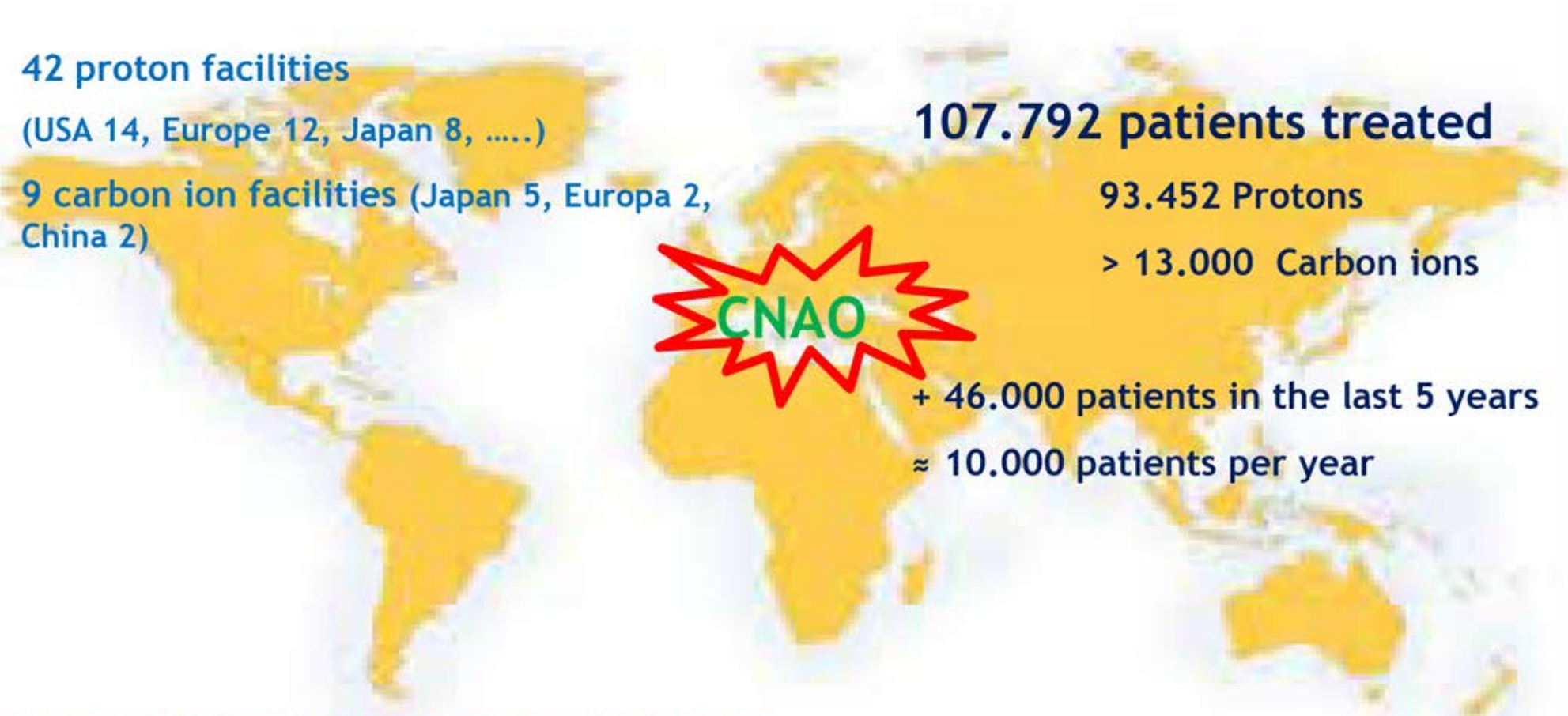
CLINICAL EXPERIENCE WITH IONS

Piero FOSSATI, MD
CNAO (Centro Nazionale di Adroterapia Oncologica)
Pavia, Italy



42 proton facilities

(USA 14, Europe 12, Japan 8, …..)

9 carbon ion facilities (Japan 5, Europa 2, China 2)

CNAO

107.792 patients treated

93.452 Protons

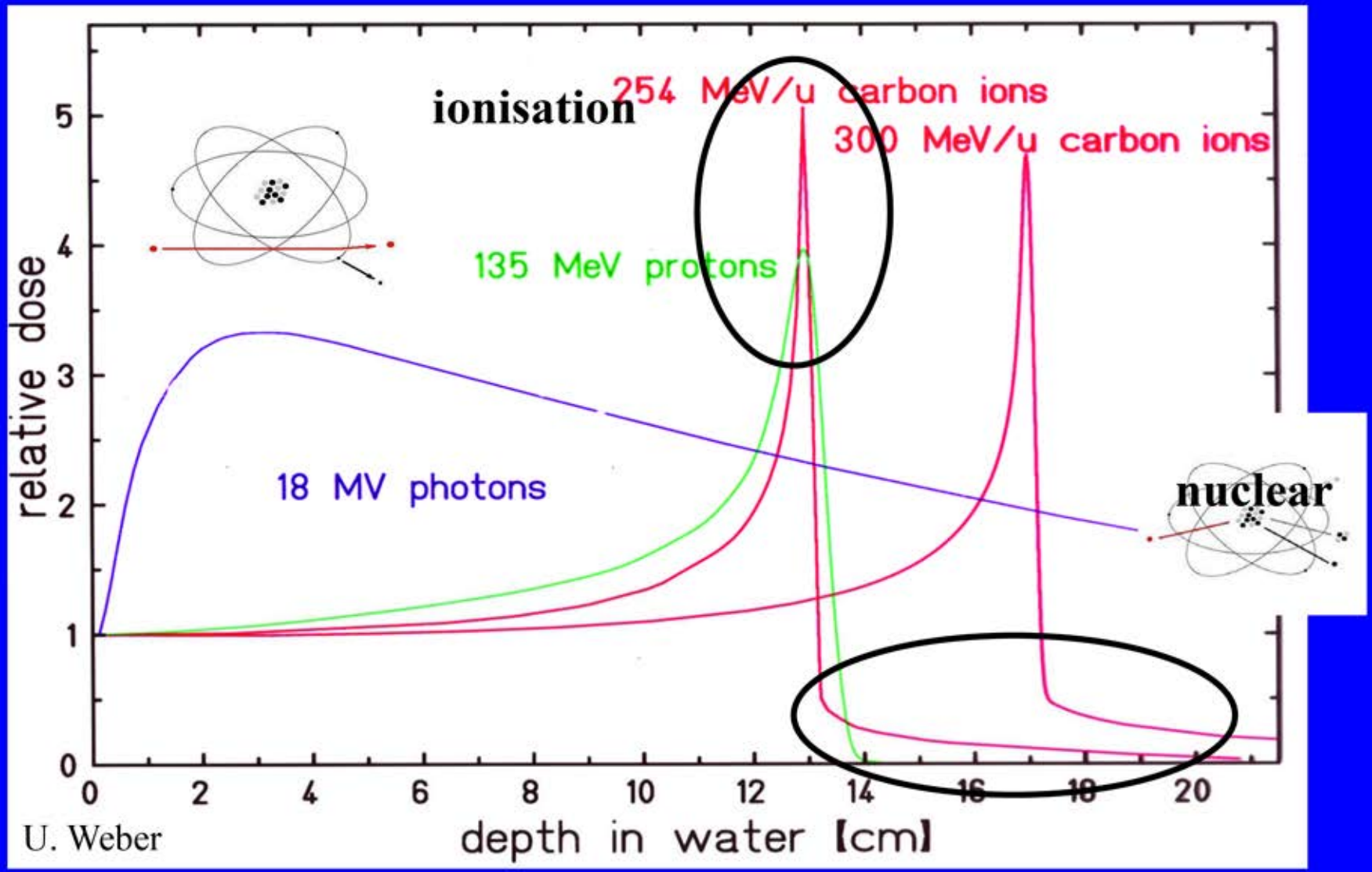
> 13.000 Carbon ions

+ 46.000 patients in the last 5 years

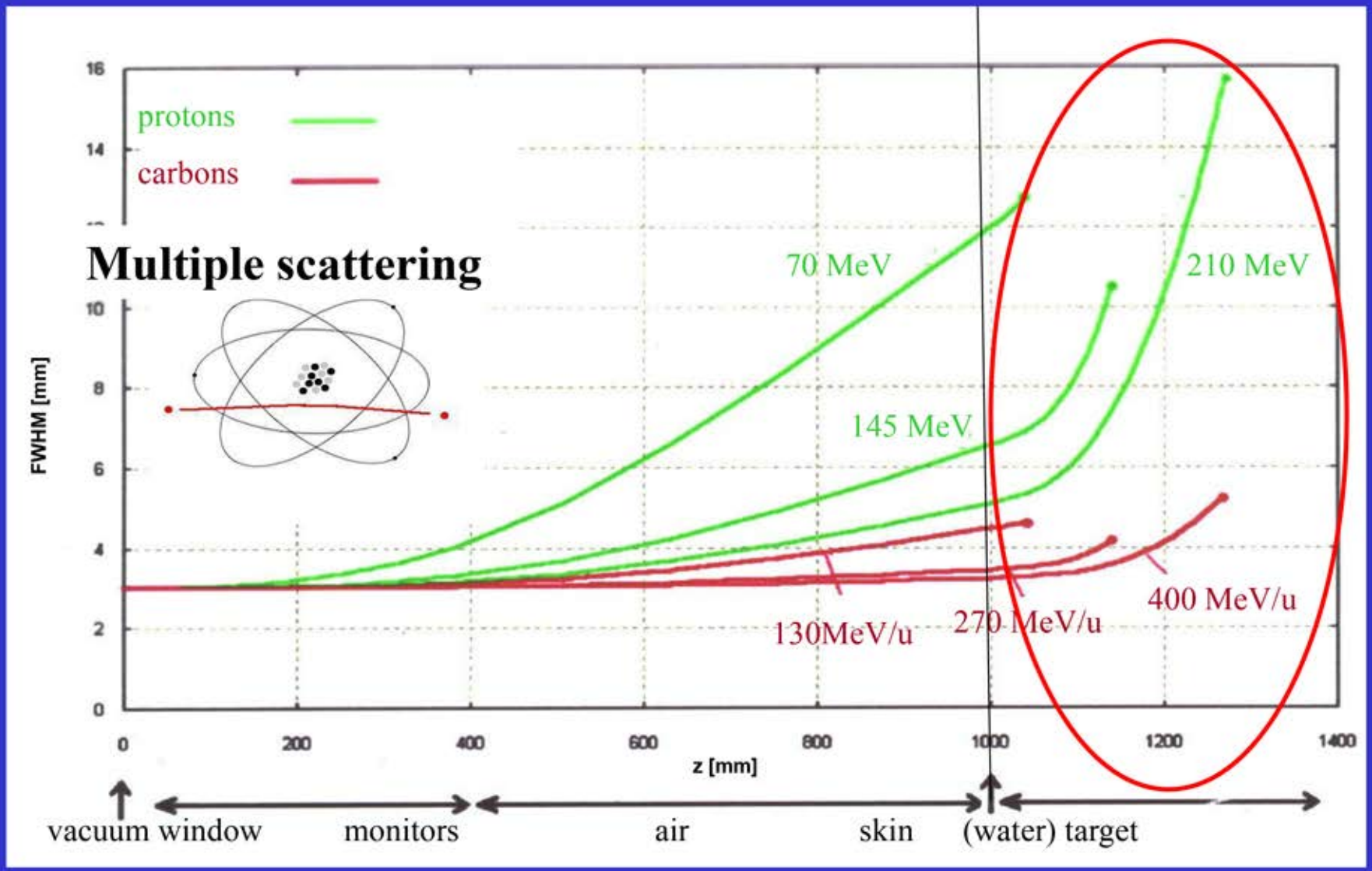
≈ 10.000 patients per year

24 particle facility about to start in 3 years

Physics


ionisation
254 MeV/u carbon ions
300 MeV/u carbon ions
135 MeV protons
18 MV photons
nuclear
relative dose
depth in water [cm]
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16
18
20
U. Weber

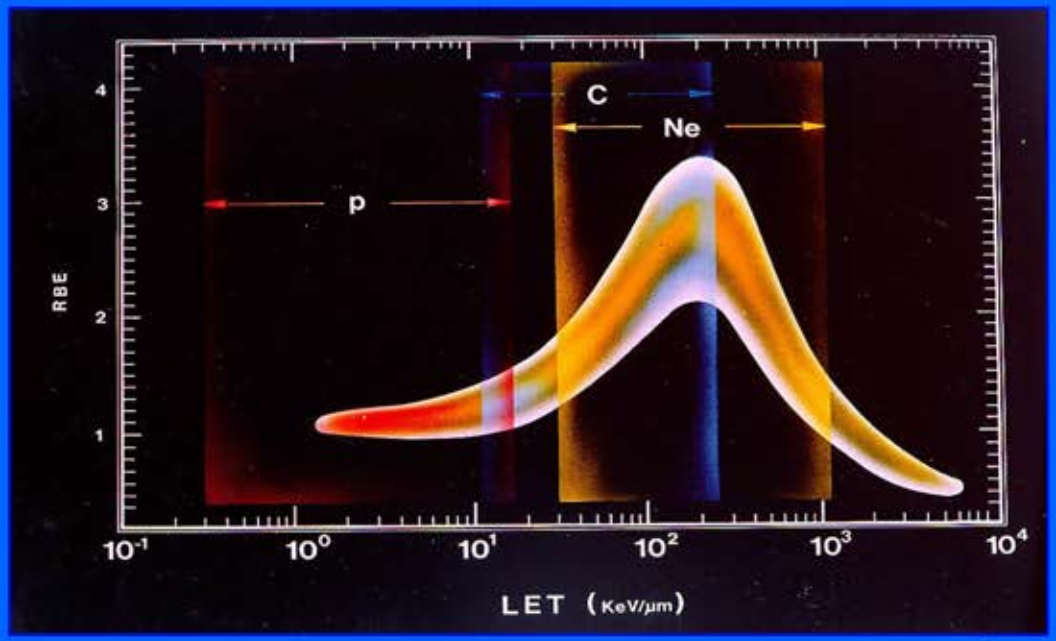
Beam scattering for a real scanning setup (exit window, monitors, air, patient)



Calc. U.Weber, RKA AG

institutCurie

BIOLOGY



Low LET

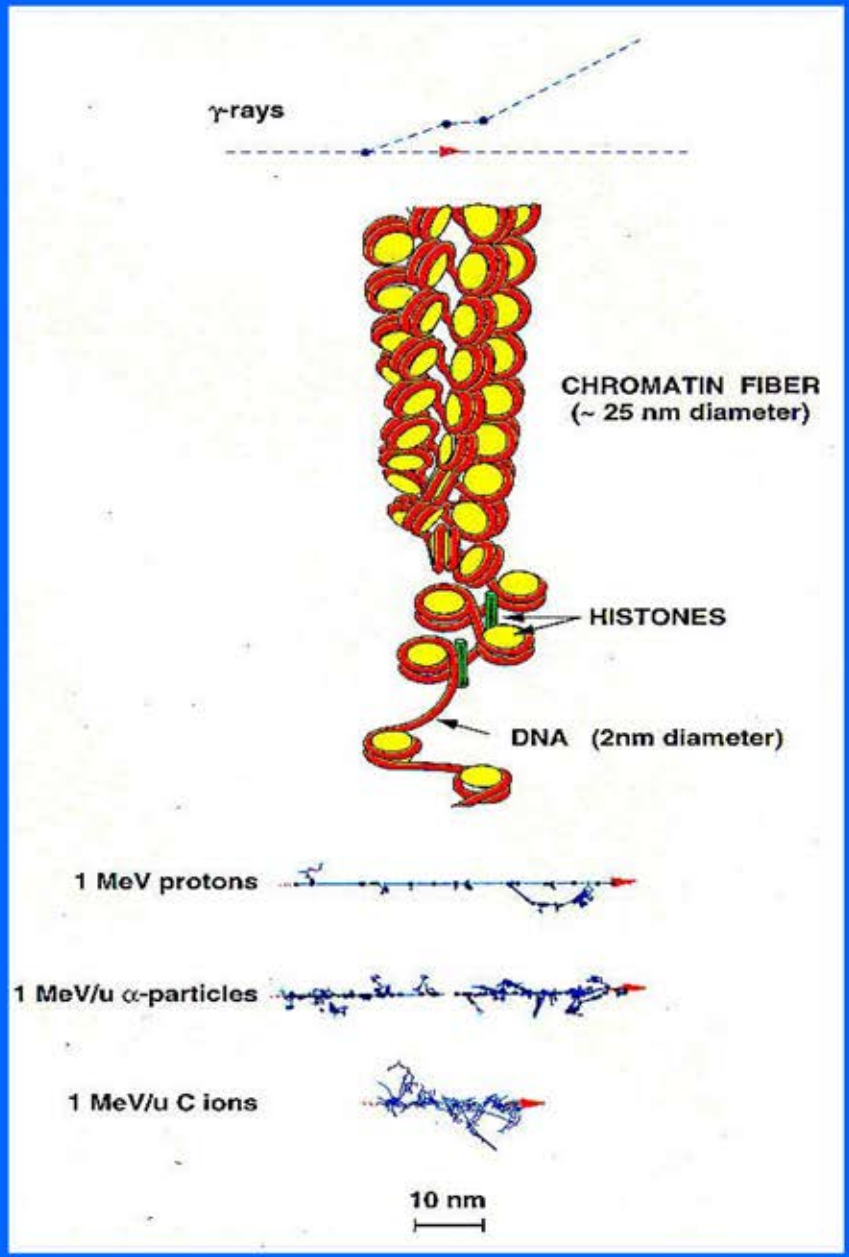
l----------l----------l---------l-----

(<20 Ke V/micron)

High LET

l---l---l---l---l---l---l---l---l--- l--- l---(>

20 – 1000 KeV/micron)



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 the radiosensitive organs ; para-spinal
- decline other therapies such as second surgery, limb amputation, concurrent chemo-radiation etc.
- unresectable or medically inoperable

Carbon Ion Clinical Trials at NIRS

Based on "high physical selectivity" & "biological effectiveness"

a) Establish safe and precise C- ion

b) Conduct phase

1. A

2. conduct comparative study, if

A total of 69 phase I and phase II protocols have been conducted at NIRS since 1994.

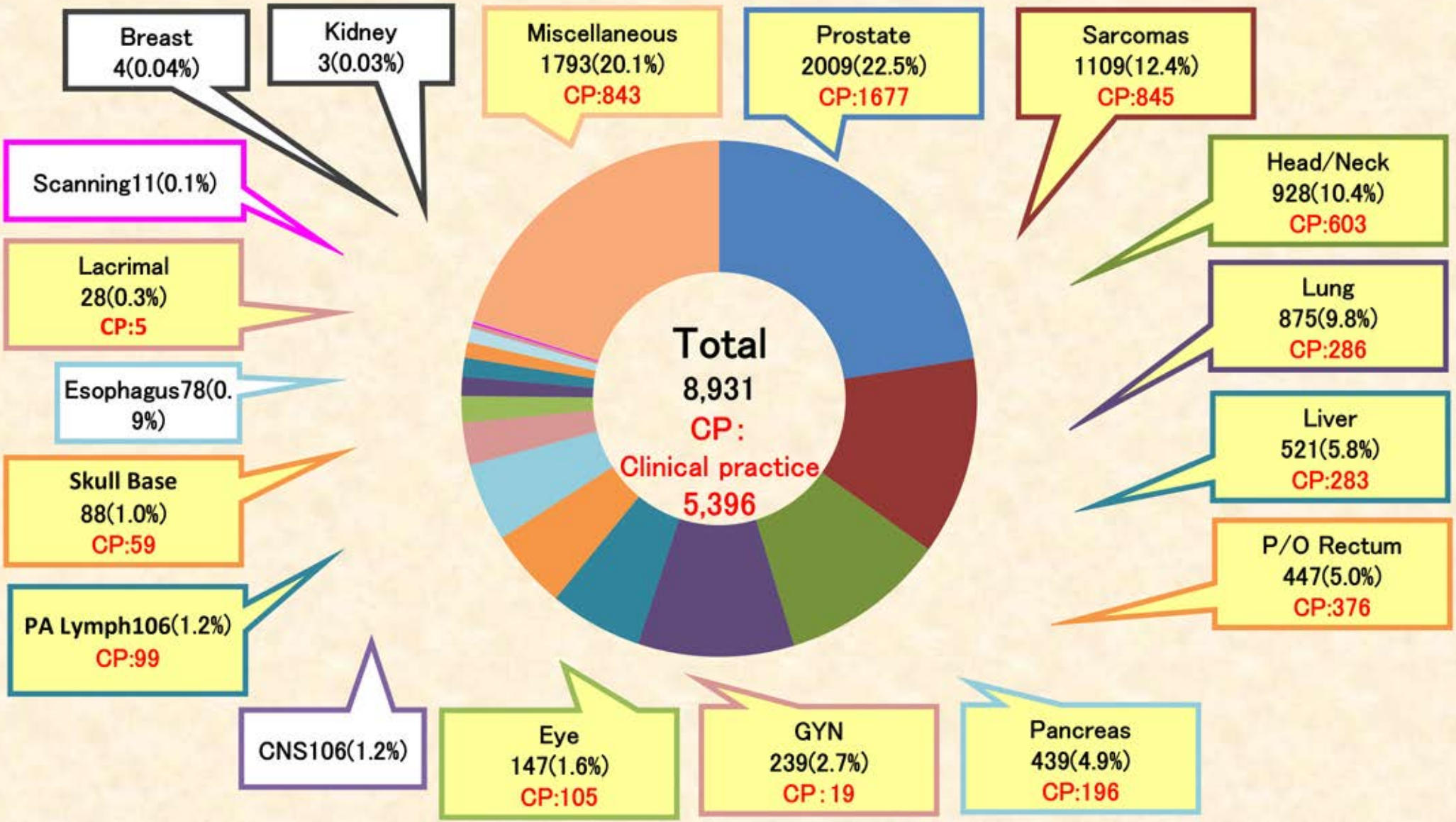
istant tumor

-fractionation in common cancer

Hypo-fractionated

To prove efficacy and safety of C-ion RT

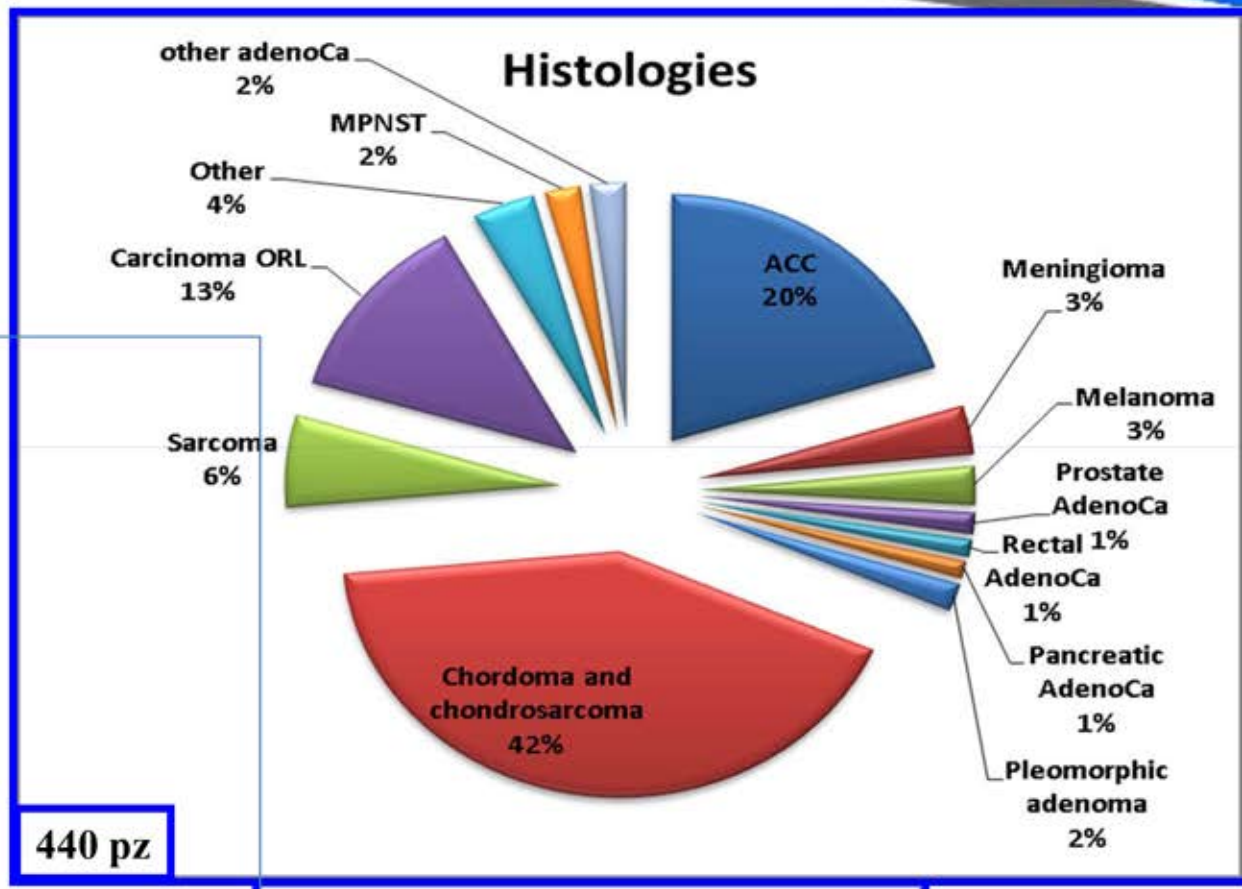
Patient Distribution Enrolled in Carbon Therapy at NIRS (Treatment: June 1994～March 2014)

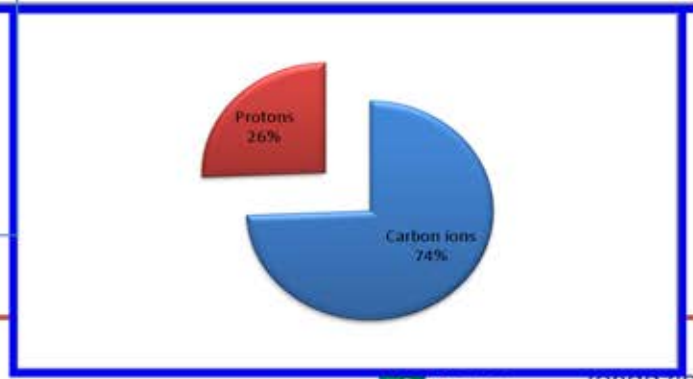


Clinical Activity at CNAO

30 Trials PHASE II

- Skull base chordoma and chondrosarcoma
- Spinal and sacral chordoma and chondrosarcoma
- Intracranial Meningioma
- Boost for locally advanced head and neck cancer
- Salivary gland tumors
- Spine and H&N bone and soft tissue sarcoma
- Mucosal melanoma
- Recurrent pleomorphic adenoma
- Reirradiation of head and neck tumors
- Orbital tumor
- High risk prostate cancer
- Locally advanced pancreatic cancer
- Reirradiation of local recurrence rectal cancer
- Hepatocarcinoma
- Hodgikin Lynphoma stage I -II





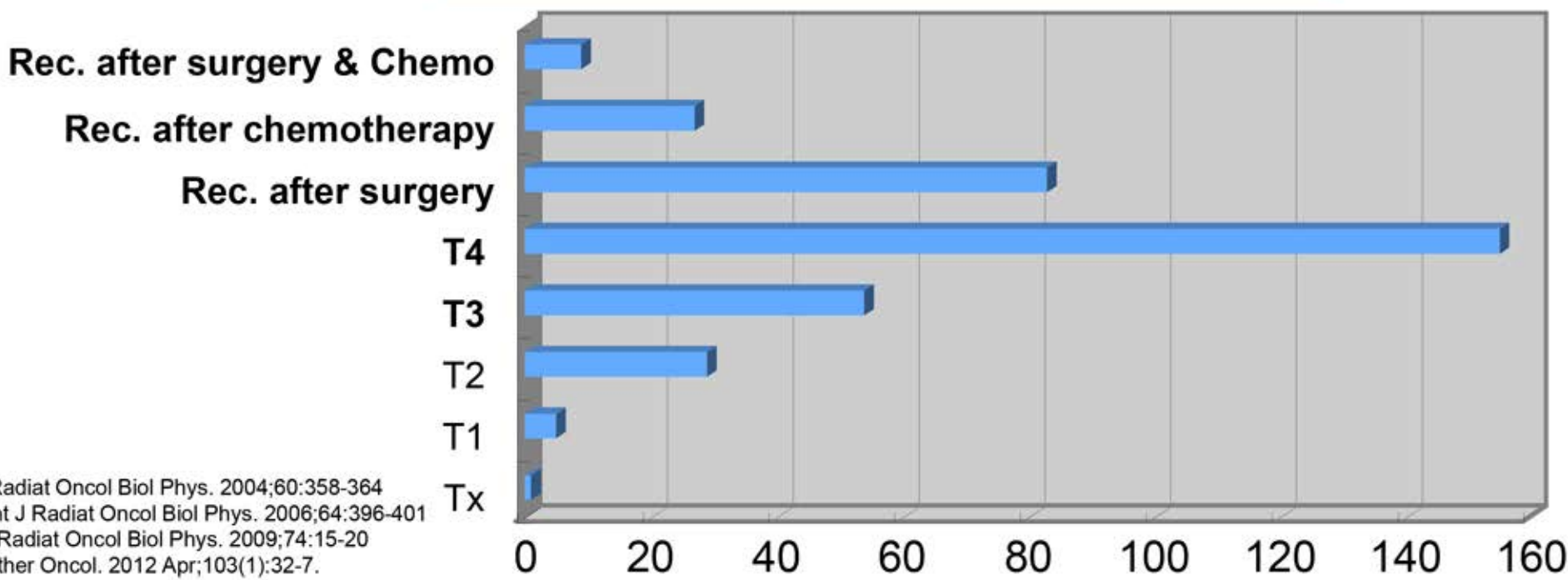
Carbon Ion Radiotherapy for Head-and-Neck Tumors

94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 →

June 1994～ April 1996～ April 1997～ ～ ongoing

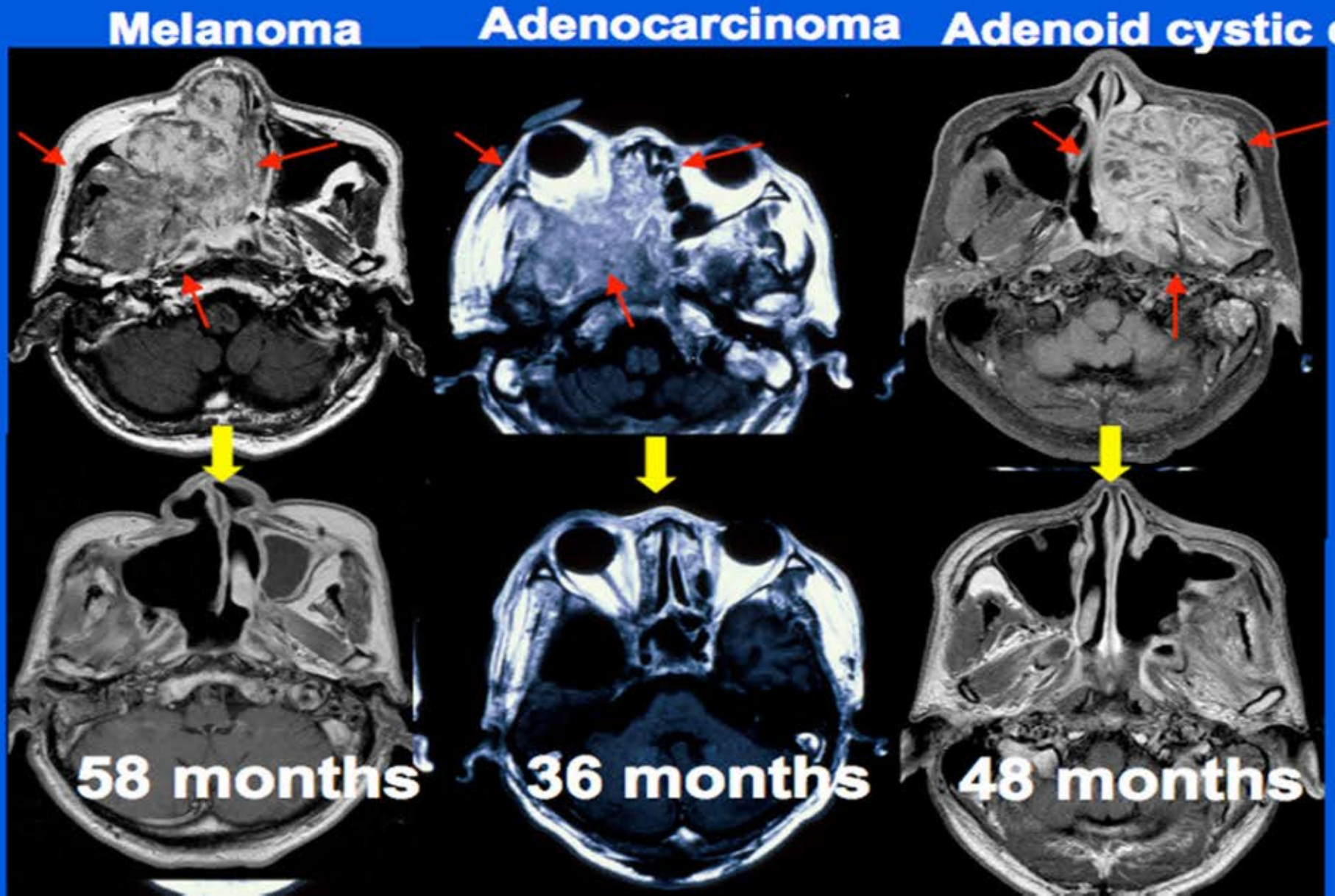
Phase I/II (9301)	Phase I/II (9504)
18 fr./4 wks	16 fr./4 wks

Phase II (9602) n=542
64 or 57.6 GyE/16 fr./4 wks

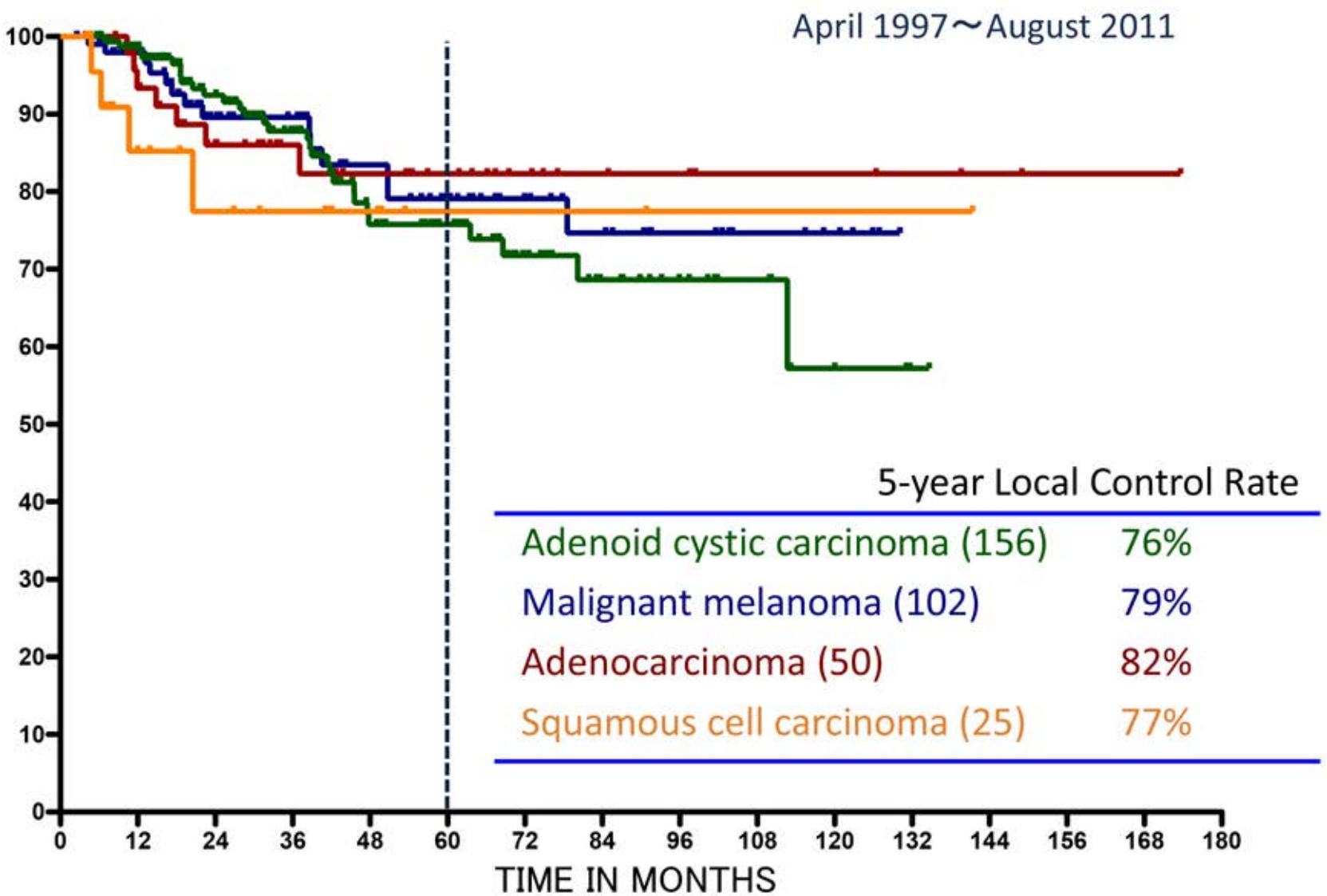


Mizoe et al. Int J Radiat Oncol Biol Phys. 2004;60:358-364
Hasegawa et al. Int J Radiat Oncol Biol Phys. 2006;64:396-401
Yanagi et al. Int J Radiat Oncol Biol Phys. 2009;74:15-20
Mizoe et al. Radiother Oncol. 2012 Apr;103(1):32-7.

Head-and-Neck Cancers

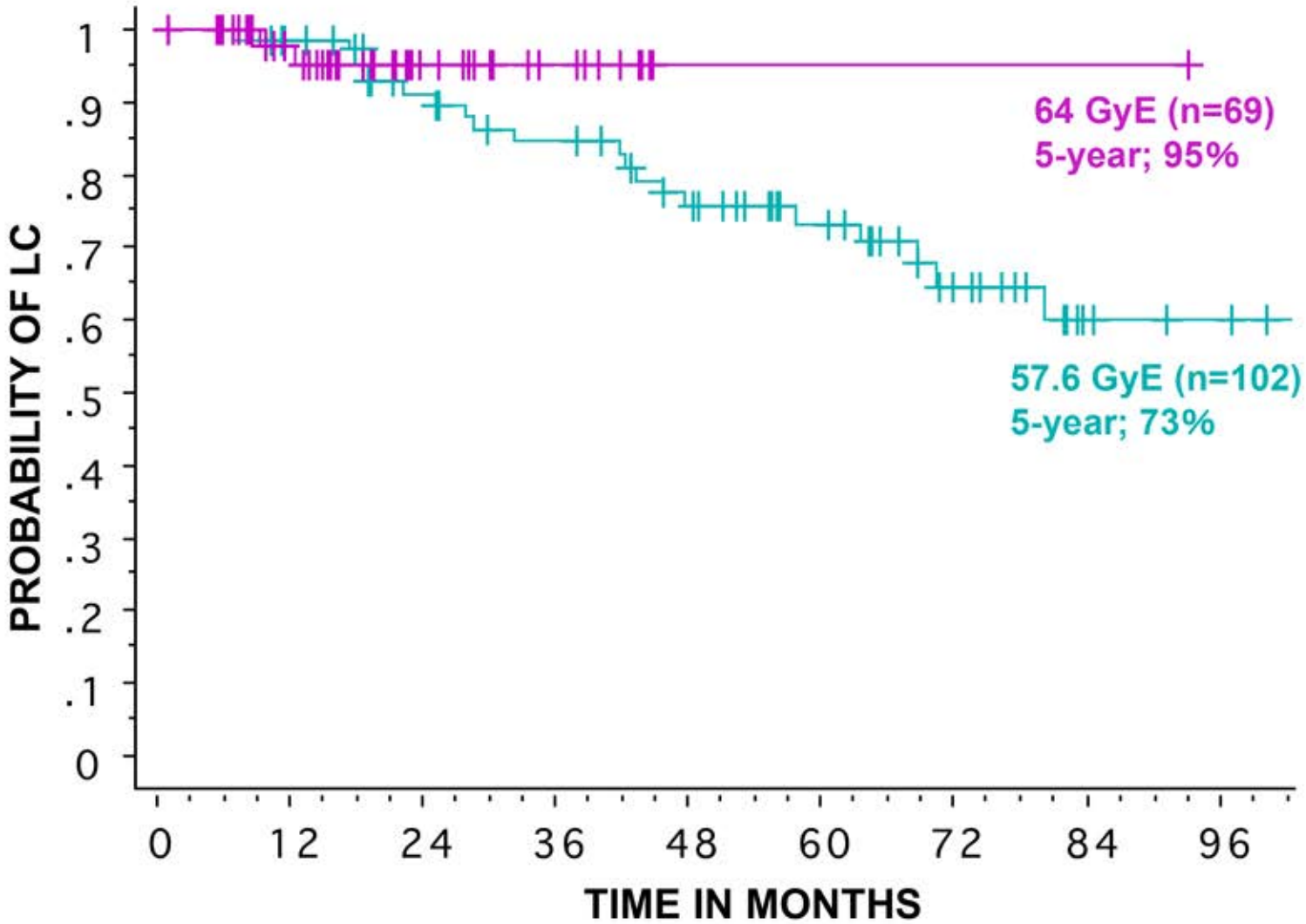


Local Control according to Histological Types



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

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

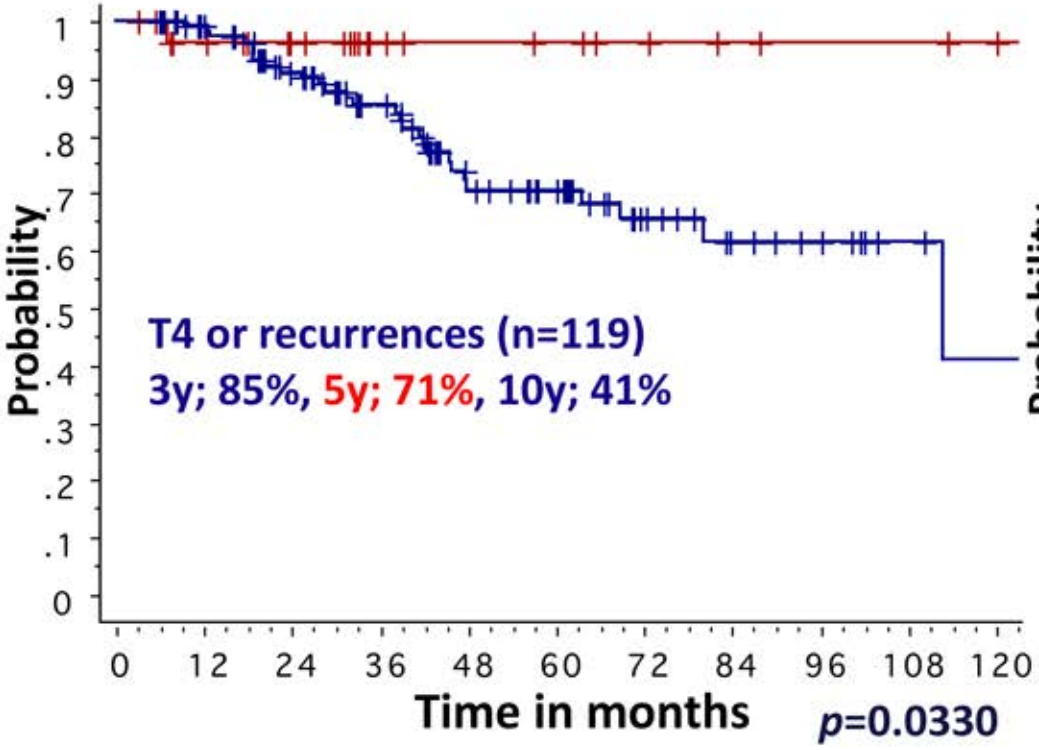


Carbon Ion Radiotherapy for Adenoid Cystic Carcinomas

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

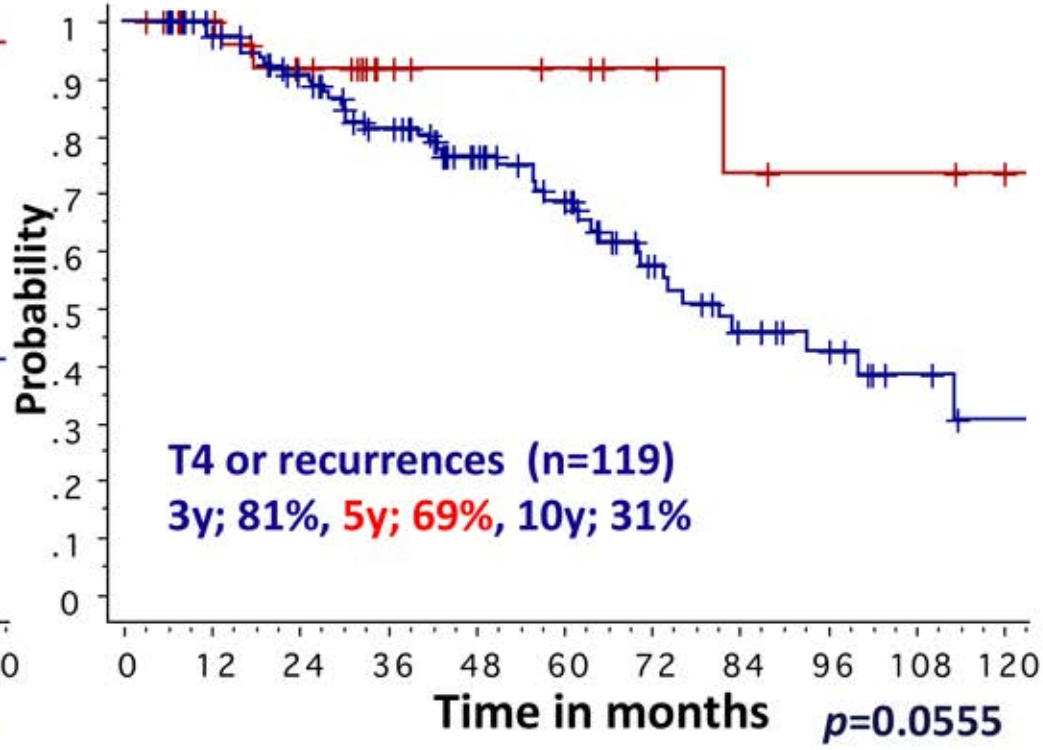
Local Control

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



Overall Survival

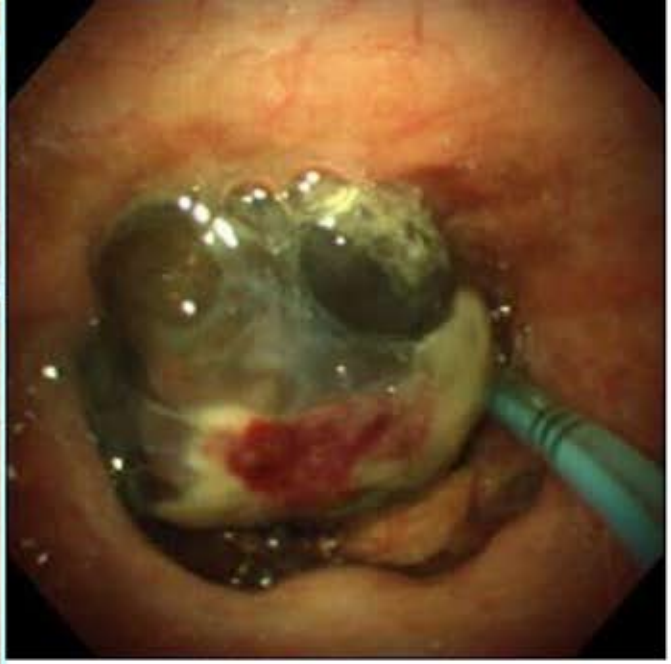
T1 to T3 (n=32)
3-5y; 92%, 10y; 74%



MELANOMA

60 Months

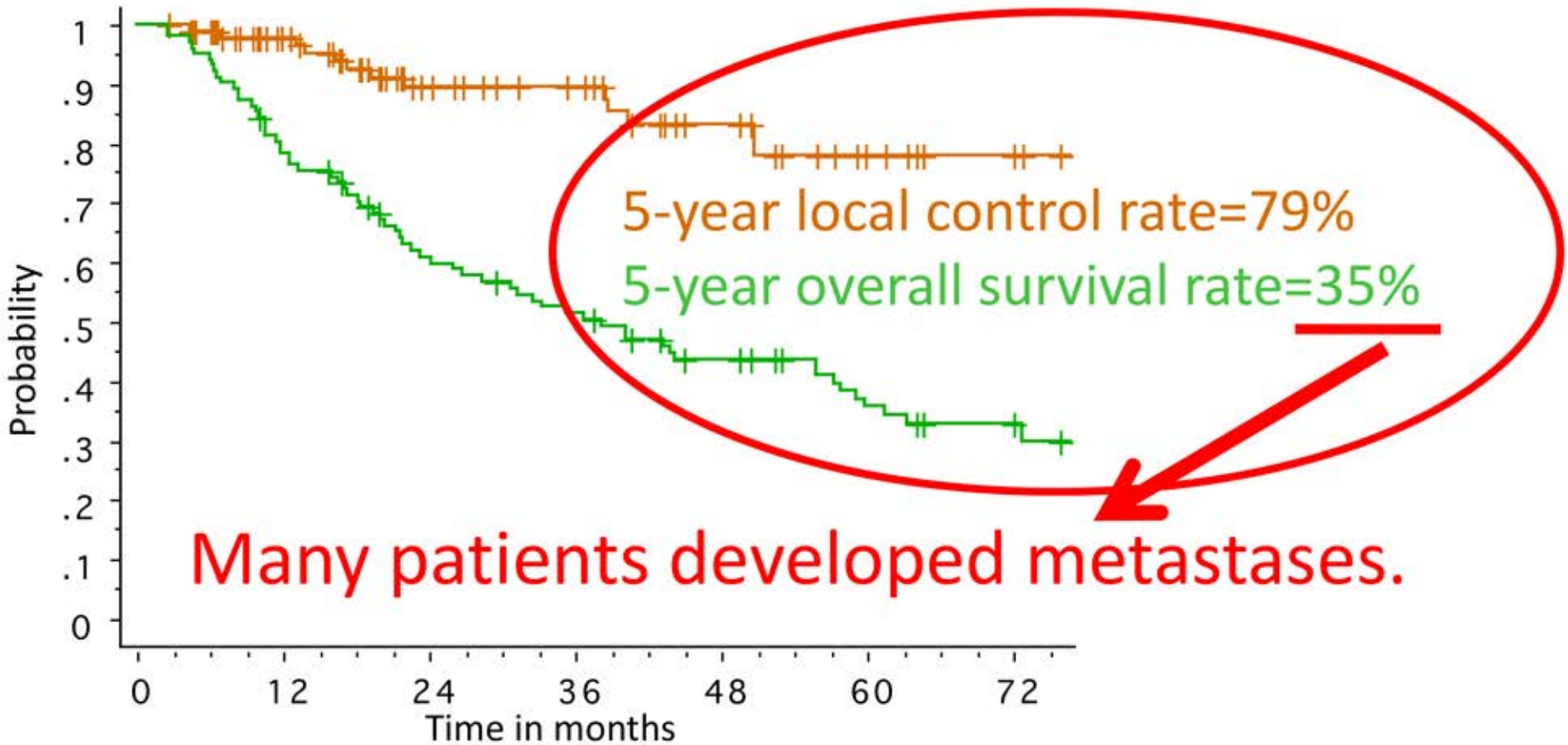
36 Months



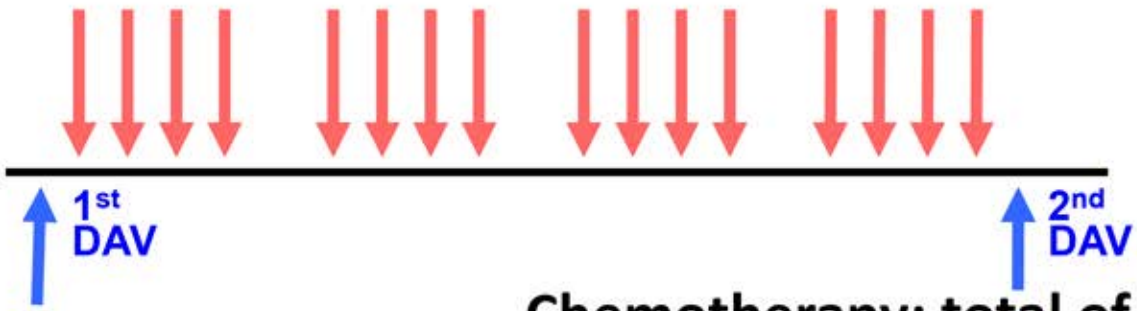
100 Months

Mucosal Malignant Melanoma(n=102)

Carbon ion radiotherapy alone: 57.6 GyE/ 16 fr.



Combined Chemotherapy and C-ion RT for Mucosal Malignant Melanomas



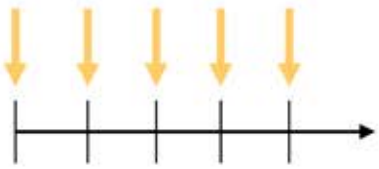
Carbon Ions
57.6 GyE/ 16 fr./ 4wks

Chemotherapy; total of 5 courses

VCR (0.7mg/m²)

ACNU (70mg/m²)

DTIC (120mg/m²)



Day 1-5

4wk interval

VCR, ACNU **VCR, ACNU** **VCR, ACNU** **VCR, ACNU**

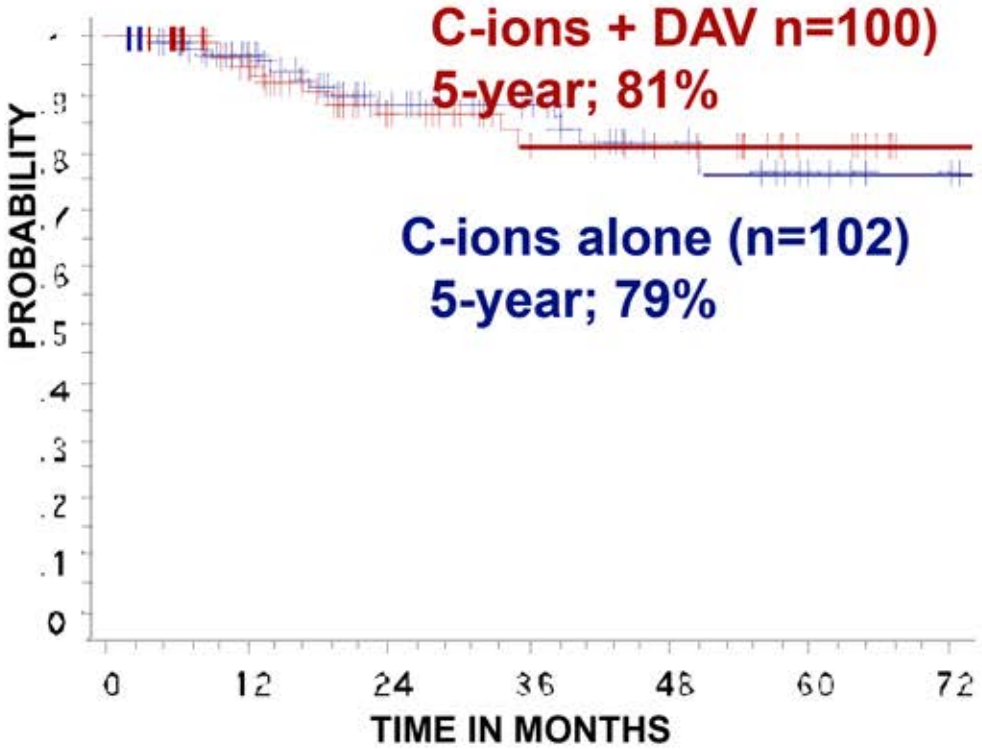
DTIC **DTIC** **DTIC** **DTIC**

Day 1-5 **Day 1-5** **Day 1-5** **Day 1-5**

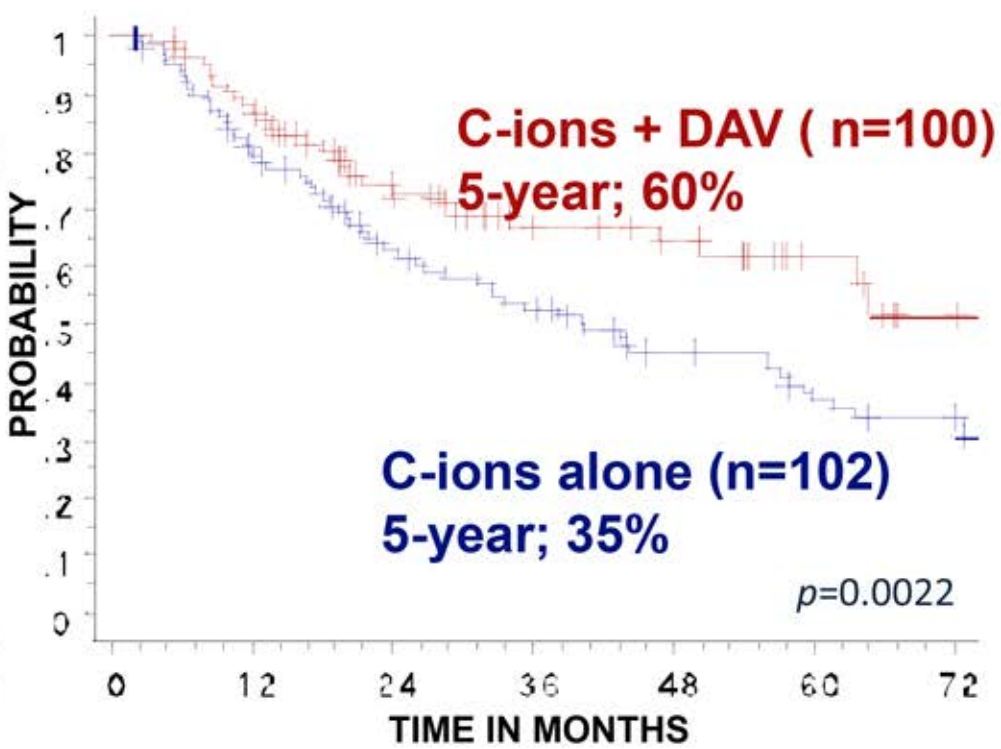
The interval between each course is 4 weeks

Combined Chemotherapy and C-ion RT for MMM

Local Control



Overall Survival



Local Control and Overall Survival of Mucosal Malignant Melanomas

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

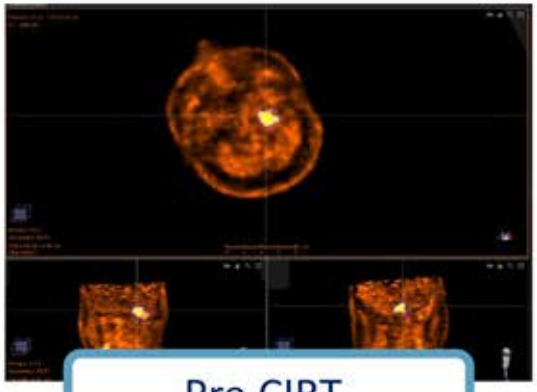
April 1997～February 2001: Carbon ions alone (102 cases)
April 2001～August 2011: Chemo-C-ions (107 cases)

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)

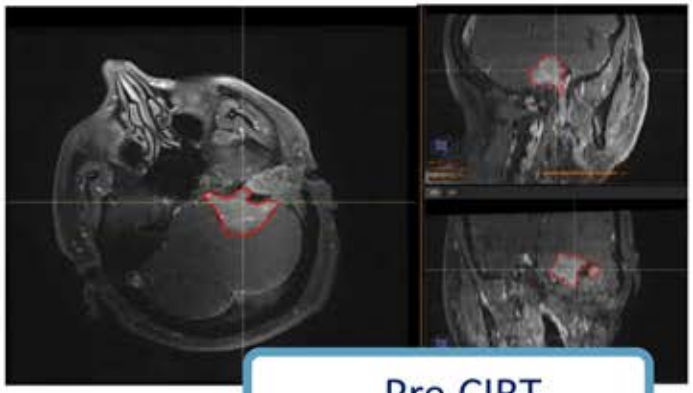
Late Radiation Morbidities		G0	G1	G2 (%)	G3 (%)
Skin	Carbon ions alone	54	43	1 (1)	0 (0)
	Chemo-C-ions	79	28	0 (0)	0 (0)
Mucosa	Carbon ions alone	64	27	3 (3)	0 (0)
	Chemo-C-ions	54	52	1 (1)	0 (0)

ACC at CNAO

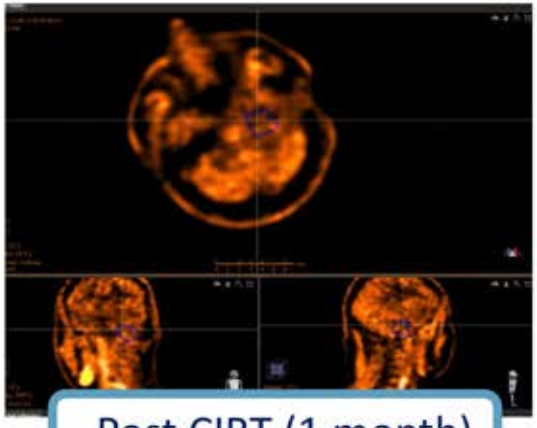
male, 45 years old, ACC recurrence after surgery



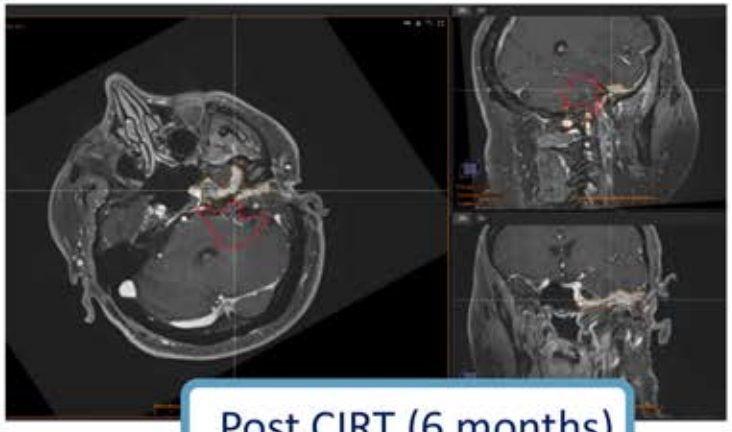
Pre CIRT



Pre CIRT

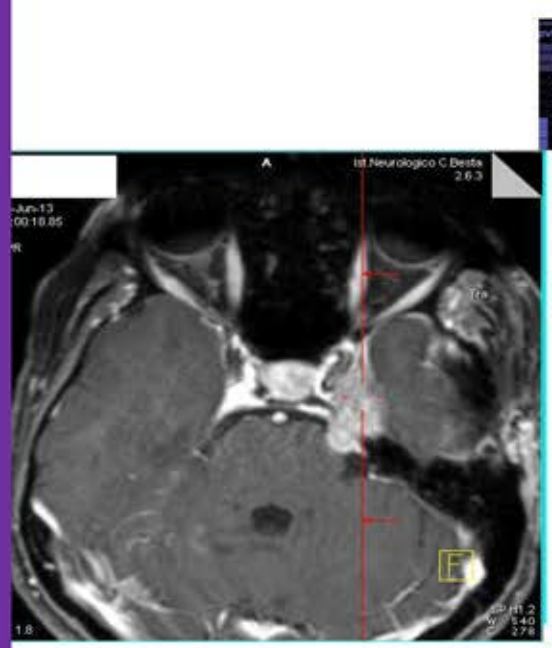


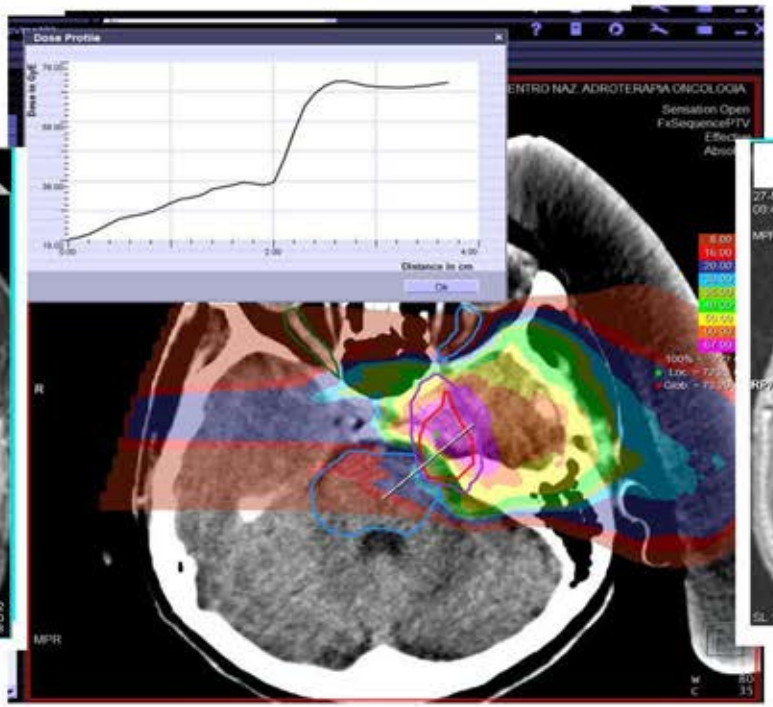
Post CIRT (1 month)

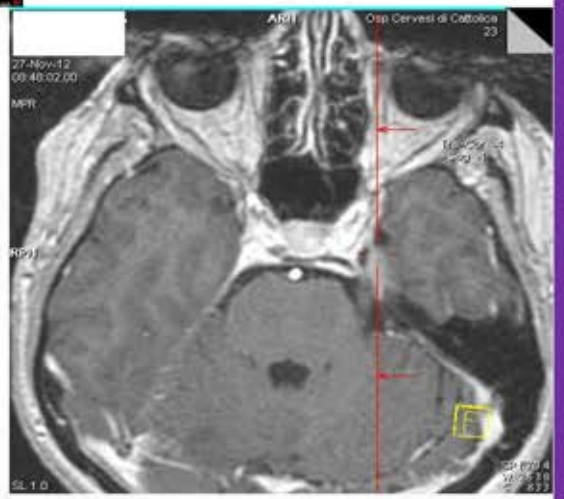


Post CIRT (6 months)

ACC CNAO







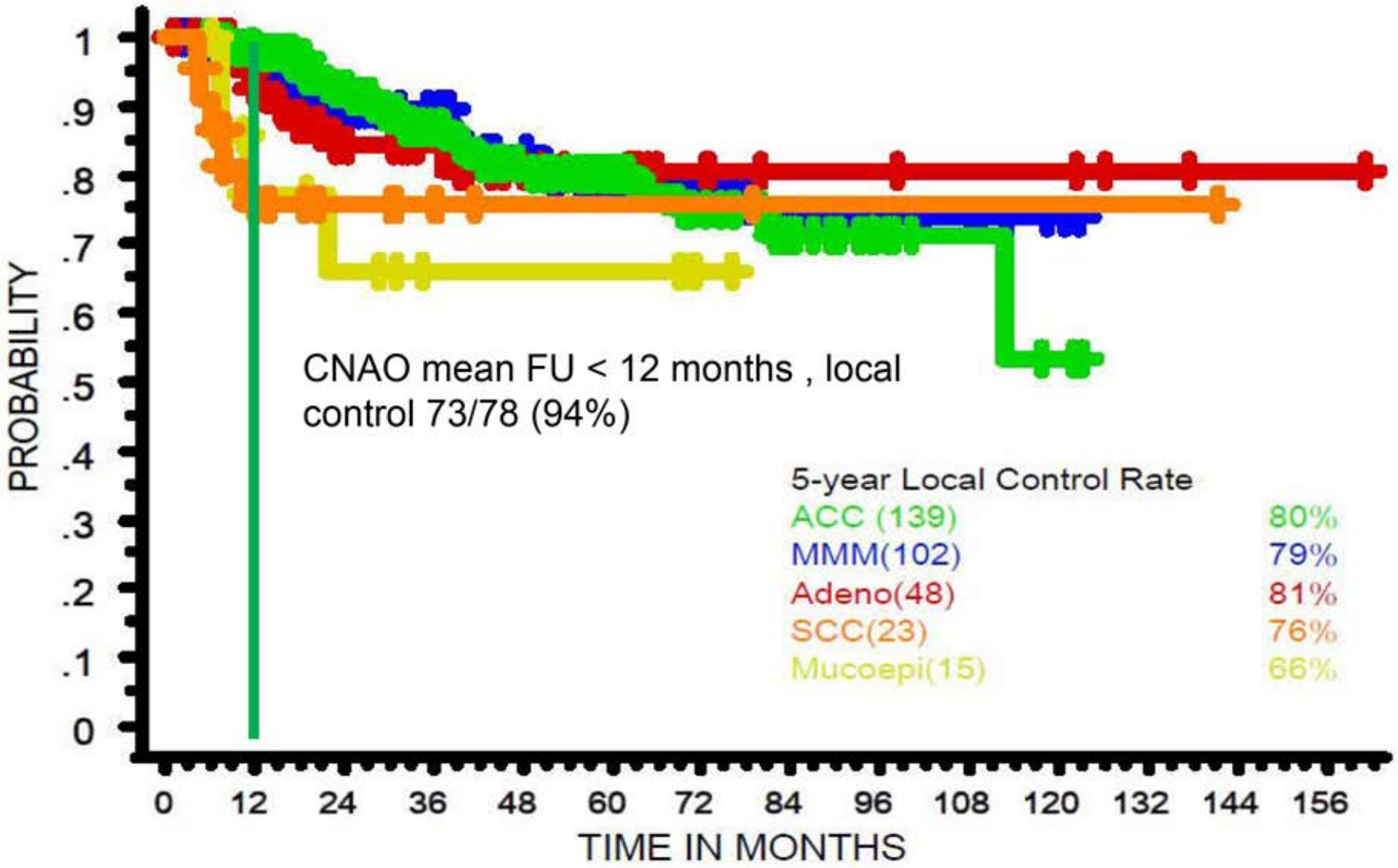
Before treatment

4.3 GyE x 16 fr= 68.8 GyE

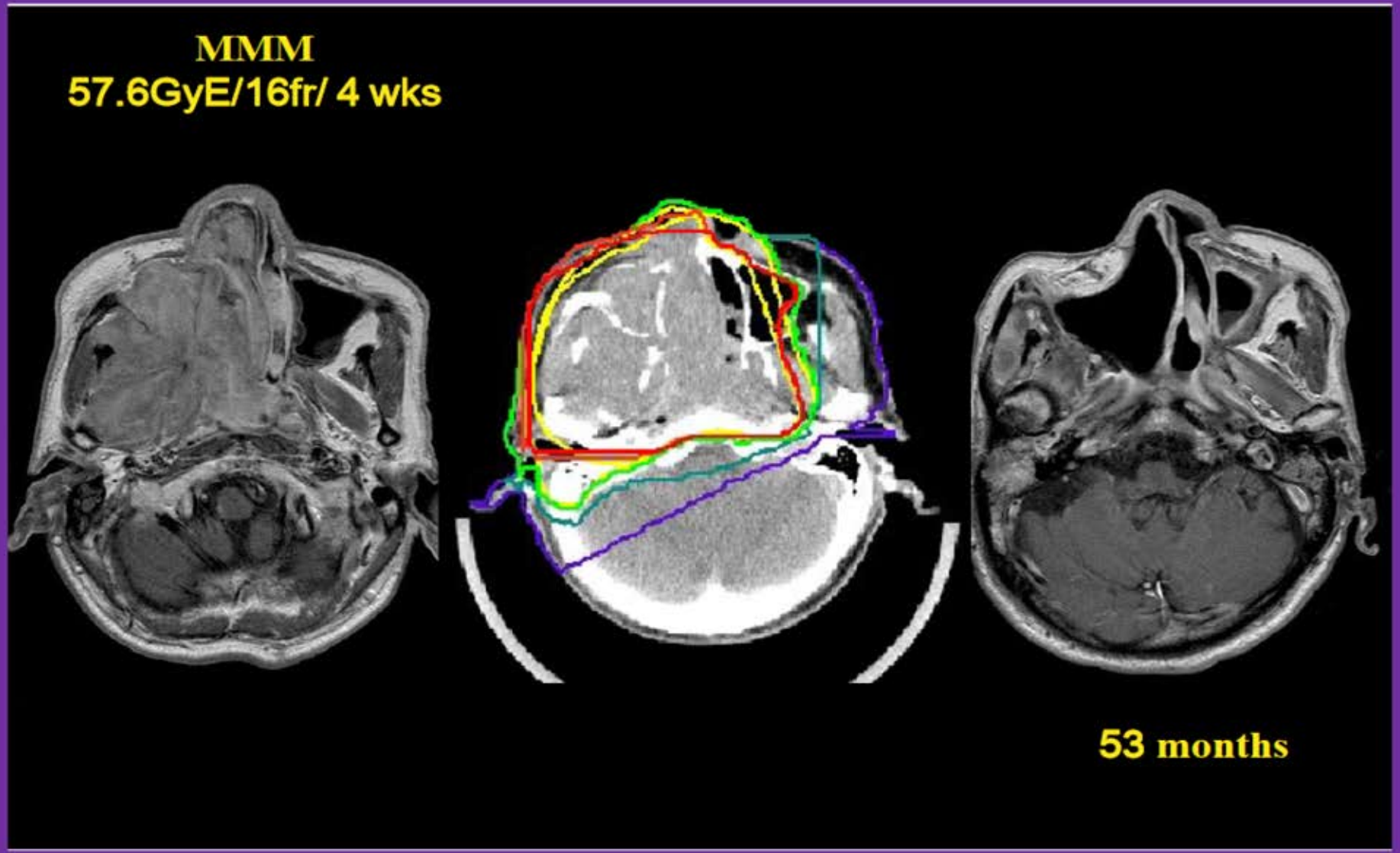
After 9 months

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

Local Control according to Histological Type (Apr 97~Aug 10)

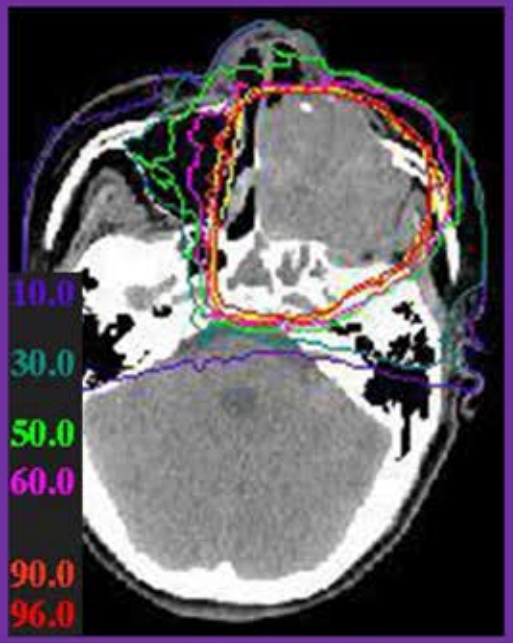


MMM NIRS

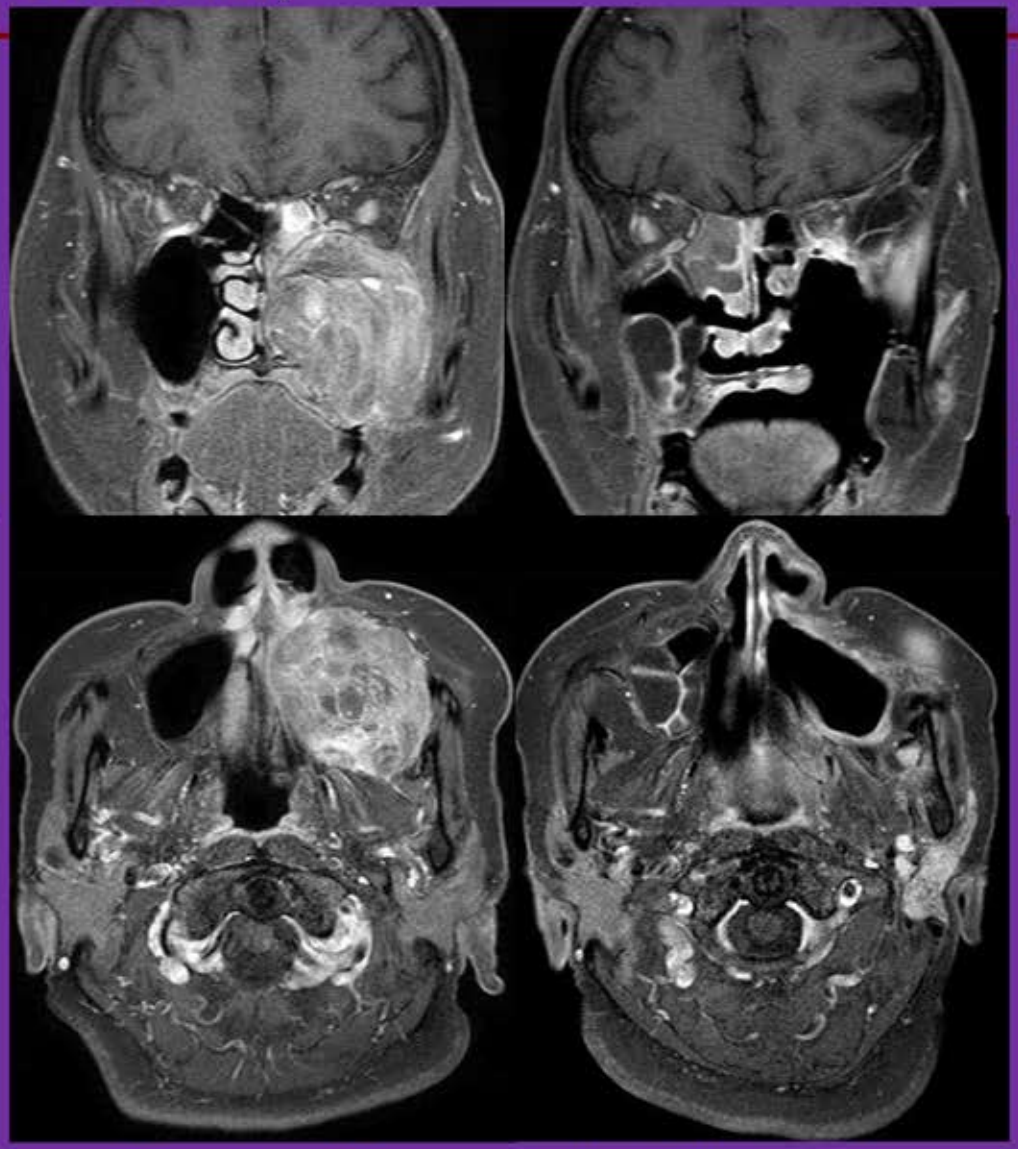


Malignant Melanoma in the Left Maxillary Sinus
(Target volume = 151.9 ml)

64 GyE/16 frs.

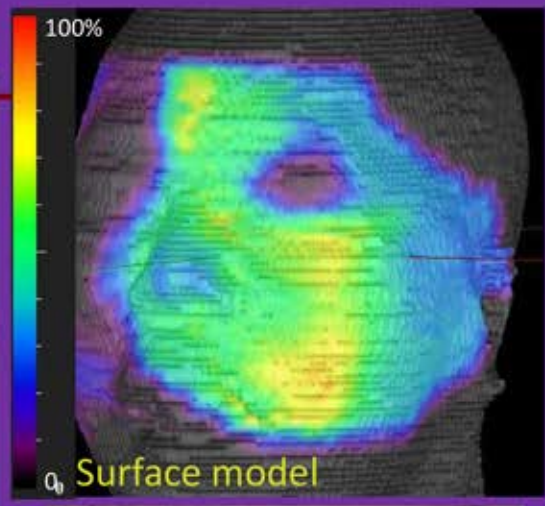


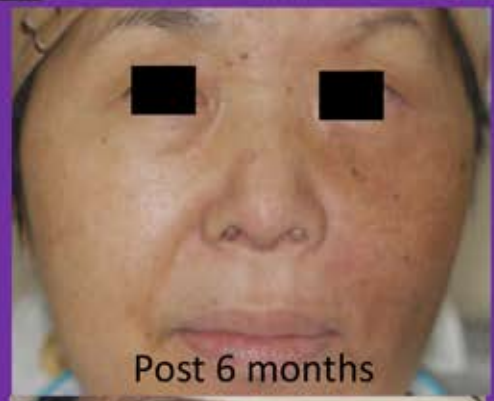
Dose distribution



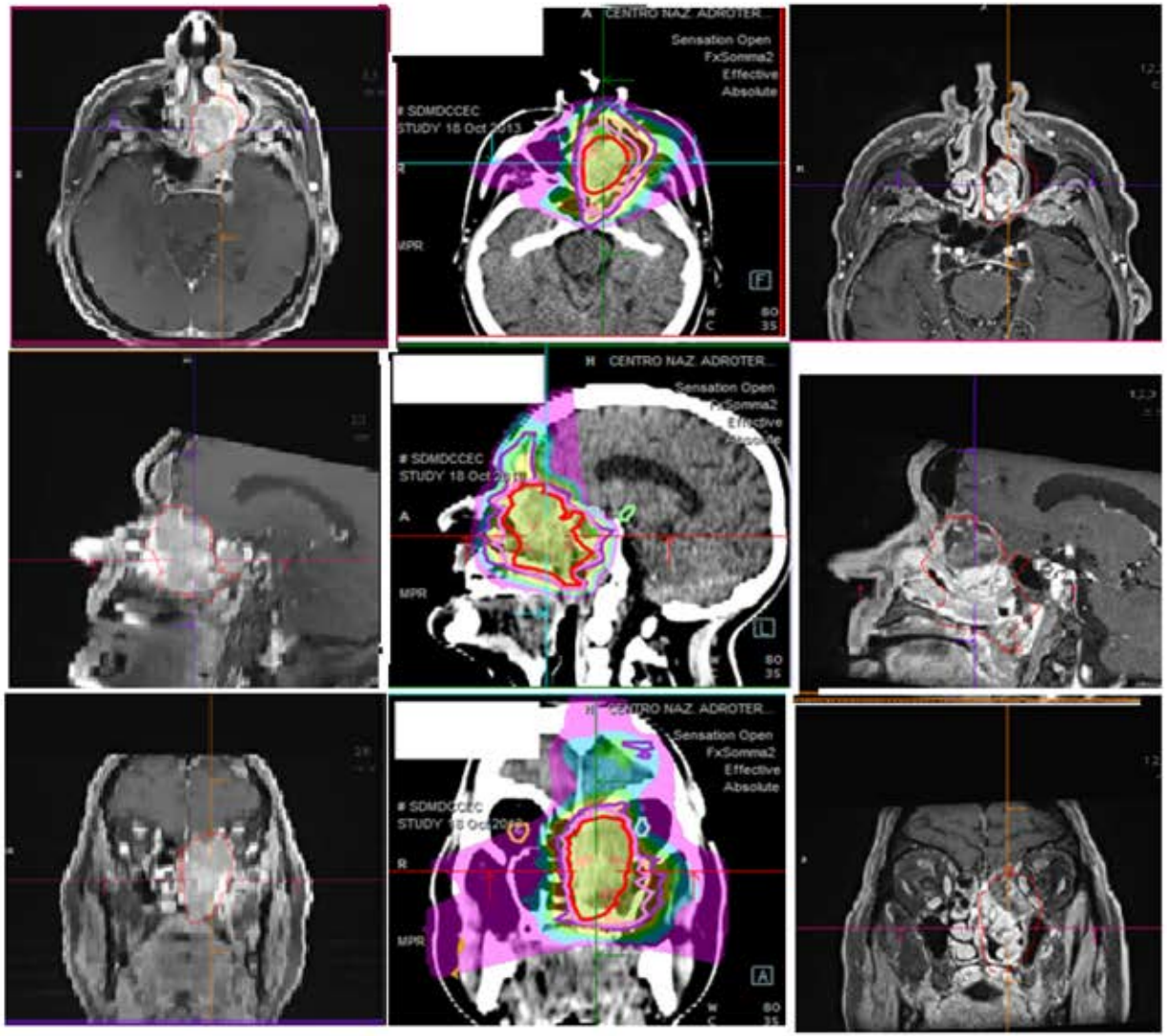
Pre c-ion RT

Post 25 months





MMM CNAO


CENTRO NAZ. ADROTER...
Sensation Open
FxSomma2
Effective
Absolute
SDMDCCEC
MPR
CENTRO NAZ. ADROTER...
Sensation Open
FxSomma2
Effective
Absolute
SDMDCCEC
MPR
CENTRO NAZ. ADROTER...
Sensation Open
FxSomma2
Effective
Absolute
SDMDCCEC
MPR

Skin toxicity

During treatment

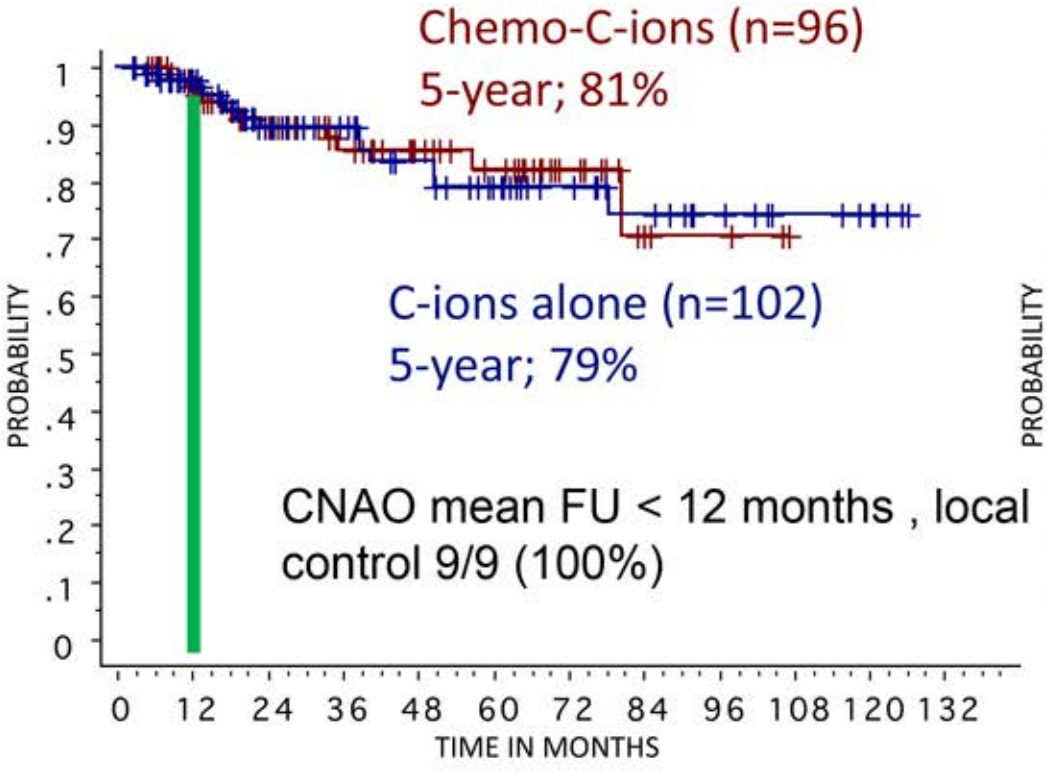
End of treatment

6 months after treatment

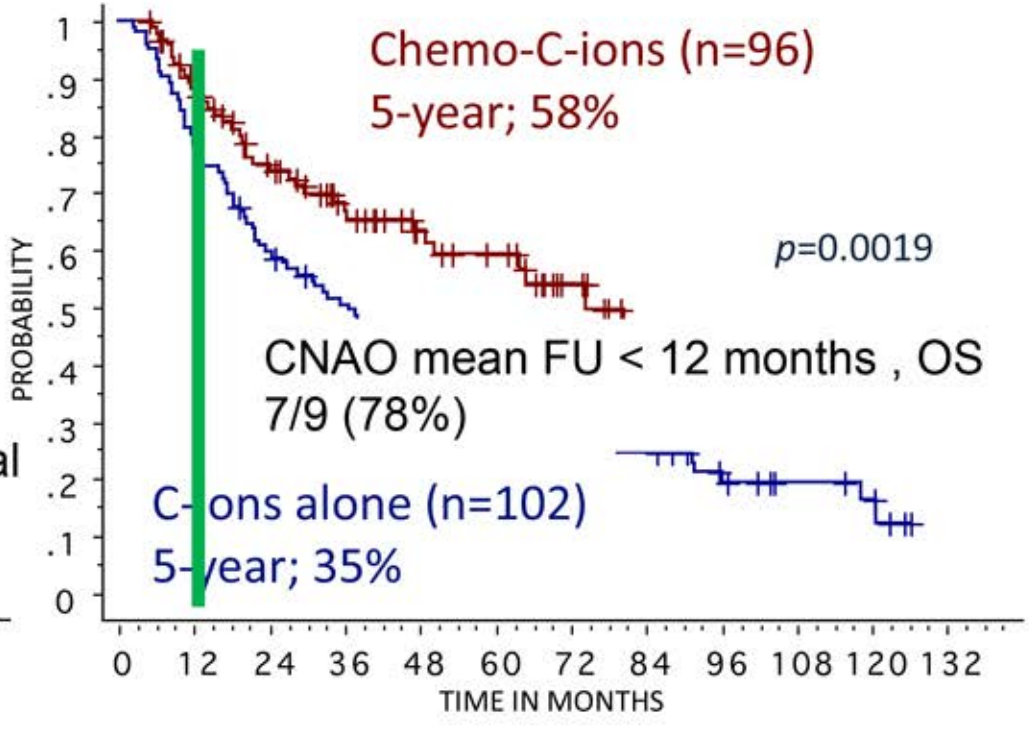
Carbon Ion Radiotherapy for Mucosal Malignant Melanomas

(Apr 97~Feb 11)

Local Control



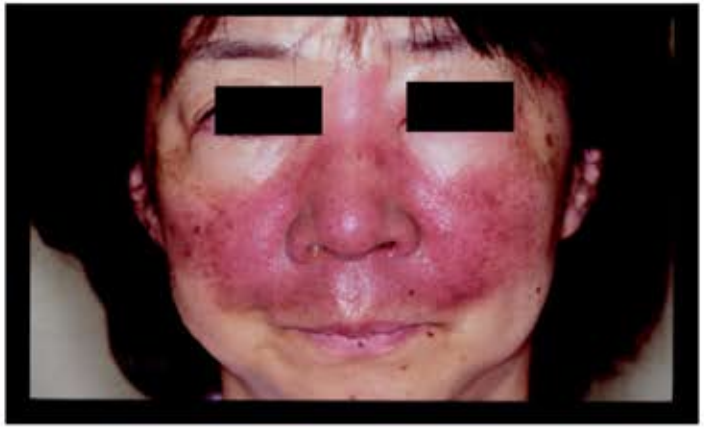
Overall Survival



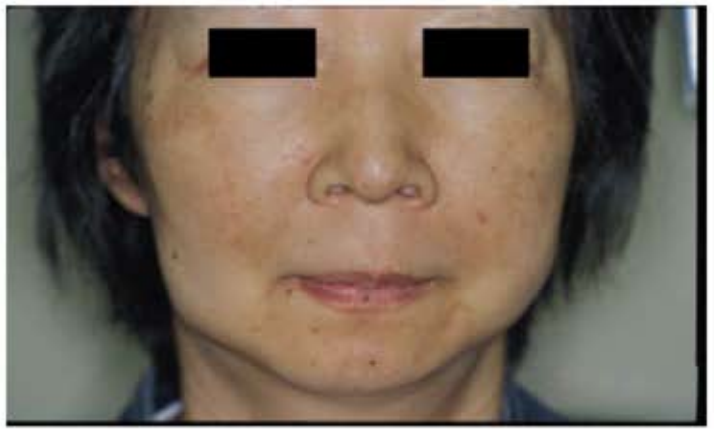
Skin toxicity NIRS

Radiation Dermatitis

G3



Maximum



6 Months after

G1/0

Skin toxicity CNAO

G1

Clinical results comparison

NIRS

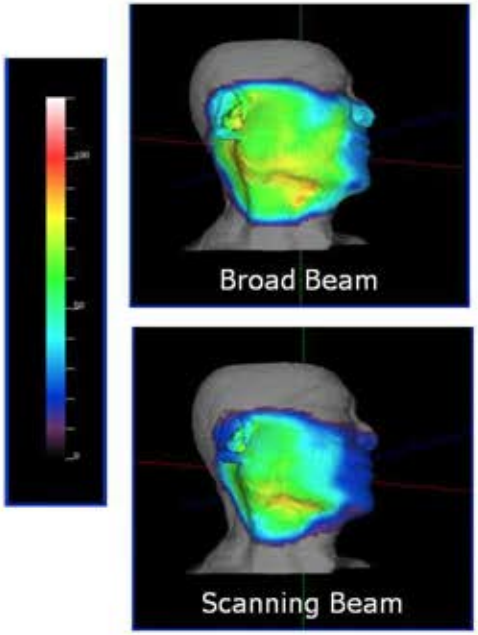
Acute Skin toxicity grade

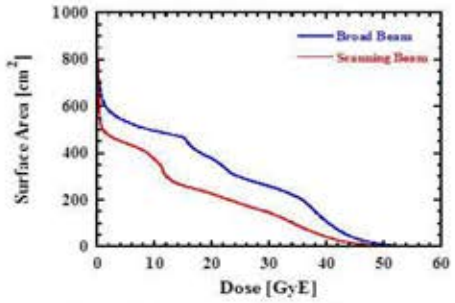
- **G2 28%**
- **G3 4%**

CNAO

Acute Skin toxicity grade

- **G2 10%**
- **G3 0%**





Dose-Surface Area Histogram

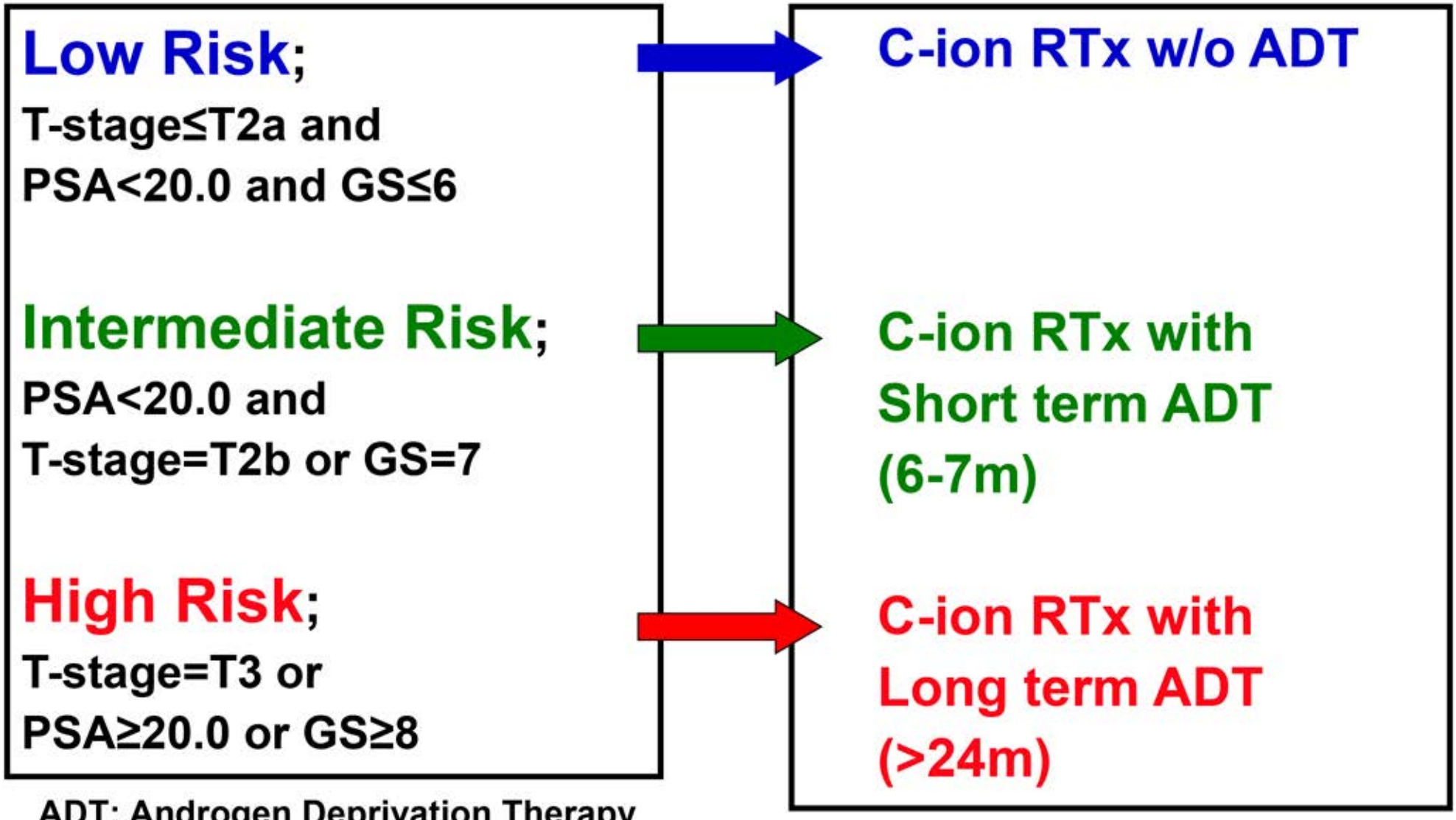
When the CNAO reaction was plotted on the schema of NIRS experience, it looks like somewhat mild reaction than NIRS experience. It may be the reflect of IMPT.

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

Risk Group & Application of Androgen Deprivation



ADT; Androgen Deprivation Therapy

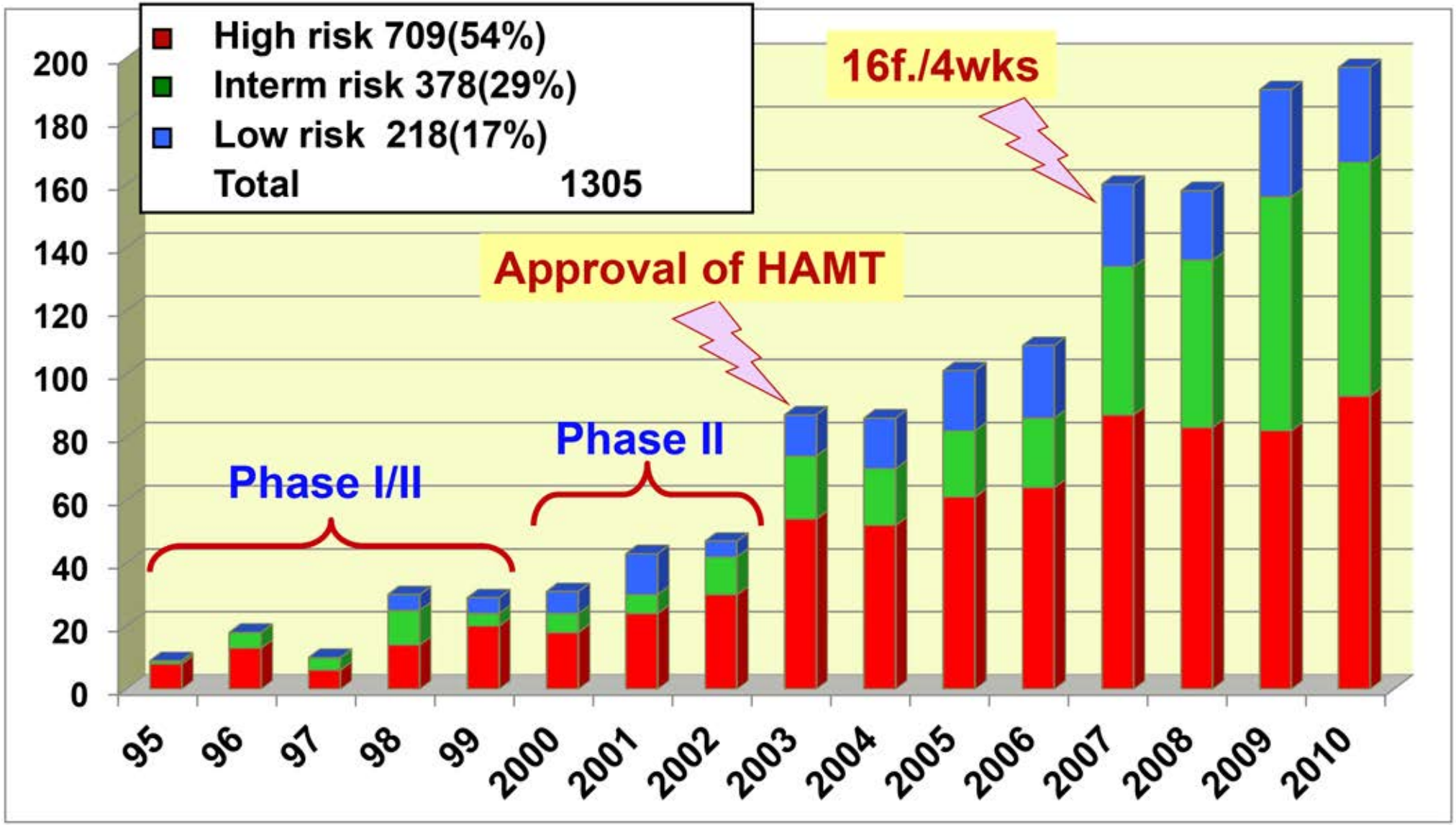
Clinical Study for Prostate Ca at NIRS

Total treated: 1305 pts. Period:95.Jun. ~ 11.Feb.
20fr / 5wks; 562pts, 16f / 4wks; 698pts, 12f / 3wks; 45pts

Protocol	Period	Dose Fractionation	No.pts
Dose Escalation	95.6~00.2	54~72GyE / 20f / 5weeks	96
Phase II ~	00.4~07.8	63~66GyE / 20f / 5weeks	466
New Fractionation	03.12~11.2	57.6GyE / 16f / 4 weeks	698
	08.4~11.2	51.6GyE / 12f / 3 weeks	45
Total	95.6~11.2		1305

H.Tsuji, et al. Proc. NIRS-KI Joint Sympo. 2010

Number of Patients



Late Radiation Toxicity

Dose GyE/f.	No. pts	Rectum G0	Rectum G1	Rectum G2	Rectum G3	Bladder/urethra G0	Bladder/urethra G1	Bladder/urethra G2	Bladder/urethra G3
66.0/20f	250	195	47	8	0	101	115	34	0
	(%)	78.0	18.8	3.2	0	40.4	46.0	13.6	0
63.0/20f	216	184	27	5	0	110	93	12	1
	(%)	85.2	12.5	2.3	0	50.9	43.1	5.6	0.5
57.6/16f	539	505	31	3	0	305	224	10	0
	(%)	93.7	5.8	0.6	0	56.6	41.6	1.9	0
Total	1005	884	105	16	0	516	432	56	1
	(%)	88.0	10.4	1.6	0	51.3	43.0	5.6	0.1

Median follow-up period:
66.0/20f;85.3m, 63.0/20f;51.2m, 57.6/16f;26.7m

H.Tsujl, et al. Proc. NIRS-Etolle Joint Sympo. 2011

Morbidity
(Comparison with other RT)

Institutes	Radiotherapy	Dose (Gy/f)	No. of pts.	Morbidity ≥ G2 Rectum	Morbidity ≥ G2 GU
Christie H.[1]	IMRT	60.0/ 20	60	9.5%	4.0%
Princess Margaret H.[2]	IMRT	60.0/ 20	92	6.3%	10.0%
Cleveland CF.[3]	IMRT	70.0/ 28	770	4.4%	5.2%
Stanford U.[4]	SRT	36.25/ 5	41	15.0%	29.0%
RTOG9406[5]	3DCRT	68.4-79.2/38-41	275	7-16%	18-29%
	3DCRT	78.0/ 39	118	25-26%	23-28%
Loma Linda U.[6]	Proton	75.0/ 39	901	3.5%	5.4%
NIRS [7]	C-ion	63.0/ 20	216	2.3%	6.1%
	C-ion	57.6/ 16	352	0.6%	1.9%

1) JH Coote et al. IJROBP 74, 2009

2) JM Martin et al. IJROBP 69, 2007

3) PA Kupelian et al. IJROBP 68, 2007

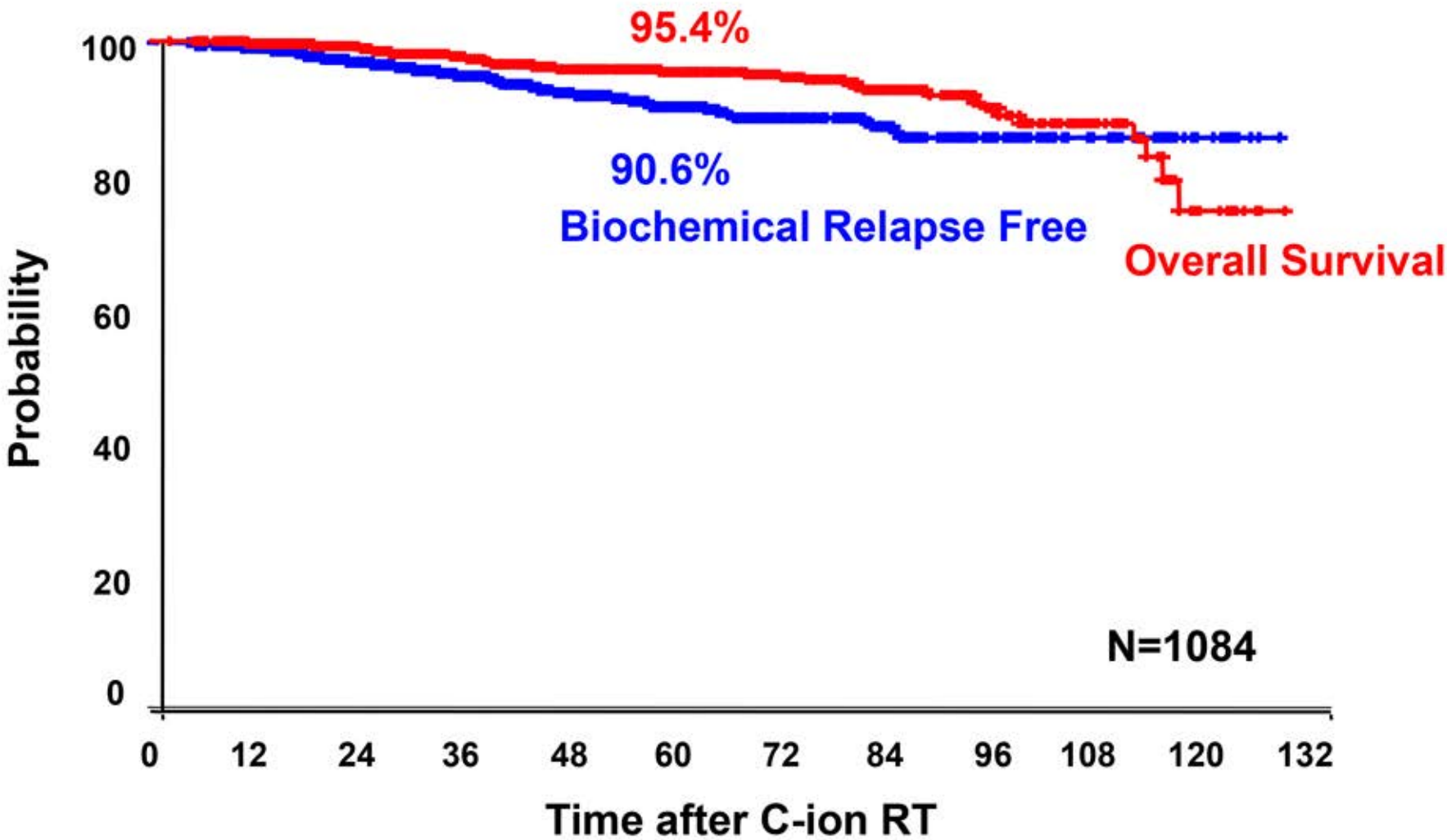
4) CR King et al. IJROBP 73, 2009

5) JM Michalski et al. IJROBP 76, 2010

6) RW Schulte et al. Strahlenther Oncol 176, 2000

7) H.Tsuji, et al. Proc. NIRS-KI Joint Sympo., 2010

Overall Survival & Biochemical relapse free Survival



H.Tsuji, et al. Proc. NIRS-Etoile Joint Sympo. 2011

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

Institutes	RTx	Dose	No. of pts.	Biochemical NED (iPSA≧20)
MDAnderson CC.[1]	Conventional	66-78Gy/33-39f	197	51%
Fox Chase CC.[2]	3DCRT	≧76Gy/38f	232	26-63%
Cleveland CF.[3]	IMRT	70Gy/28f	293(High risk)	72%
Loma Linda U.[4]	Proton	75CGE/45f	901	45%
NIRS [5]	Carbon	63-66/20, 57.6/16	266	89%

1) A Pollack et al. IJROBP 48, MR Storey et al.IJROBP 48, 2000
2) GE Hanks et al. IJROBP 46, 2000
3) PA Kupelian et al. IJROBP 68, 2007
4) JD Slater et al. IJROBP 59, 2004
5) H.Tsuji, et al. Proc. NIRS-KI Joint Sympo., 2010

Comparison of Overall Survival Rate between C-ion RT vs. RTOG meta analysis

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	65-70/35	443	82%	338	68%	324	52%
RT+ Short Hormone		70	82%	88	70%	57	54%
RT+ Long Hormone		114	76%	138	79%	103	63%
Carbon	66.0,63.0/20, 57.6/16						
RT+ Short Hormone		121	99%	-	-		-
RT+ Long Hormone		260	100%	321	94%	143	87%

*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

§*Carbon:* H.Tsuji, et al. Proc. NIRS-KI Joint Sympo., 2010

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

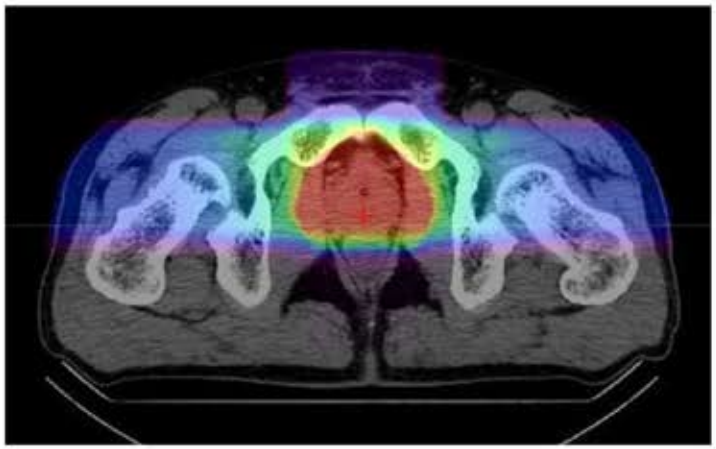
Fixed dose; 51.6GyE

>>> just finished with 46 patients.

So far, no severe toxicity, no

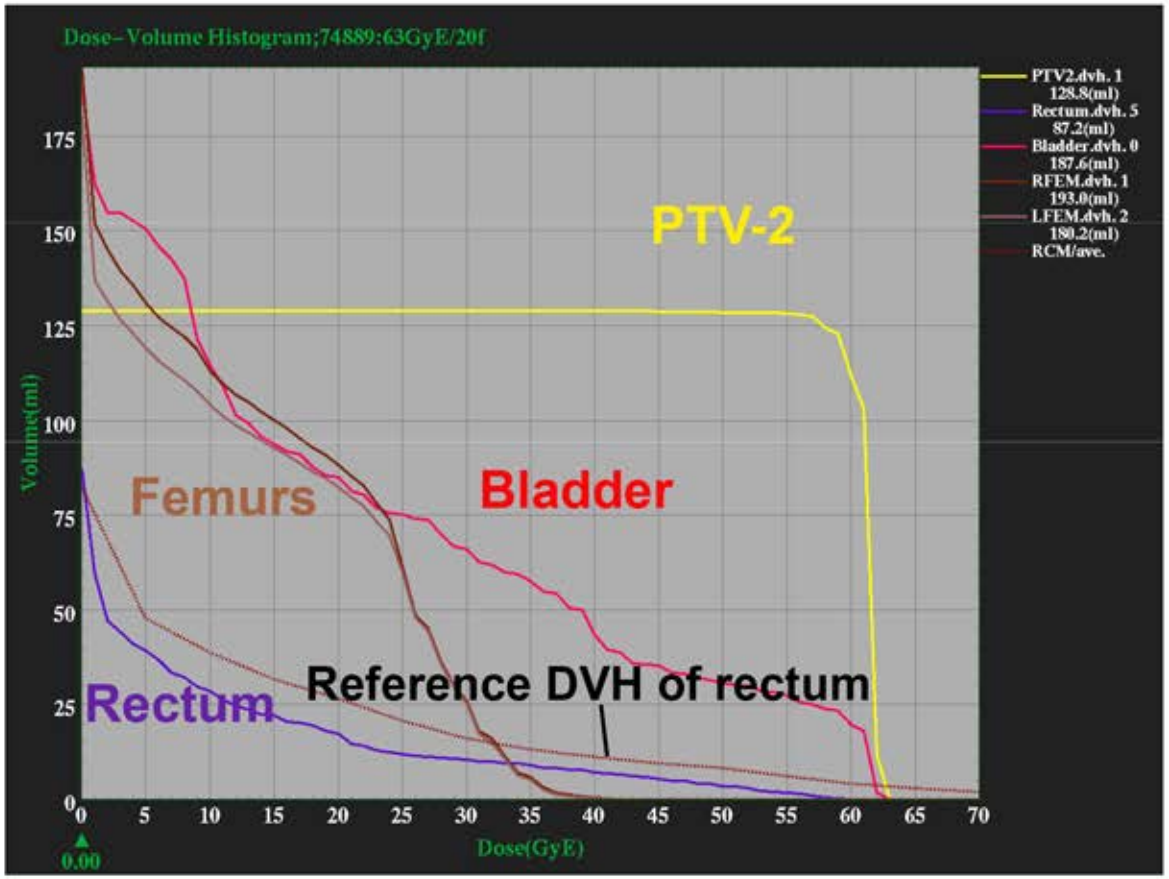
More Hypofracionation

Dose Constraint with Rectum DVH



Dose-Constraints

OARs	Constraints
Rectum	
Dmax	≤ 66GyE/20f
V_{50}	< 8cc
Bladder	
Dmax	≤ 66GyE/20f
V_{50}	< 50cc



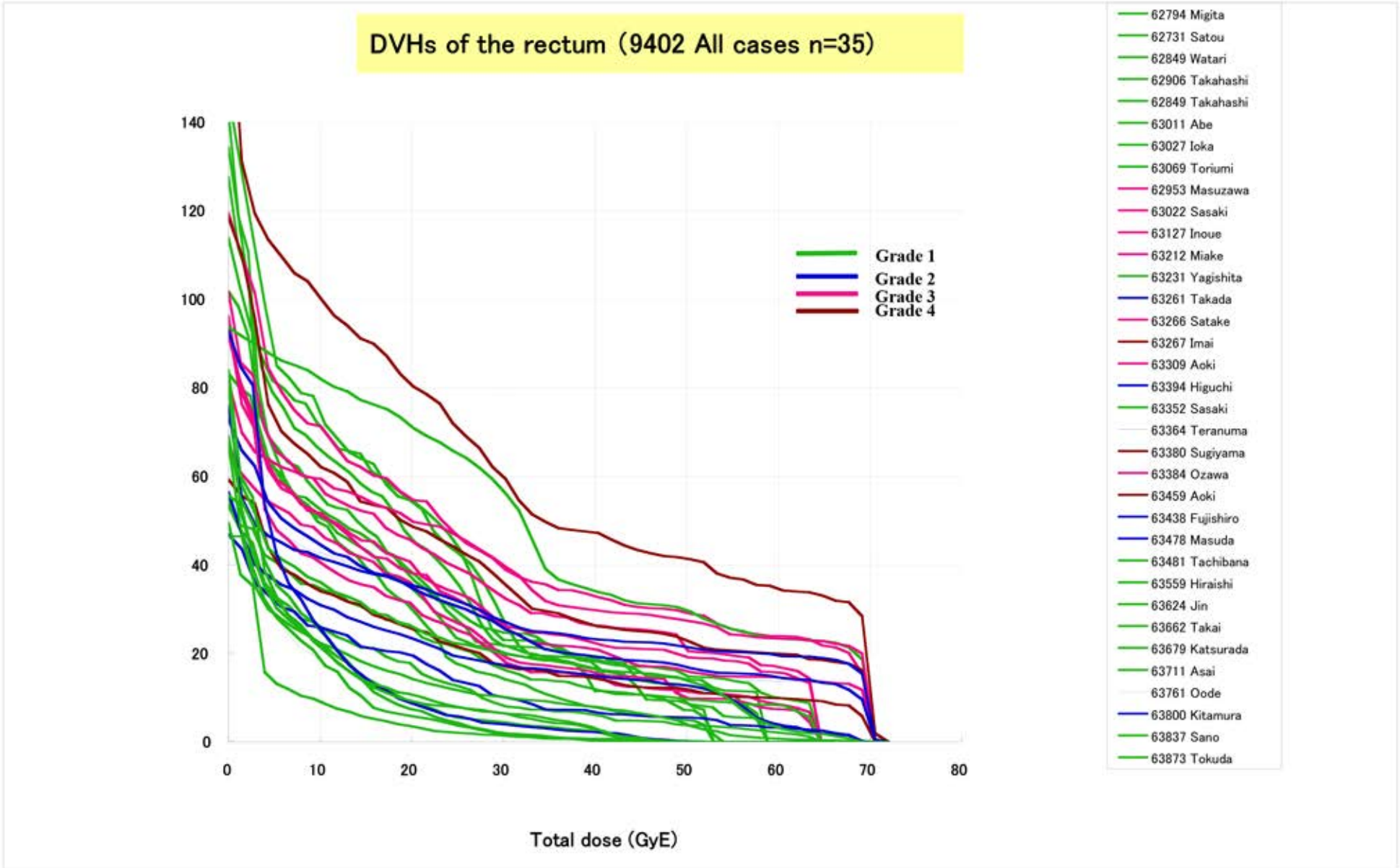
Reference DVH: Average DVH of the patients with grade 0~1 rectal toxicity

DVH below the reference DVH at high dose level.

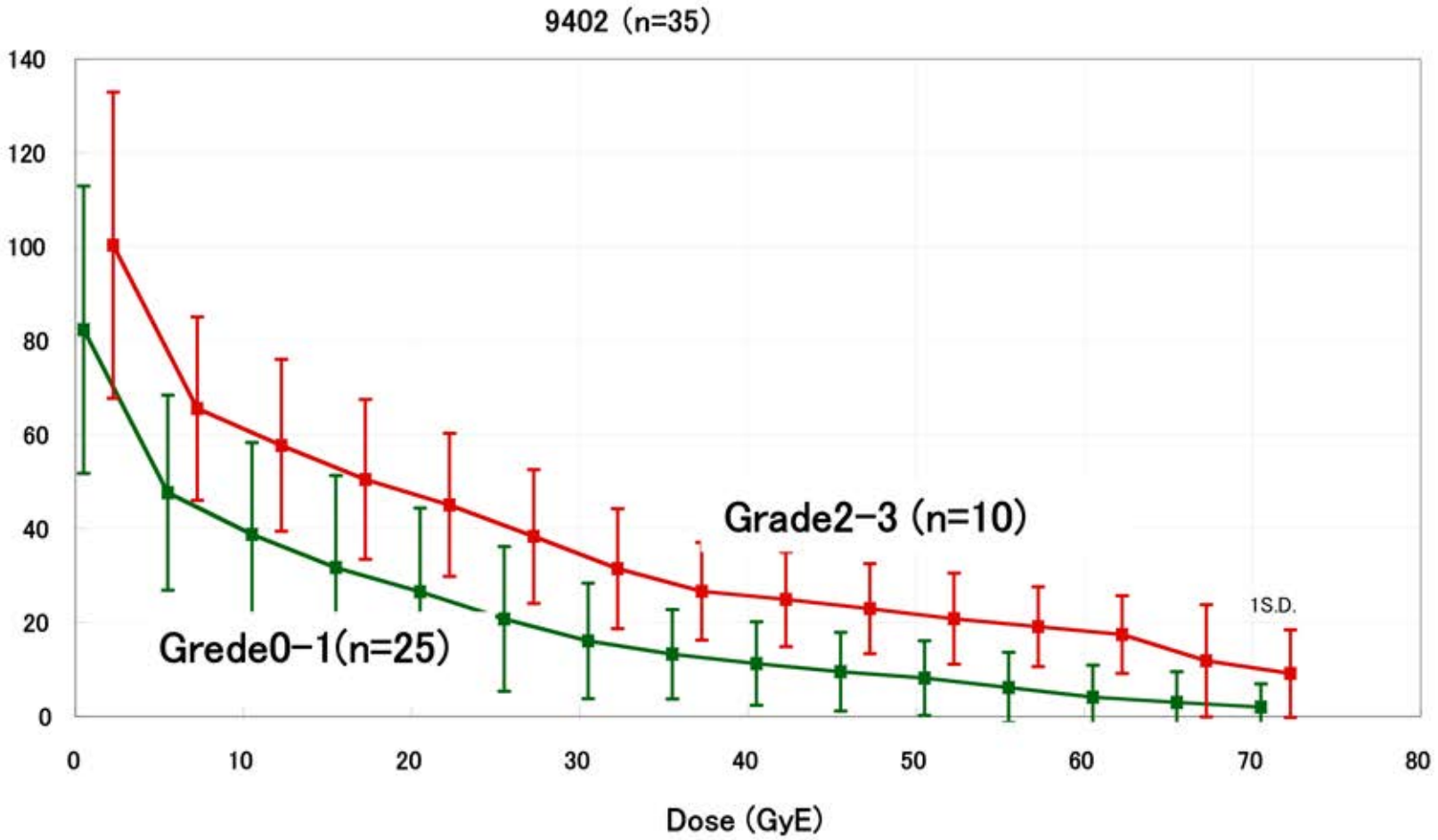
Dose Constraints for GI Tract in C-ion RT

Volume	Dose limits		
	20 fractions	16 fractions	ED in 2Gy/f.
Rectum ***(α/β=3.0)***			
Max	66.0GyE (100%)	60.8GyE (82.6%)	83.2Gy
5%	60.0GyE (90.9%)	56.0GyE (76.1%)	72.0Gy
10%	50.0GyE (75.8%)	46.4GyE (63.0%)	55.0Gy
20%	30.0GyE (45.5%)	28.8GyE (39.1%)	27.0Gy
Small intestine ***(α/β=10.0)***			
Max	50.0GyE	48.0GyE	52.0Gy

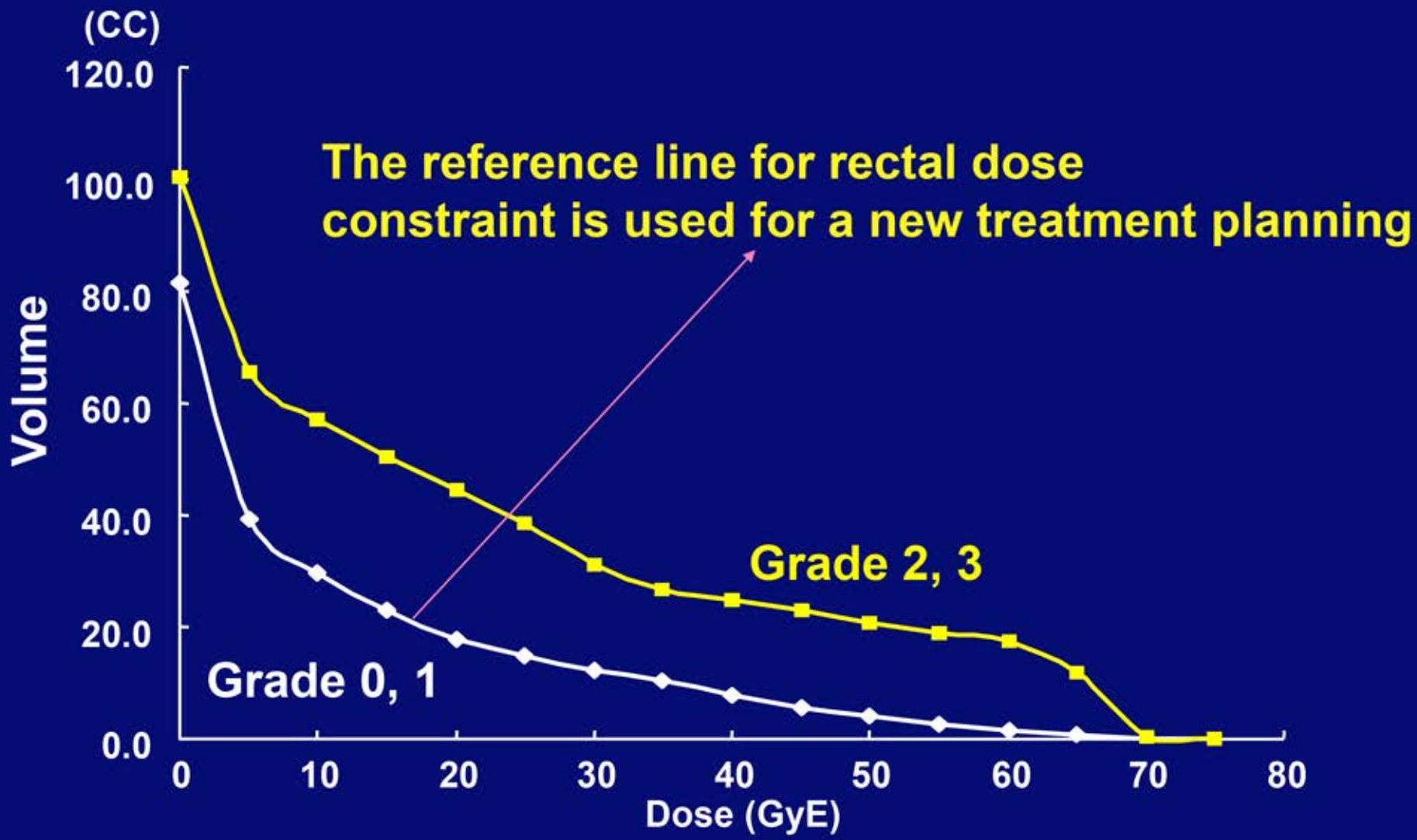
DVHs of the Rectum in Carbon Ion Therapy for Prostate ca



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)



Pancreas

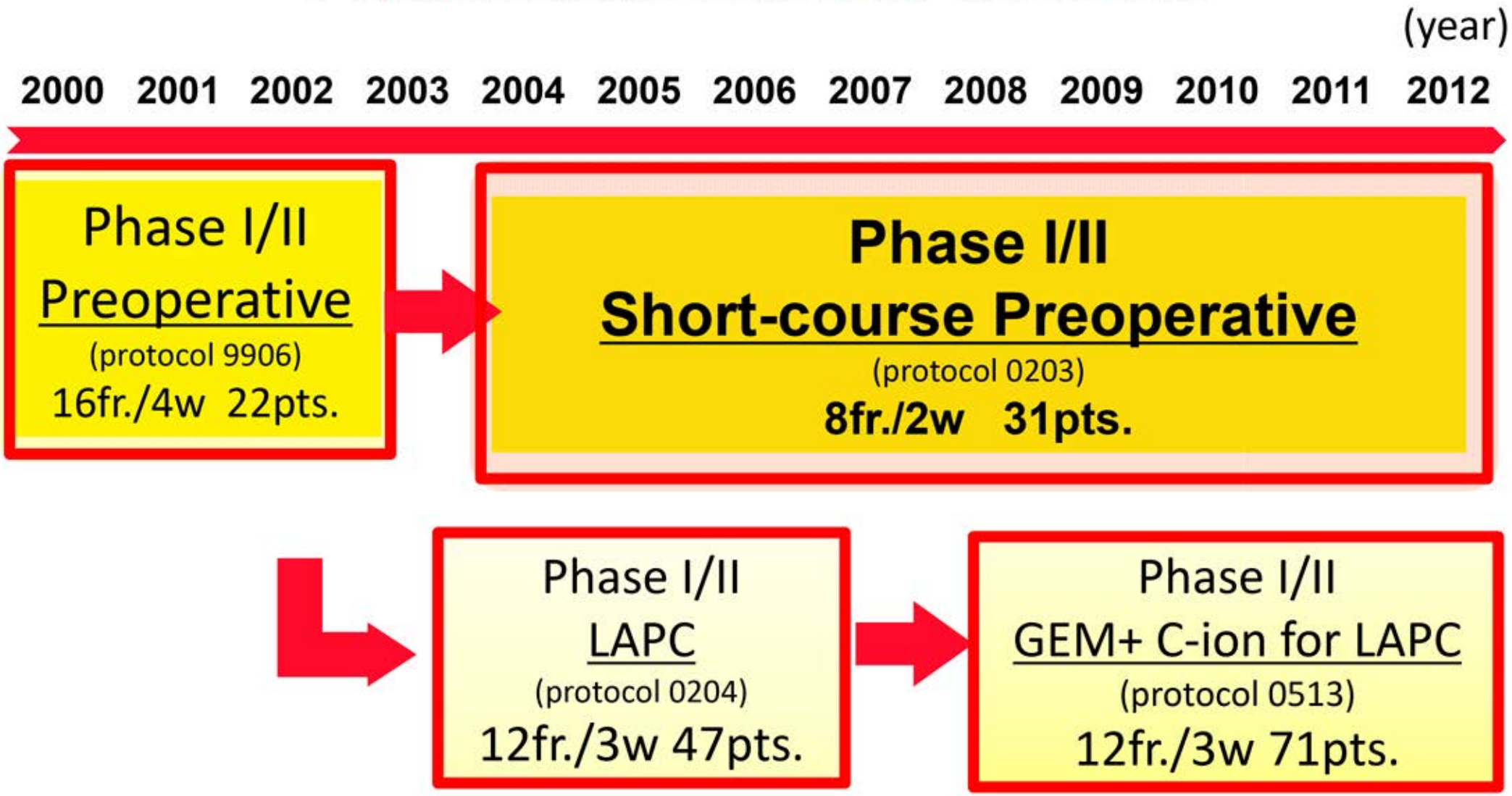
Table 3
Estimated numbers of new cancer cases and deaths from cancer (thousands), age-standardised rates (ASRs) (per 100,000) by sex and cancer site in Europe in 2012.

	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	29.7	2.7	11.9	2.7	17.9	2.8	20.9	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	39.9	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				.0				.3				
Testis				.8				.4				
Kidney				.2	43.4	8.1				.2	17.7	2.8
Bladder	151.2	14.4	118.3	26.9	32.9	5.3	32.4	4.3	39.5	8.5	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

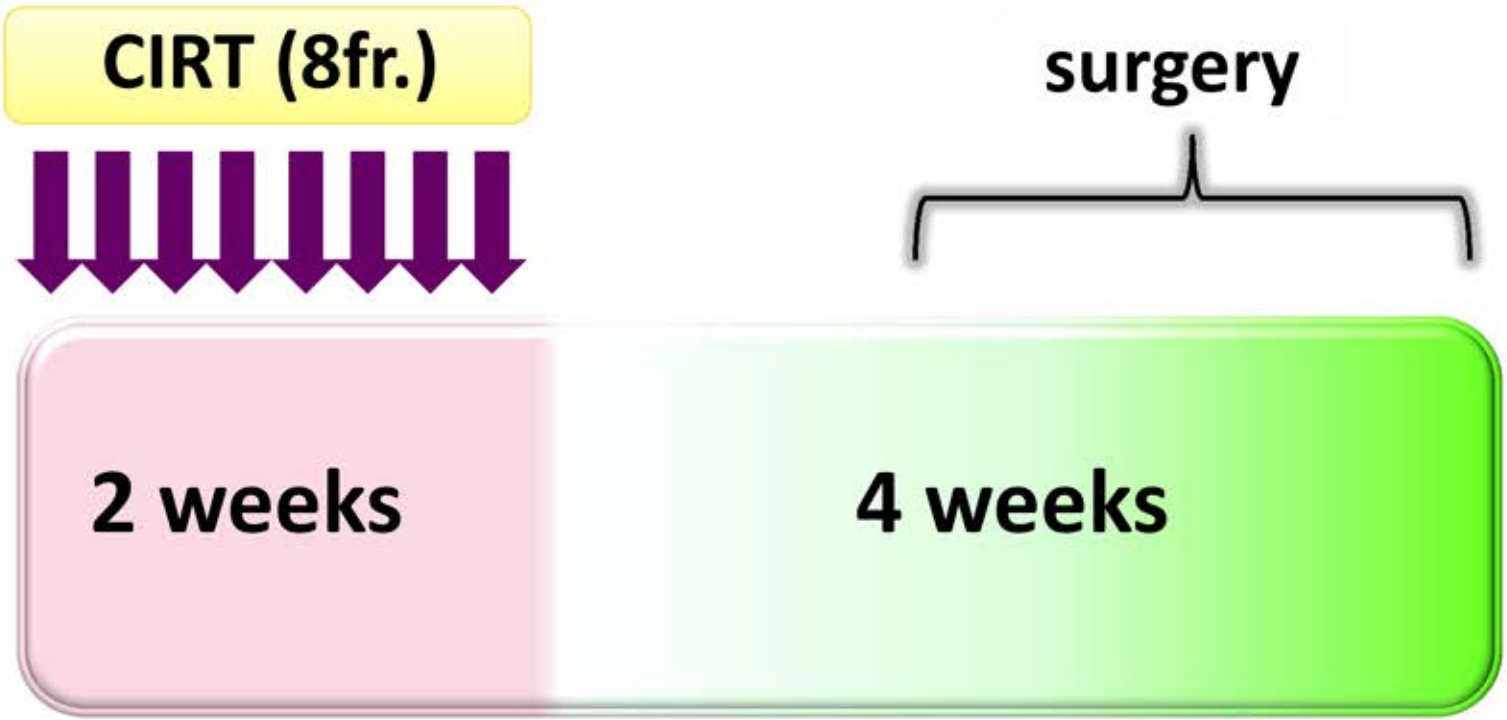
103.000 New cases

104.000 New deaths

C-ion RT Clinical Trials for Pancreatic Cancer at NIRS



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	4	3
3	33.6GyE		
4	35.2GyE		
5	36.8GyE		

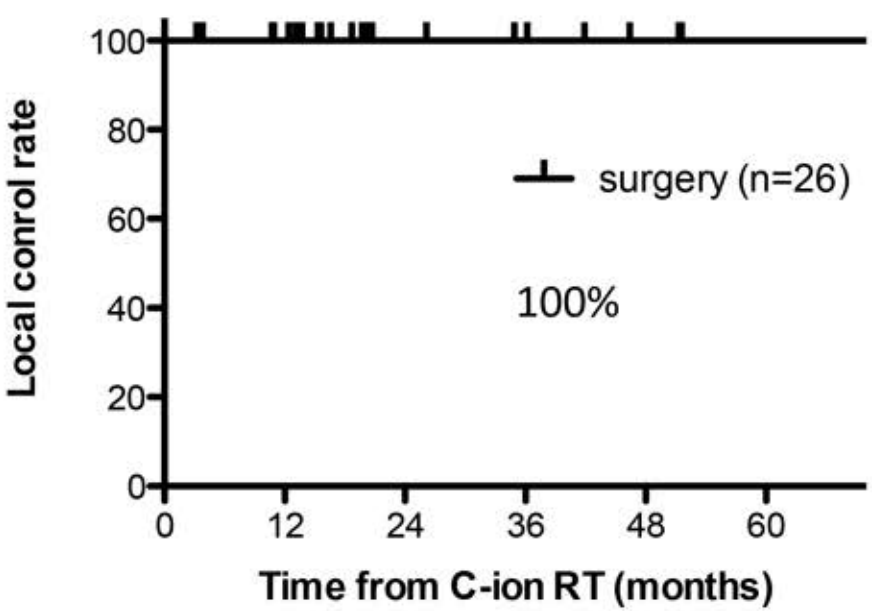
2006～
resection rate
95%

Acute and Late toxicity

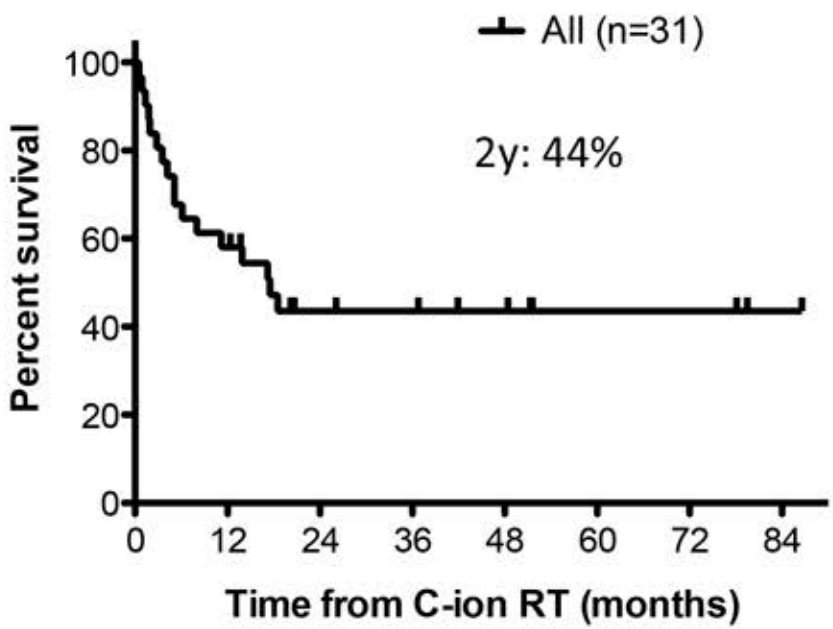
	Acute toxicities (NCI-CTC)						Late toxicities (RTOG/EORTC)					
	n	G0	G1	G2	G3	G4	n	G0	G1	G2	G3	G4
skin	26	26	0	0	0	0	26	26	0	0	0	0
GI	26	25	1	0	0	0	26	26	0	0	0	0
Liver	26	25	0	0	1	0	26	26	0	0	0	0
Portal Vein	26	26	0	0	0	0	26	25	0	0	0	1
Leakage	26	26	0	0	0	0	26	26	0	0	0	0

Preoperative C-ion RT

Local Control

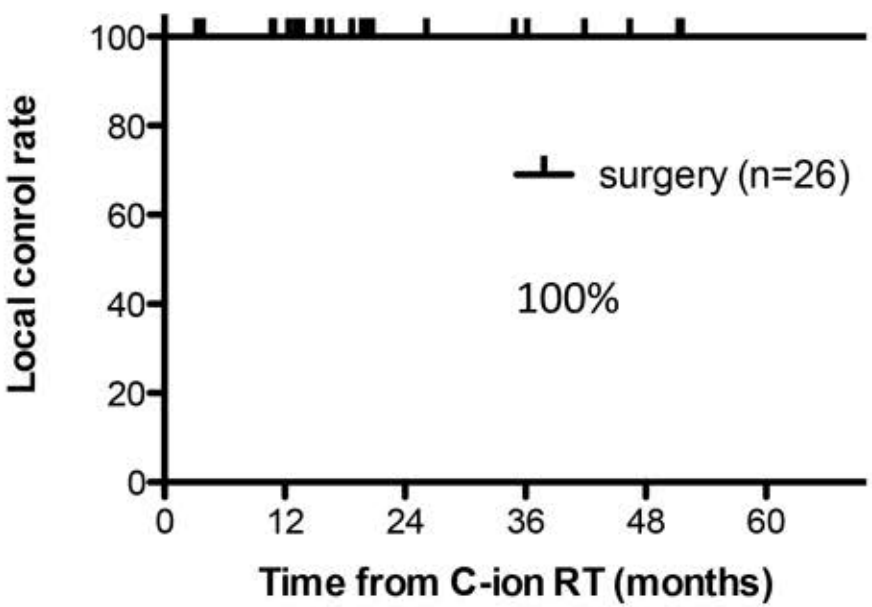


DMFS
(Distant Metastasis Free Survival)

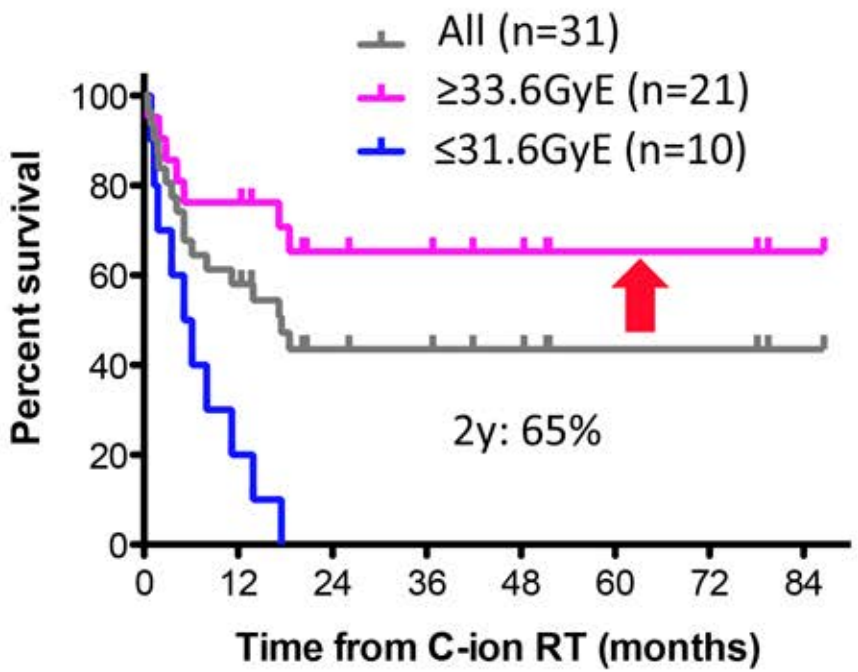


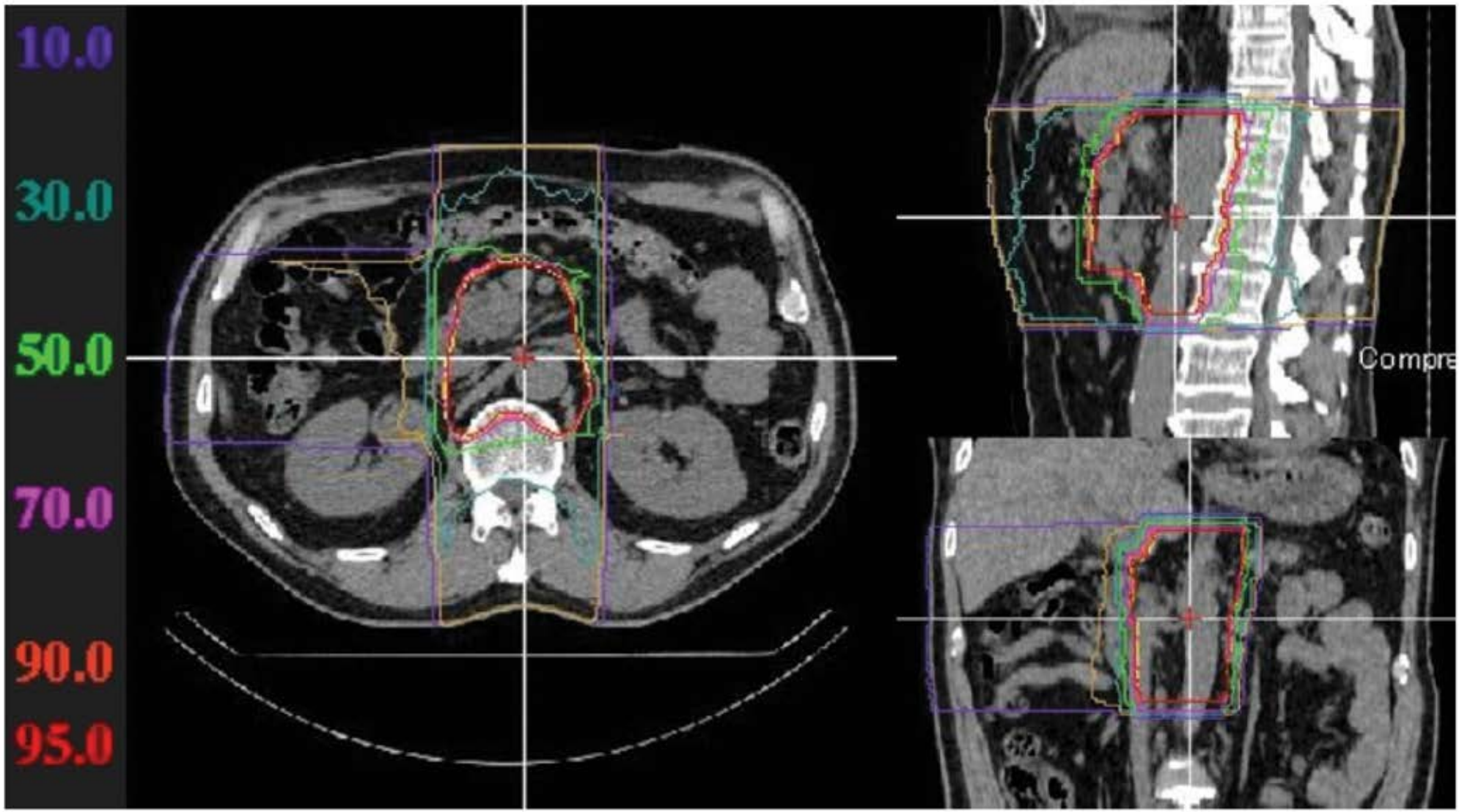
Preoperative C-ion RT

Local Control



DMFS
(Distant Metastasis Free Survival)

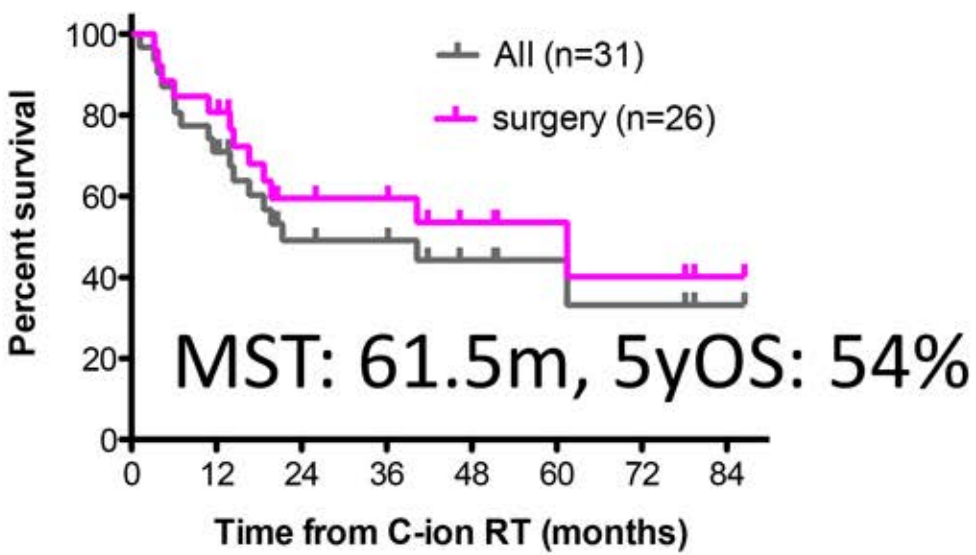



10.0
30.0
50.0
70.0
90.0
95.0
Compre

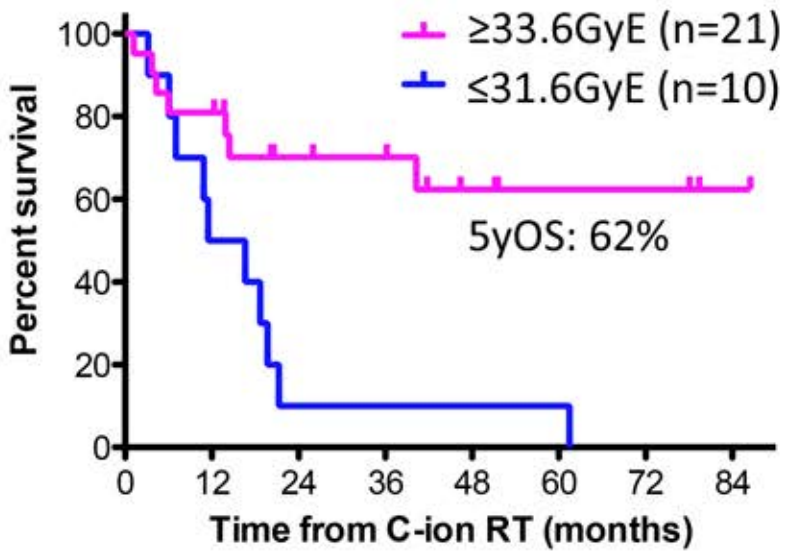
Preoperative C-ion RT

	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%**

Overall Survival

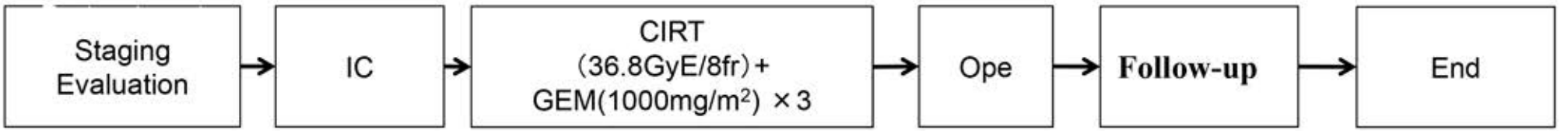


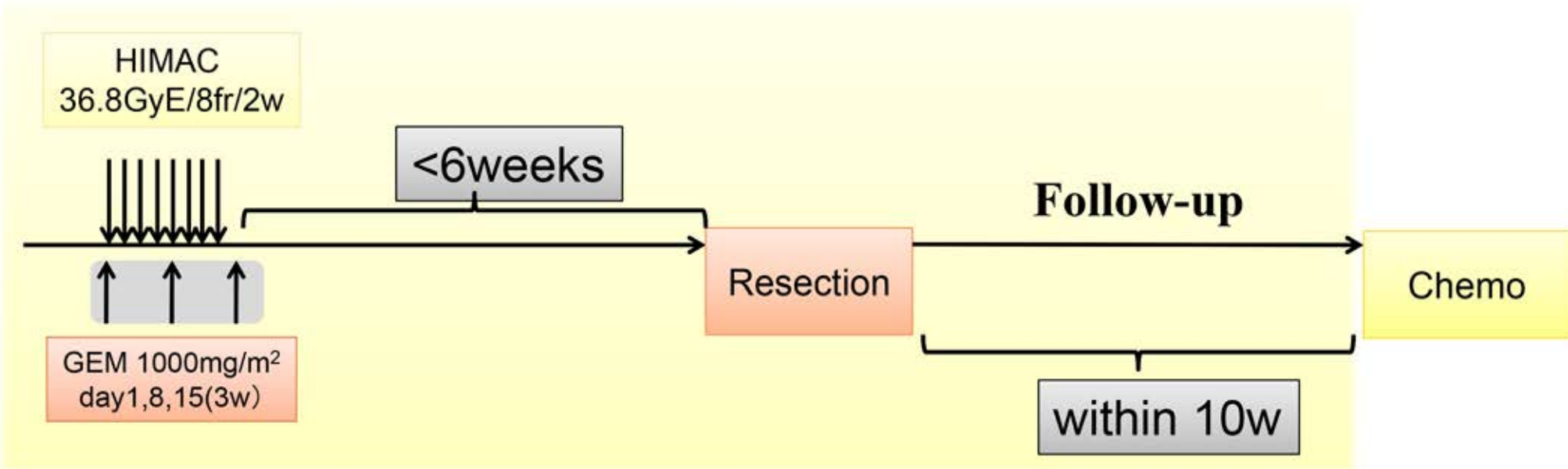
Overall Survival by Dose



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

Schema for New Protocol





C-ion RT Clinical Trials for Pancreatic Cancer

(year)

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

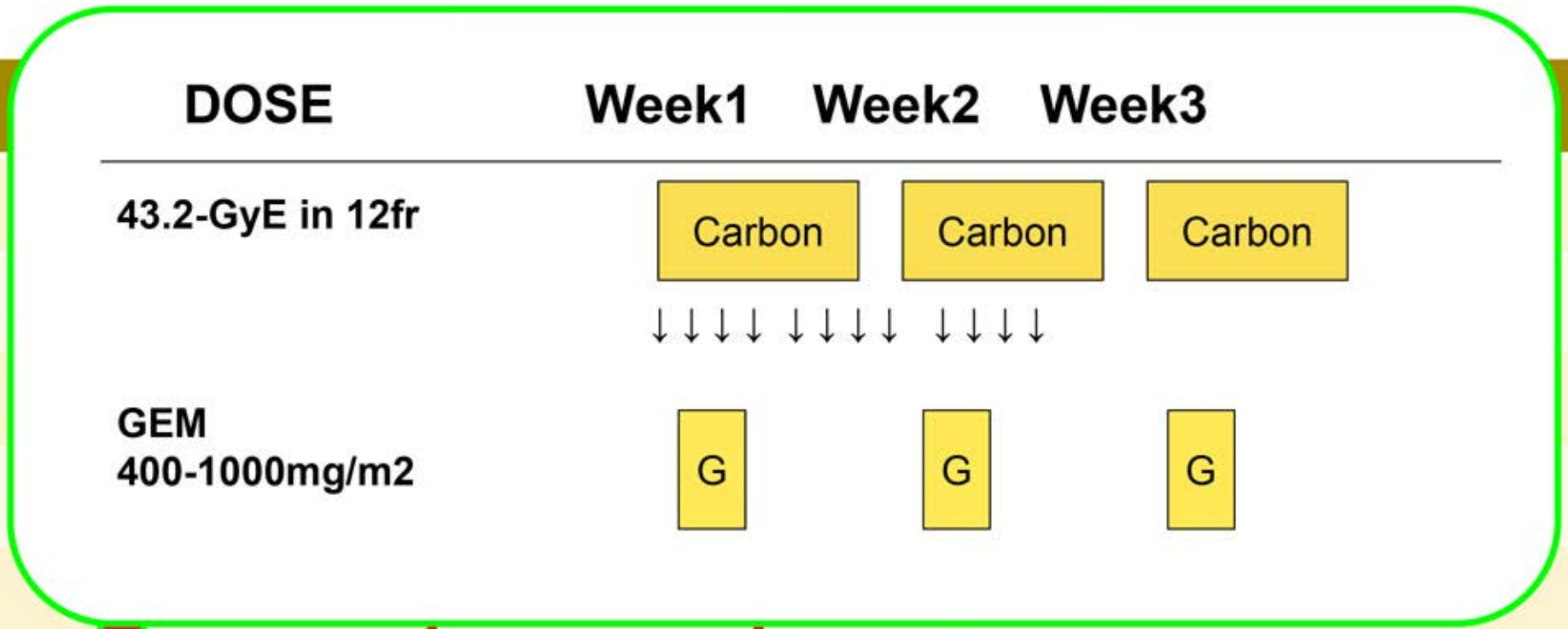
Phase I/II
Preoperative
(protocol 9906)
16fr./4w 22pts.

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

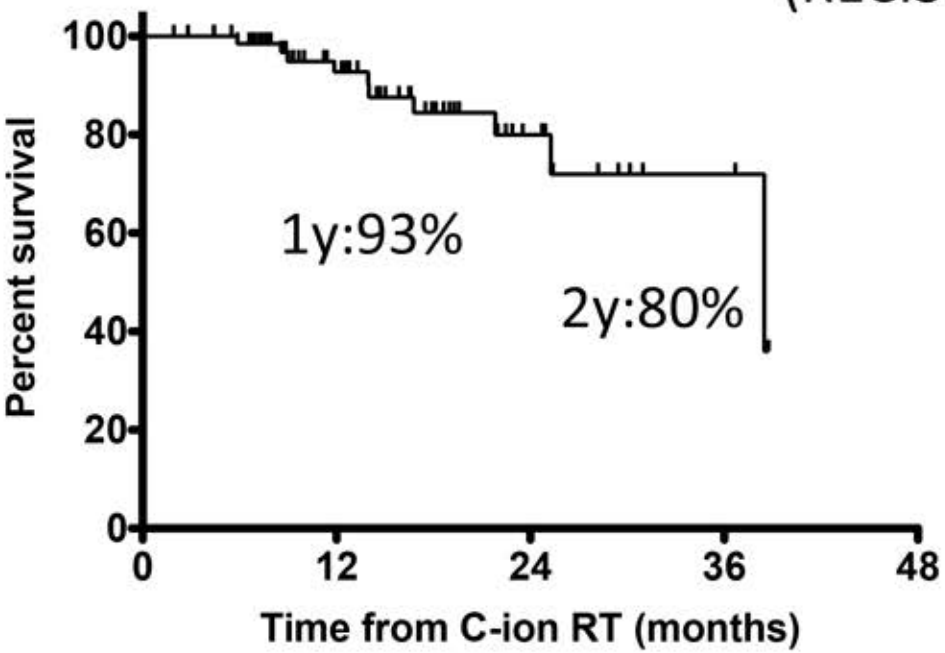


50.4GyE	1000mg/m^2	11
52.8GyE	1000mg/m^2	11
55.2GyE	1000mg/m^2	11

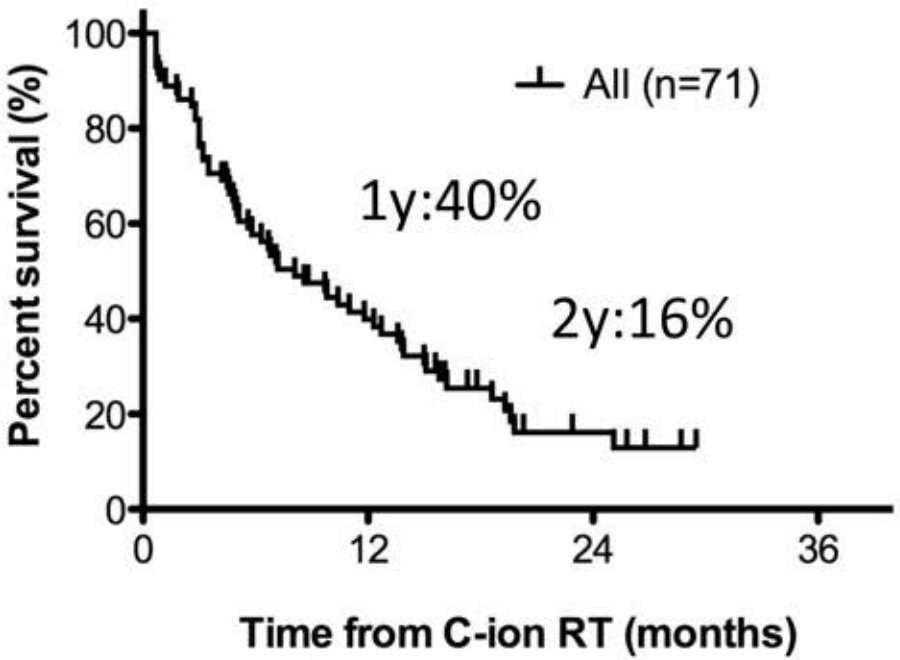
GEM+C-ion RT for LAPC

FFLP
(Freedom From Local Progression)

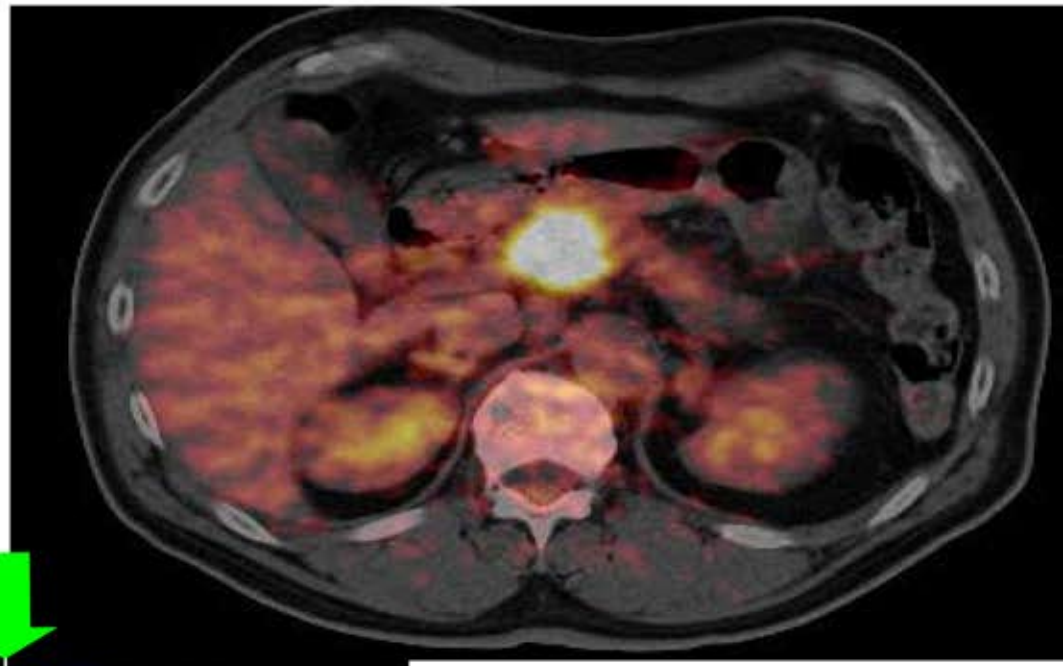
(RECIST)

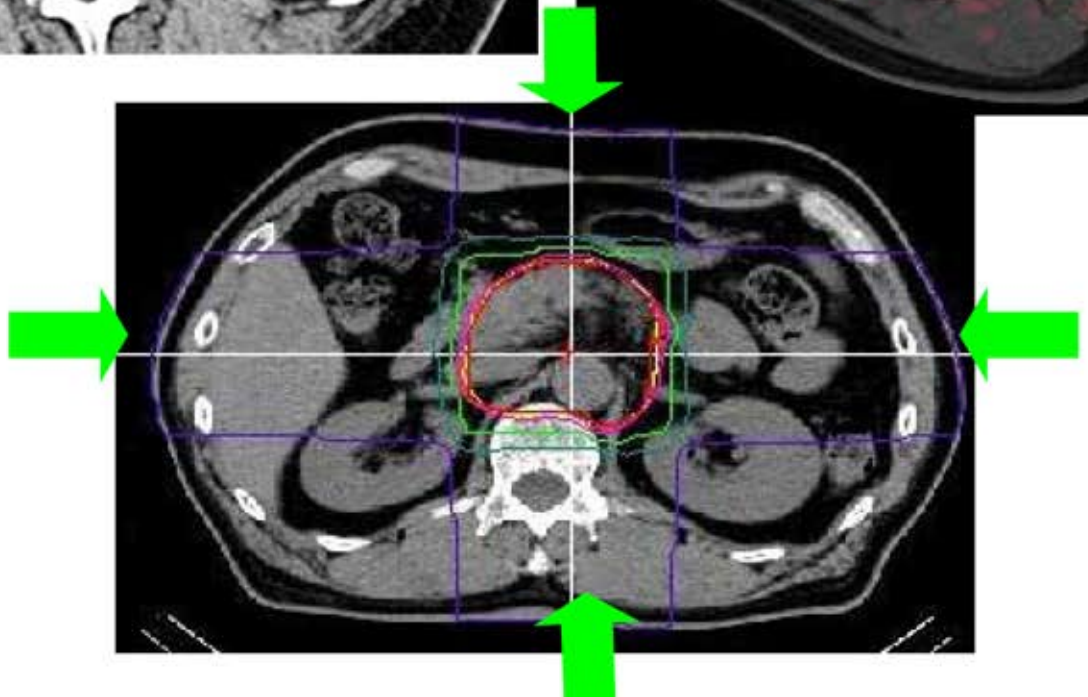


DMFS
(Distant Metastasis Free Survival)



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



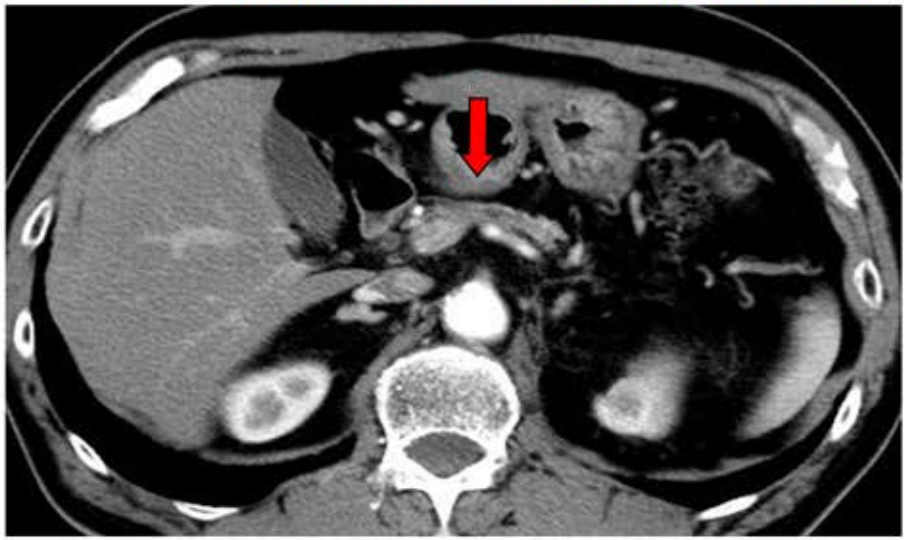


50.4GyE / 12fr

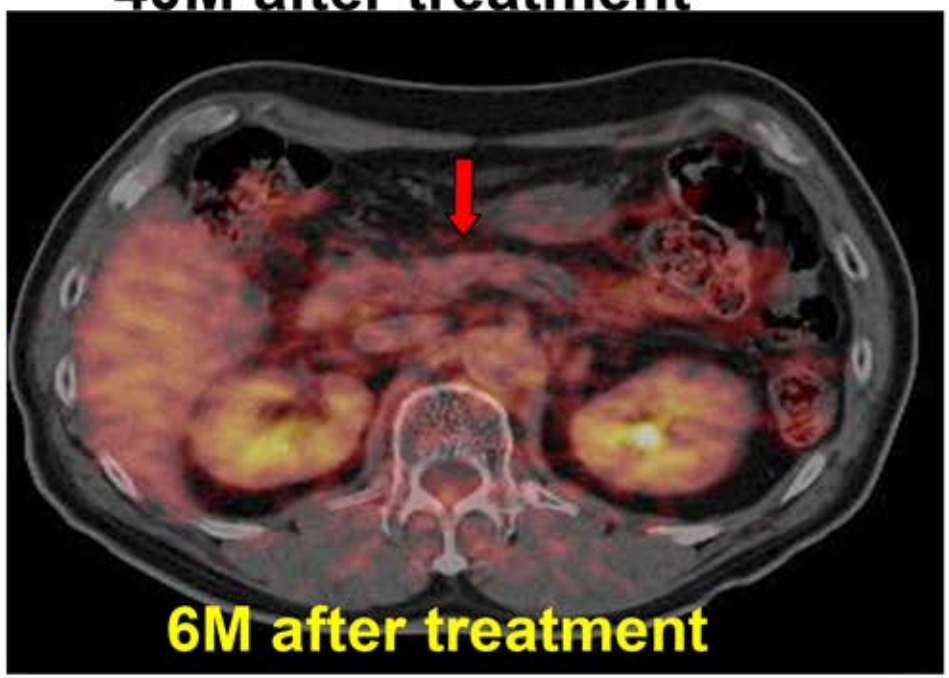
50.4GyE / 12fr

Alive at 50M after treatment

Before Treatment



40M after treatment



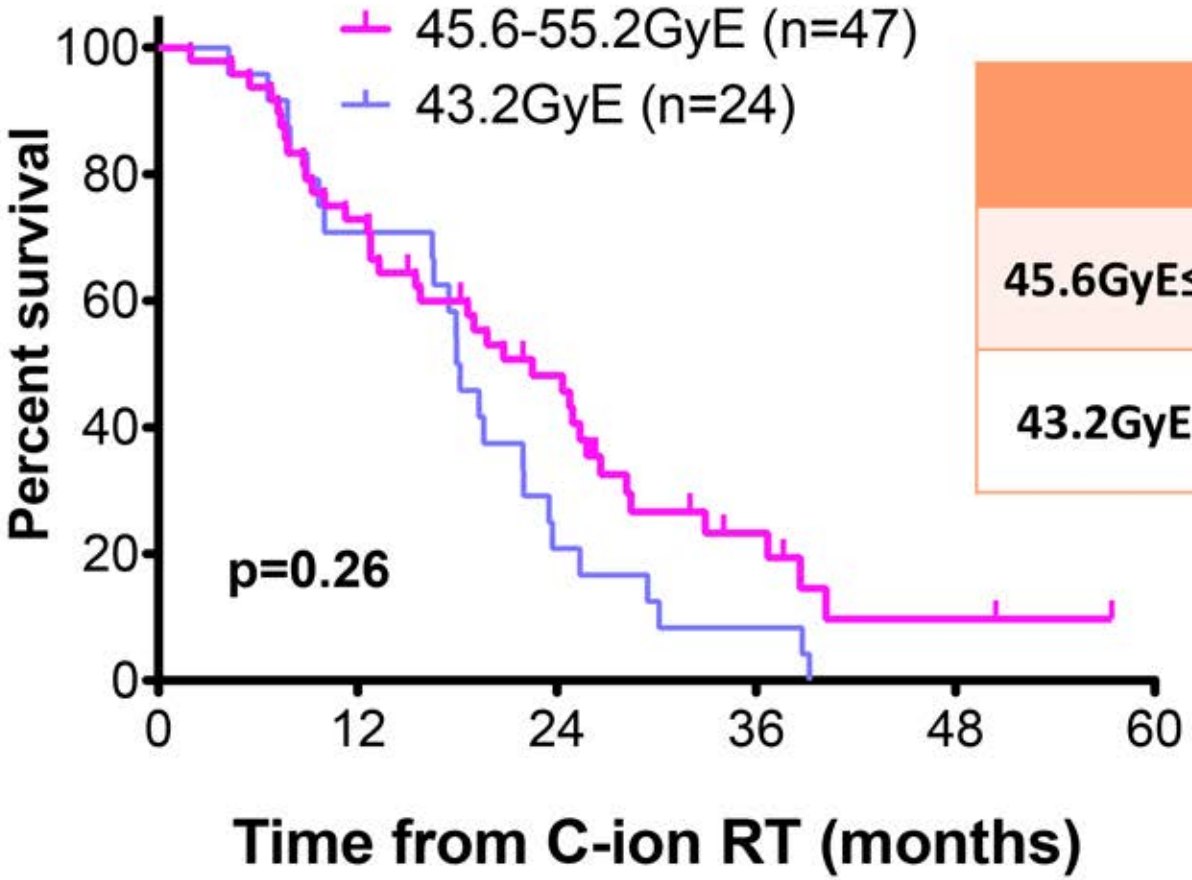
Upper gastrointestinal acute and late Grade2-3 toxicity by total dose

Carbon・GEM	n	0	1	2	3	4	5
43.2GyE・400・700・1000mg/m²	24	24	0	0	0	0	0
45.6GyE・1000mg/m²	7	7	1	0	0	0	0
48.0GyE・1000mg/m²	8	8	1	0	0	0	0
50.4GyE・1000mg/m²	11	10	0	1	1	0	0
52.8GyE・1000mg/m²	11	10	1	3	0	0	0
55.2GyE・1000mg/m²	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 TPNindicated ≥24 hrs

GEM+C-ion RT for LAPC

Overall Survival



	n	MST (m)	1y-OS	2y-OS	3y-OS
45.6GyE≤	47	22.5	73%	23.2%	
43.2GyE	24	18.0	72%	21%	8%

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

Table 1 The impact of photon and carbon ion irradiation on metastatic potential of tumor cells.

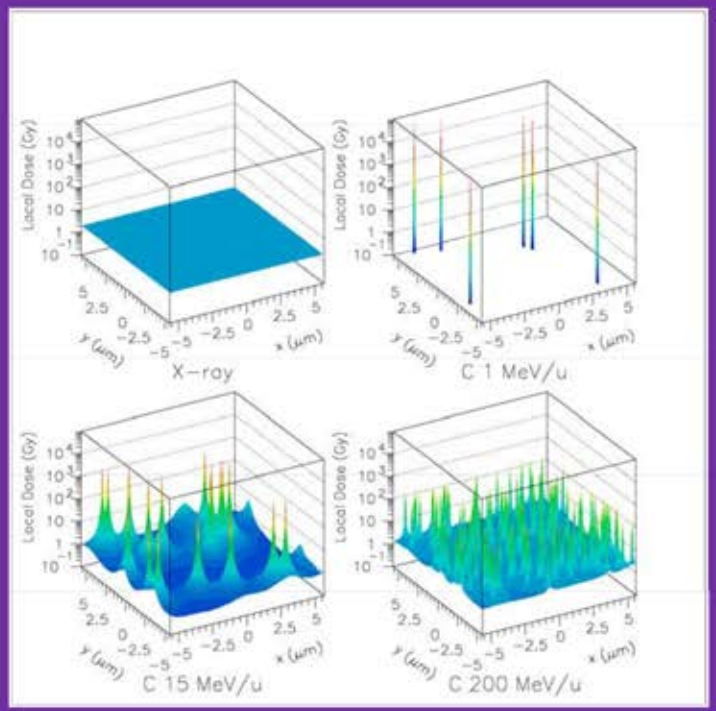
The impact of irradiation on metastatic potential of tumor cells	Biological mechanisms	Reference
The effects of irradiation on the processes of angiogenesis and metastasis	(1) Photon irradiation enhanced MMP-2 activity resulting in the promotion of tumor invasion and metastasis.	[6,15,16,17]
	Strategy to counteract metastasis: Combination MMP inhibitor with ionizing radiation to target invasion and metastasis might improve the efficacy of radiotherapy.	[17,18]
	(2) Carbon ion irradiation decreased angiogenesis by affecting both tumor cells and endothelial cells.	[23]
The influence of irradiation on migration and metastatic potential of tumor cells	(1) Photon irradiation promoted cell migration and invasion concomitant with up-regulation of αvβ3 integrin.	[26]
	(2) Carbon ion irradiation decreased cell migration and invasion, inhibited MMP-2 activity, and decreased number of metastasis in vivo.	
	Carbon ion radiotherapy may be superior to convential photon beam therapy in possible preventive effect on metastases of irradiated tumor cells.	
The effect of irradiation on epidermal growth factor receptor signaling	(1) Migration of glioma U87 EGFR++ cells and LN229 EGFR++ cells: Photon irradiation increased migration of U87 cells and decreased LN229 cells.	[29]
	Heavy ion irradiation decreased migration of both cell lines.	
	(2) Phosphorylation of EGFR, Akt, ERK1/2: Photon increased phosphorylation.	[29]
	Heavy ion: phosphorylation remained unchanged.	
	(3) Treatment strategy: Photon radiotherapy with tyrosine kinase inhibitor vandetanib to inhibit GBM growth might improve the treatment result.	[35]
The effect of irradiation on PI3K/Akt pathway	(1) Photon irradiation increased invasiveness of tumor cells: mediated by PI3K/Akt/ NF-κB signal transduction pathway.	[39]
	Strategy to counteract invasion: treatment with PI3K inhibitor LY294002 decreased tumor cell invasion.	[9]
	(2) Carbon ion irradiation suppressed the metastatic potential of tumor cells by suppressing the PI3K/Akt signaling pathway.	[40]
The effect of irradiation on Rho signaling pathway	(1) Carbon ion irradiation suppressed invasiveness and motility of tumor cells via inactivation of EGFR/PI3K/Rho signaling pathway.	[7]
	Carbon beam irradiation suppressed the migration and invasion of non-small lung cancer cells more effectively than did photon irradiation.	
The influence of irradiation on integrin family of adhesion molecule	(1) Integrin α2β1 and EGFR cooperatively promote invasiveness of ionizing radiation (IR)-survived lung cancer cells.	[9]
	(2) Photon irradiation induced up-regulation of β1-integrin in invasive breast cancer.	[44,45]
	(3) Carbon ion irradiation inhibited integrin expression and suppressed glioma cell migration.	[5]

BEWARE: in carbon ion non uniform phsical dose is prescribed according to RBE models

All models used in the clinics are based on a very simple concept

Less dose where there is more LET

My GyE is not equivalent to your GyE !!



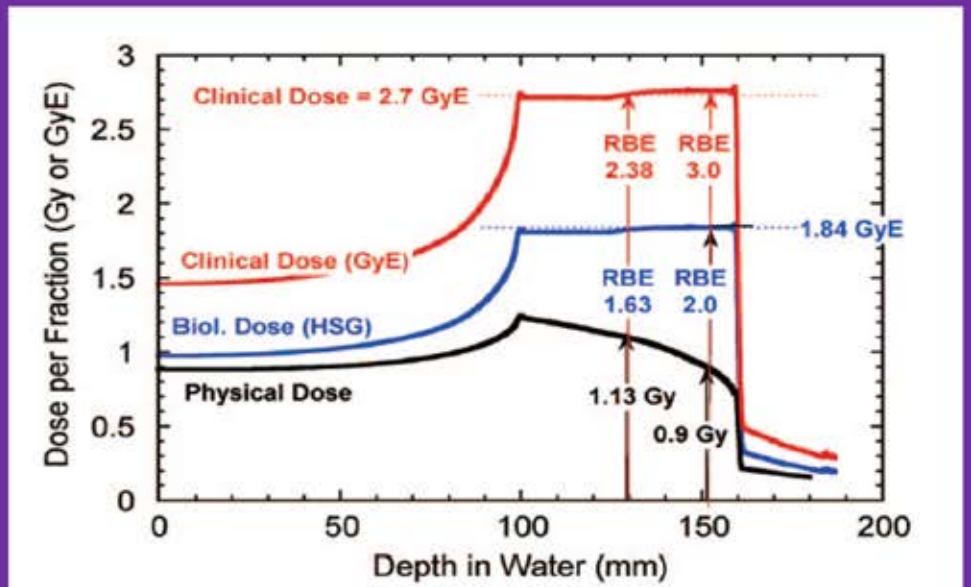
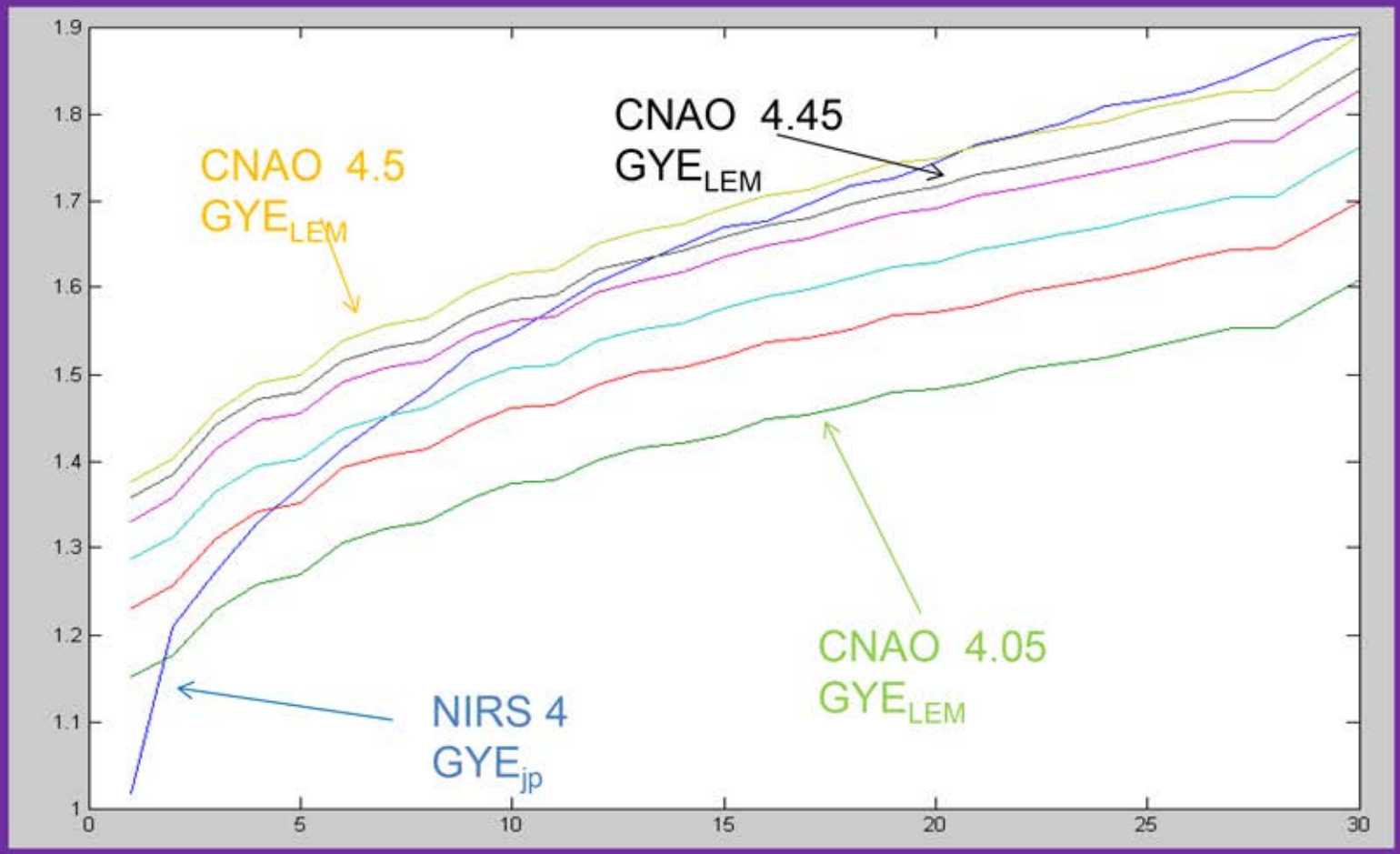


Fig. 5. Schematic method used to determine RBE at the center of SOBP for the clinical situation.

The problem is difficut but there are possible solutions



IOP PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. 57 (2012) 7543–7554 doi:10.1088/0031-9155/57/22/7543

Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy

Piero Fossati[1,2,4,5], Silvia Molinelli[1], Naruhiru Matsufuji[3], Mario Ciocca[1], Alfredo Mirandola[1], Andrea Mairani[1], Junetsu Mizoe[1,3], Azusa Hasegawa[3], Reiko Imai[3], Tadashi Kamada[3], Roberto Orecchia[1,2,4] and Hirohiko Tsujii[3]

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[2] Dipartimento di Scienze e Tecnologie Biomediche, Università di Milano, Milano, Italy
[3] Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
[4] Istituto Europeo di Oncologia, Milano, Italy

Final results

Prescription doses (GyE) (16 fractions, 4 fractions per week)								
Indication	NIRS dose	CNAO dose						
		Opposed ports		Orthogonal ports		Single port		
		quadratic errors		quadratic errors		quadratic errors		MC
		Cubes	Spheres	Cubes	Spheres	Cubes	Spheres	Spheres
Head and neck non mesenchymal cancer	3.60	4.20	4.15	4.20	4.15	4.20	4.15	4.19
Skull base chordoma and hondrosarcoma	3.80	4.35	4.30	4.35	4.30	4.35	4.30	4.33
Head and neck non mesenchymal cancer	4.00	4.50	4.40	4.50	4.45	4.50	4.45	4.47
Spinal chordoma and chondrosarcoma	4.20	4.65	4.60	4.70	4.60	4.70	4.60	4.64
Head and neck sarcoma	4.40	4.80	4.70	4.80	4.70	4.80	4.70	4.75
Bone and soft tissue sarcoma	4.40	4.80	4.75	4.80	4.75	4.80	4.75	4.78

End of alloted time

- Thank you
- The rest is for self study/ discussion / lunch time

Volumes

- What should we treat ?

Radiation field

CTV 1 Main tumor ＋N2 nodes and plexus → 9 fractions

CTV 2　GTV+ 0.5cm margin → last 3 fractions

N2 nodes are frequently metastatic

Staging according to JPS

Fig. 15. Lymph node station numbers

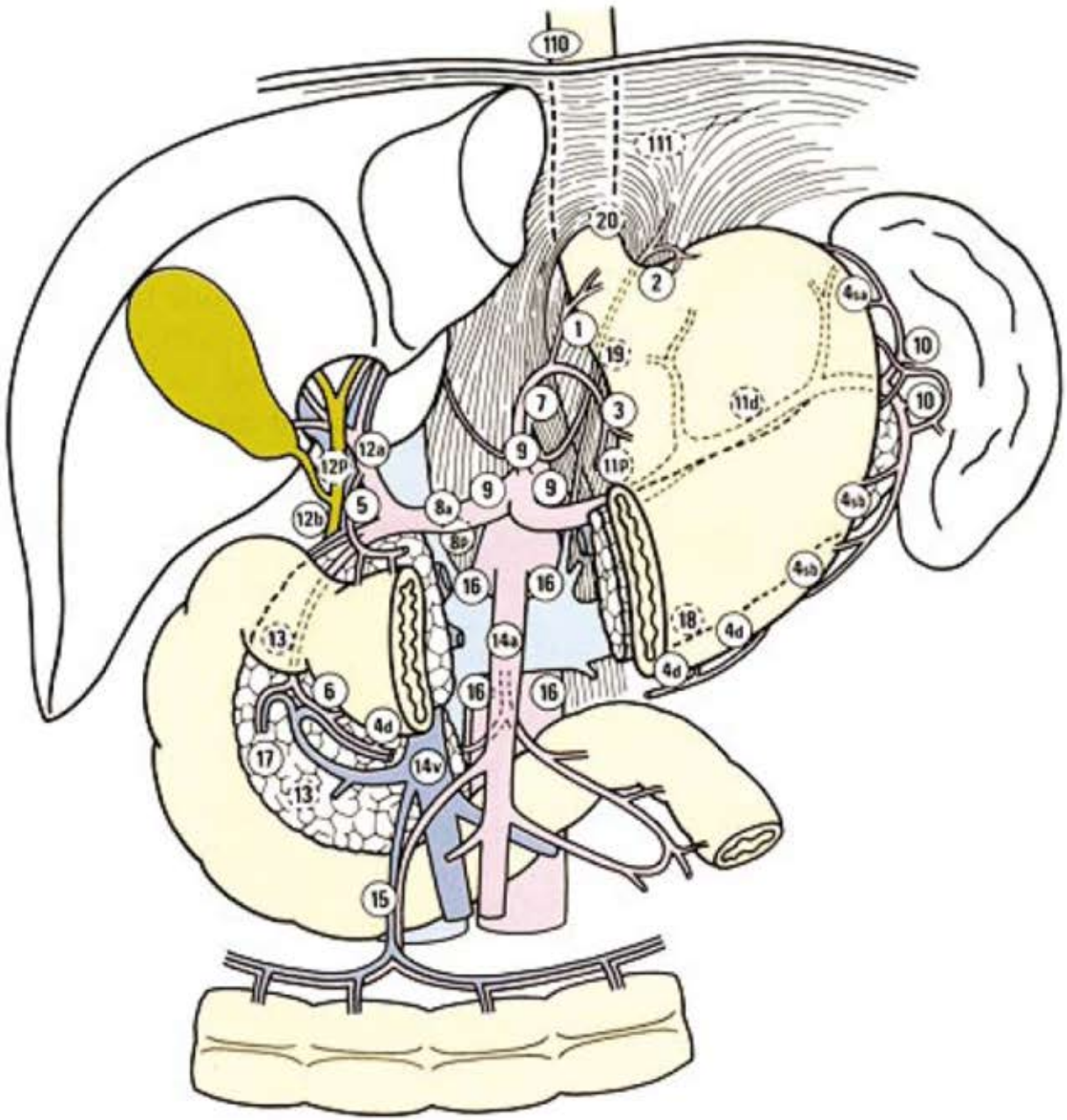


Table 3 Classification of lymph nodes according to groups

	Head	Body and tail
Group 1 lymph nodes	13a, 13b, 17a, 17b	8a, 8p, 10, 11p, 11d, 18
Group 2 lymph nodes	6, 8a, 8p, 12a, 12b, 12p, 14p, 14d	7, 9, 14p, 14d, 15
Group 3 lymph nodes	1, 2, 3, 4, 5, 7, 9, 10, 11p, 11d, 15, 16a2, 16b1, 18	5, 6, 12a, 12b, 12p, 13a, 13b, 17a, 17b, 16a2, 16b1

(3) Lymph node metastasis

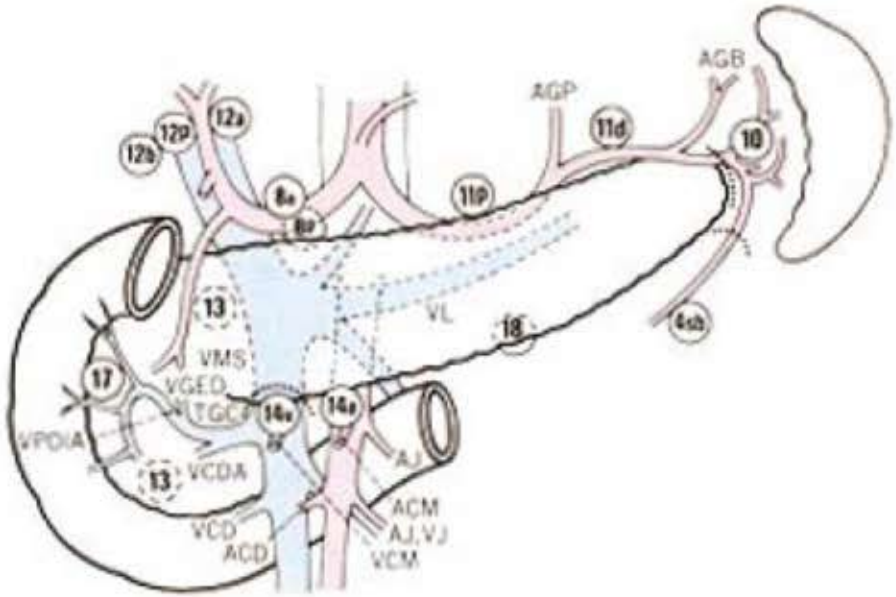
N0: No evidence of lymph node metastasis

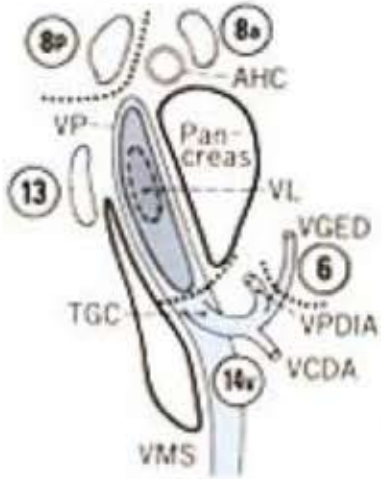
N1: Metastasis to Group 1 lymph nodes alone

N2: Metastasis to Group 2 lymph nodes

N3: Metastasis to Group 3 lymph nodes

NX: Lymph node metastasis cannot be assessed





APIS : A. phrenica inferior sinistra
AGB : Aa. gastricae breves
AGES : A. gastroepiploica sinistra
VGED : V. gastroepiploica dextra
VCDA : V. colica dextra accessoria
VCM : V. colica media
VCD : V. colica dextra
VJ : V. jejunalis
AGP : A. gastrica posterior

AHC : A. hepatica communis
VP : V. portae
VL : V. lienalis
VMS : V. mesenterica superior
VPDIA : V. pancreaticoduodenalis inferior anterior
TGC : Truncus gastrocolicus
ACM : A. colica media
AJ : A. jejunalis

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	0/23	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	

Sun et al. Radiation Oncology 2010, 5:28
http://www.ro-journal.com/content/5/1/28

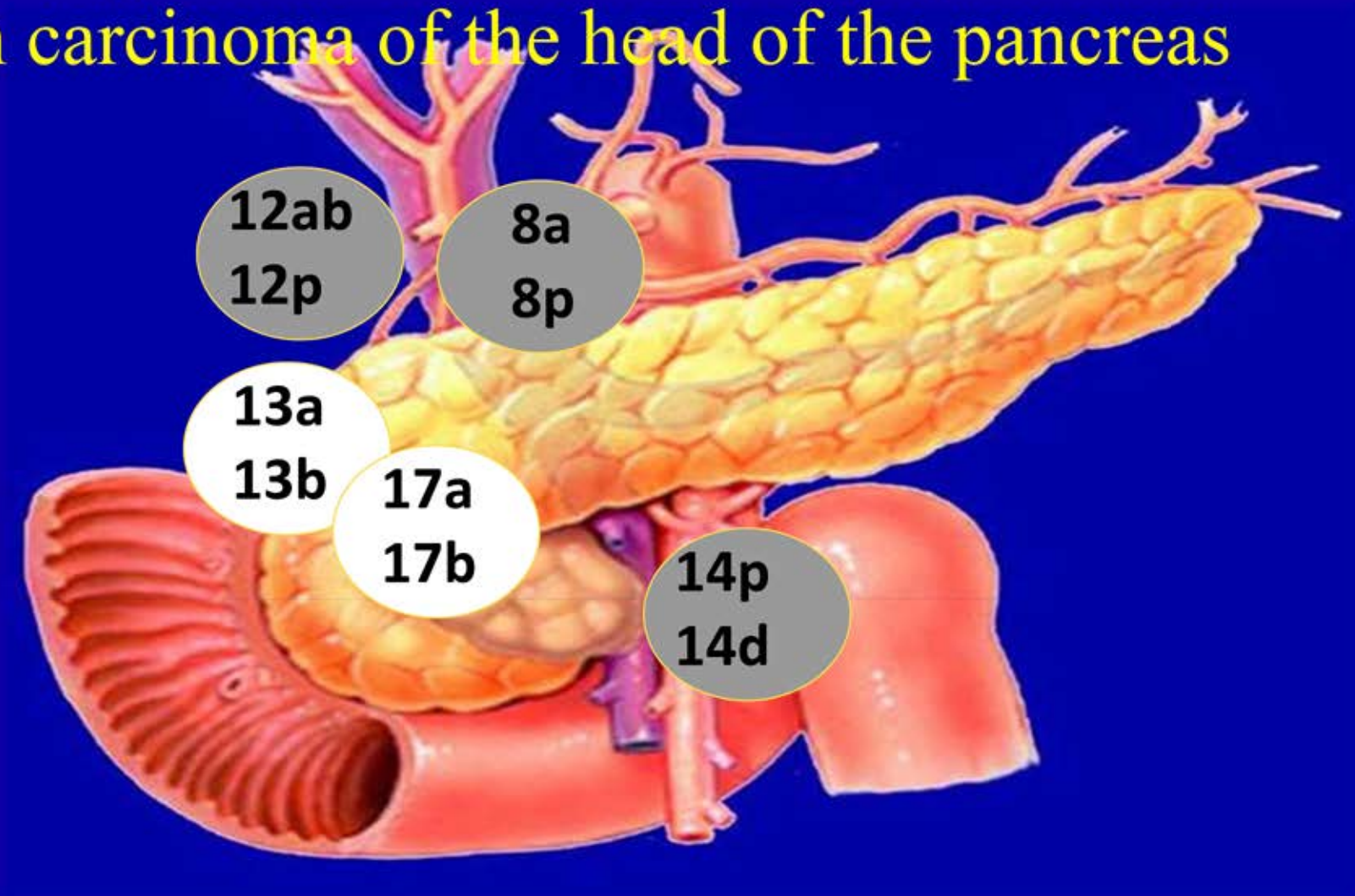
RADIATION ONCOLOGY

RESEARCH Open Access

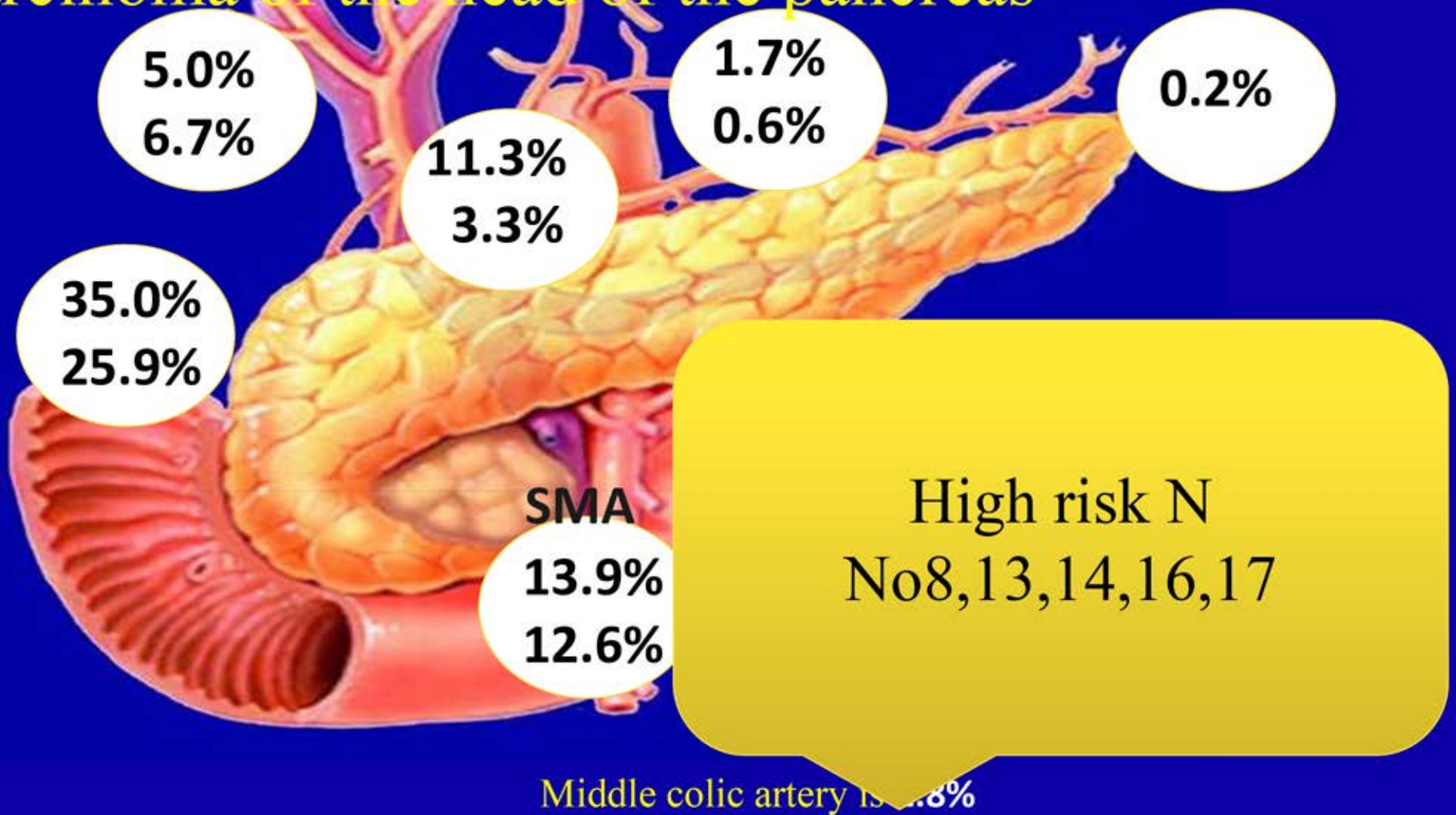
Proposing the lymphatic target volume for elective radiation therapy for pancreatic cancer: a pooled analysis of clinical evidence

Wenjie Sun[1*], Cheng N Leong[2], Zhen Zhang[3*], Jiade J Lu[1,2]

Group classification of the lymph nodes in carcinoma of the head of the pancreas



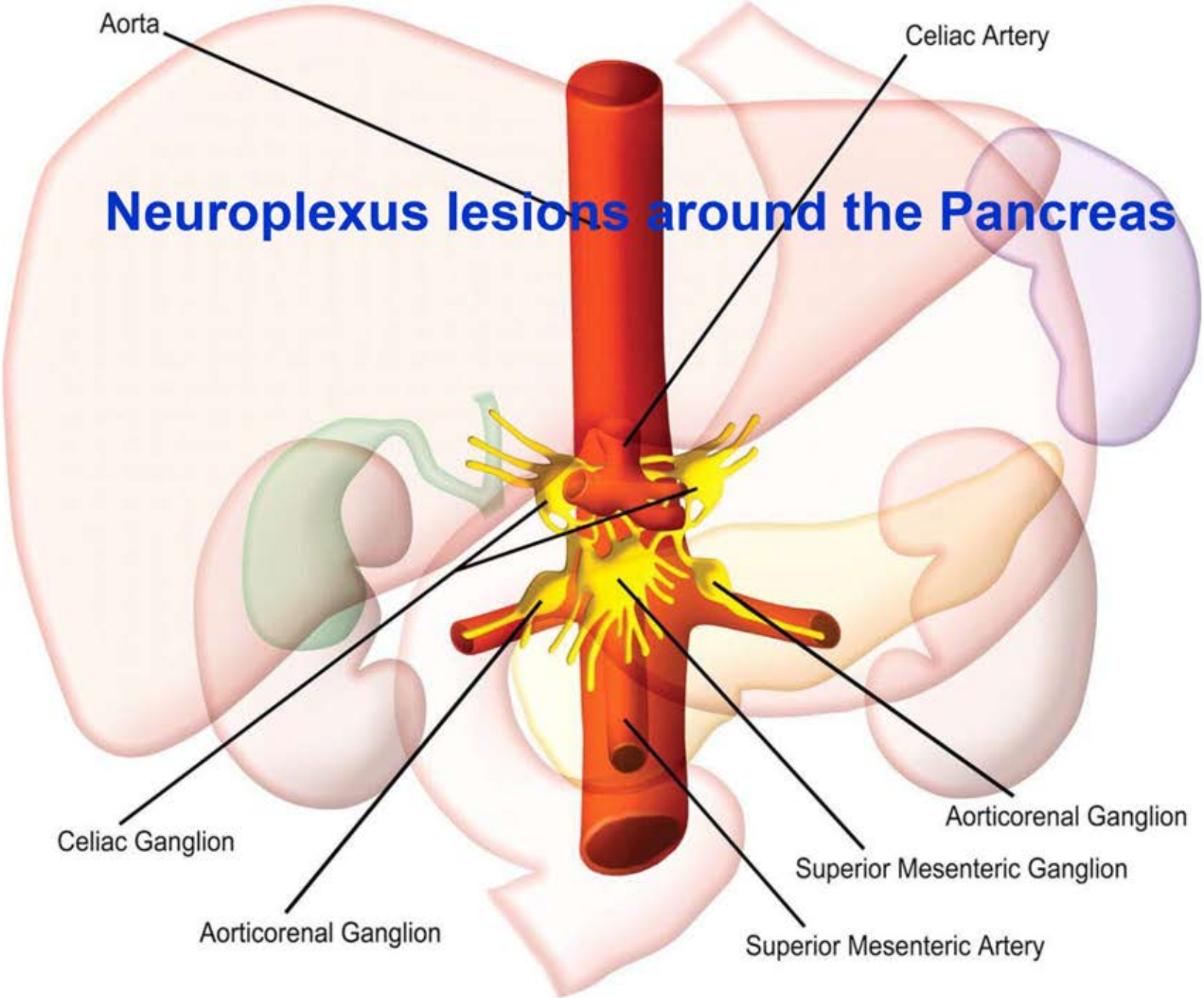
The frequency of lymph node metastasis in carcinoma of the head of the pancreas



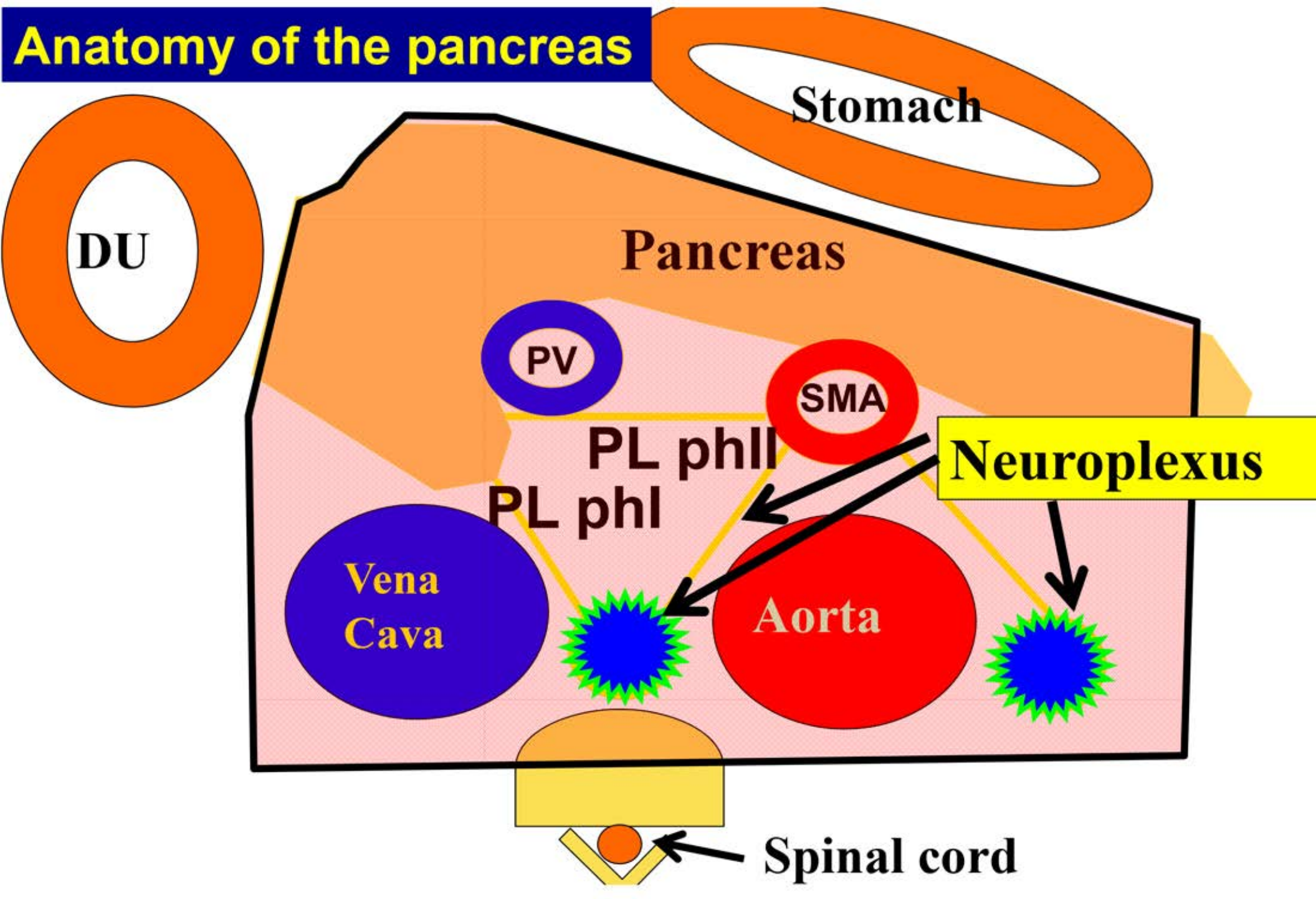
Presence or absence of nerve plexus invasion in resected cases

	Number of cases （%）
Plexus invasion （−）	1338(51.1%)
Plexus invasion （＋）	748(28.6%)
Unknown	531(20.3%)

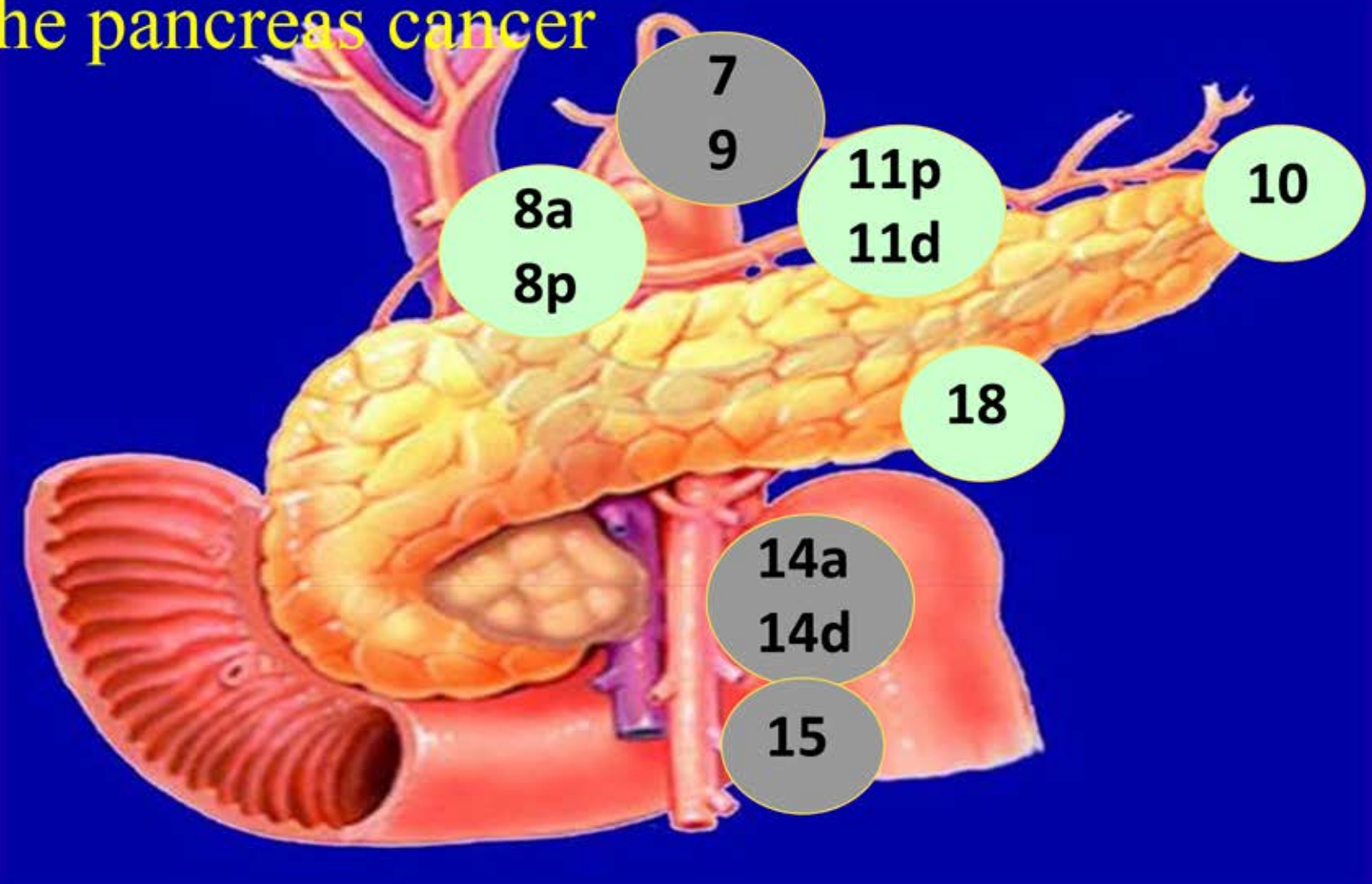
pancreatic cancer registered since 2007


Aorta
Celiac Artery
Neuroplexus lesions around the Pancreas
Celiac Ganglion
Aorticorenal Ganglion
Superior Mesenteric Artery
Superior Mesenteric Ganglion
Aorticorenal Ganglion

Anatomy of the pancreas



Classification group of lymph nodes in the body of the pancreas cancer



The frequency of lymph node metastasis in cancer of the pancreatic body

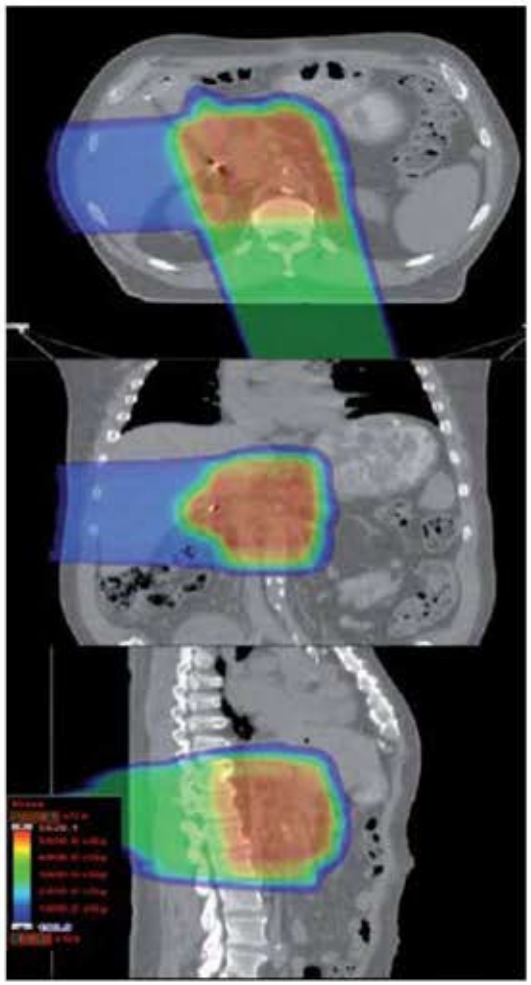
Technique

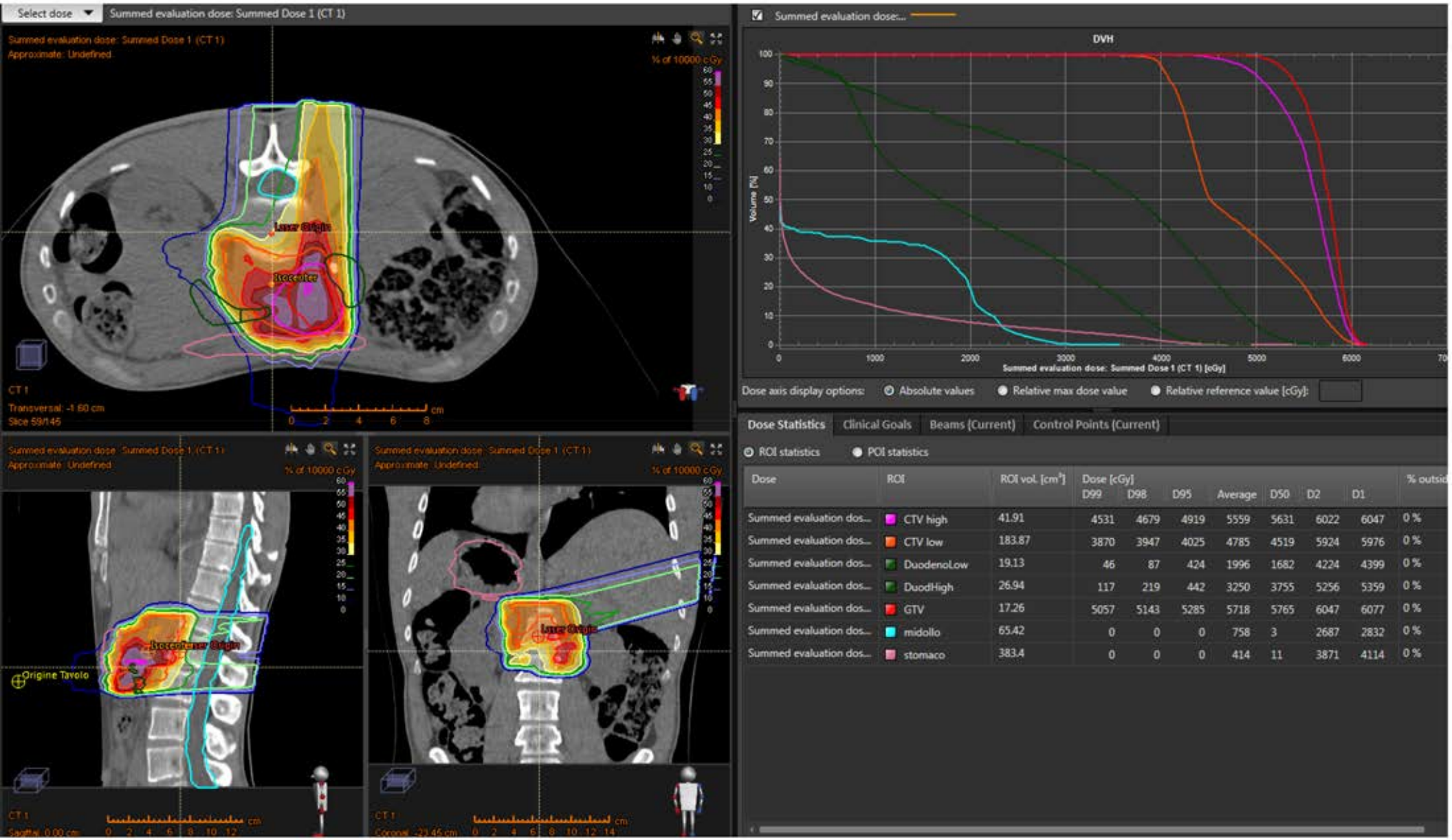
- NIRS: passive fields , 4 ports simulation in both prone and supine position, uncertainties in bowel filling is compensated with PTV margins
- CNAO: active , avoid passing through bowel

Pancreas at CNAO

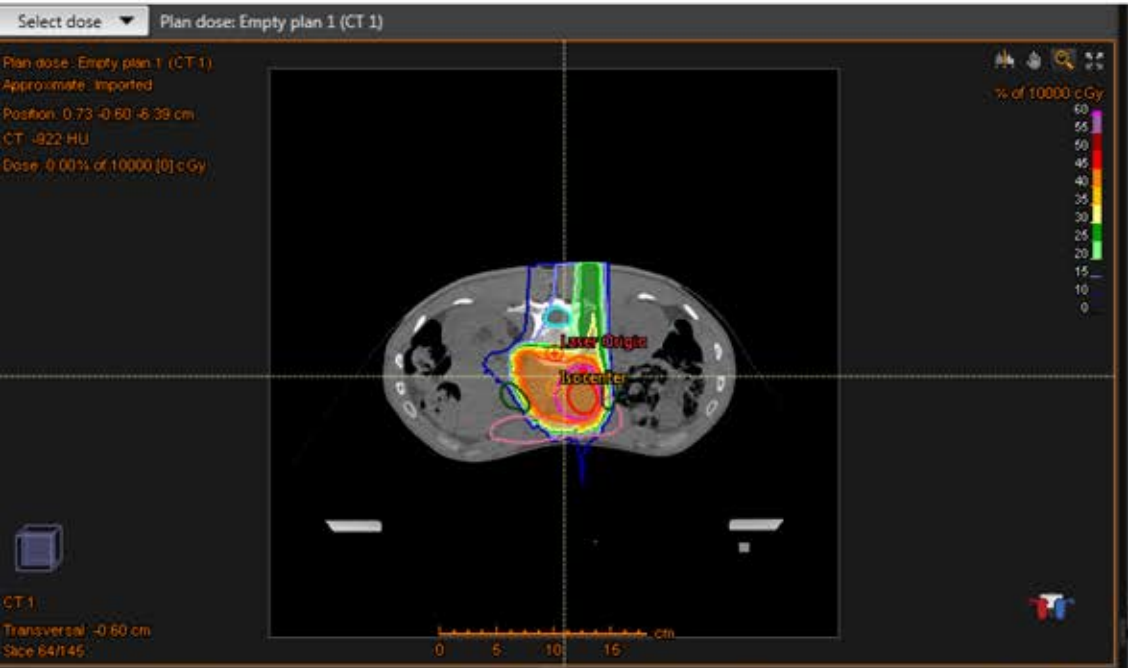
- Abdominal compression
- Multiple set up
- 4D CT scan
- 4D MR
- Respiratory gating
- 5 times rescanning
- Weekly replanning
- Plan robustness (hand made)

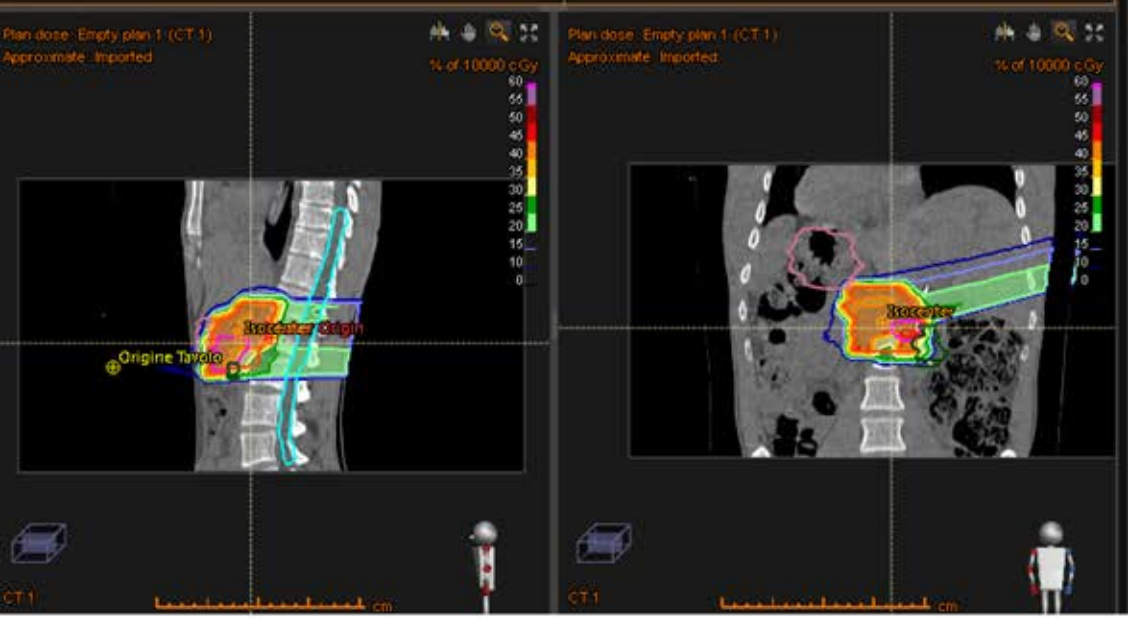
Better from the back

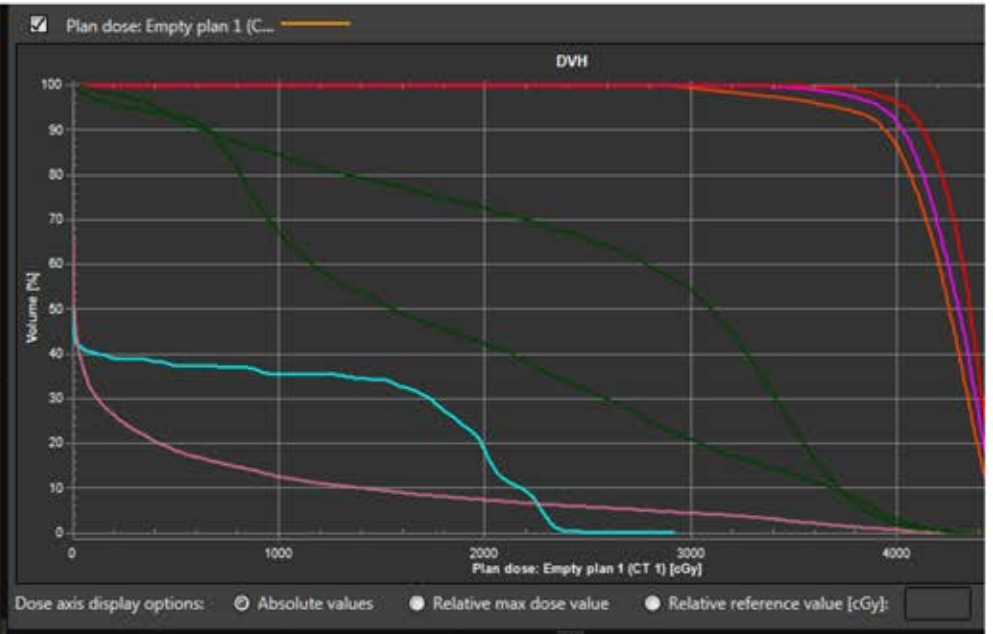




Dose	ROI	ROI vol. [cm³]	Dose [cGy] D99	D98	D95	Average	D50	D2	D1	% outsid
Summed evaluation dos...	CTV high	41.91	4531	4679	4919	5559	5631	6022	6047	0 %
Summed evaluation dos...	CTV low	183.87	3870	3947	4025	4785	4519	5924	5976	0 %
Summed evaluation dos...	DuodenoLow	19.13	46	87	424	1996	1682	4224	4399	0 %
Summed evaluation dos...	DuodHigh	26.94	117	219	442	3250	3755	5256	5359	0 %
Summed evaluation dos...	GTV	17.26	5057	5143	5285	5718	5765	6047	6077	0 %
Summed evaluation dos...	midollo	65.42	0	0	0	758	3	2687	2832	0 %
Summed evaluation dos...	stomaco	383.4	0	0	0	414	11	3871	4114	0 %



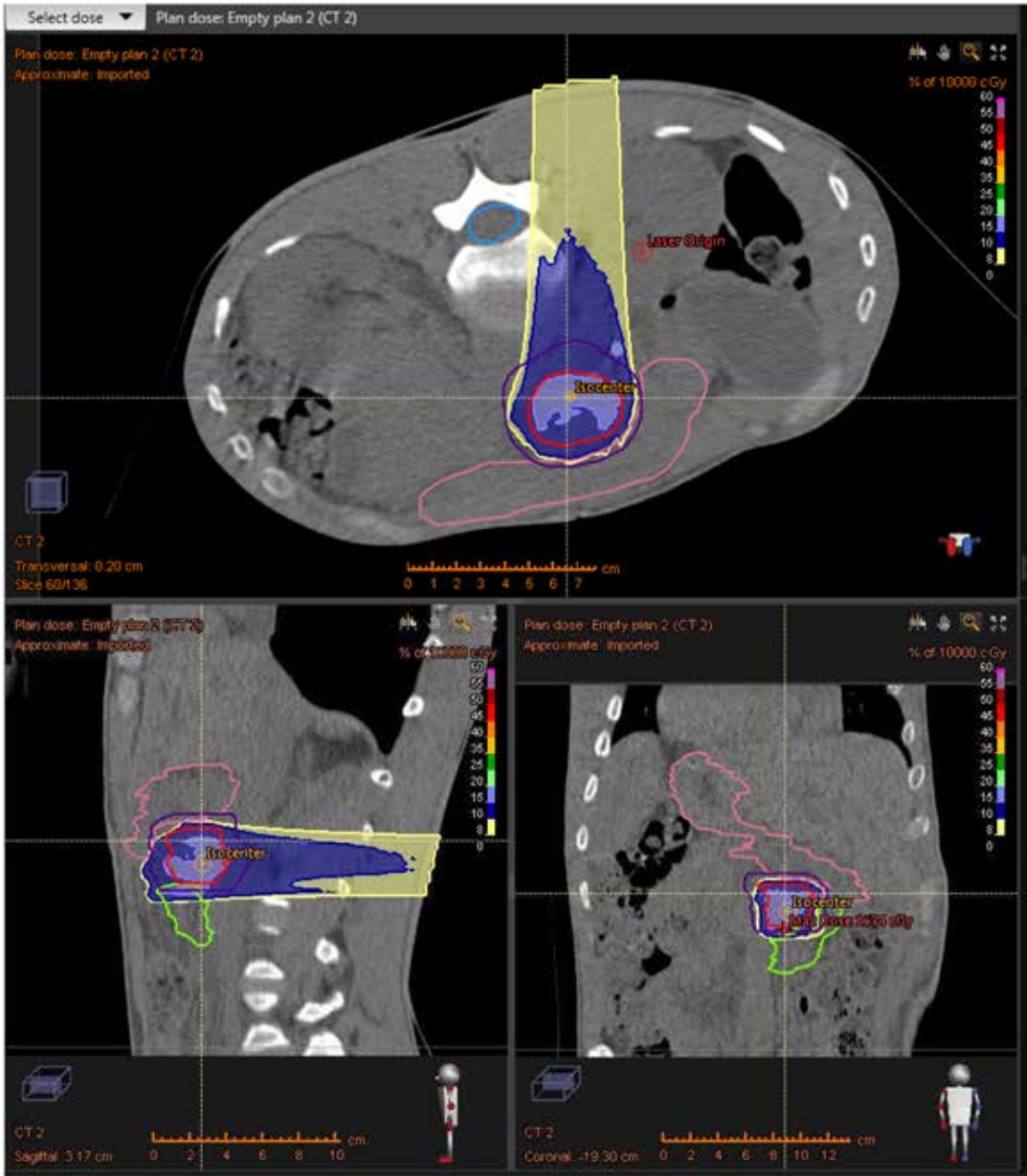


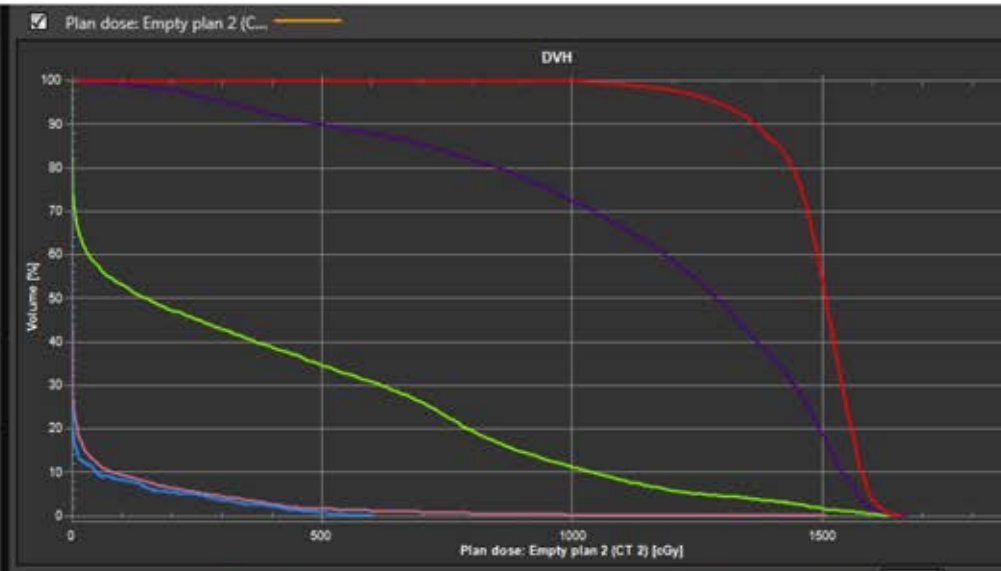


Dose Statistics | Clinical Goals | Beams (Current) | Control Points (Current)

ROI statistics | POI statistics

Dose	ROI	ROI vol. [cm³]	Dose [cGy] D99	D98	D95	Average	D50	D2	D1
Plan dose: Empty plan 1...	CTV high	41.9	3584	3737	3924	4269	4304	4551	45
Plan dose: Empty plan 1...	CTV low	183.88	3082	3272	3712	4203	4259	4525	45
Plan dose: Empty plan 1...	DuodenoLow	19.14	31	63	269	1861	1555	4064	41
Plan dose: Empty plan 1...	DuodHigh	26.93	103	203	410	2612	3100	3987	40
Plan dose: Empty plan 1...	GTV	17.27	3802	3898	4043	4328	4358	4556	45
Plan dose: Empty plan 1...	midollo	65.39	0	0	0	732	2	2327	23
Plan dose: Empty plan 1...	stomaco	383.41	0	0	0	389	11	3621	38



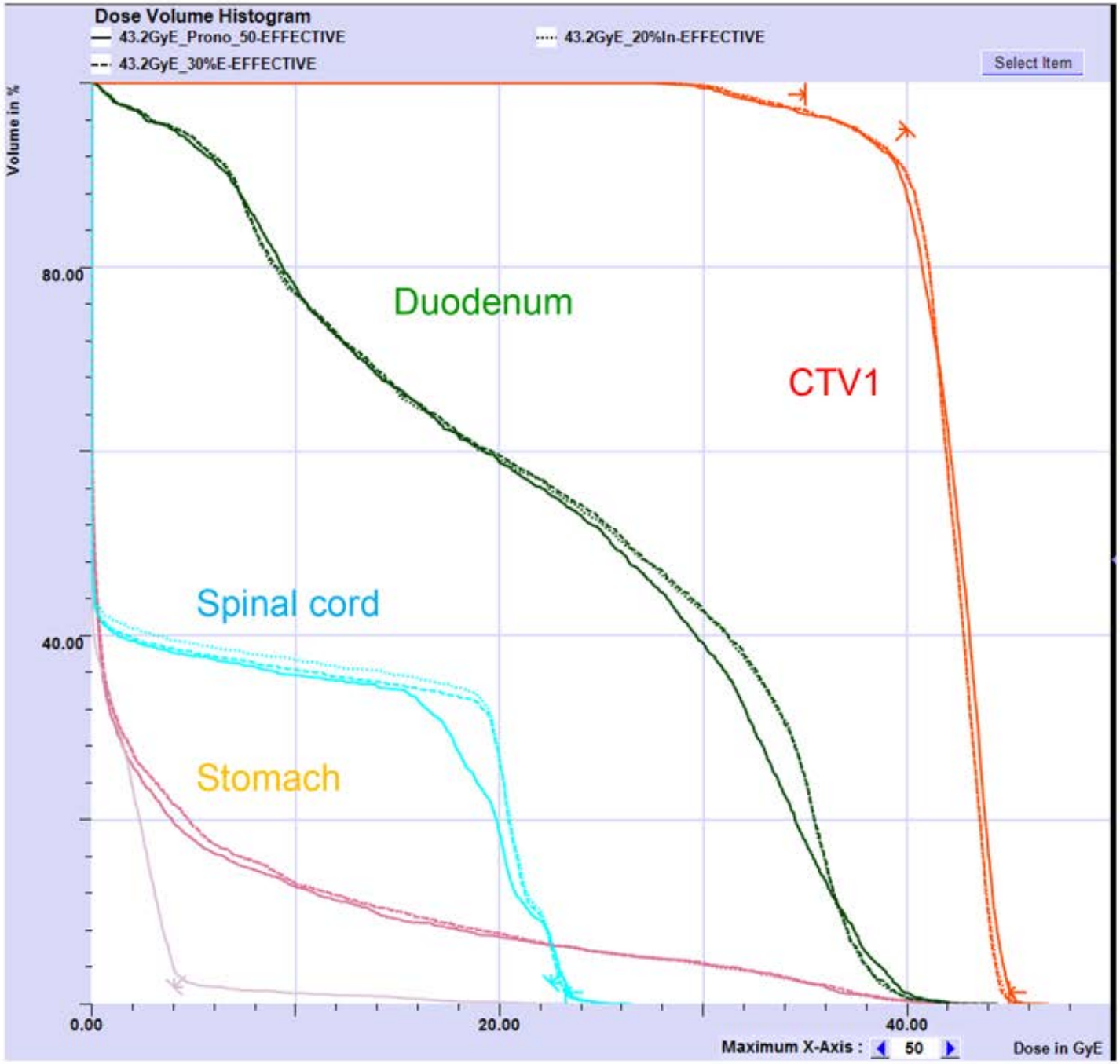


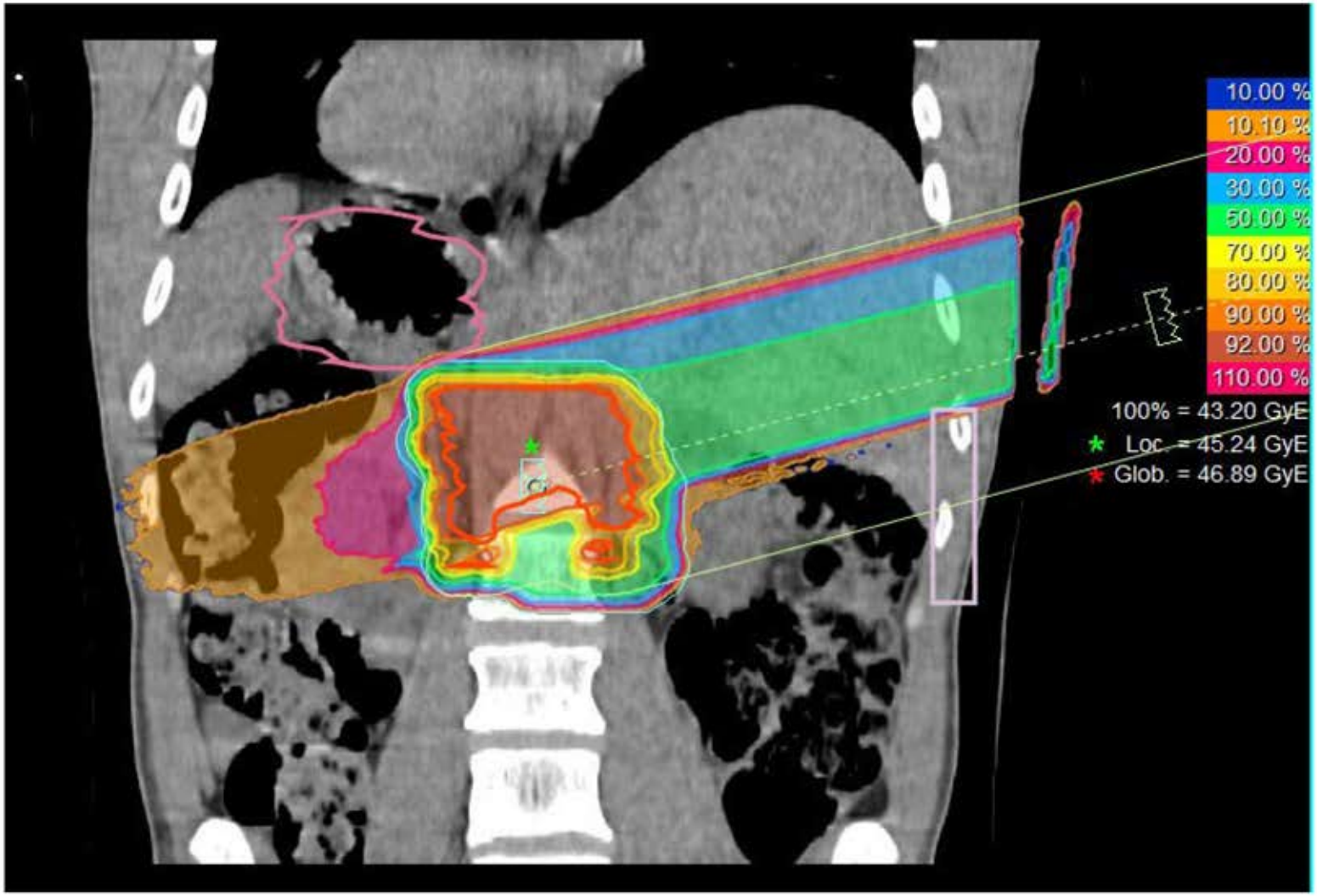
Dose axis display options: Absolute values | Relative max dose value | Relative reference value [cGy]:

Dose Statistics | Clinical Goals | Beams (Current) | Control Points (Current)

ROI statistics | POI statistics

Dose	ROI	ROI vol. [cm³]	Dose [cGy] D99	D98	D95	Average	D50	D2	D1
Plan dose: Empty plan 2...	duodenotilt	91.67	0	0	0	374	148	1479	1545
Plan dose: Empty plan 2...	GTVBOOST	23.42	1105	1188	1292	1487	1507	1614	1626
Plan dose: Empty plan 2...	MIDOLLO_boost	38.72	0	0	0	27	0	410	474
Plan dose: Empty plan 2...	PTVBOOST	87.57	125	186	304	1160	1287	1592	1607
Plan dose: Empty plan 2...	stomaco	288.1	0	0	0	36	1	432	638

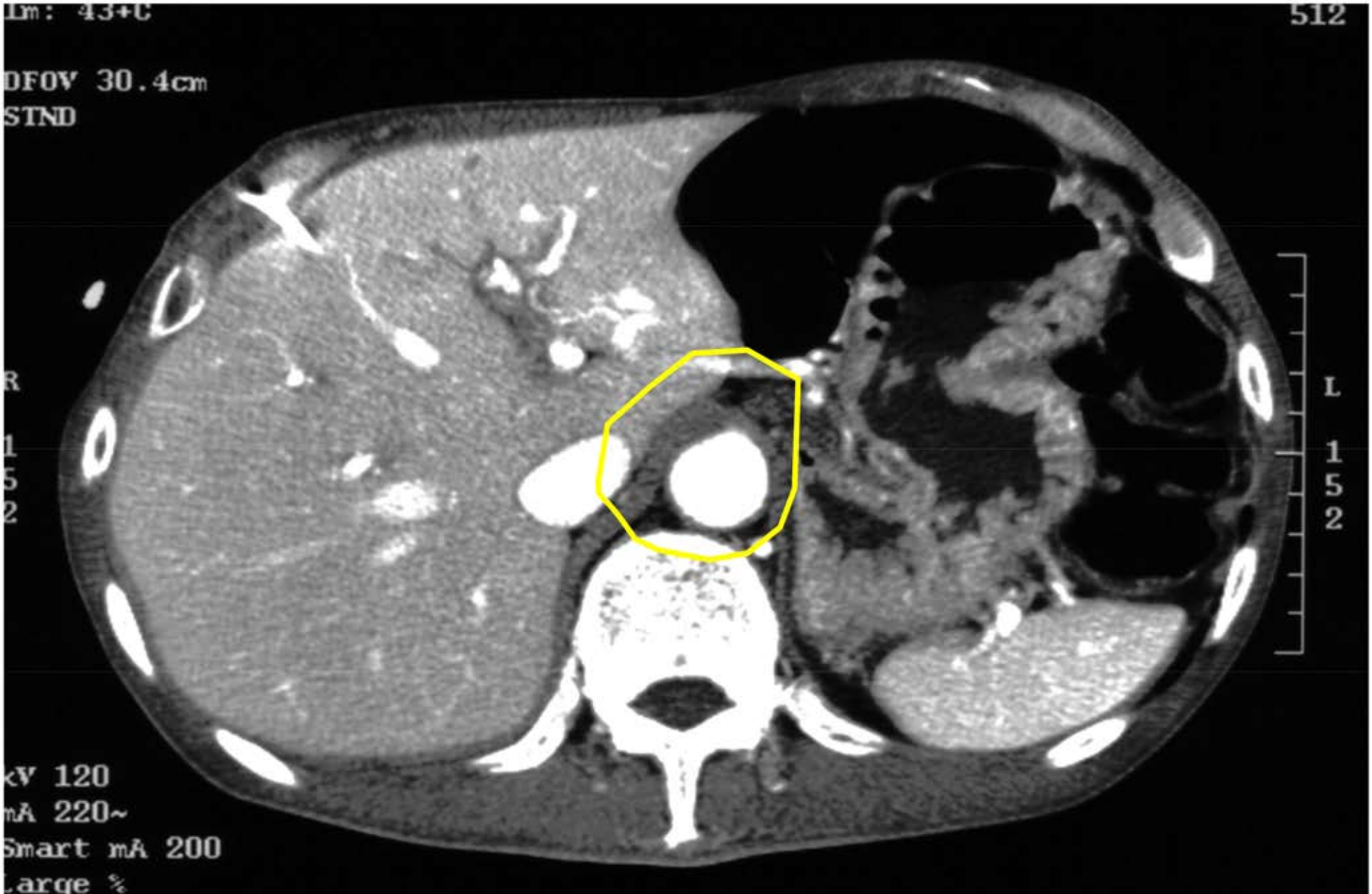

Dose Volume Histogram
43.2GyE_Prono_50-EFFECTIVE
43.2GyE_20%In-EFFECTIVE
43.2GyE_30%E-EFFECTIVE
Select Item
Volume in %
80.00
40.00
Duodenum
CTV1
Spinal cord
Stomach
0.00
20.00
40.00
Maximum X-Axis :
50
Dose in GyE

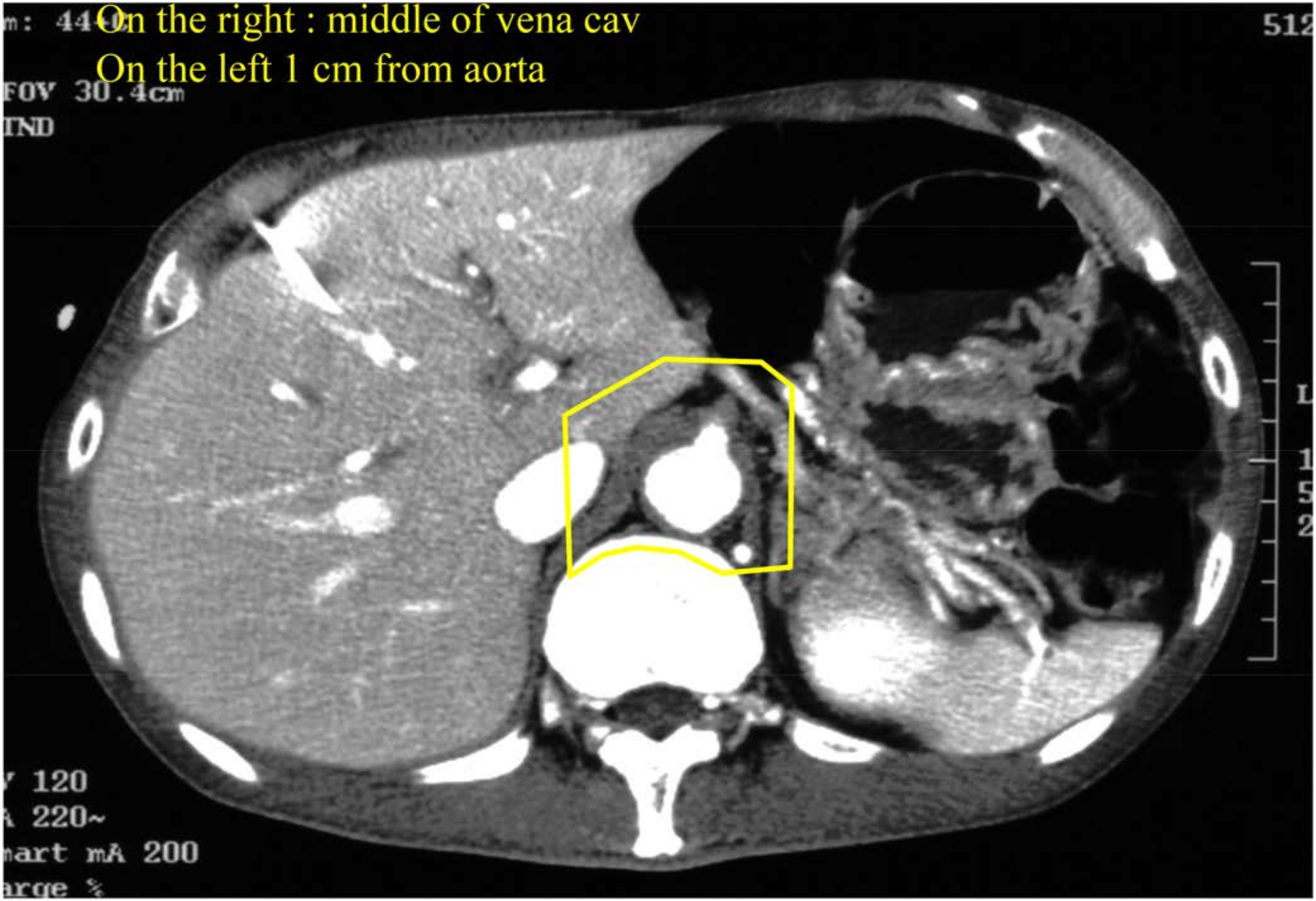

10.00 %
10.10 %
20.00 %
30.00 %
50.00 %
70.00 %
80.00 %
90.00 %
92.00 %
110.00 %
100% = 43.20 GyE
Loc. = 45.24 GyE
Glob. = 46.89 GyE

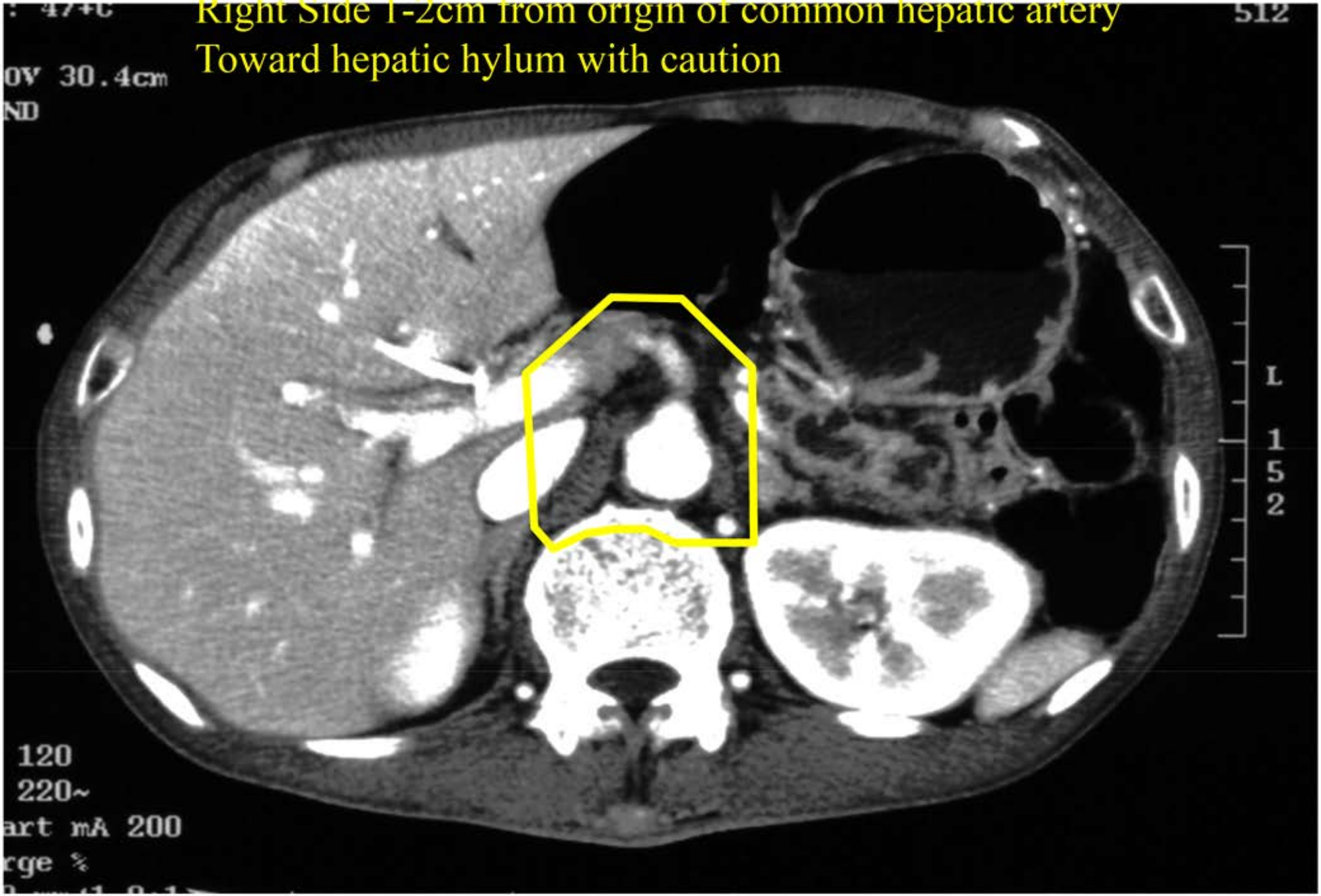
Example of NIRS volumes (Homework)

- Pancreas head
- CTV1

Cranial margin 1-2cm above celiac artery origin



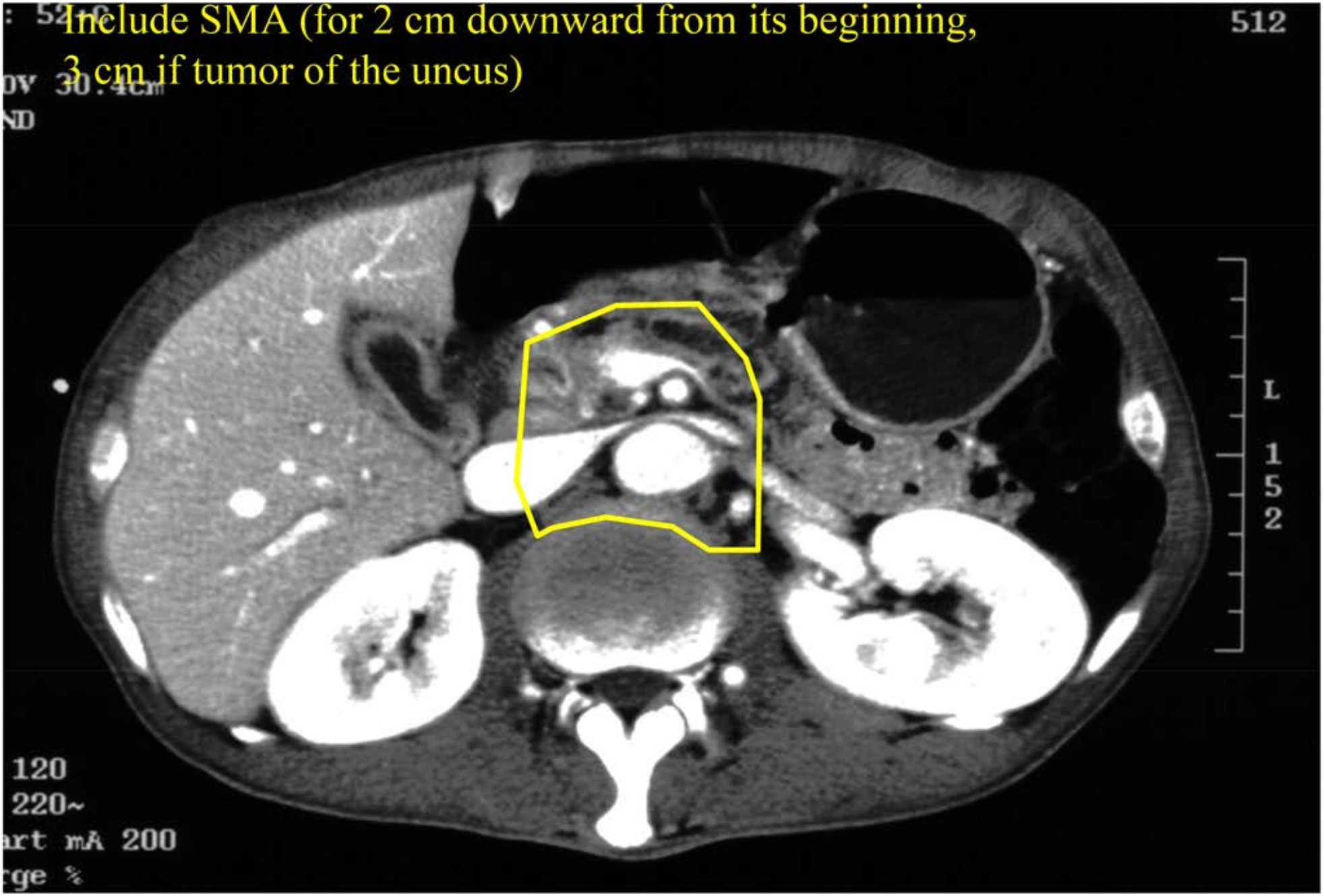

On the right : middle of vena cav
On the left 1 cm from aorta
FOV 30.4cm
512
120
220~
mart mA 200


Right Side 1-2cm from origin of common hepatic artery
Toward hepatic hylum with caution
512
OV 30.4cm
ND
L
152
120
220~
art mA 200
rge %

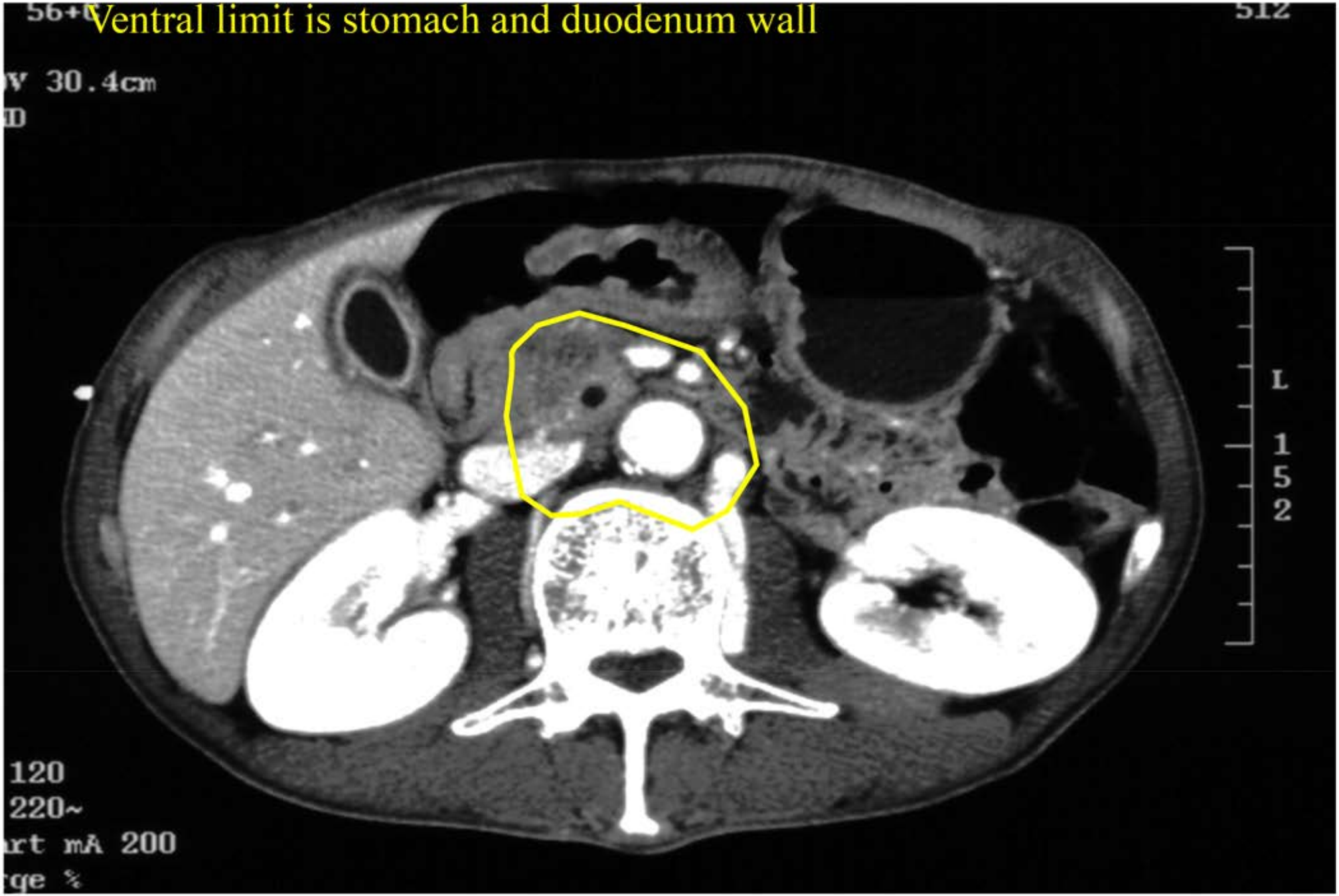

512
OV 30.4cm
ND
L
1
5
2
120
220~
art mA 200
rge %

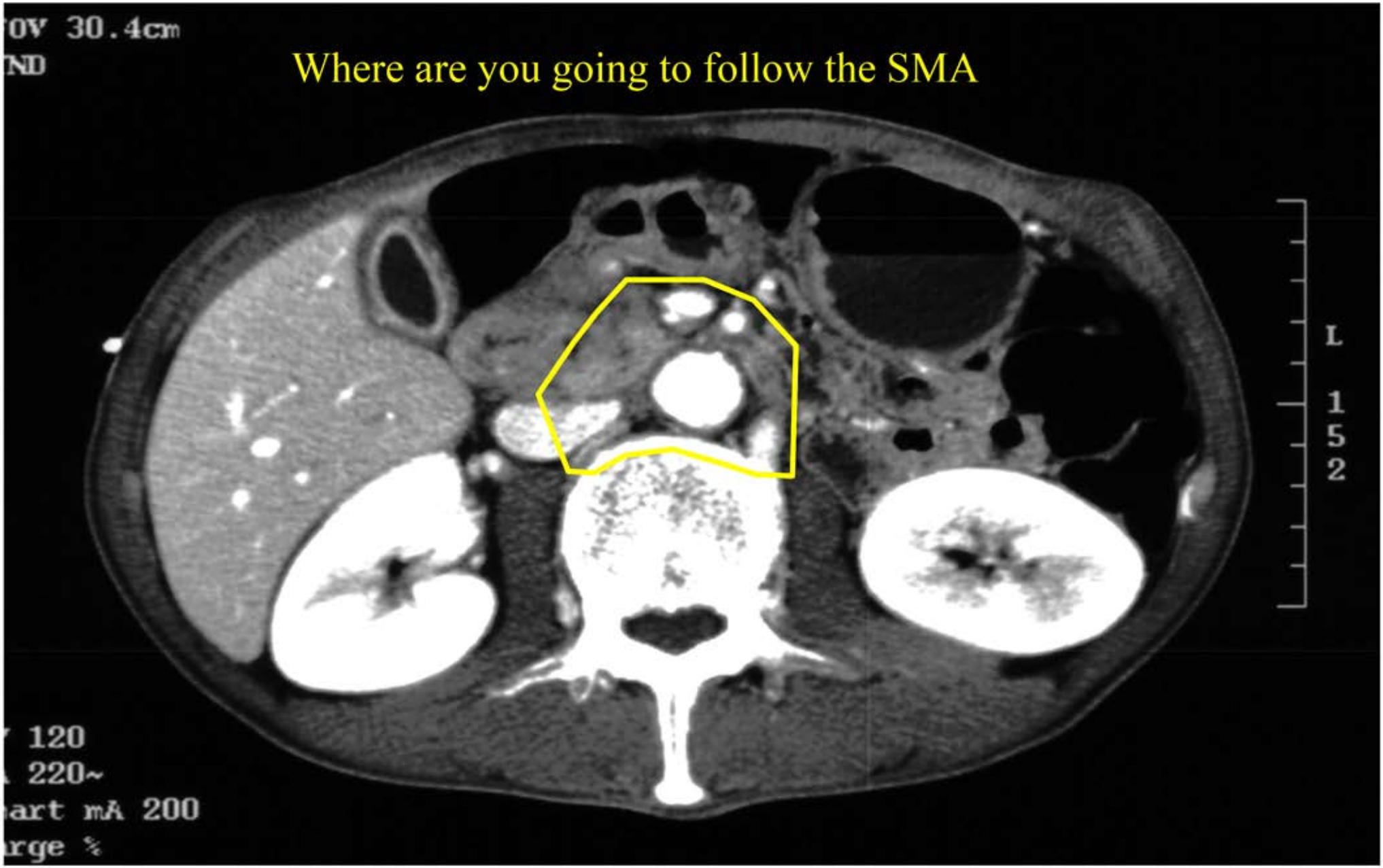

: 50+C
Exclude upper bile duct
512
OV 30.4cm
ND
L
1
5
2
120
220~
art mA 200
rge %


V 30.4cm
D
L
152
120
220~
rt mA 200
ge %

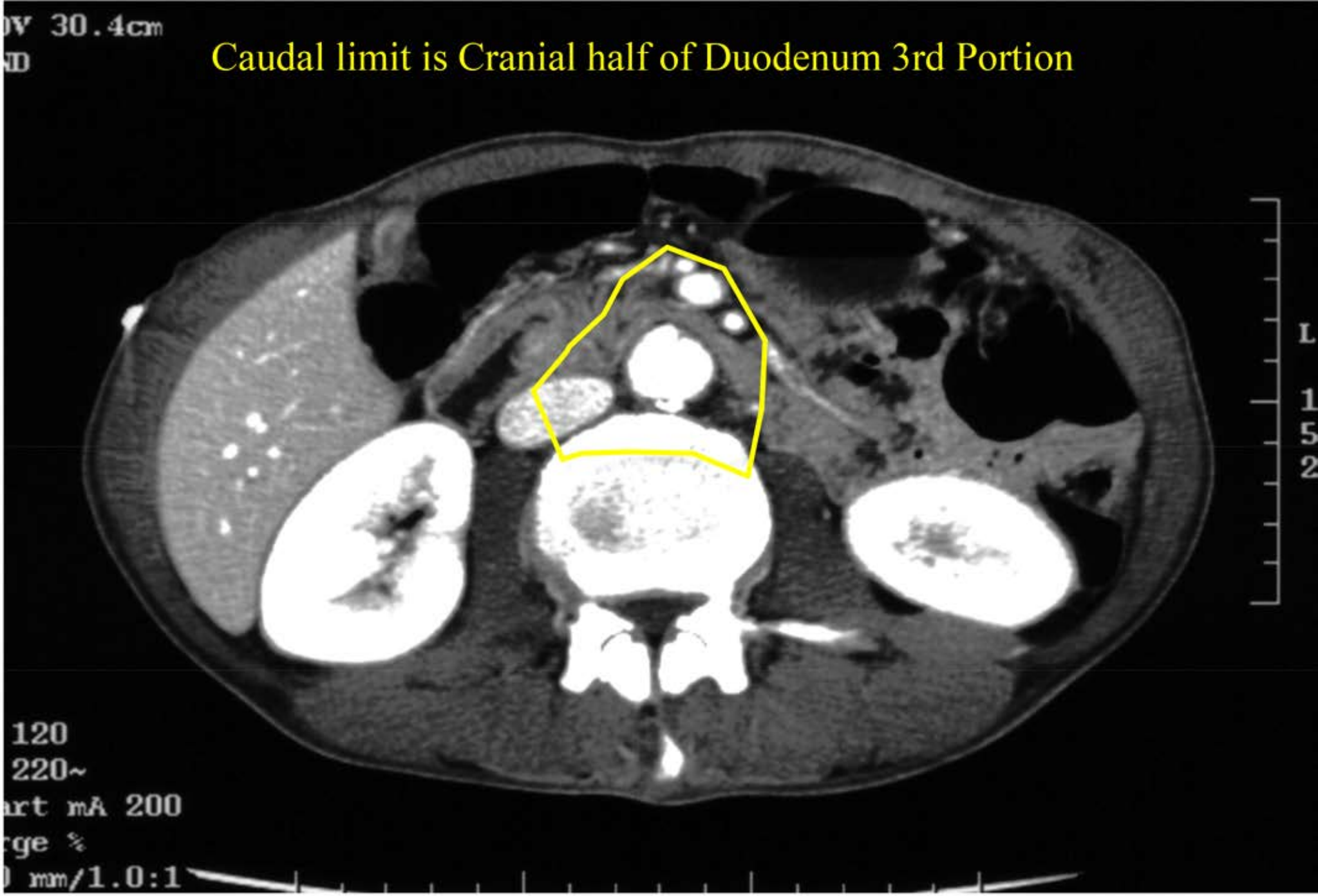

Include SMA (for 2 cm downward from its beginning,
3 cm if tumor of the uncus)
512
L
152
120
220~
mA 200


DV 30.4cm
ND
L
1
5
2
120
220~
art mA 200
rge %


Ventral limit is stomach and duodenum wall
512
W 30.4cm
L
152
120
220~
rt mA 200


Where are you going to follow the SMA


DV 30.4cm
ND
L
1
5
2
120
220~
art mA 200
rge %


Caudal limit is Cranial half of Duodenum 3rd Portion