; ^bK.G.Jebsen Colorectal Cancer Research Centre; ^cDepartment of Medical Physics, Oslo University Hospital, Norway; ^dDepartment of Oncology, Aarhus University Hospital, Denmark; ^eCentre for Cancer Treatment, Mount Vernon Hospital, Northwood, UK; ^fUniversity of Oslo, Norway

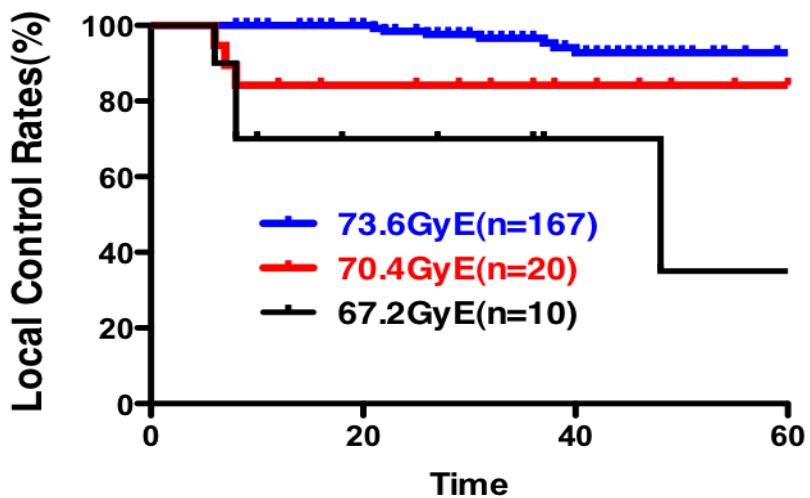
reported. **Conclusions:** Reirradiation of rectal cancer to limited volumes is feasible. When curative resection is possible, the goal is radical resection and long-term survival, and hyperfractionated chemoradiotherapy should be preferred to limit late toxicity. Reirradiation yielded good symptomatic relief in palliative treatment.

Carbon ion therapy Clinical Trials for p/o Local Recurrence of Rectal Cancer

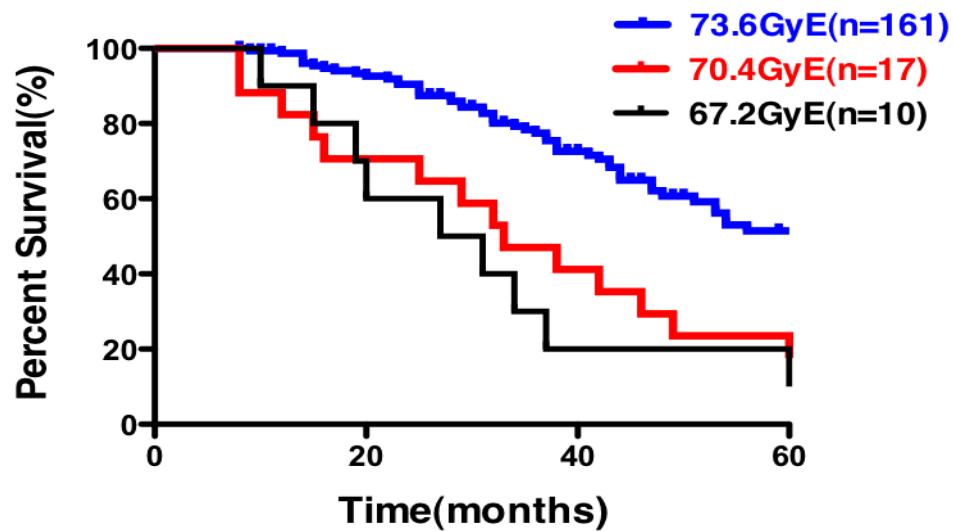


Local Control Rates and Survival Rates

Local Control Rates



Survival Rates



Local Control	3y	5y
67.2GyE	70.0%	35.0%
70.4GyE	84.2%	84.2%
73.6GyE	96.6%	92.8%

Survival Rates	3y	5y
67.2GyE	30.0%	20.0%
70.4GyE	47.0%	23.5%
73.6GyE	78.4%	51.4%

Acute and Late toxicities in LRRC

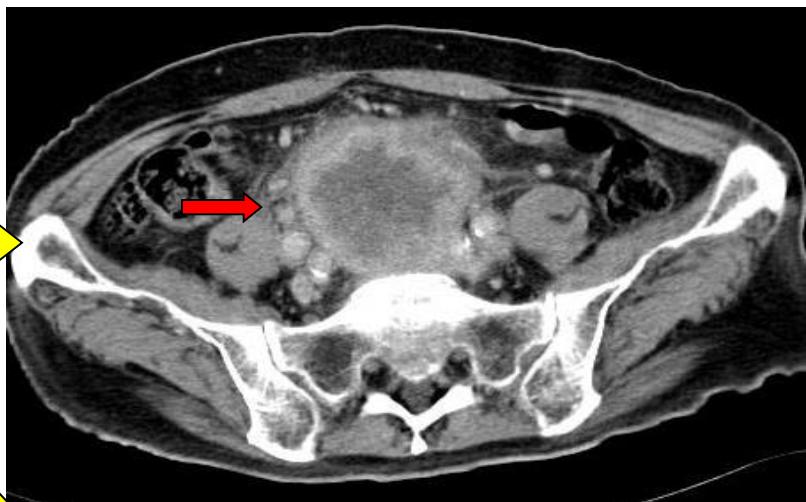
(202 lesions in 189 patients)

	Acute (NCI-CTC)			G3≤	Late (RTOG/EORTC)			G3≤
	n	G1	G2		n	G1	G2	
Skin	202	159	8	0 %	202	84	1	1 %
GI tract	202	1	4	0 %	202	1	1	0.5 %
Urinary	202	1	0	0 %	202	1	2	0 %

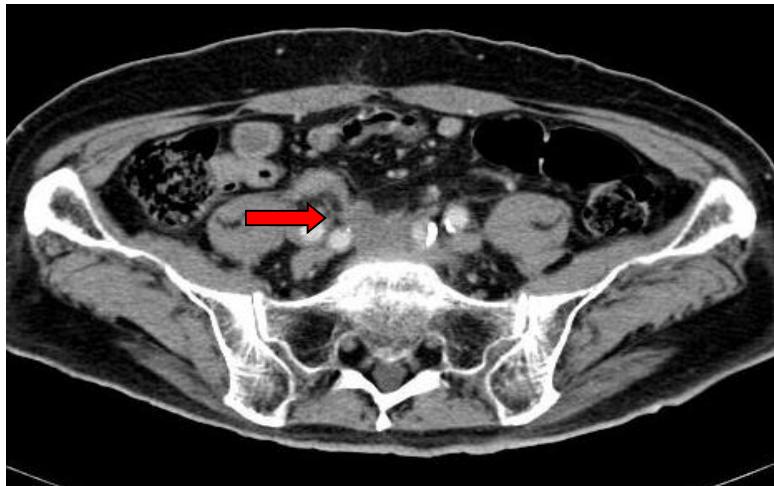
Recurrent Rectal Cancer : 66y M 67.2GyE/16Fr



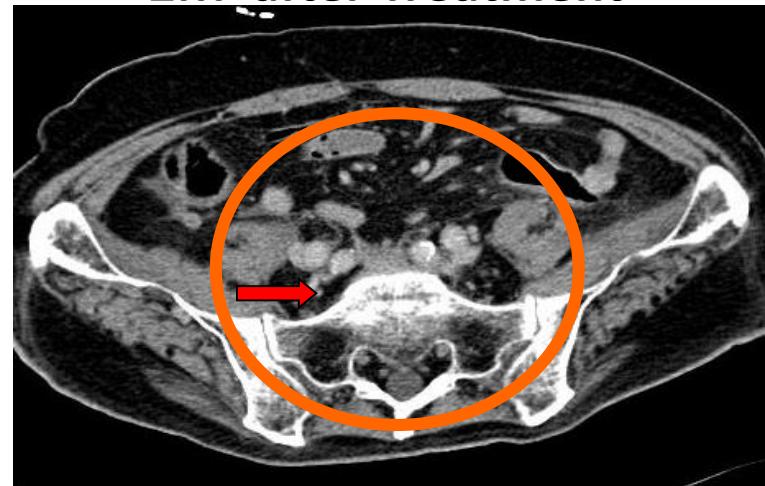
Before Treatment



2M after Treatment

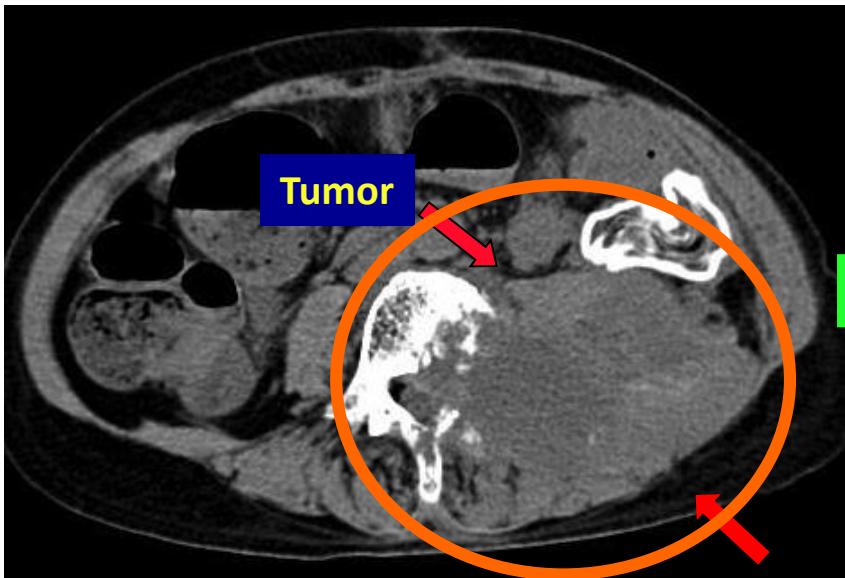


4M after Treatment

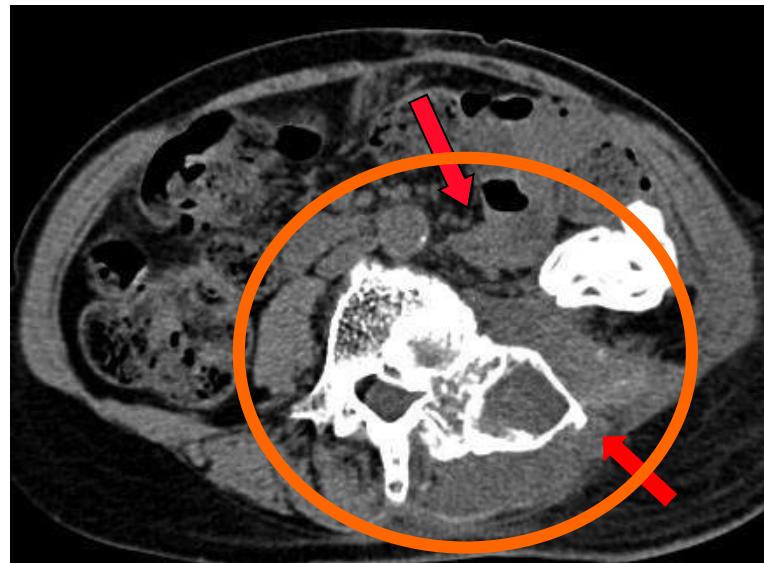


24M after Treatment

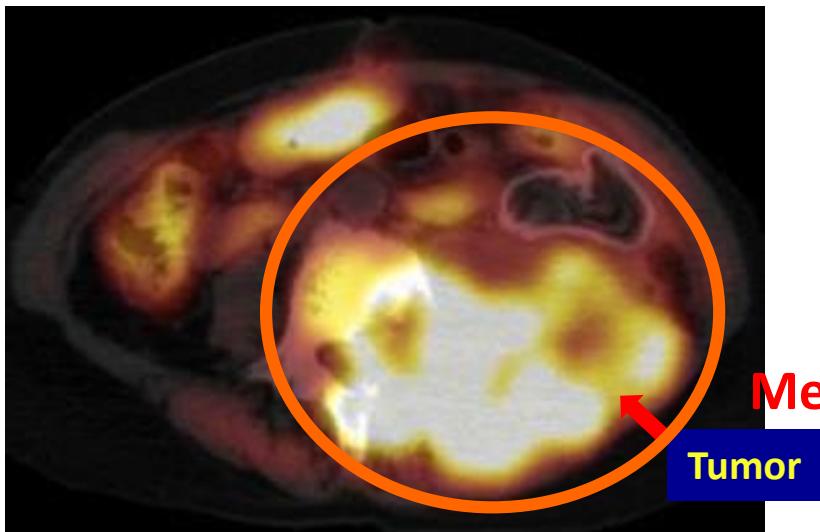
Recurrent Rectal Cancer : 69y F 73.6GyE/16Fr



Before Treatment



12M after Treatment

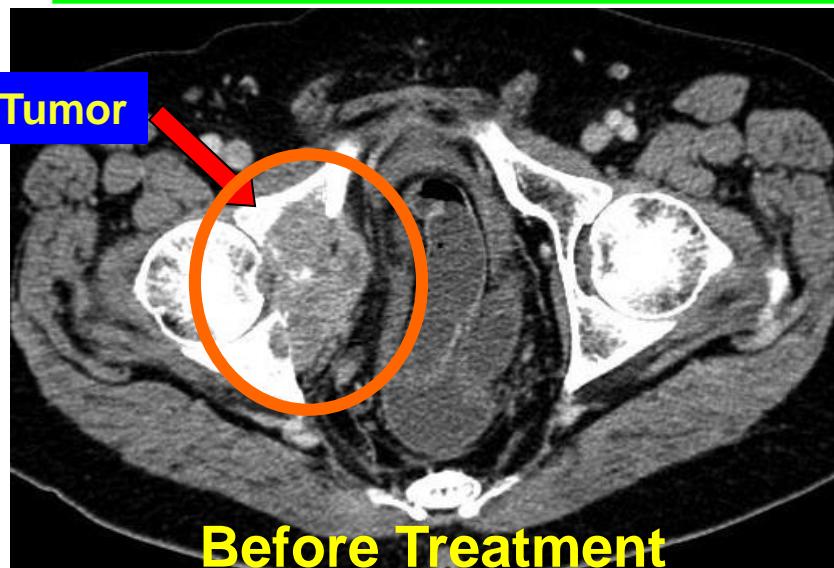


Methionine PET
Tumor



6M after Treatment

Recurrent Rectal Cancer : 65y M 73.6GyE/16Fr



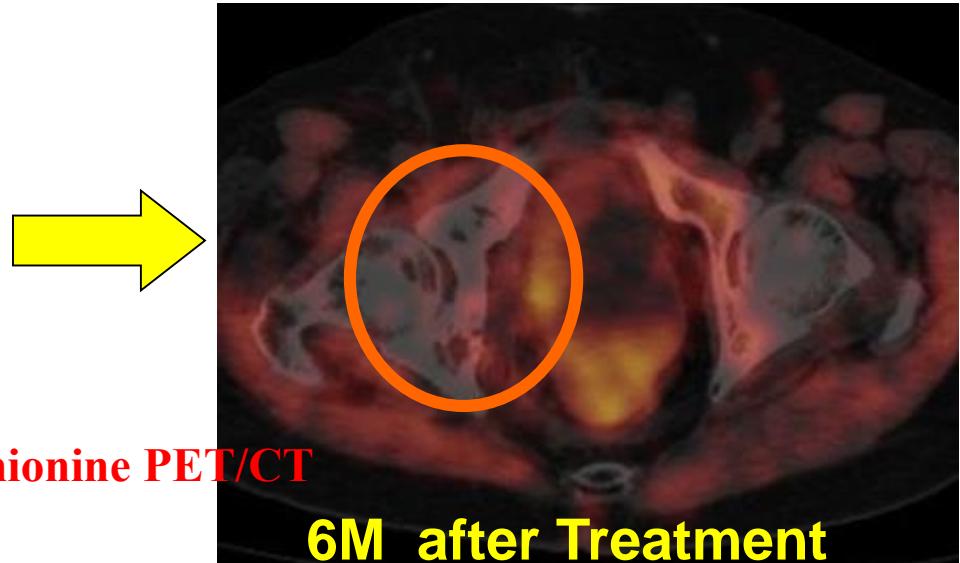
Before Treatment



12M after Treatment



Before Treatment



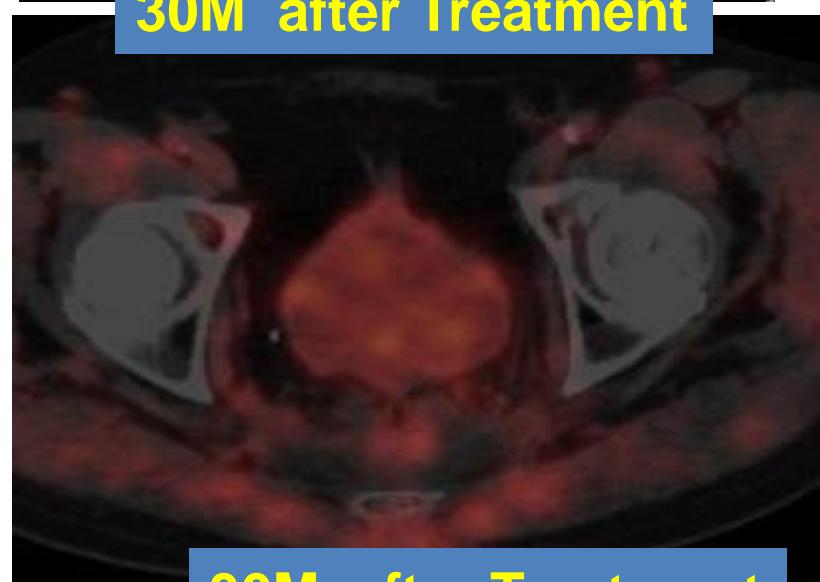
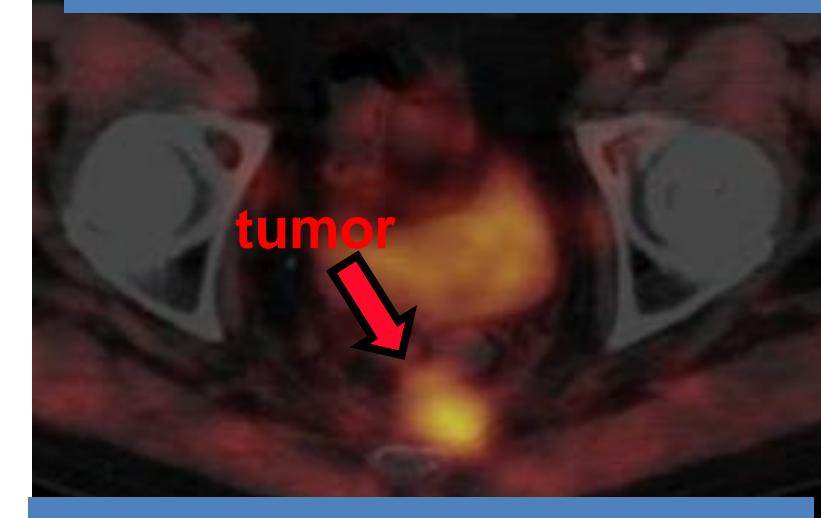
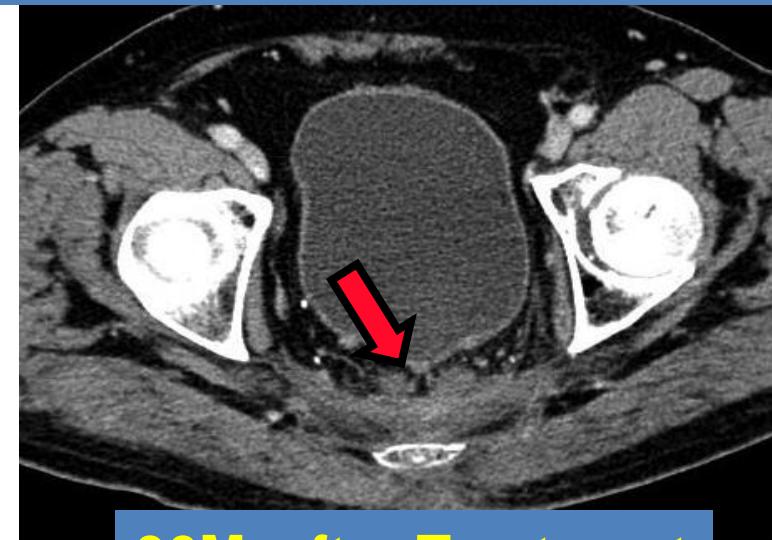
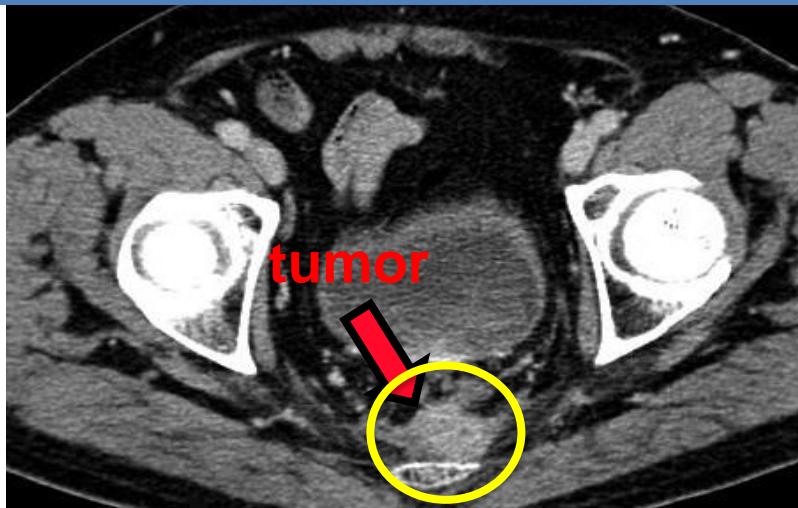
Methionine PET/CT

6M after Treatment

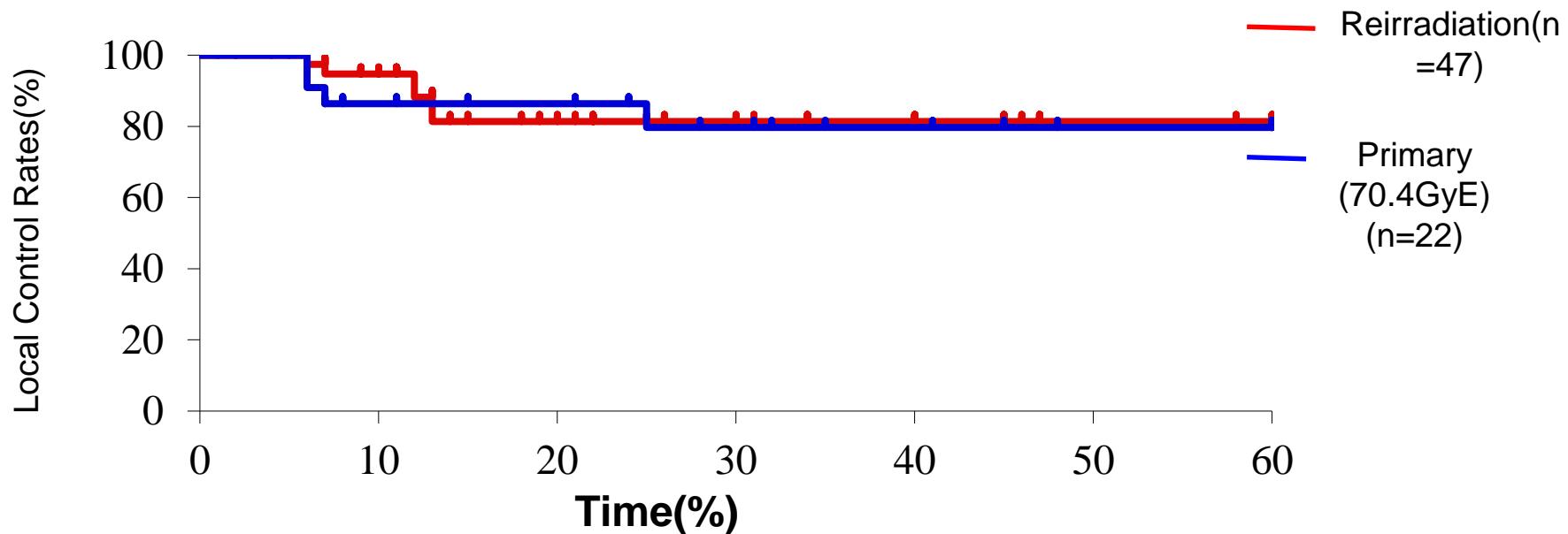
Re-irradiation of Rectal Cancer P/O Local Recurrence Patients and Treatment Characteristics (2006.4~2013.1 : 47Cases)

Age	61y(37~76y)	
Male／Female	Male／Female=38:9	
	Presacrum	20
The dose of Carbon Ion is 70.4GyE/16fr		
	Perineal	8
Indication for prior treatment	Neo- or Adjuvant	16
	For recurrent tumor	31
Prior Rad Dose	48.5Gy(20-70)	
Retreatment Interval	28.3 months(4-156)	

Case :74y M X-ray 60Gy/30fr. → Carbon70.4GyE/16fr.

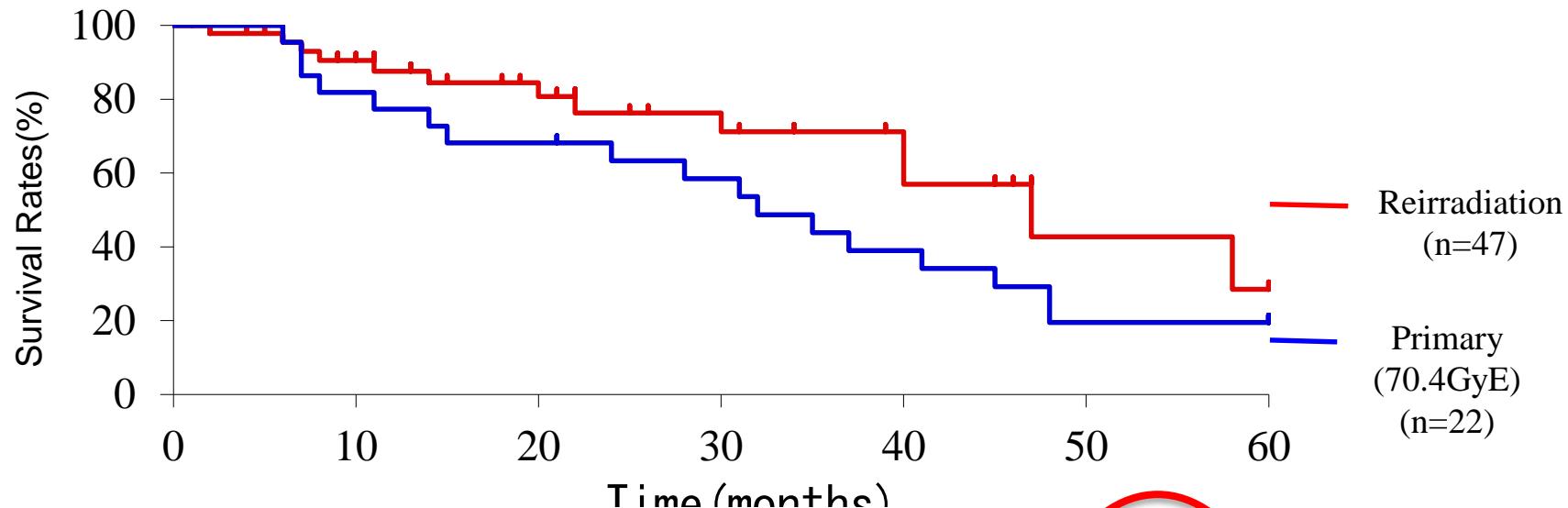


Local Control Rate of locally recurrent rectal cancer by primary CIRT and CIRT as reirradiation



	Number	1y	3y	5y
Reirradiation by CIRT	47	88.2%	81.4%	81.4%
Primary CIRT (70.4GyE)	22	86.4%	79.7%	79.7%

Overall Survival Curves of locally recurrent rectal cancer by primary CIRT and CIRT as reirradiation



Author	Year	N	Total Dose	ToxicityG3	5y-Survival	Local Control
Modiuddin M	2002	34	70-108Gy (85.8Gy)	Acute 4%	Surg 22%	44%
		69		Late 26%	15%	
Das P	2010	18	64-109Gy(86Gy)	Acute 4%	Surg 44%	
		32		Late 26%	12%	
NIRS	2014	47	90-140GyE (118GyE)	Acute 17% Late 25%	30%	81% (5y)

Comparison between Maximum Normal Tissue Damage by primary CIRT and CIRT as re-irradiation

- Primary CIRT : 70.4GyE/16回・・17cases
- Reirradiation by CIRT: 70.4GyE/16回・・47cases

	Neuropathy					Gastrointestinal				
Toxicity	No	G0	G1	G2	G3	No	G0	G1	G2	G3
Primary CIRT	17	6	6	4	1	17	10	4	3	0
Re-irradiation	47	20	19	6	2	46	37	1	3	5*

*3 grade 3 were attributed to operations for spacer insertion before treatment

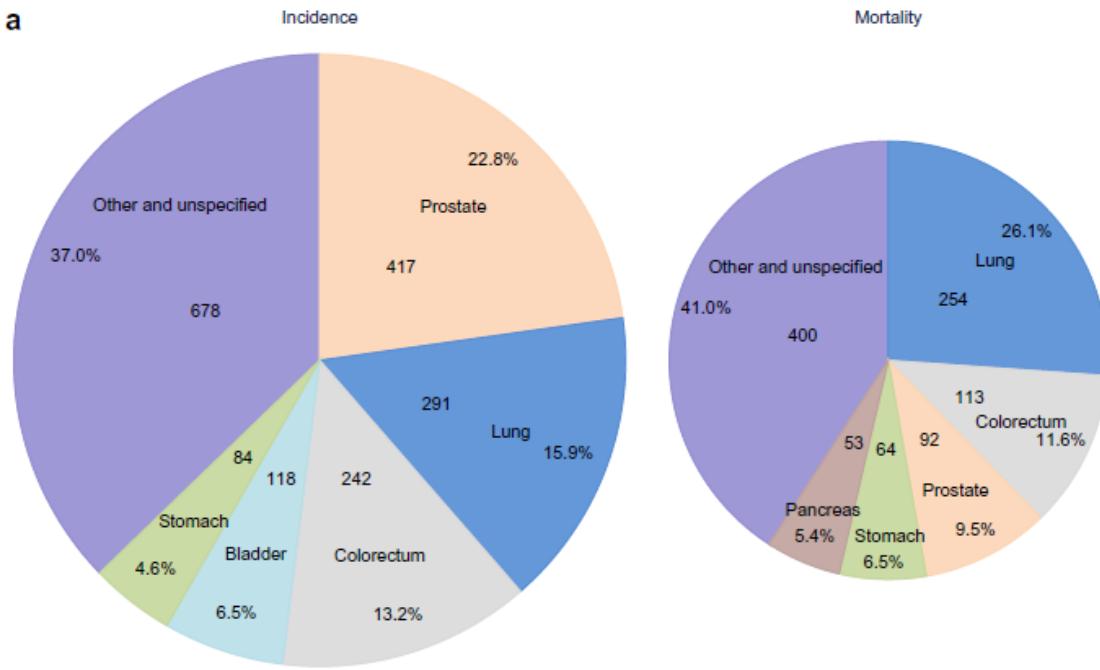
GASTROINTESTINAL CANCERS (J MEYER, SECTION EDITOR)

Particle Radiation Therapy for Gastrointestinal Cancers

Makoto Shinoto¹ • Daniel K. Ebner^{2,3} • Shigeru Yamada²

Pancreas cancer is bad

a



> 90.000 cases per year in Europe

European Journal of Cancer (2013) 49, 1374–140



Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012

J. Ferlay^{a,*}, E. Steliarova-Foucher^a, J. Lortet-Tieulent^a, S. Rosso^b,
J.W.W. Coebergh^{c,d}, H. Comber^e, D. Forman^a, F. Bray^a

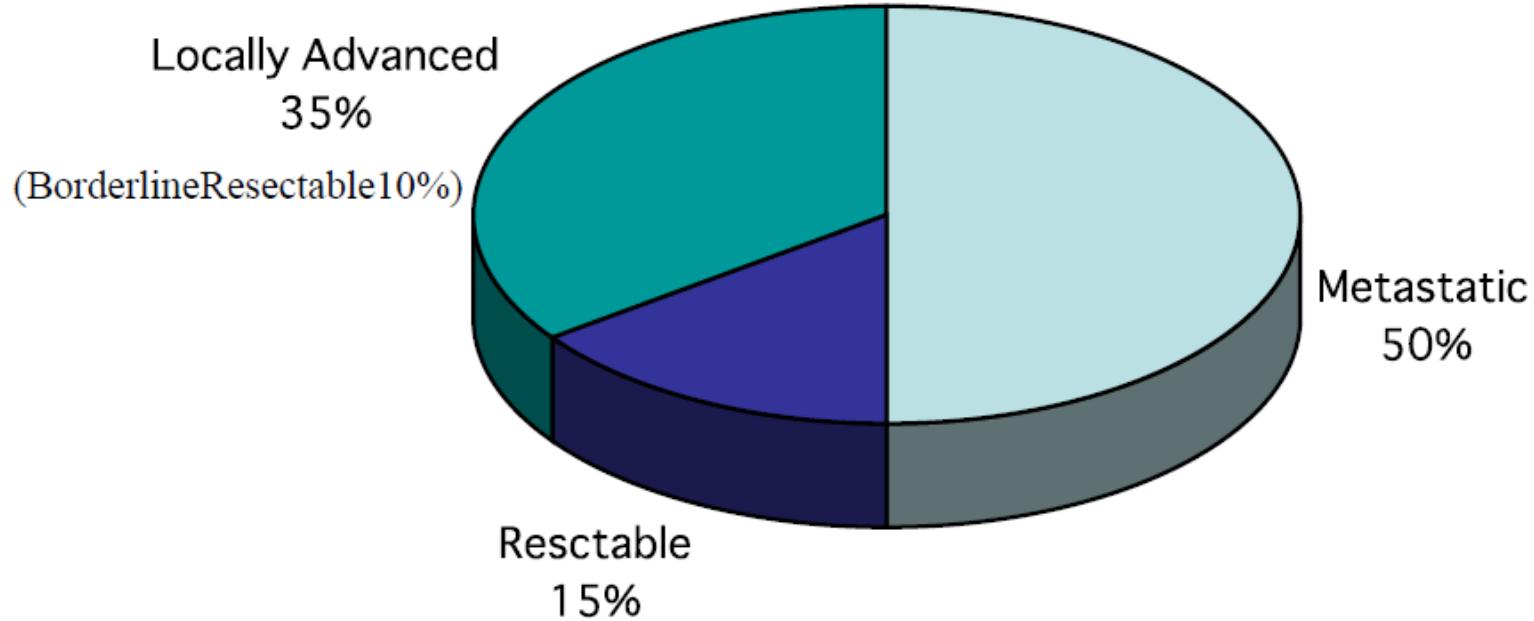
Table 3

Estimated numbers of new cancer cases and deaths from cancer (thousands), age-standardised rates (ASRs) (per 100,000) by sex and cancer site in Europe in 2012.

	Incidence						Mortality					
	Both sexes		Male		Female		Both sexes		Male		Female	
	Cases	ASR (E)	Cases	ASR (E)	Cases	ASR (E)	Deaths	ASR (E)	Deaths	ASR (E)	Deaths	ASR (E)
Oral cavity and pharynx	99.6	11.0	73.9	18.2	25.8	4.9	43.7	4.7	34.2	8.4	9.4	1.6
Oesophagus	45.9	4.7	35.1	8.4	10.8	1.8	39.5	3.9	30.3	7.1	9.2	1.4
Stomach	139.6	13.7	84.2	19.5	55.4	9.3	107.3	10.3	63.6	14.6	43.7	7.0
Colon and rectum	446.8	43.5	241.6	55.7	205.2	34.7	214.7	19.5	113.2	25.2	101.5	15.4
Liver	63.4	6.2	42.8	10.0	20.6	3.3	62.1	5.9	39.9	9.1	22.2	3.4
Gallbladder	20.7	2.7	11.9	2.7	17.9	2.8	20.0	1.9	7.9	1.8	13.0	2.0
Pancreas	103.8	10.1	51.9	12.1	51.8	8.3	104.5	9.9	52.6	12.2	51.9	8.1
Larynx	39.4	4.4	36	8.8	3.9	0.8	19.8	2.1	18.1	4.3	1.7	0.3
Lung	409.9	41.9	290.7	68.3	119.2	21.6	353.5	35.2	254.4	59.1	99.0	17.2
Melanoma of skin	100.3	11.1	47.2	11.4	53.1	11.0	22.2	2.3	12.1	2.8	10.1	1.8
Breast					463.8	94.2					131.2	23.1
Cervix uteri					58.3	13.4					24.4	4.9
Corpus uteri					98.9	19.3					23.7	3.9
Ovary					65.5	13.1					42.7	7.6
Prostate												
Testis												
Kidney												
Bladder	151.2	14.4	118.3	26.9	32.9	5.3	52.4	4.5	59.5	6.5	12.9	1.8
Brain, nervous system	57.1	6.6	30.7	7.8	26.4	5.6	45.0	4.9	24.6	6.0	20.4	4.0
Thyroid	52.9	6.3	12.3	3.1	40.7	9.3	6.3	0.6	2.1	0.5	4.3	0.7
Hodgkin lymphoma	17.6	2.3	9.3	2.5	8.3	2.1	4.6	0.5	2.6	0.6	2.0	0.4
Non-Hodgkin lymphoma	93.4	9.8	49.5	11.9	43.9	8.0	37.9	3.5	20.3	4.6	17.5	2.7
Multiple myeloma	38.9	3.8	20.5	4.7	18.4	3.1	24.3	2.2	12.2	2.7	12.1	1.8
Leukaemia	82.3	8.8	46.4	11.3	35.9	6.9	53.8	5.1	29.5	6.7	24.3	3.9
All sites but non-melanoma skin cancers	3439.6	355.7	1829.1	429.9	1610.5	306.3	1754.6	168.0	975.9	222.6	778.6	128.8

**103.000
New cases**

**104.000
New deaths**



C-ion RT Clinical Trials for Pancreatic Cancer at NIRS

(year)

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012

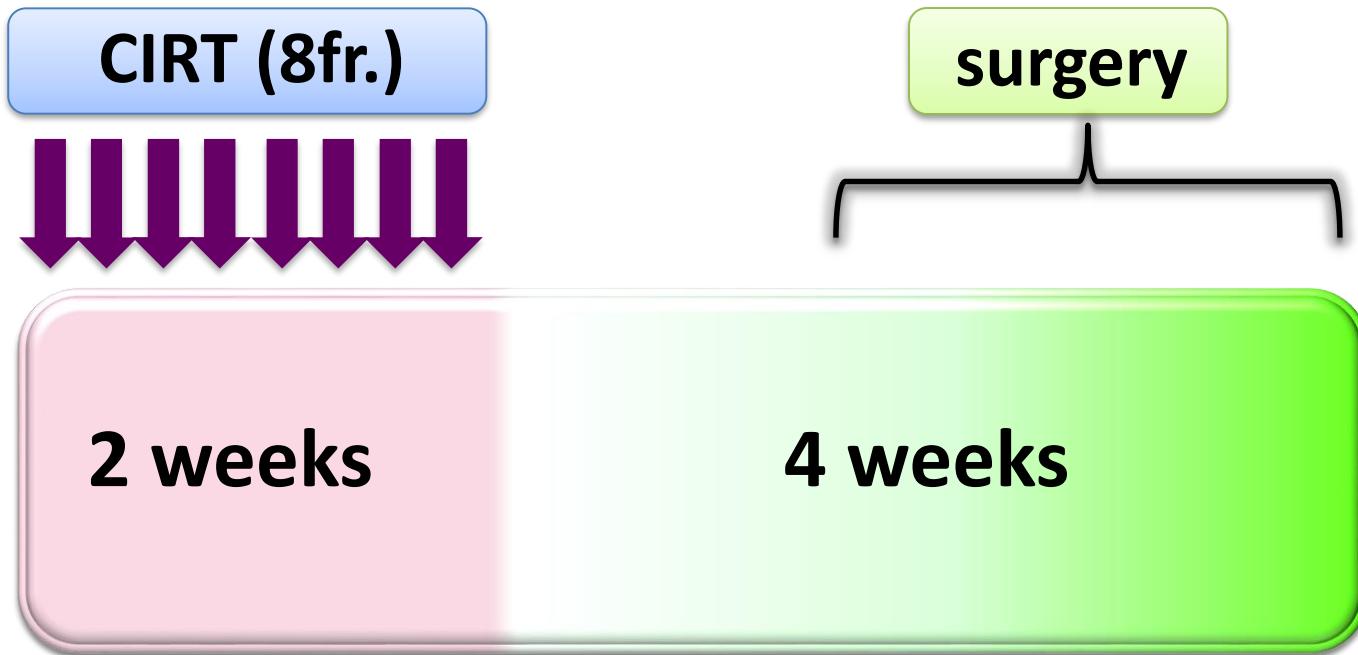
Phase I/II
Preoperative
(protocol 9906)
16fr./4w 22pts.

Phase I/II
Short-course Preoperative
(protocol 0203)
8fr./2w 31pts.

L
→
Phase I/II
LAPC
(protocol 0204)
12fr./3w 47pts.

→
Phase I/II
GEM+ C-ion for LAPC
(protocol 0513)
12fr./3w 71pts.

Schedule of C-ion RT and surgery



**Surgery was performed within 4 weeks
from the completion of CIRT**

Shinoto et al. Cancer 2013

Dose escalation in Pre-op Panc ca

Dose level	C-ion RT (GyE)	# of patients	# of patients with resection
1	30.0GyE	6	3
2	31.6GyE		3
3	33.6GyE		
4	35.2GyE		
5	36.8GyE		

R1 → 10 %, N+ ?

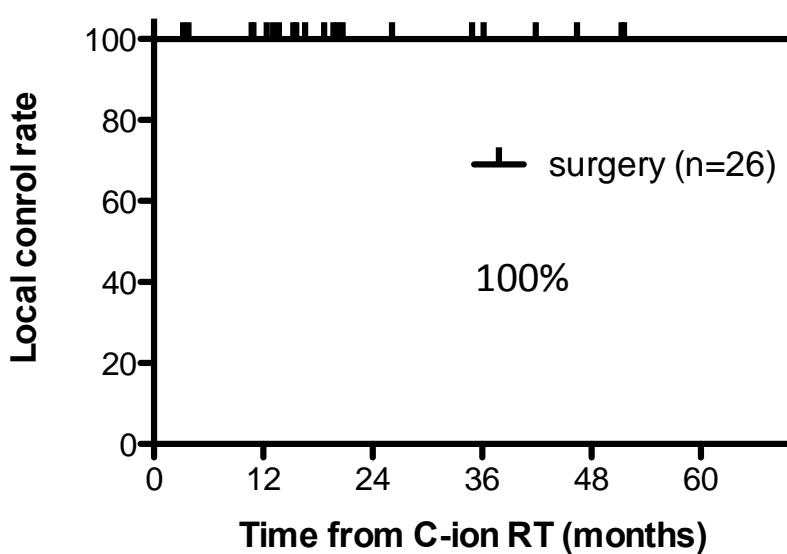
2006～
resection rate
95%

Acute and Late toxicity

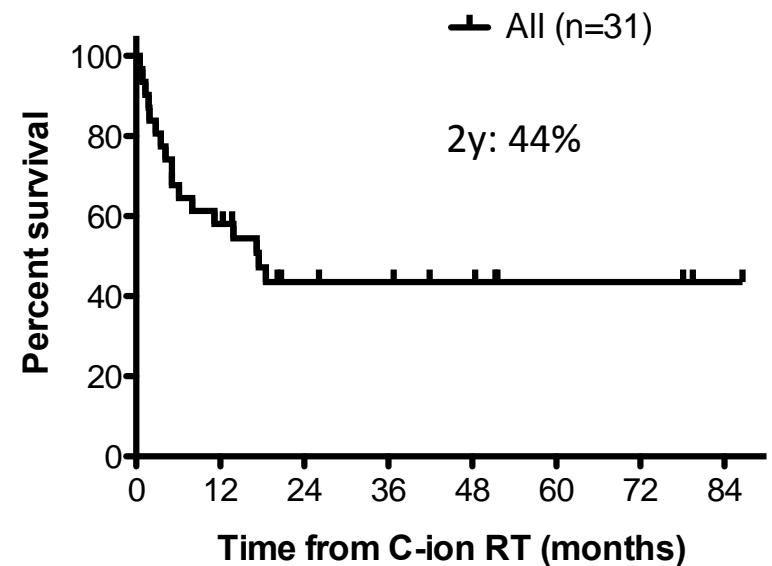
	Acute toxicities (NCI-CTC)						Late toxicities (RTOG/EORTC)					
	n	G0	G1	G2	G3	G4	n	G0	G1	G2	G3	G4
skin	26	26	0	0	0	0	26	26	0	0	0	0
GI	26	25	1	0	0	0	26	26	0	0	0	0
Liver	26	25	0	0	1	0	26	26	0	0	0	0
Portal Vein	26	26	0	0	0	0	26	25	0	0	0	1
Leakage	26	26	0	0	0	0	26	26	0	0	0	0

Preoperative C-ion RT

Local Control

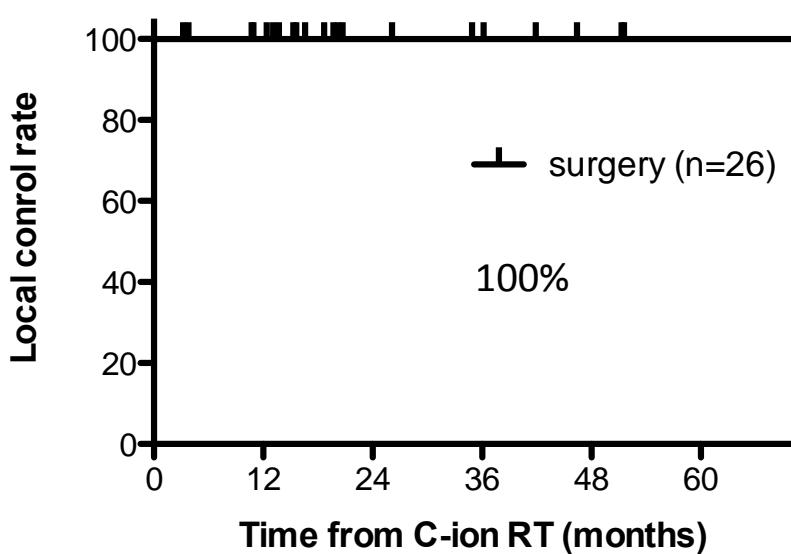


DMFS (Distant Metastasis Free Survival)



Preoperative C-ion RT

Local Control



DMFS (Distant Metastasis Free Survival)

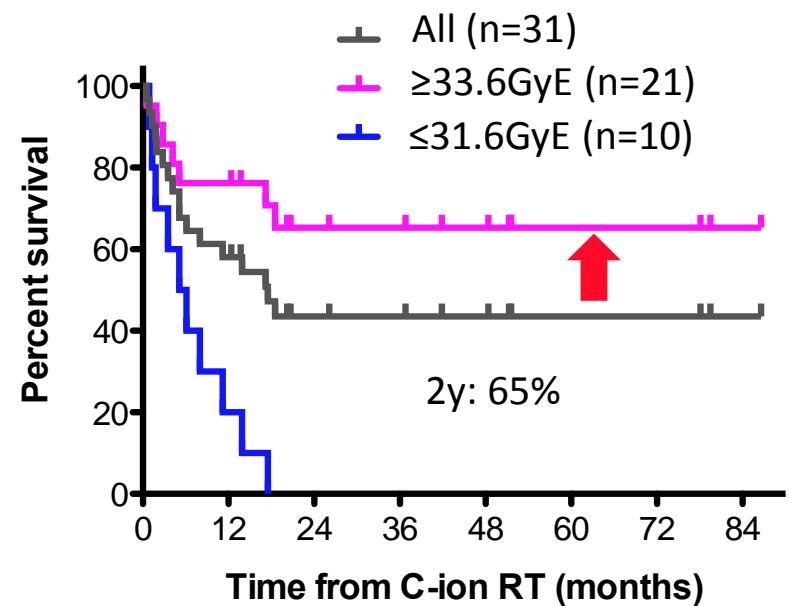


Fig. 15. Lymph node station numbers

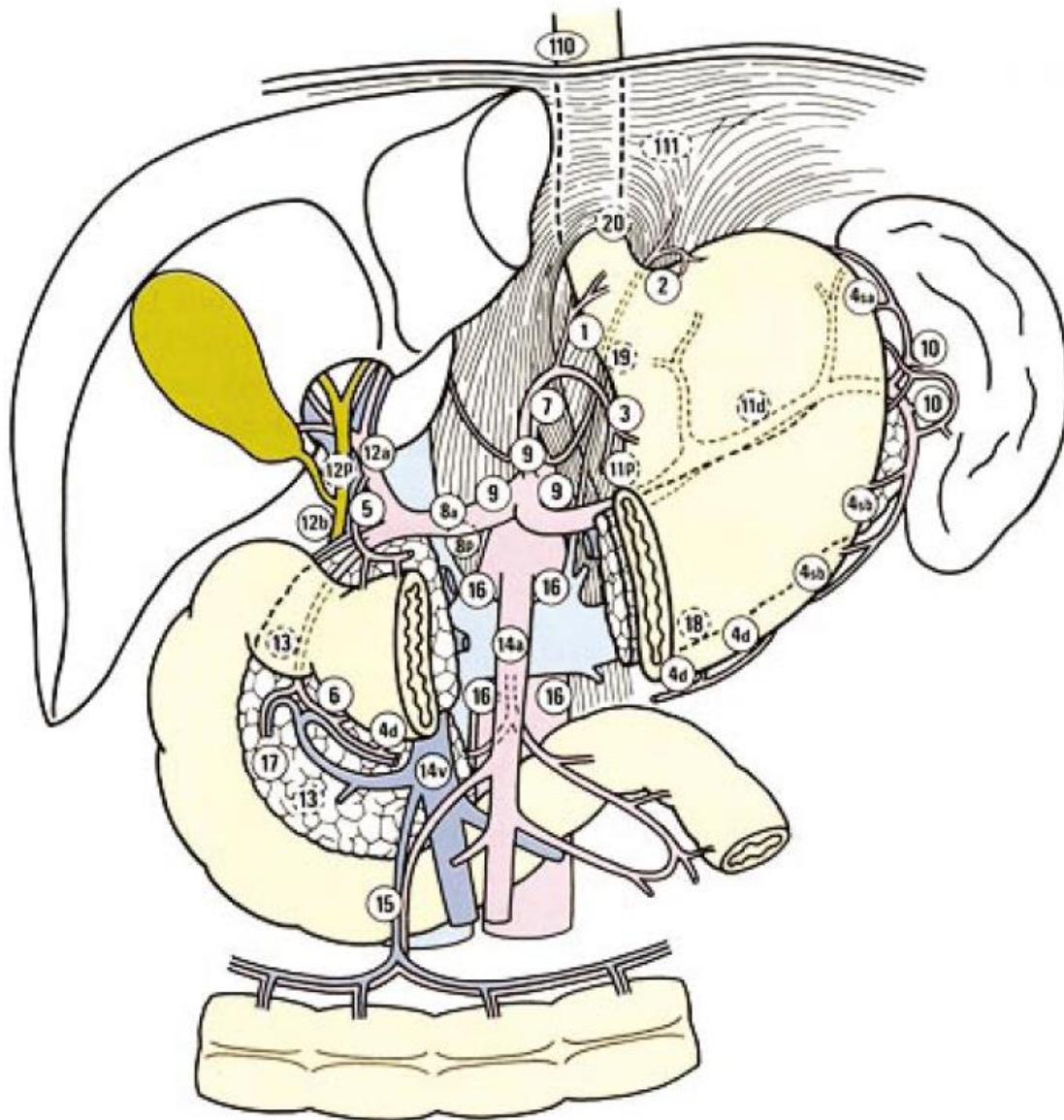


Table 2 Metastatic rates of all groups of lymph nodes (According to JPS Classification)

No. Group No. Study	1 RC	2 LC	3 LCS	4 GCS	5 SP	6 IP	7 LGA	8 CHA	9 CT	10 HS	11 SA	12 HDL	13 PPD	14 SMA	15 MCA	16 PA	17 APD	18 IB	
Pancreatic Head Cancer																			
1									8/175	2/175		31/175	65/175	17/175		39/175	41/175		
2	12/ 2974	8/ 2768	48/ 3796	57/ 3928	72/ 3973	298/ 4167	70/ 3697	728/ 7453	130/ 3697	23/ 2759	121/ 8260	921/12400	2588/ 8503	1182/ 7962	97/3364	501/ 5134	1524/ 8148	84/3266	
3*									5/76	3/76	0/76	1/76	11/76	75/76	26/76	0/76	14/76	35/76	0/76
4	0/96	0/96	0/96	0/96	0/96	0/96	0/96	12/96	6/96	1/96	3/96	14/96		11/96	0/96	10/96	0/96		
5(6) #		0/42	0/42	0/42	1/42	0/42	6/42	2/42	0/42	2/42	9/42	29/42	16/42	0/42	7/42	17/42	5/20		
7			0/100	12/100			6/100	9/100			3/100		22/100	3/100					
12			0/44	1/44	0/44	6/44	2/44	0/44	2/44	6/44	28/44	15/44	0/44	7/44	14/44	4/44			
13																9/34			
14					21/178	0/178	17/178	2/178	0/178	14/178	33/178	83/178	50/178	2/178	34/178	51/178	3/178		
15		0/50	0/50																
16						2/81	9/81	2/81	1/81		12/81	40/81	38/81	5/81	15/81	30/81			
17							6/49	2/49		6/49	48/49	18/49		9/49	27/49				
Total (head)	12/ 3070	8/ 2864	48/ 3984	57/ 4116	72/ 4255	333/ 4627	72/ 4138	795/ 8119	166/ 4538	27/ 3451	143/ 8696	1046/ 13241	2956/ 9148	1395/ 8803	107/ 3981	645/ 5909	1739/ 8793	96/3680	
¹ Total rate (head) %	0.39	0.28	1.2	1.38	1.69	7.2	1.74	9.79	3.66	0.78	1.64	7.9	32.31	15.85	2.69	10.92	19.78	2.61	
Pancreatic Body/tail Cancer																			
3*									5/23	1/23	1/23	11/23	3/23	1/23	1/23	1/23	4/23	9/23	
9	0/30	0/30	1/30	0/30	0/30	1/30	0/30	1/30	4/30	1/30	5/30	0/30	0/30	4/30	0/30	4/30	1/30	2/30	
11								5/20	2/20	1/20	10/20	3/20	1/20	2/20	1/20	4/20	0/20	7/20	
Total (body/tail)	0/30	0/30	0/30	0/30	0/30	1/30	0/30	11/73	7/73	3/73	26/73	6/73	2/73	7/73	2/73	12/73	1/73	18/73	
¹ Total rate (Body/tail)%	0	0	0	0	0	3.33	0	15.07	9.59	4.11	35.62	8.22	2.74	9.59	2.74	16.44	1.37	24.66	
General Pancreatic Cancer																			
8										0/22		0/22	10/22	1/22	1/22		2/22		
10										0/8		0/8	4/8		4/8		2/8		
18						1/10					1/10	1/10	1/10			6/10			

For tumor of the head of the pancreas stations number 8,13,14,16,17 will be included in CTV1

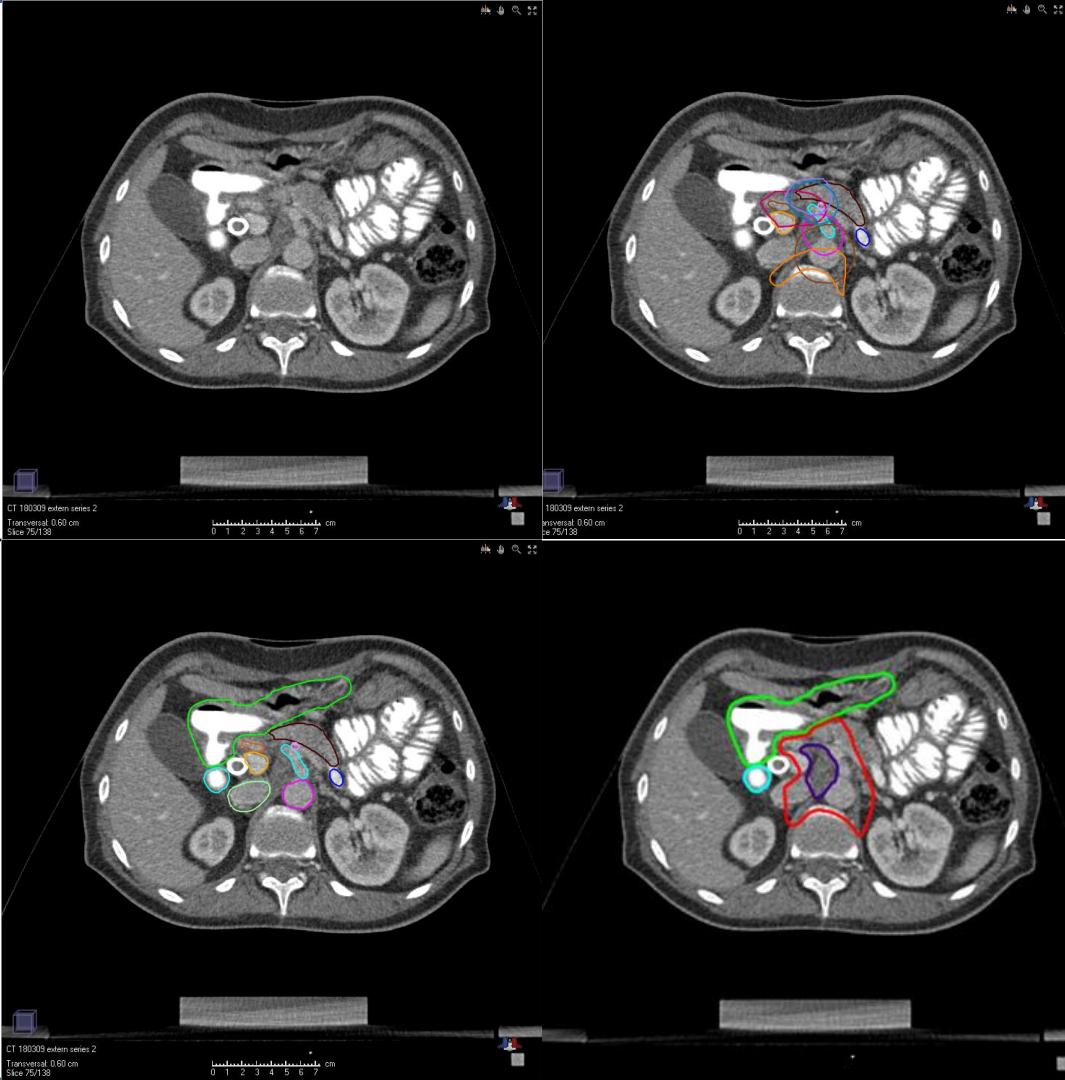
Pancreatic head tumor			
Lymph node group	JPS Classification [32]	%	Recommended margins
Common hepatic artery lymph nodes	Group 8	9.8	10 mm margin around the common hepatic artery, from the origin of the artery (correspond to the superior border of the pancreas), on the anterior surface of the portal vein upper to the hilum of the liver
Posterior pancreaticoduodenal lymph nodes	Group 13	32.3	10 mm margin around the inferior - posterior pancreaticoduodenal artery
Superior mesenteric artery lymph nodes	Group 14	15.8	10 mm margin around the origin of superior mesenteric artery
Paraaoortic lymph nodes	Group 16	10.9	10 mm margin around the abdominal aorta, between the celiac artery and the inferior mesenteric artery
Anterior pancreaticoduodenal lymph nodes	Group 17	19.8	10 mm margin around the superior - anterior pancreaticoduodenal artery

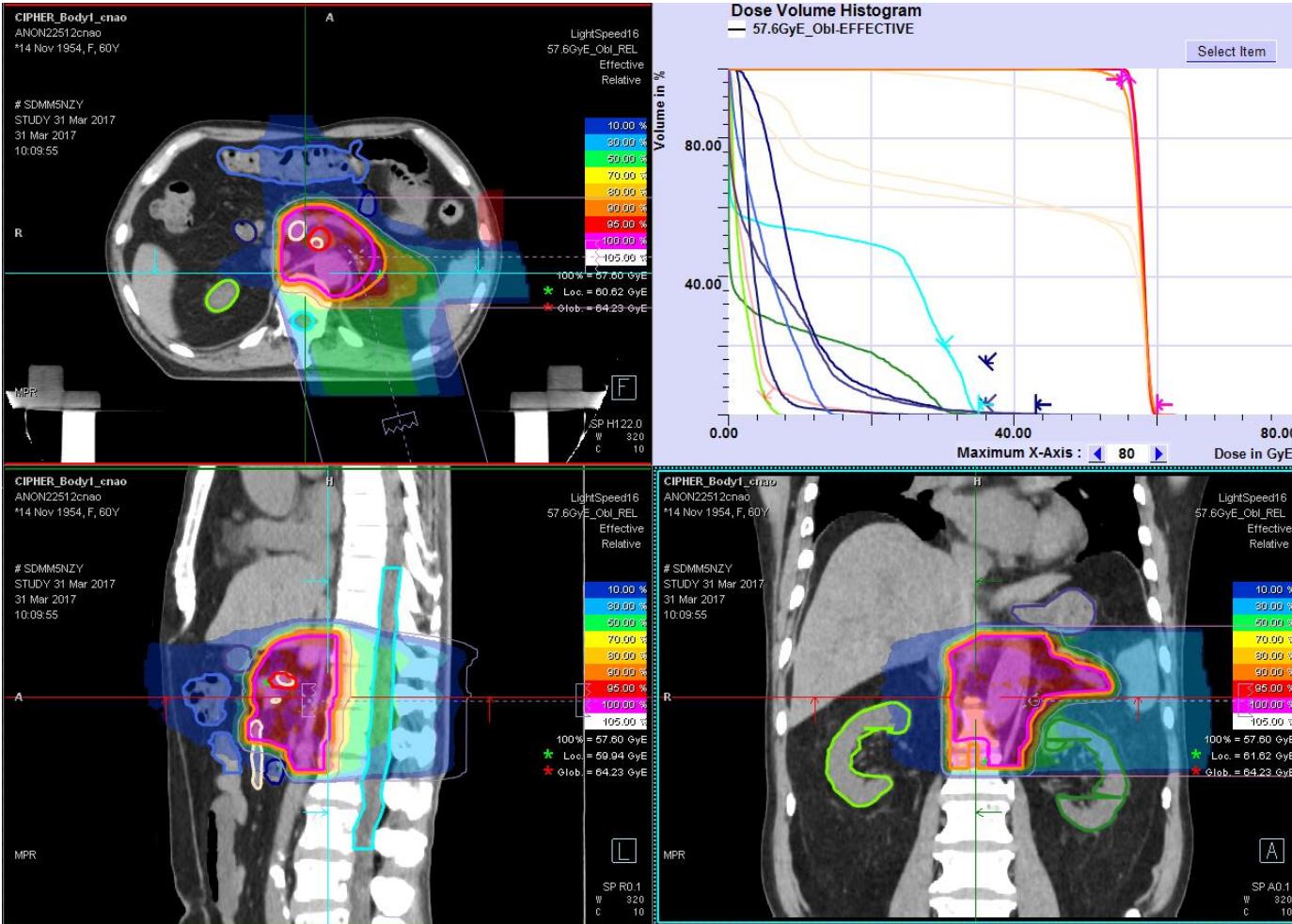
Modified from Caravatta et al. Radiation Oncology 2012,

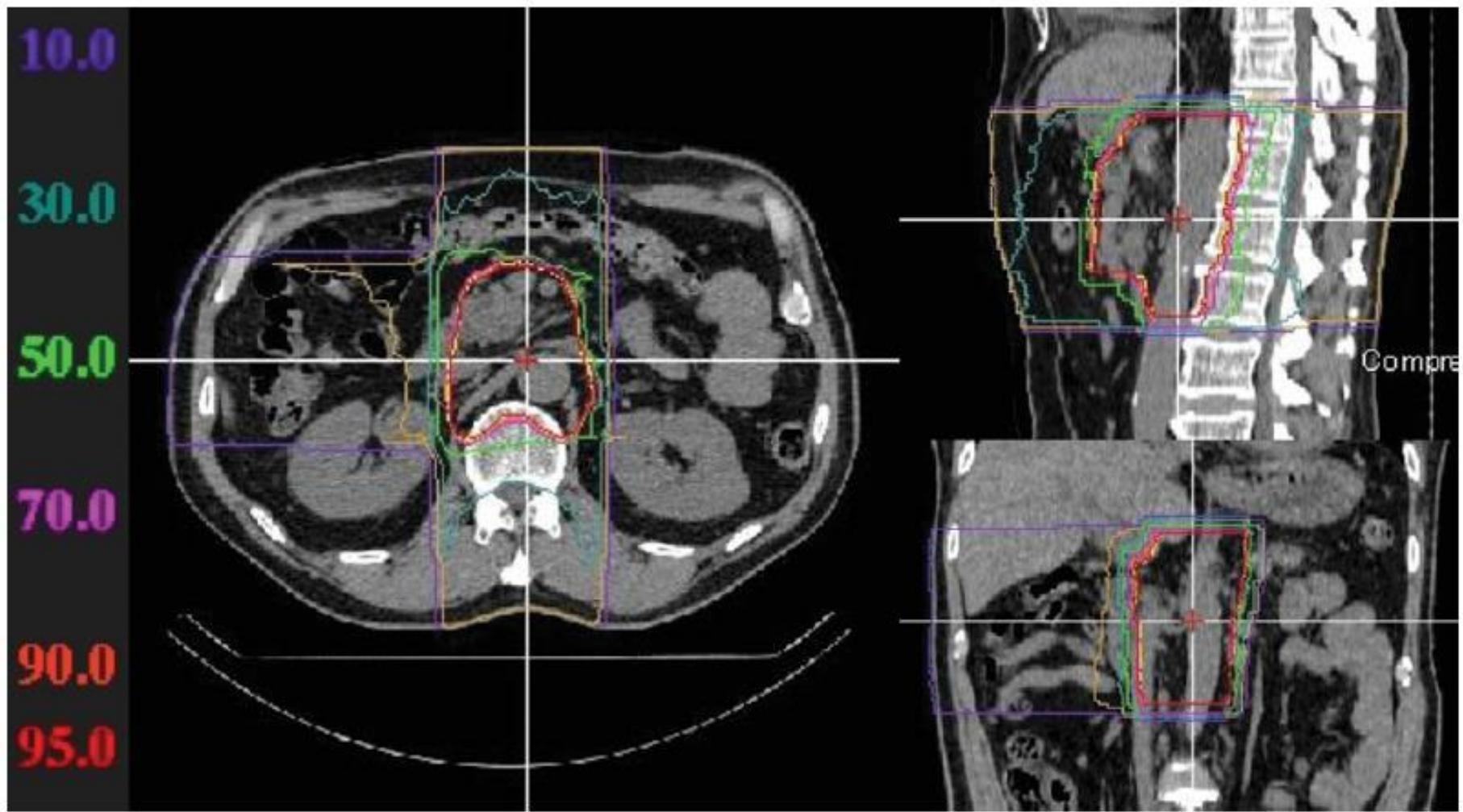
For tumors of the body/tail of the pancreas stations number 8,9 ,11,14,16,18

Pancreatic body/tail tumor			
Lymph node group	JPS Classification [32]	%	Recommended margins
Common hepatic artery lymph nodes	Group 8	15.1	10 mm margin around the common hepatic artery, from the origin of the artery (correspond to the superior border of the pancreas), on the anterior surface of the portal vein upper to the hilum of the liver
Celiac trunk lymph nodes	Group 9	9.6	10 mm margin around the celiac trunk
Splenic artery lymph nodes	Group 11	35.6	10 mm margin around the splenic artery
Superior mesenteric artery lymph nodes	Group 14	9.6	10 mm margin around the origin of superior mesenteric artery
Paraaortic lymph nodes	Group 16	16.4	10 mm margin around the abdominal aorta, between the celiac artery and the inferior mesenteric artery
Inferior body lymph nodes	Group 18	24.7	10 mm margin around the inferior pancreatic artery

Modified from Caravatta et al. Radiation Oncology 2012,

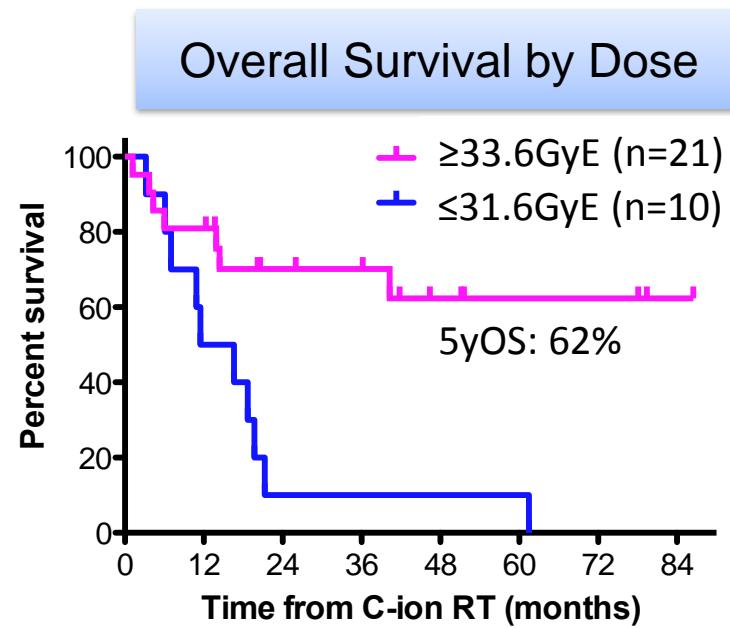
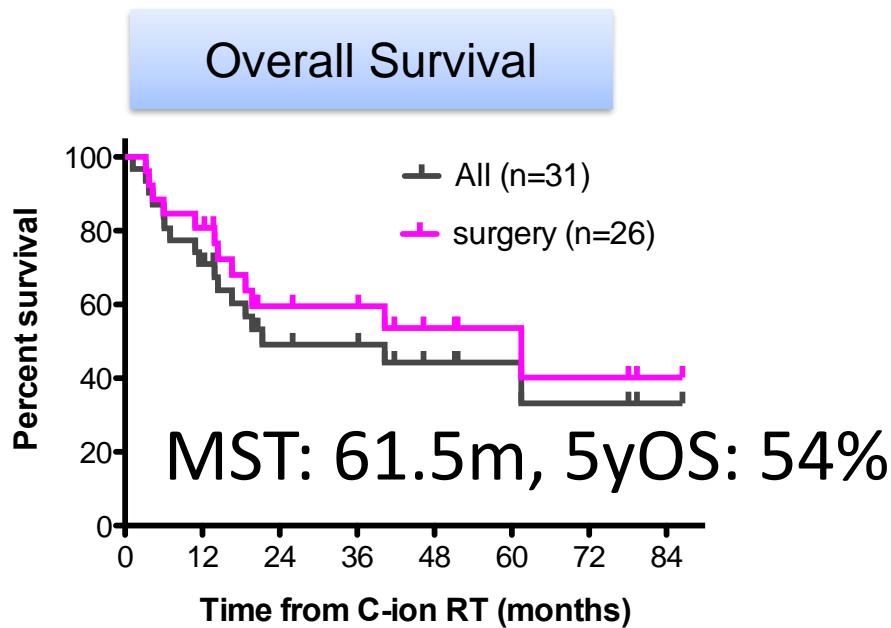






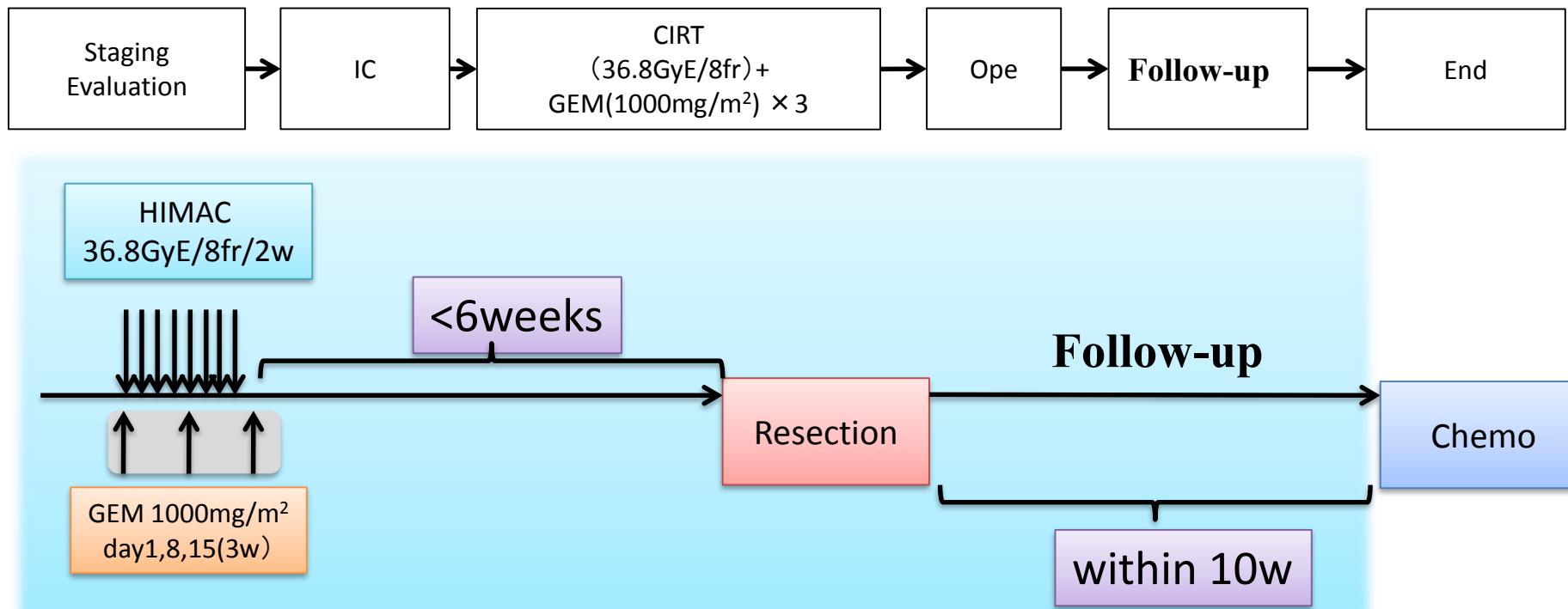
Preoperative C-ion RT

	year	n	treatment	Survival		
				MST	3-yr	5-yr
CONKO-001	98-04	182	surgery only	20.2m	21%	12%
		186	surgery+GEM	22.1m	34%	23%
NIRS	03-13	26	CIRT + surgery	61.5m	60%	54%



A phase I/II clinical trial of carbon ion radiotherapy and concurrent gemcitabine chemotherapy for patients with preoperative pancreatic cancer

Schema for New Protocol



Original Article

Phase 1 Trial of Preoperative, Short-Course Carbon-Ion Radiotherapy for Patients With Resectable Pancreatic Cancer

Makoto Shinoto, MD^{1,2}; Shigeru Yamada, MD, PhD¹; Shigeo Yasuda, MD, PhD¹; Hiroshi Imada, MD, PhD¹; Yoshiyuki Shioyama, MD, PhD³; Hiroshi Honda, MD, PhD²; Tadashi Kamada, MD, PhD¹; Hirohiko Tsujii, MD, PhD¹; Hiromitsu Saisho, MD, PhD⁴; and Working Group for Pancreas Cancer

BACKGROUND: The authors evaluated the tolerance and efficacy of carbon-ion radiotherapy (CIRT) as a short-course, preoperative treatment and determined the recommended dose needed to reduce the risk of postoperative local recurrence without excess injury to normal tissue. **METHODS:** Patients radiographically defined with potentially resectable pancreatic cancer were eligible. A preoperative, short-course, dose-escalation study was performed with fixed 8 fractions in 2 weeks. The dose of irradiation was increased by 5% increments from 30 gray equivalents (GyE) to 36.8 GyE. Surgery was to be performed 2 to 4 weeks after the completion of CIRT. **RESULTS:** The study enrolled 26 patients. At the time of restaging after CIRT, disease progression with distant metastasis or refusal ruled out 5 patients from surgery. Twenty-one of 26 patients (81%) patients underwent surgery. The pattern of initial disease progression was distant metastasis in 17 patients (65%) and regional recurrence in 2 patients (8%). No patients experienced local recurrence. The 5-year survival rates for all 26 patients and for those who underwent surgery were 42% and 52%, respectively. **CONCLUSIONS:** Preoperative, short-course CIRT followed by surgery is feasible and tolerable without unacceptable morbidity. *Cancer* 2013;119:45–51. © 2012 American Cancer Society.

KEYWORDS: preoperative, short course, carbon-ion radiotherapy, pancreatic cancer, phase 1.

C-ion RT Clinical Trials for Pancreatic Cancer

(year)

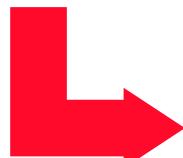
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012

Phase I/II
Preoperative
(protocol 9906)
16fr./4w 22pts.

Phase I/II
Short-course Preoperative
(protocol 0203)
8fr./2w 31pts.



Phase I/II
LAPC
(protocol 0204)
12fr./3w 47pts.



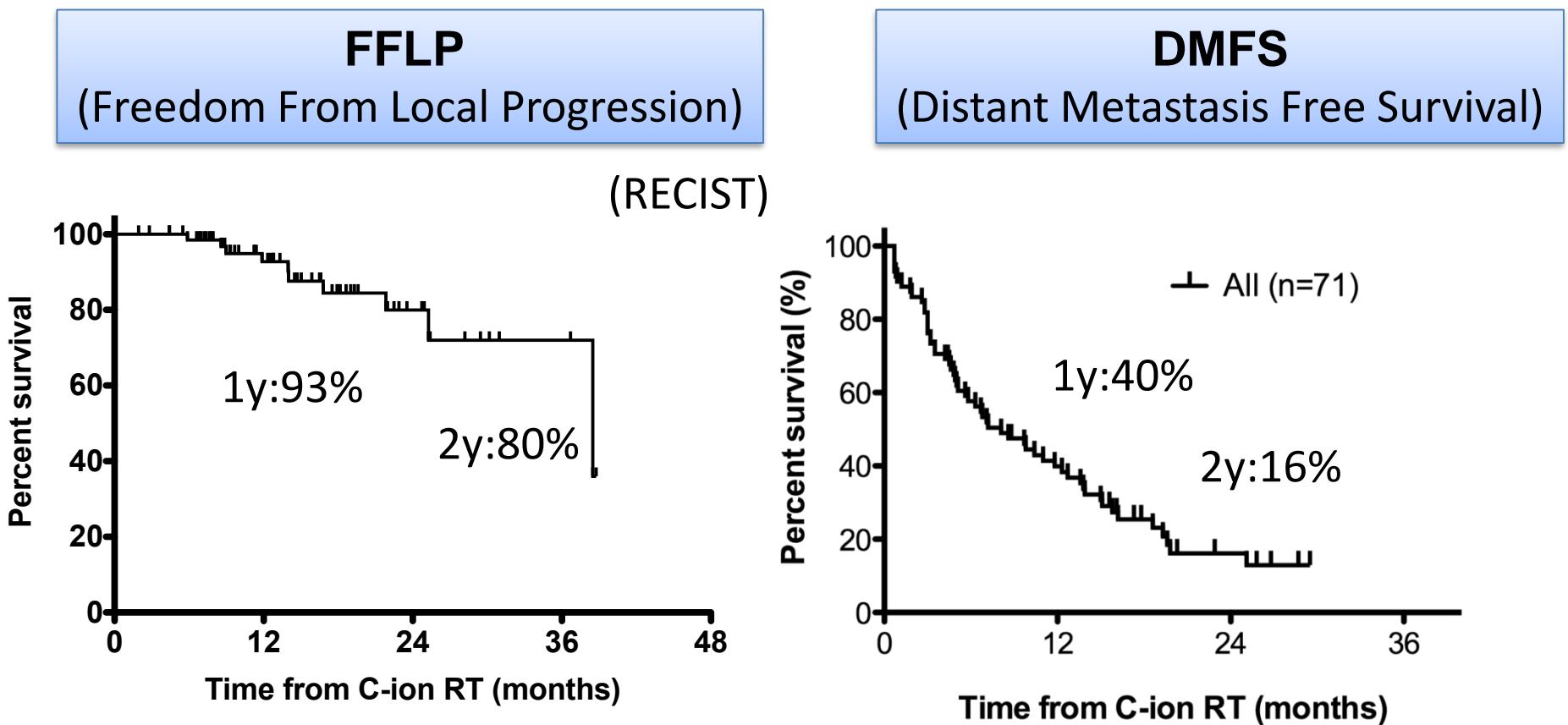
Phase I/II
GEM+ C-ion for LAPC
(protocol 0513)
12fr./3w 71pts.



Dose escalation

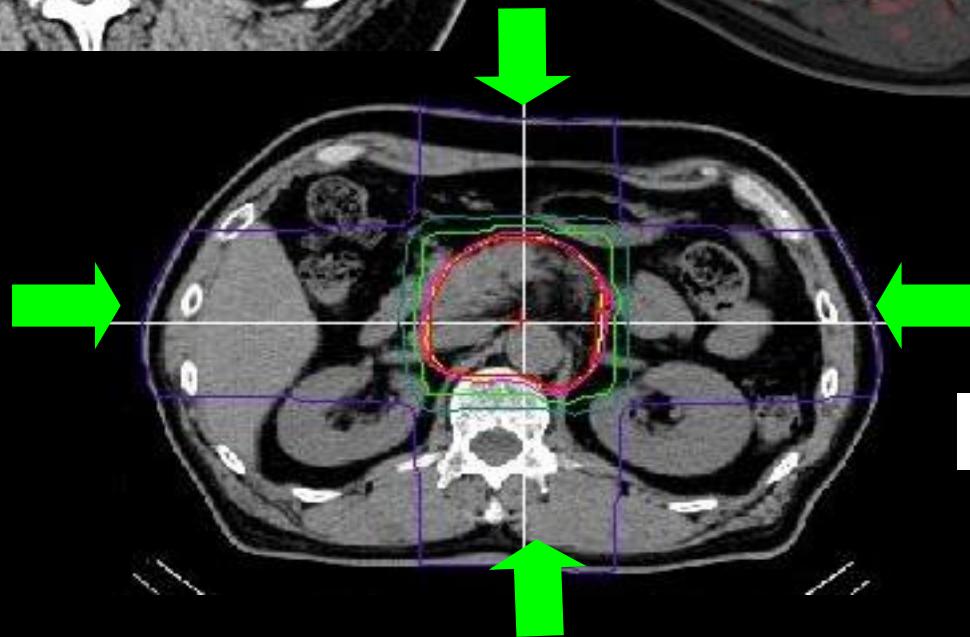
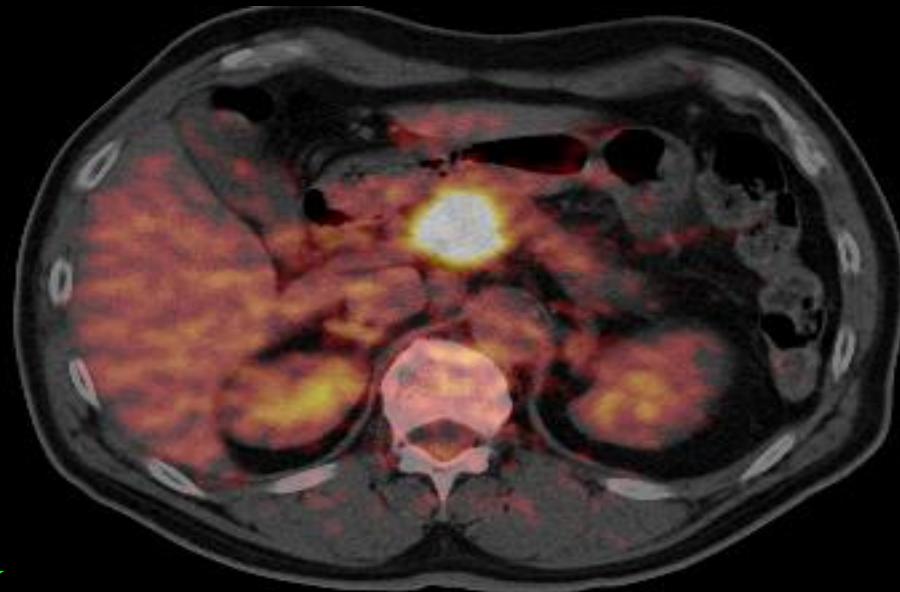
DOSE	Week1	Week2	Week3
43.2-GyE in 12fr	Carbon ↓↓↓↓	Carbon ↓↓↓↓	Carbon ↓↓↓↓
GEM 400-1000mg/m ²	G	G	G
50.4GyE · 1000mg/m ²			11
52.8GyE · 1000mg/m ²			11
55.2GyE · 1000mg/m ²			11

GEM+C-ion RT for LAPC



Case 1: 66y Male

Pbh 35mm×25mm Stage IVa
TS2,N0,S+,RP+,CH-,DU-,PV+A+



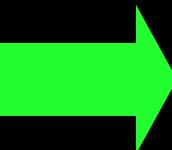
Case 1: 66y Male

50.4GyE / 12fr

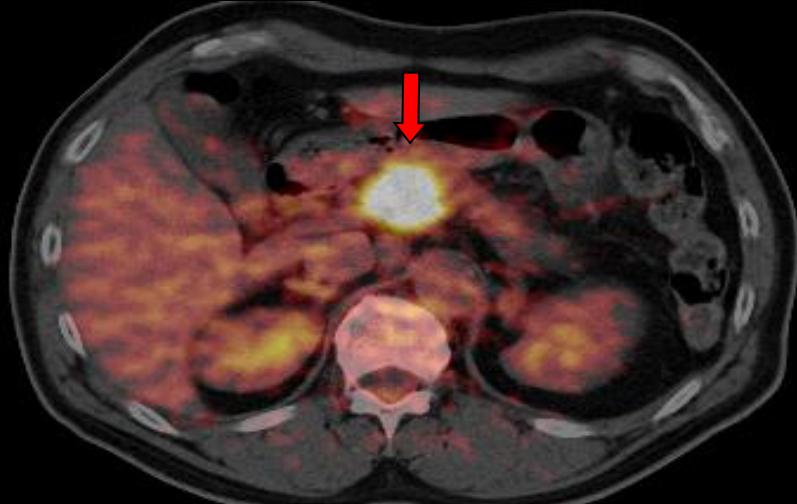
Alive at 50M after treatment



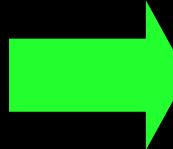
Before Treatment



40M after treatment



Before Treatment



6M after treatment

Upper gastrointestinal acute and late Grade2-3 toxicity by total dose

Carbon·GEM	n	0	1	2	3	4	5
43.2GyE · 400·700·1000mg/m ²	24	24	0	0	0	0	0
45.6GyE ·1000mg/m ²	7	7	1	0	0	0	0
48.0GyE ·1000mg/m ²	8	8	1	0	0	0	0
50.4GyE ·1000mg/m ²	11	10	0	1	1	0	0
52.8GyE ·1000mg/m ²	11	10	1	3	0	0	0
55.2GyE ·1000mg/m ²	10	5	0	5	0	0	0

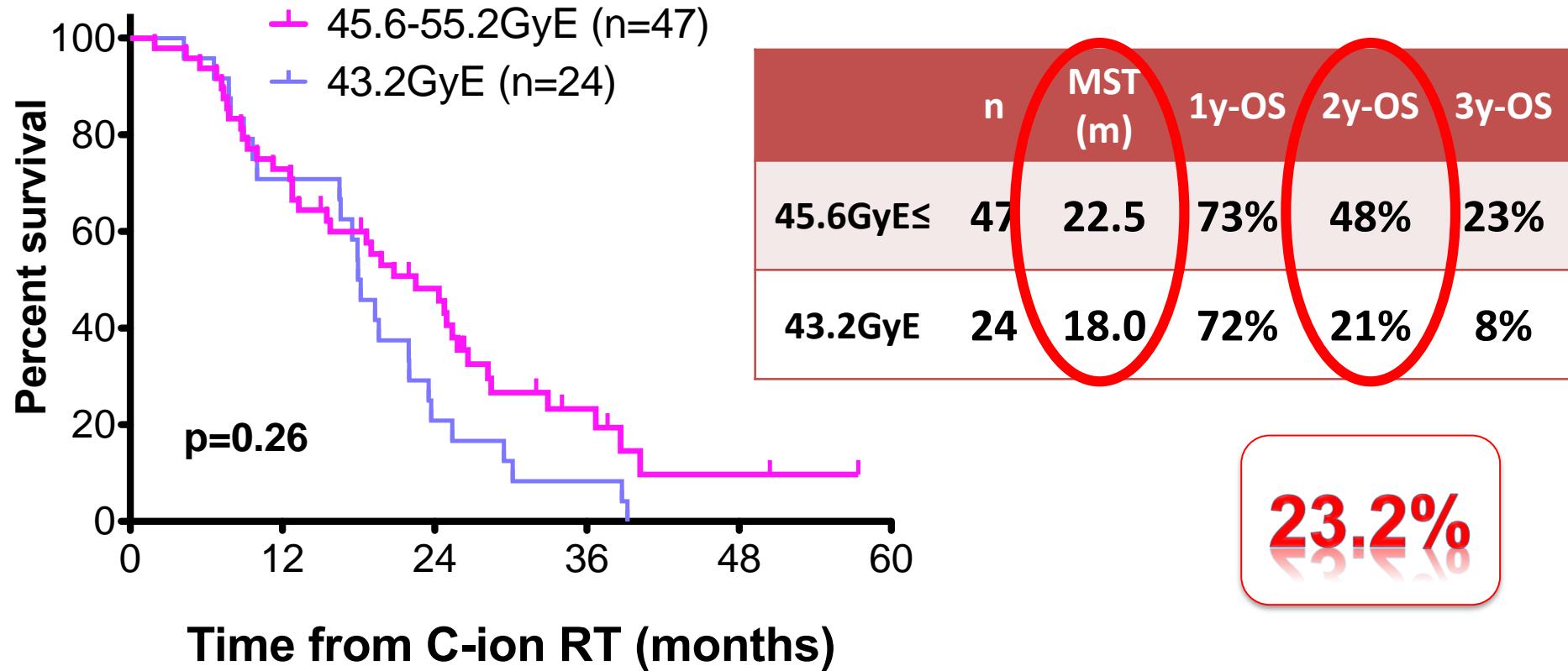
Grade1 : Asymptomati.

Grade2 : Symptomatic; altered GI function

Grade3 : Symptomatic and severely altered GI; IV fluids, tube feedings, or TPN indicated ≥24 hrs

GEM+C-ion RT for LAPC

Overall Survival



GEM+C-ion RT for locally advanced pancreatic cancer

	Year	n	Treatment	Dose	Survival	
					1yr	2yr
ECOG	2008	34	GEM+RT	50.4Gy	50%	12%
		37	GEM	-	32%	4%
Ishii	2010	50	GEM	-	64%	14%
Sudo	2011	34	S-1+RT	50.4Gy	71%	25%
Small	2011	28	GEM+BZ*+RT	36Gy/15fr.	45%	17%
Schellenberg	2011	20	GEM+SBRT	25Gy/1fr.	50%	20%
NIRS	2014	47	GEM+CIRT	45.6-55.2 GyE	73%	48%

*Bevacizumab

Chemoradiotherapy for locally advanced Pancreatic Cancer

Author	Year	n	Radiation	Chemo	DOSE	Dose /Fr	GI ulcer ≥ grade 3	Survival(OS)		
								MST	1-y OS	2-y OS
Loehrer	2011	34	3DCRT	GEM	50.4 Gy	1.8Gy		11.0	50%	12%
Ikeda	2013	60	3DCRT	s-1	50.4 Gy	1.8Gy	2%	16.2	72%	-
Schellenberg	2011	20	SBRT	none	25 Gy	25 Gy	5%	11.8	50	20
Ben-Josef	2012	50	IMRT	GEM	50-60 Gy	2.0-2.4 Gy	8%	14.8	-	30
Terashima	2012	50	Proton	GEM	50.0-70.2 GyE	2.5-2.7 GyE	10%	-	76.8 %	-
Sachsman	2014	11	Proton	Cape	59.4 Gy (RBE)	1.8 Gy E(RBE)	0%	18.4m	61%	31%
NIRS Phasel/II	2015	42	Carbon	GEM	45.6-55.2 GyE	3.8-4.6 GyE	2%	24m	80%	48%
NIRS Phasell	2015	64	Carbon	GEM	55.2 GyE	4.6 GyE	2%	24.2m	87%	53%
J-CROS Retro	2016	52	Carbon	GEM	55.2 GyE	4.6 GyE	4%	26.2m	81%	60%

GEM:Gemcitabine Cape:Capecitabine CIRT:Carbon-ion Radiotherapy

Courtesy of H Tsujii

Clinical Investigation

Carbon Ion Radiation Therapy With Concurrent Gemcitabine for Patients With Locally Advanced Pancreatic Cancer

Makoto Shinoto, MD,^{*,†,‡} Shigeru Yamada, MD, PhD,^{*}
Kotaro Terashima, MD, PhD,[†] Shigeo Yasuda, MD, PhD,^{*}
Yoshiyuki Shiroyama, MD, PhD,[†] Hiroshi Honda, MD, PhD,[†]
Tadashi Kamada, MD, PhD,^{*} Hirohiko Tsujii, MD, PhD,^{*}
and Hiromitsu Saisho, MD, PhD,[§] the Working Group for Pancreas
Cancer

^{*}Hospital of Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan; [†]Ion Beam Therapy Center, SAGA HIMAT Foundation, Tosu, Japan;

[‡]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; and [§]Department of Internal Medicine and Clinical Oncology, Kaken Hospital, Chemotherapy Research Institute, Chiba, Japan

Received Sep 17, 2015, and in revised form Dec 14, 2015. Accepted for publication Dec 15, 2015.

Vielen Dank für ihre Aufmerksamkeit

