Status of Carbon Therapy

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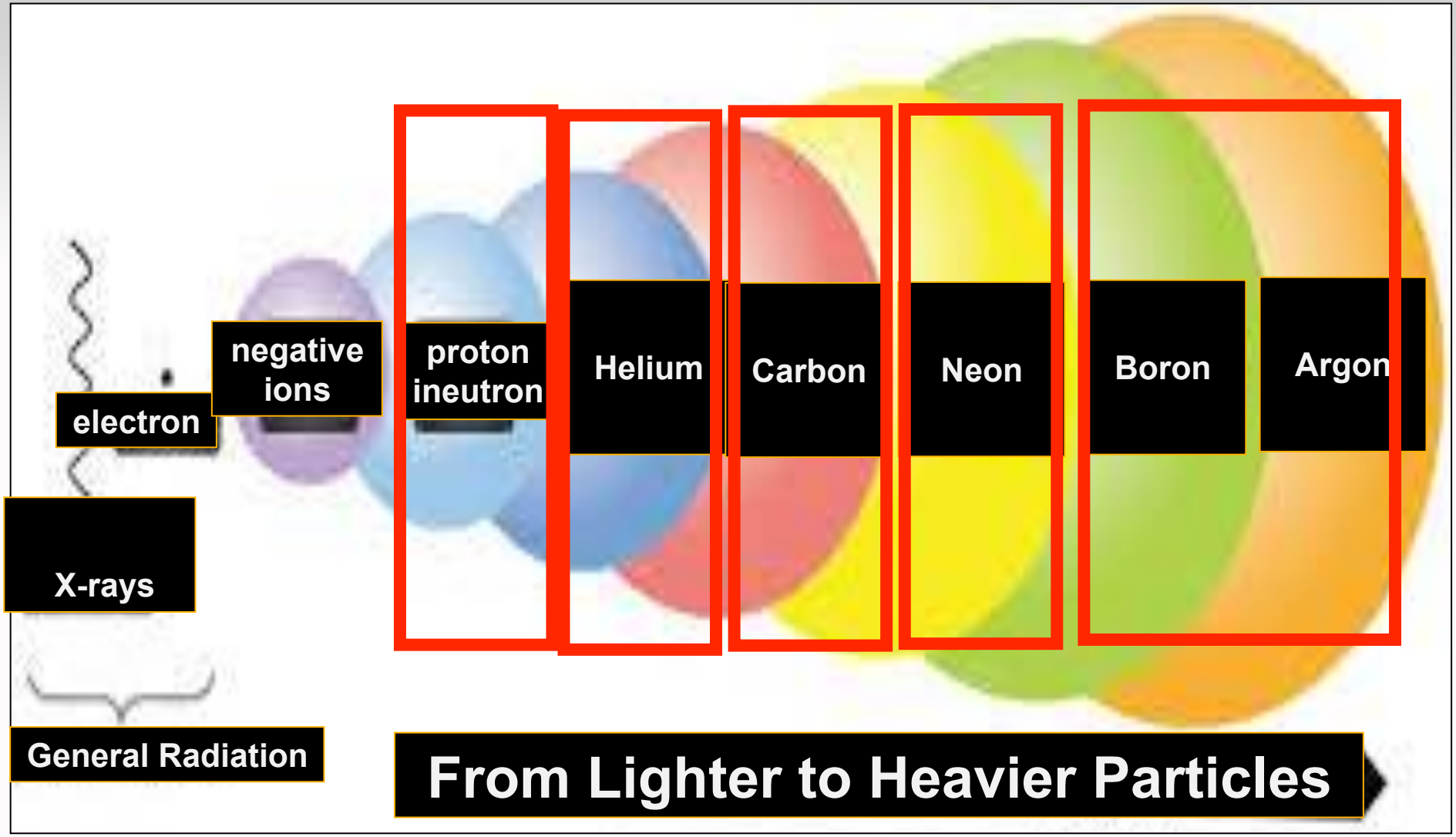
ENLIGHT Meeting
Utrecht
15th September 2016

UNIVERSITÀ DEGLI STUDI DI MILANO

IEO European Institute of Oncology

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

Particle Therapy



Experience with light ions at LBL

1314 patients treated from 1975 to 1992

64% with He (low-LET), 32% with Ne

347 uveal melanoma (He only), 194 pancreas (55% He), 94 chordoma (85% He), esophagus, biliary tract, salivary glands, paranasal sinuses, lung, prostate, ...

International Journal of Radiation Oncology biology • physics
www.redjournal.org

- Phase III RCT
- Helium ions vs iodine125 plaque brachytherapy
- Significant improvement in LC
- Long term follow up
- No difference in OS

Clinical Investigation

Long-term Results of the UCSF-LBNL Randomized Trial: Charged Particle With Helium Ion Versus Iodine-125 Plaque Therapy for Choroidal and Ciliary Body Melanoma

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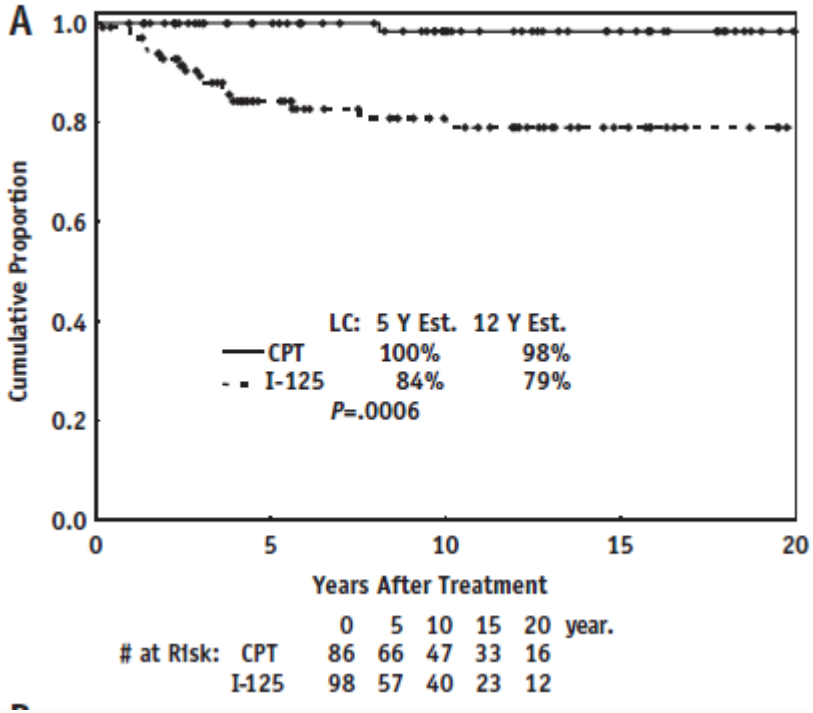
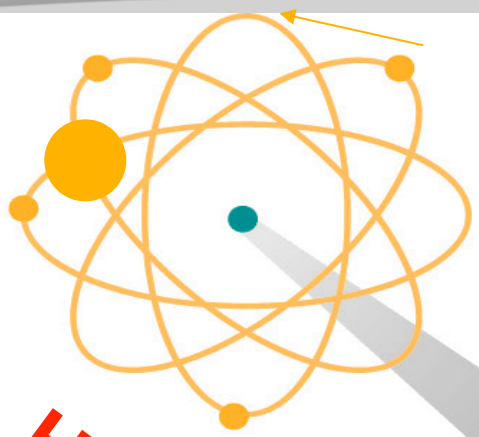


Fast neutrons & Neon ions

Tumour site or type	Local control rates after treatment with [a]	
	Fast neutrons (pooled data)	Neon ions (Berkeley)
Salivary gland tumours	67%	80% (25-30%)
Paranasal sinuses	67%	63% (≈20%)
Fixed cervical lymph nodes	69% (55%)	
Sarcomas	53%	45% (30-40% [b])
Prostatic adenocarcinoma	77%	100% (30-70% [b])

BEVALAC complex

(SuperHILac linear accelerator + Bevatron)



Electrons (X-rays):

Carbon ion is 12×2000 times heavier than electron

Hadrontherapy

Nucleus of Carbon made of 6 protons (p) and 6 neutrons (n)

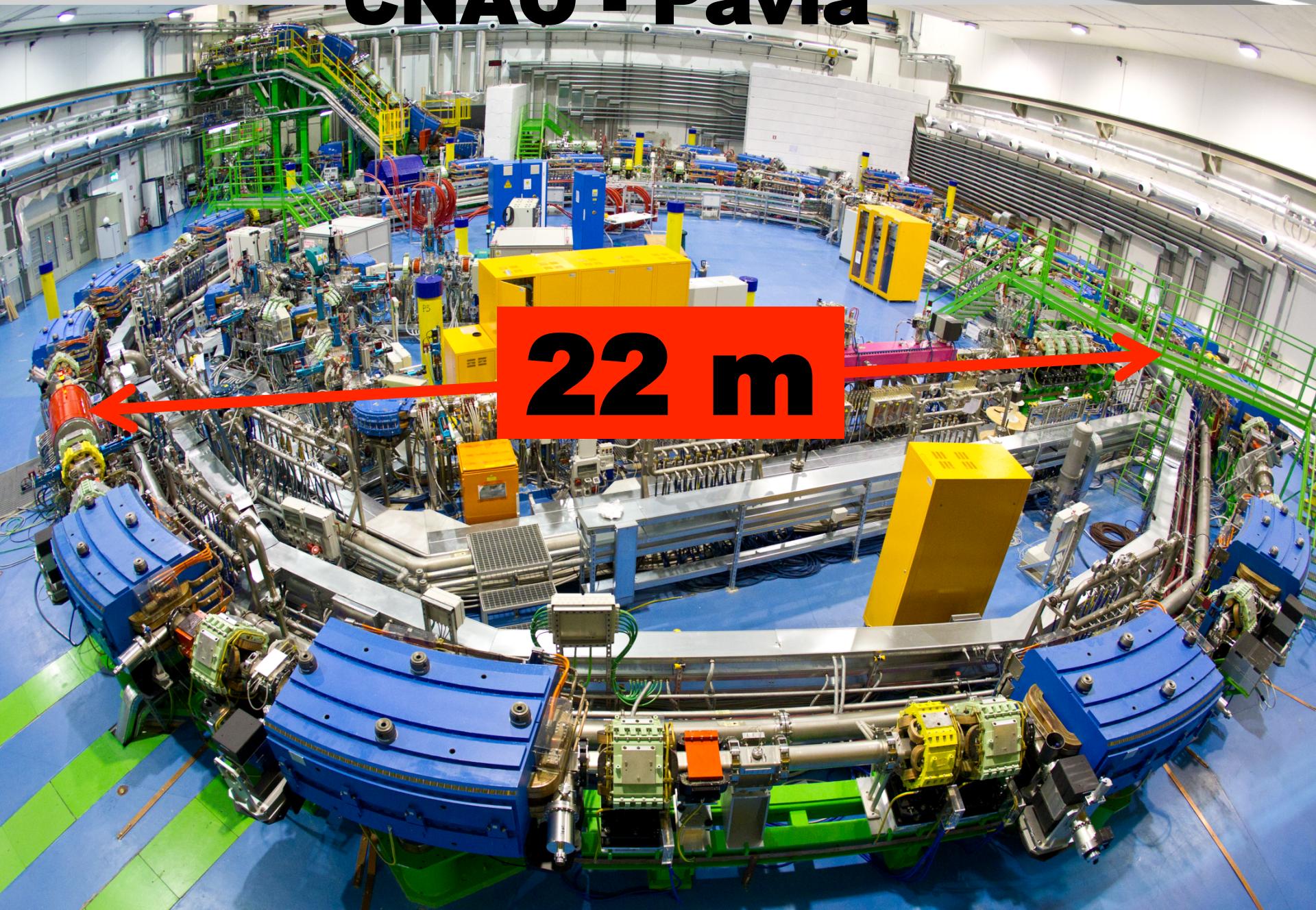
p

n

Simplest nucleus: the proton (p)

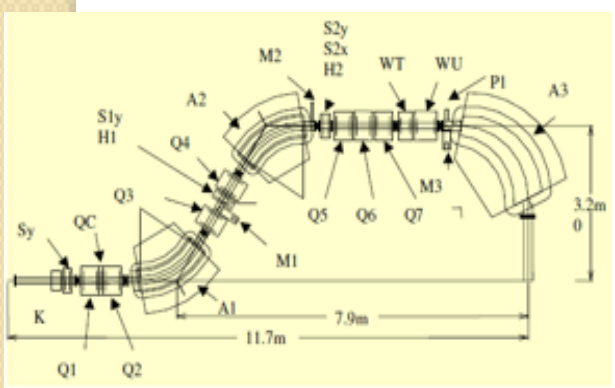
Proton is 2000 times heavier than electron

CNAO - Pavia



Gantry size

Conventional RT

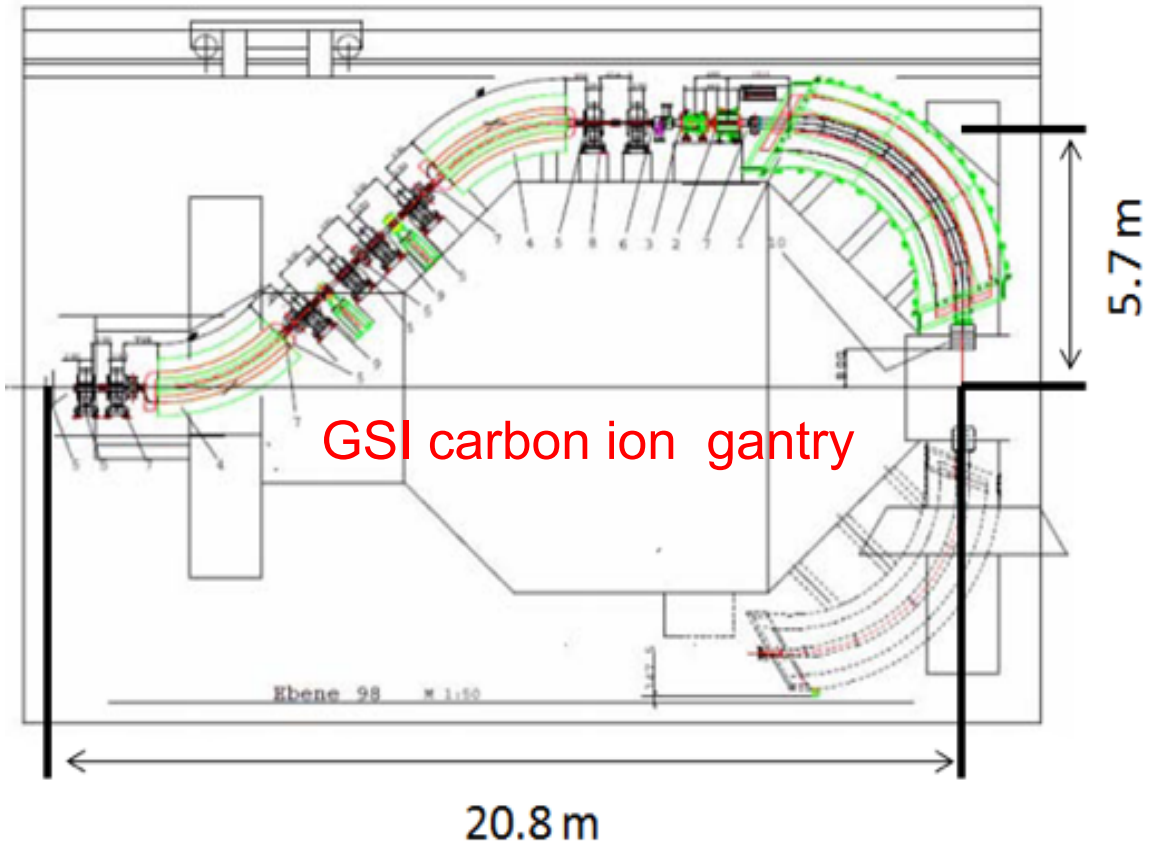


Proton Gantry
Bρ < 2.4 Tm

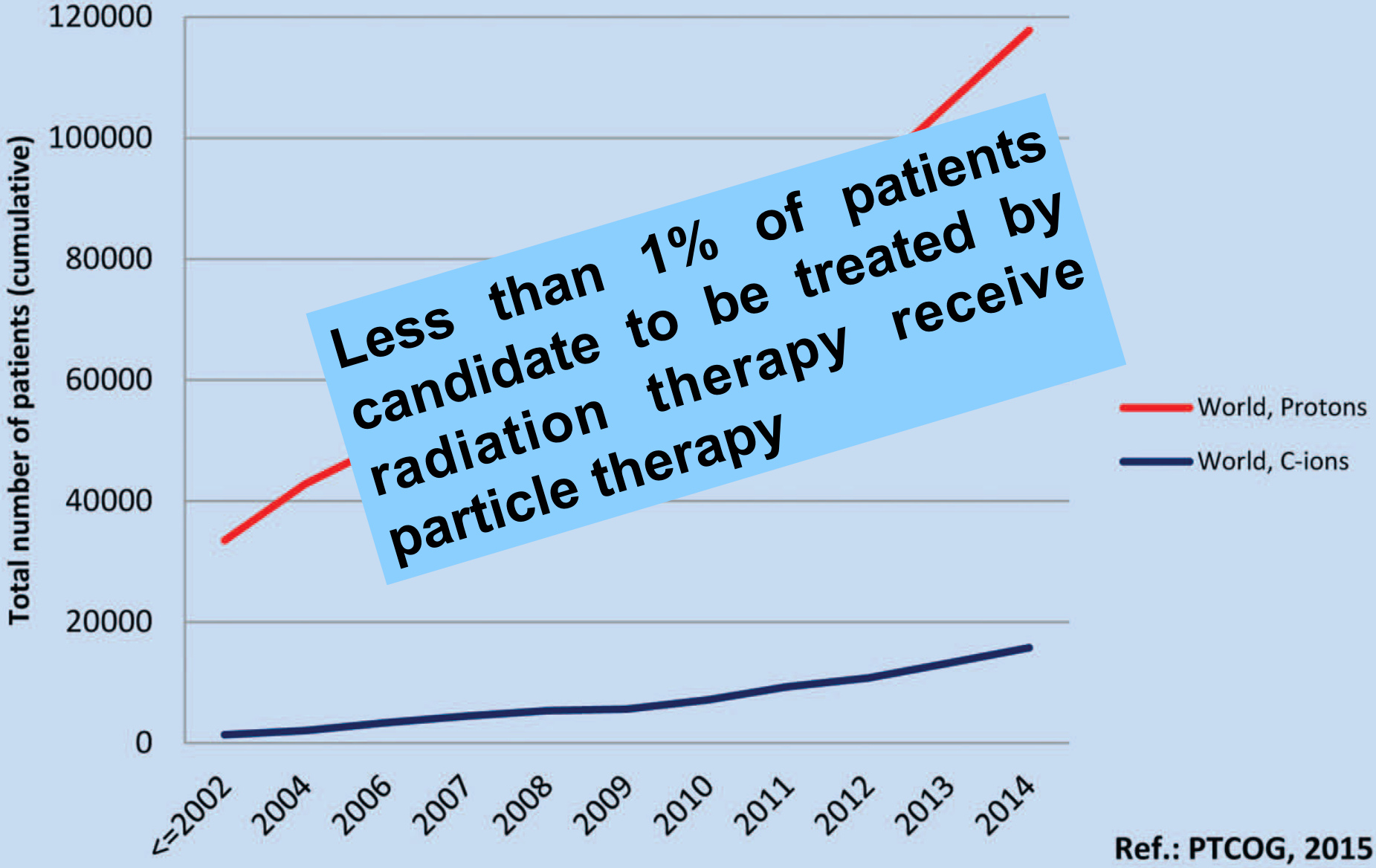
PSI proton gantry

(Courtesy M. Pullia)

Carbon Ion Gantry
Bρ < 6.4 Tm

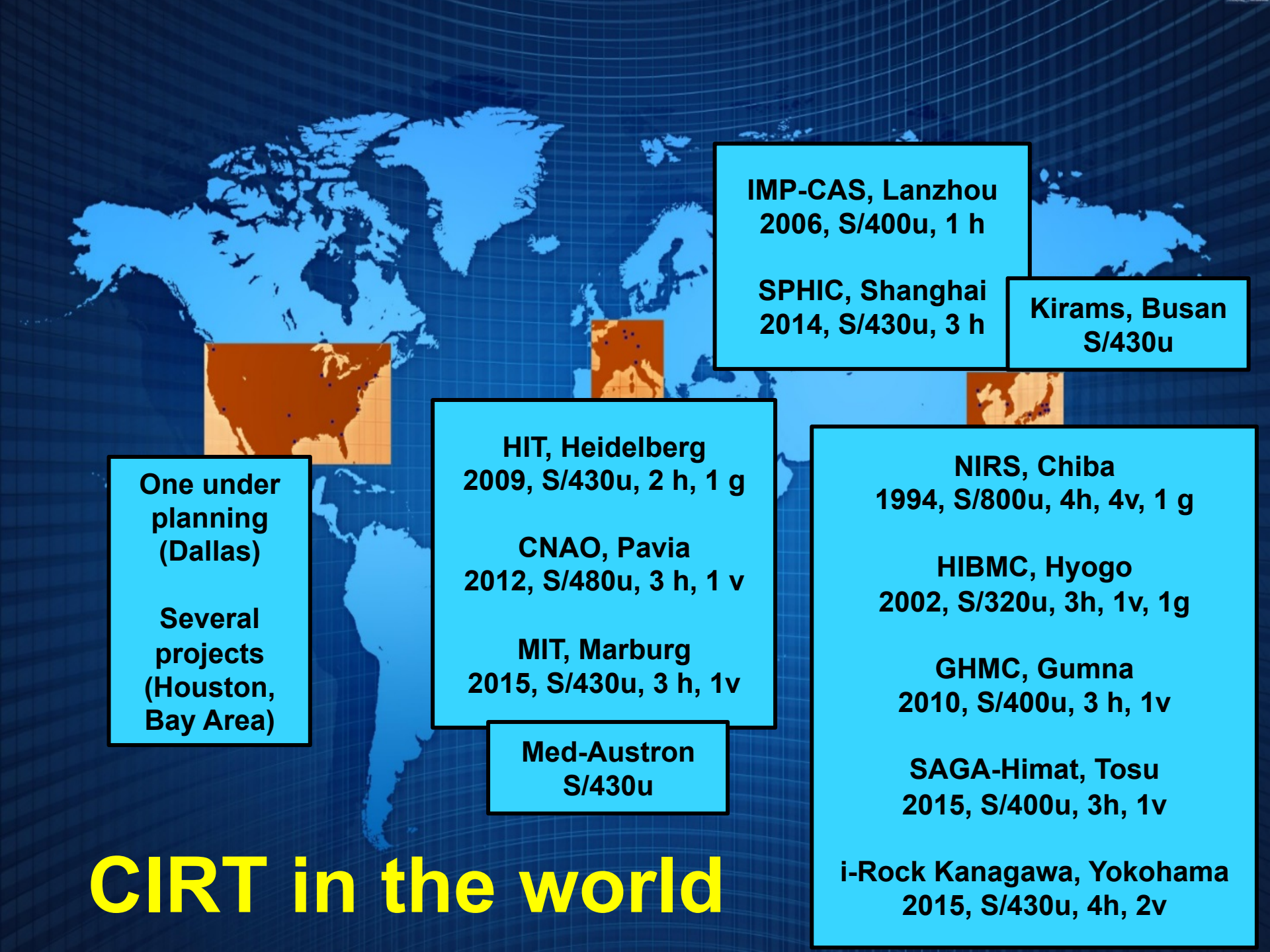


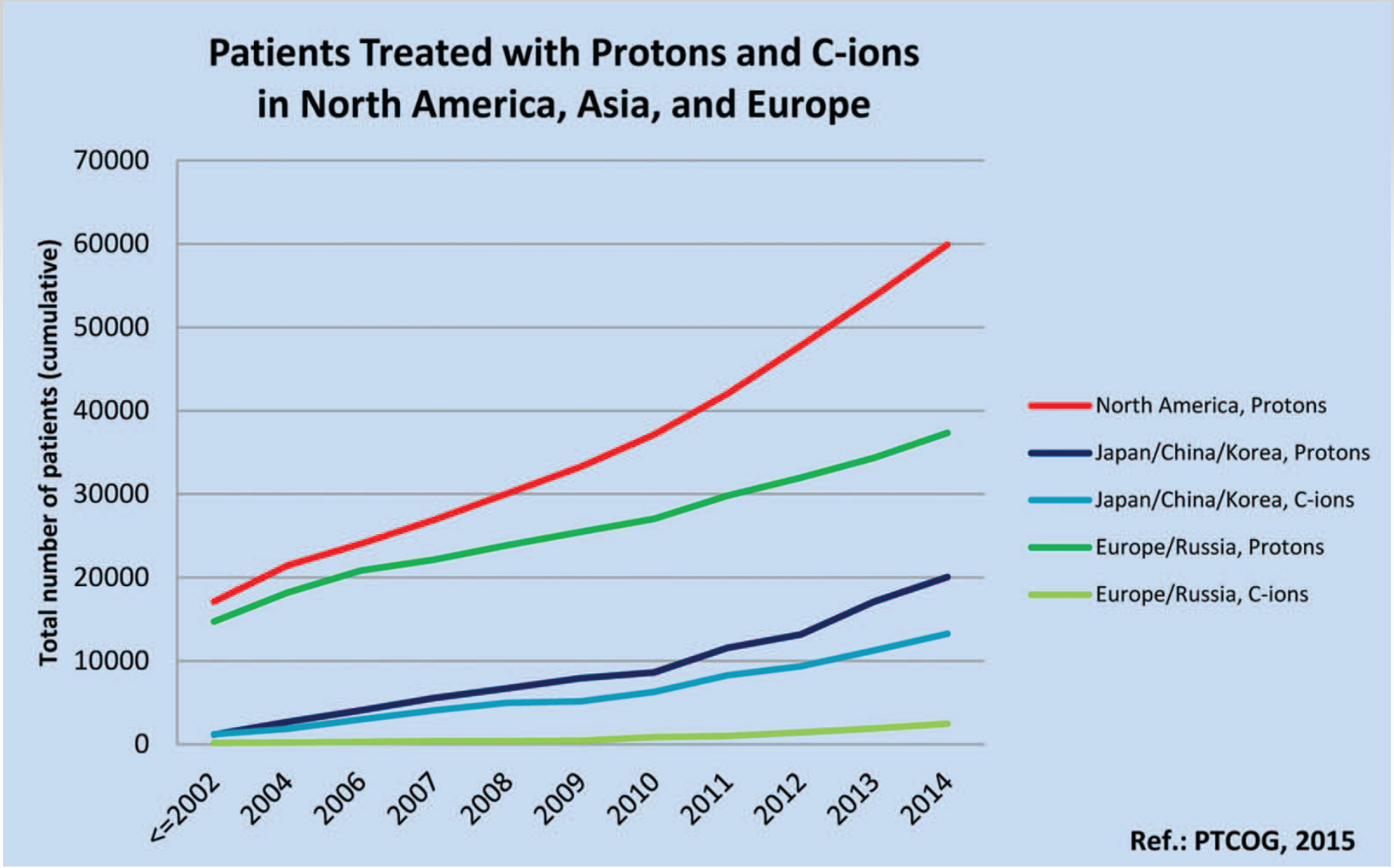
Patients Treated with Protons and C-ions Worldwide



Less than 1% of patients candidate to be treated by radiation therapy receive particle therapy

Ref.: PTCOG, 2015

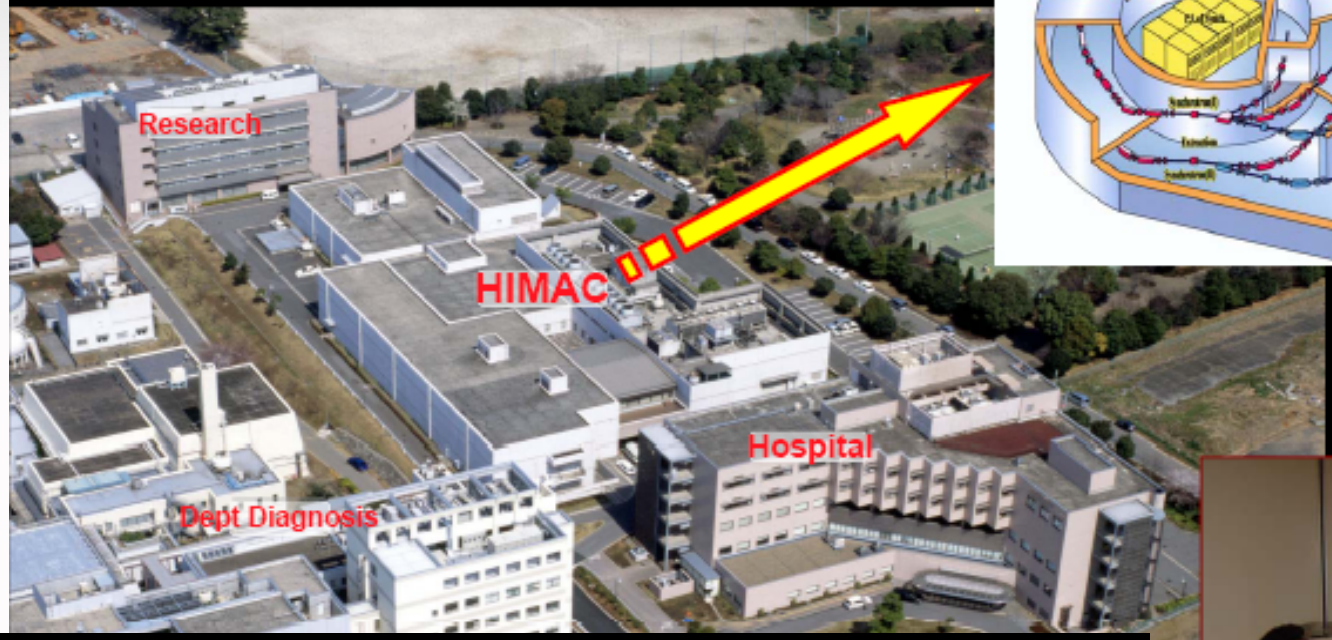

IMP-CAS, Lanzhou
2006, S/400u, 1 h
SPHIC, Shanghai
2014, S/430u, 3 h
Kirams, Busan
S/430u
One under planning (Dallas)
Several projects (Houston, Bay Area)
HIT, Heidelberg
2009, S/430u, 2 h, 1 g
CNAO, Pavia
2012, S/480u, 3 h, 1 v
MIT, Marburg
2015, S/430u, 3 h, 1v
Med-Austron
S/430u
NIRS, Chiba
1994, S/800u, 4h, 4v, 1 g
HIBMC, Hyogo
2002, S/320u, 3h, 1v, 1g
GHMC, Gumna
2010, S/400u, 3 h, 1v
SAGA-Himat, Tosu
2015, S/400u, 3h, 1v
i-Rock Kanagawa, Yokohama
2015, S/430u, 4h, 2v
CIRT in the world

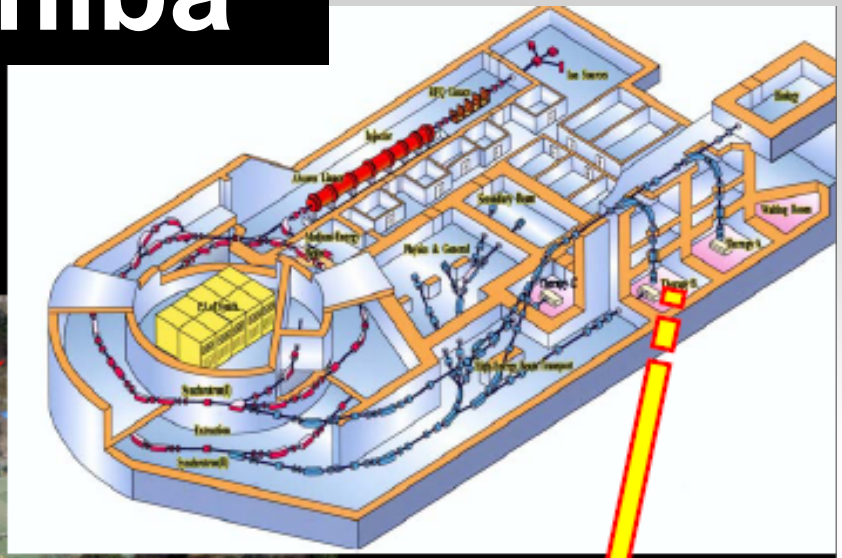

Patients Treated with Protons and C-ions
in North America, Asia, and Europe
Total number of patients (cumulative)
70000
60000
50000
40000
30000
20000
10000
0
<=2002
2004
2006
2007
2008
2009
2010
2011
2012
2013
2014
North America, Protons
Japan/China/Korea, Protons
Japan/China/Korea, C-ions
Europe/Russia, Protons
Europe/Russia, C-ions
Ref.: PTCOG, 2015

Carbon ion at Chiba

HIMAC

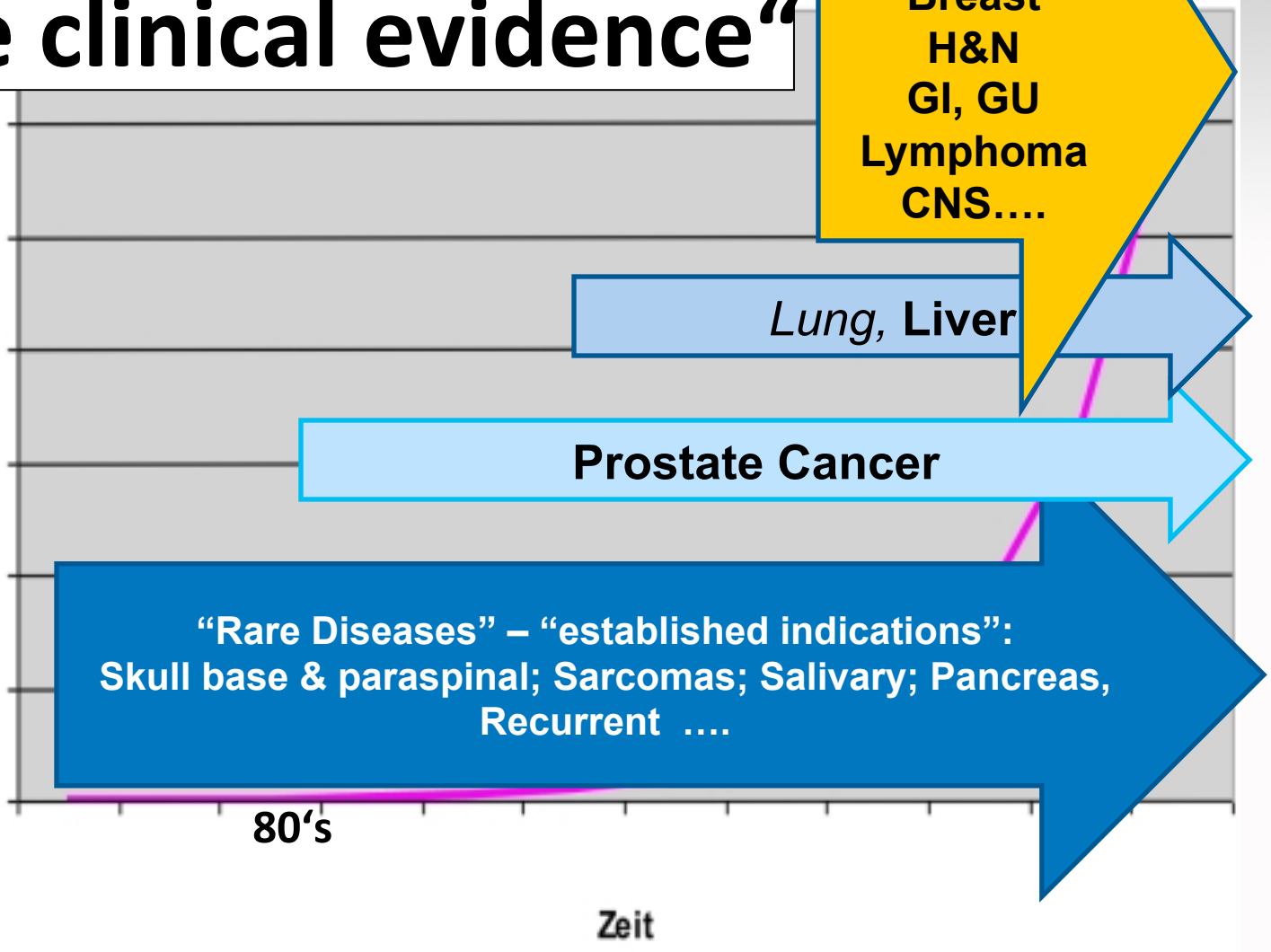
(Heavy Ion Medical Accelerator in Chiba)





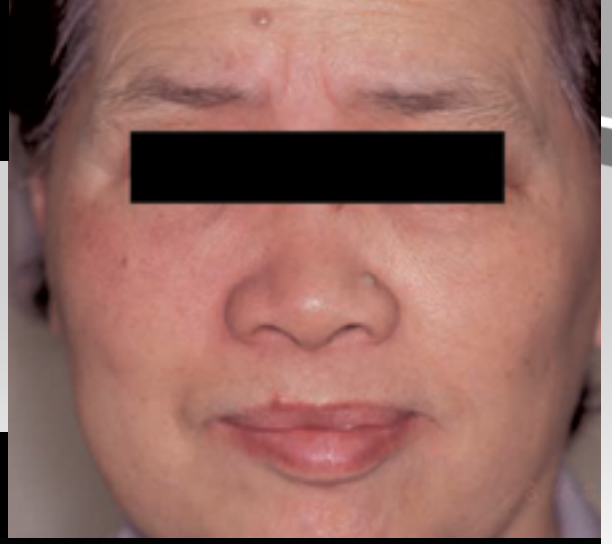
Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience: a review Panel report. Lancet Oncol 2015

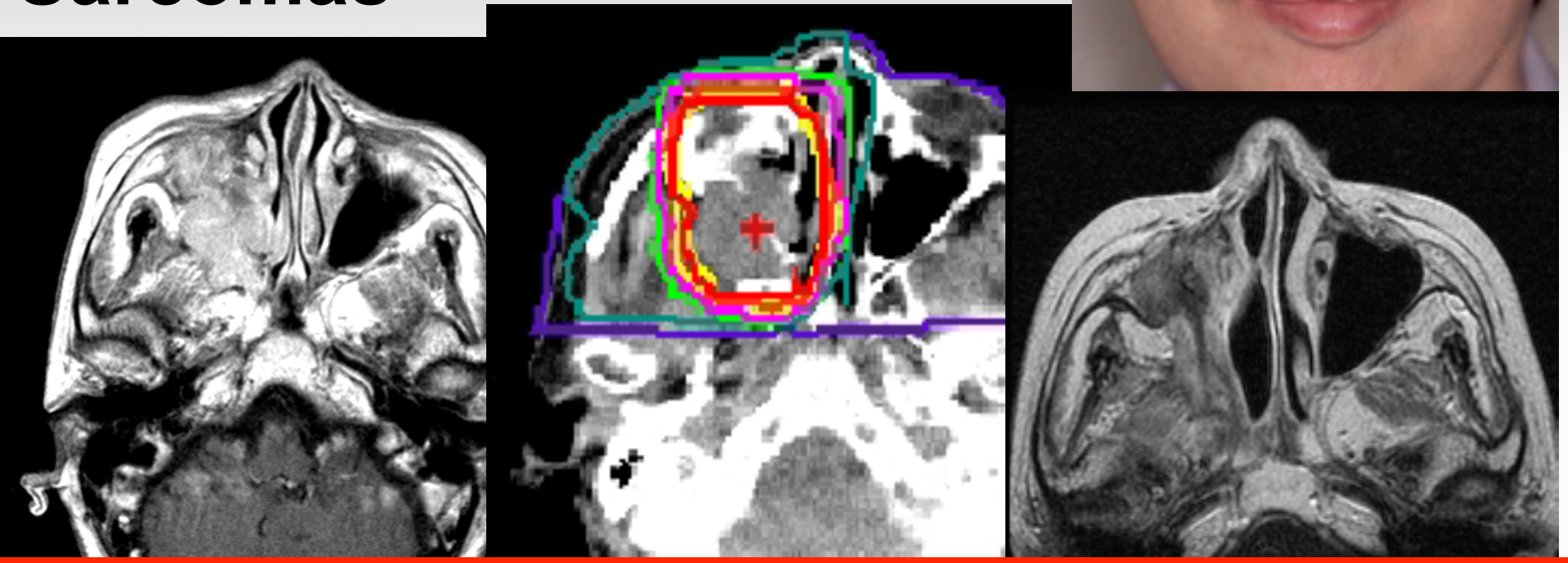
Carbon Ion therapy: „the clinical evidence“



Carbon ion at Chiba

Bone and Soft Tissue Sarcomas

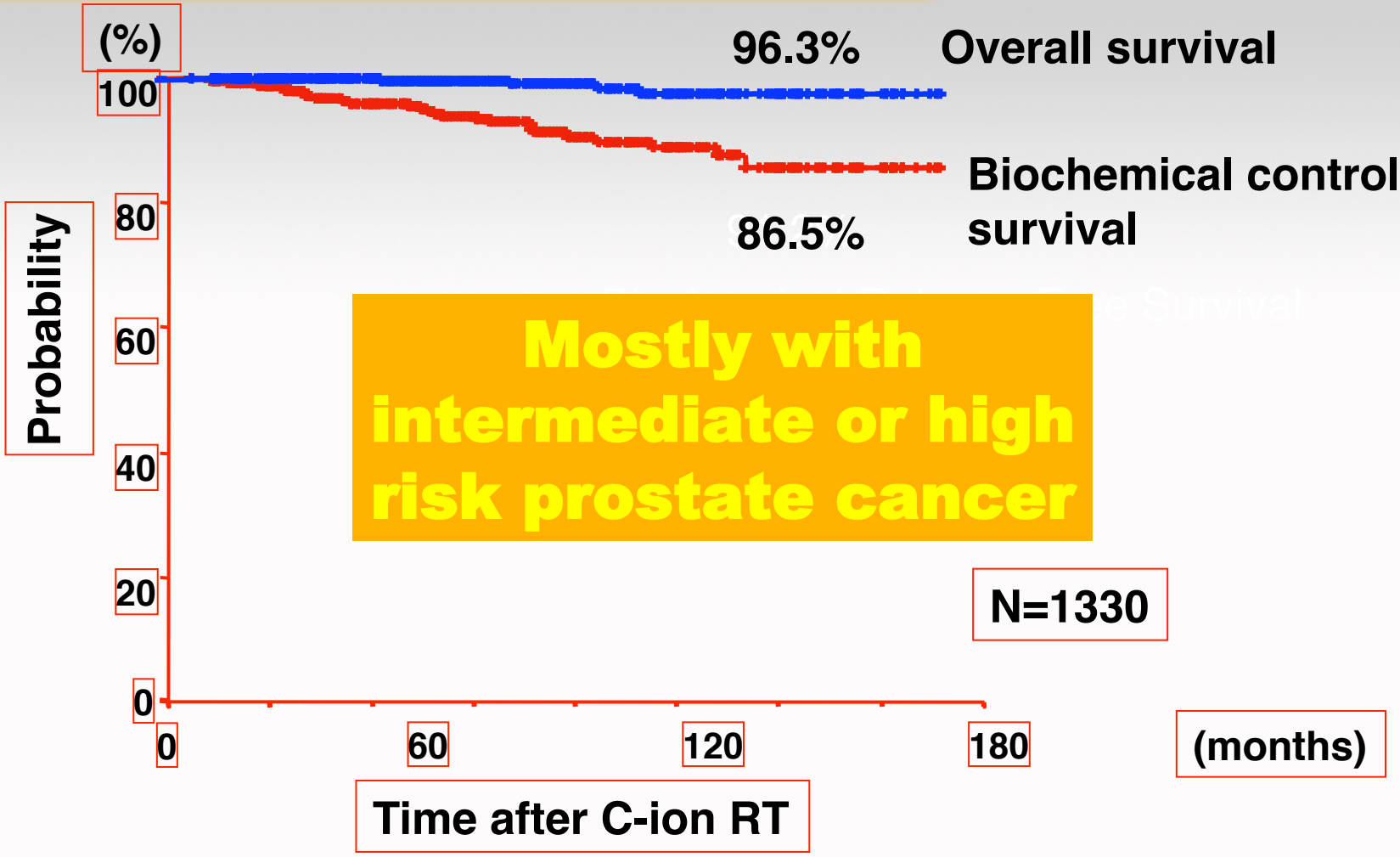




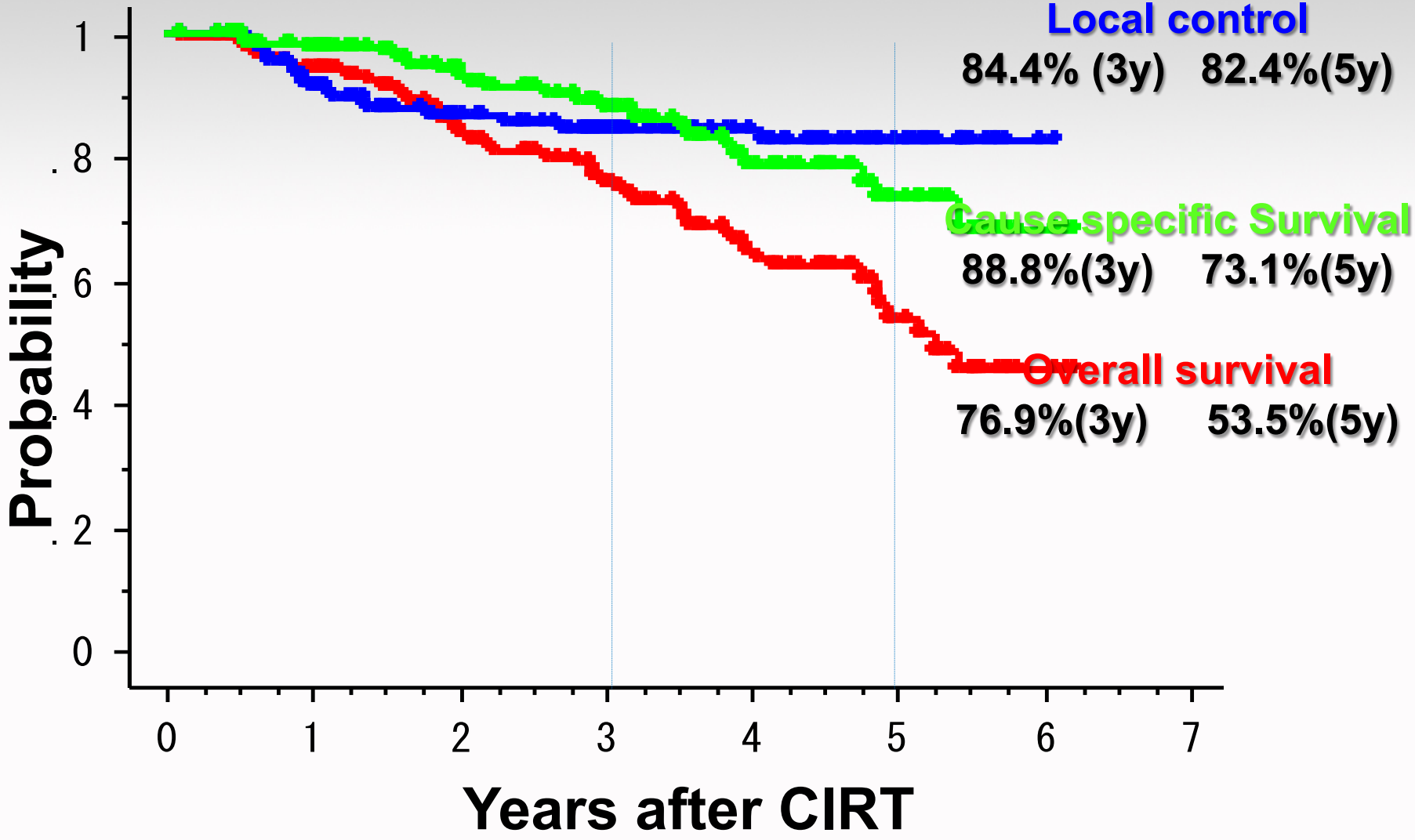
Local Control a 5 years over 80%
Overall Survival over il 60%

(Lancet Oncol, 2015)

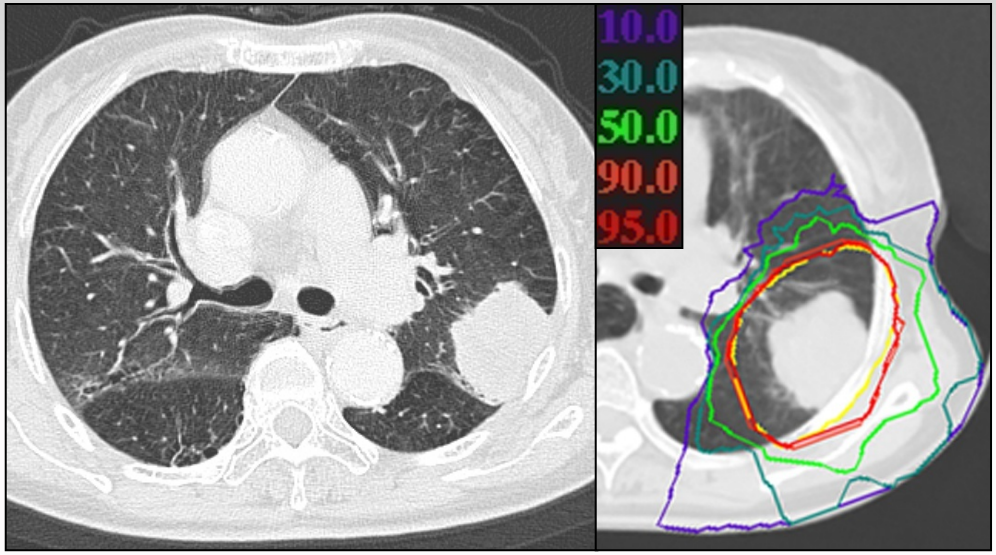
Prostate cancer.
OS and Biochemical Control

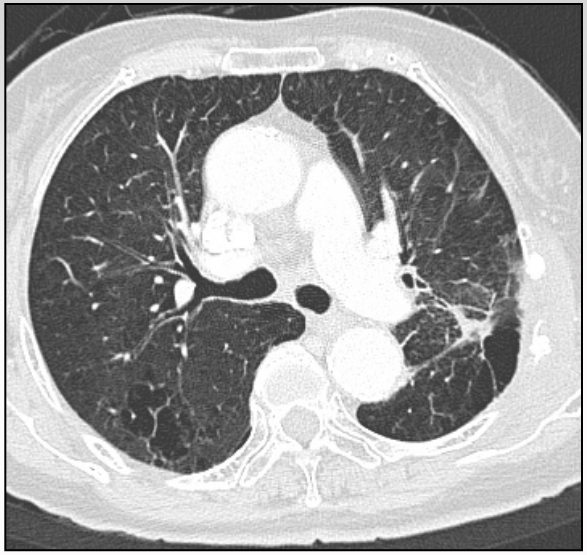


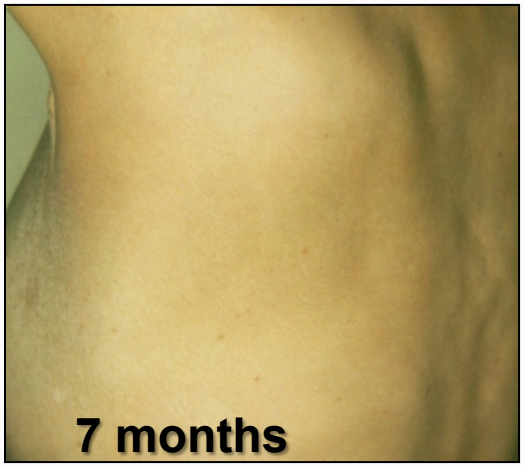
Lung cancer, Local control and survivals in ≥36.0GyE (36.0 - 48.0GyE)



cT2N0M0 Squamous cell carcinoma 40.0GyE/single fraction







18 mo after CIRT

Grade 1 adverse reaction

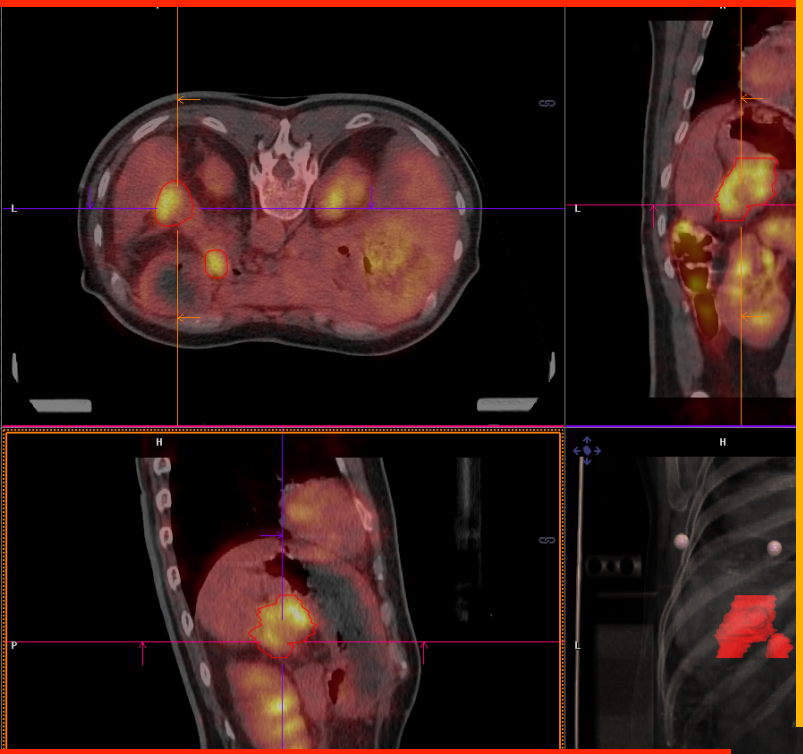
Carbon ion at Chiba

Pancreatic Cancer

Median Survival

About the double

standard RTOG/U



CHIPER: a prospective multi-center randomised phase III trial of CIRT versus conventional RT for locally advanced unresectable pancreatic cancer

Lancet Oncol, 2015

Sistema Sanitario Regione Lombardia

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

The question is …

- Is CIRT evidence based ?

- Sometimes stated as:

  «it costs more but

  is it worth more?»

ws and
trol Trials

Carbon and Standard of Care (SOC)

CD Schlaff et al, Radiat Oncol, 2014

Tumor	
ACC Head&Neck	
Pancreas	
Rectum (recurrent)	
Cervix (recurrent)	
Prostate	

France-Hadron: a prospective multi-center randomised phase III trial of CIRT versus conventional RT for locally advanced H&N sarcoma and ACC

Some randomised trials will start soon……

How to reproduce the Japanese results?

- All clinical results from Japan (NIRS, Hyogo and Gunma) are based on Kanai Model
- All clinical results from Europe (GSI, HIT and CNAO) are based on LEM I Model with an idealized chordoma cell line as reference

IOP PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

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

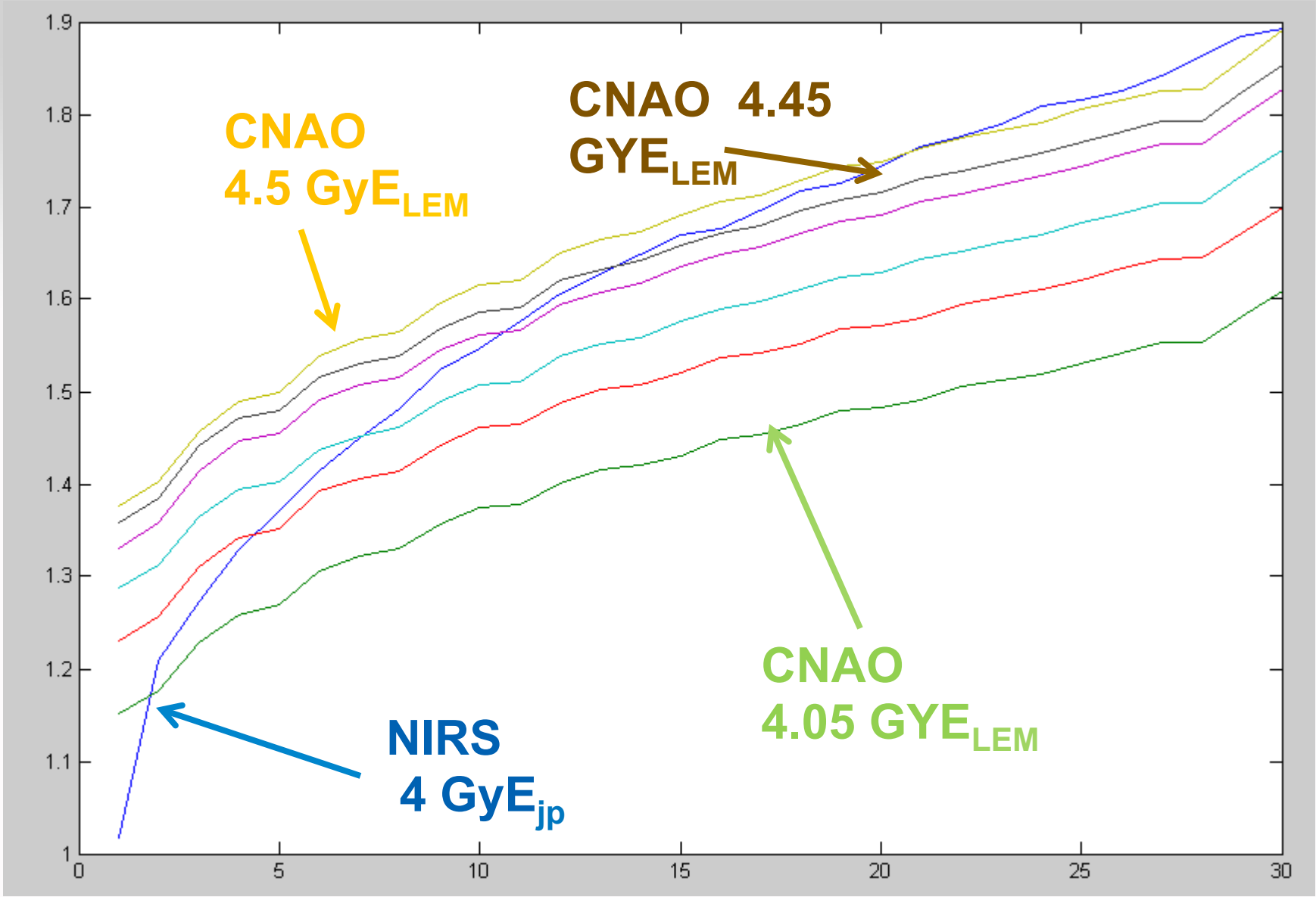
Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy

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]

[1] Centro Nazionale di Adroterapia Oncologica (CNAO), Pavia, Italy
[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

Hiplan TPS (Chiba)
Siemens Syngo-VA11 PT-Planning (CNAO)
Fluka MC

Physical dose in SOBP



Clinical results comparison

NIRS

- ACC 57.6 – 64 GyE

Adenoid cystic carcinoma

- MMM 57.6 – 64 GyE

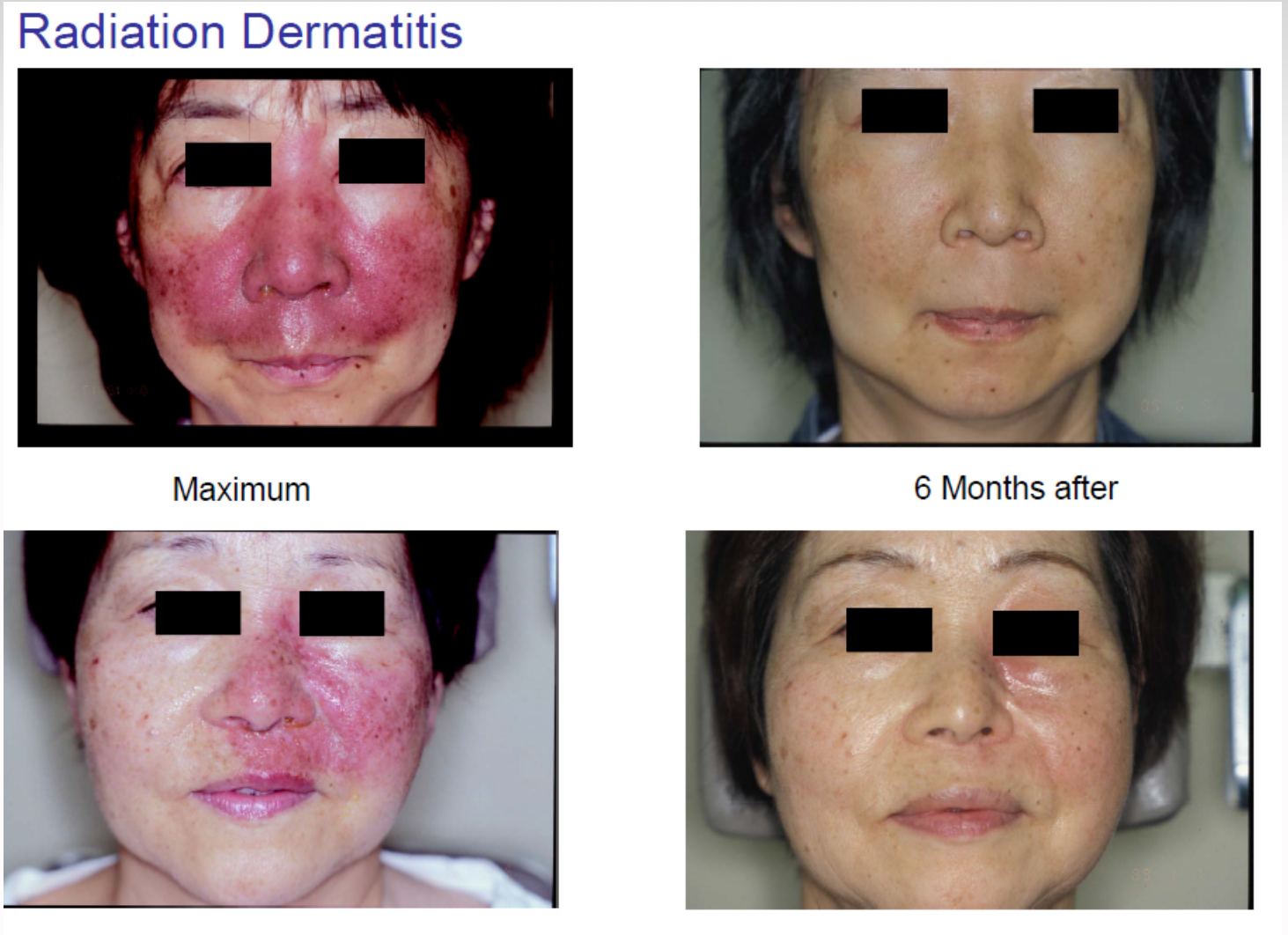
Malignant mucosal melanoma

CNAO

- ACC 68.8 GyE
- MMM 68.8 GyE

Skin toxicity at NIRS

G3



G0/1

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

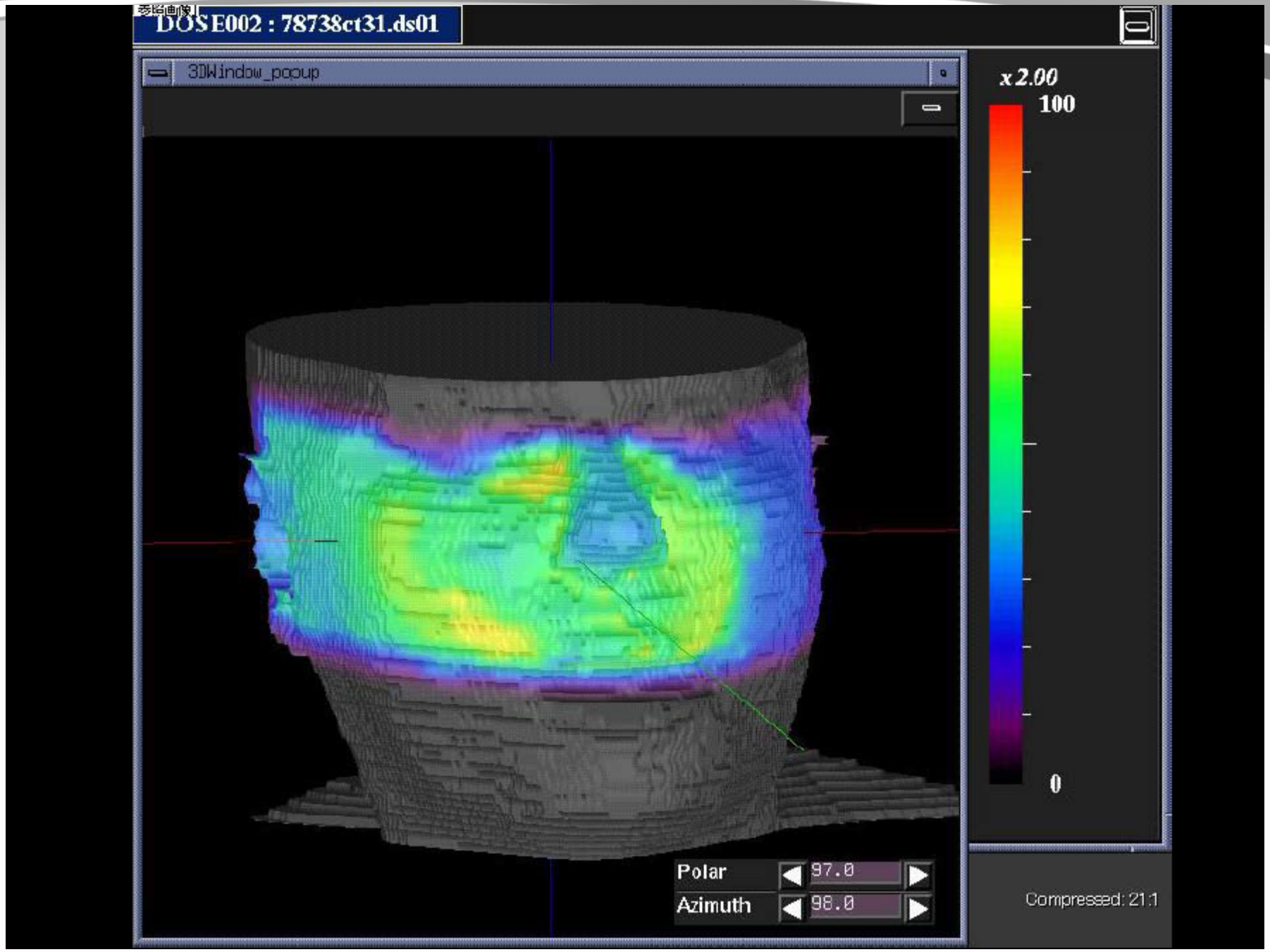
Acute Radiation Morbidities

	Acute Skin (RTOG)			
Dose (n)	G0 (%)	G1 (%)	G2 (%)	G3 (%)
57.6 GyE (255)	19 (8)	136 (53)	85 (33)	15 (6)
64.0 GyE (134)	9 (7)	102 (76)	22 (16)	1 (1)
Total (389)	28 (7)	238 (61)	107 (28)	16 (4)

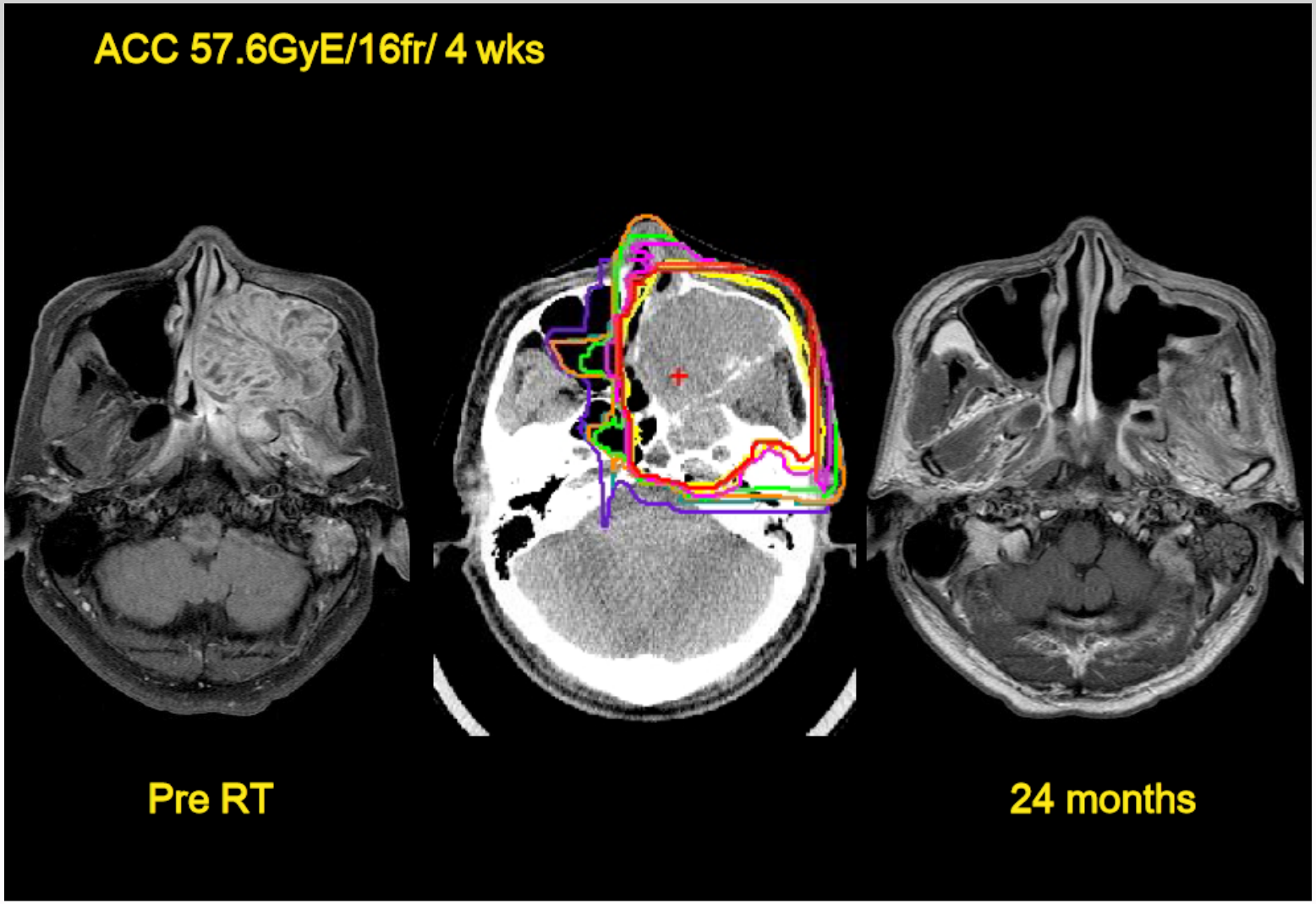
	Acute Mucosa (RTOG)			
Dose (n)	G0 (%)	G1 (%)	G2 (%)	G3 (%)
57.6 GyE (246)	29 (11)	99 (41)	92 (38)	26 (10)
64.0 GyE (128)	12 (9)	44 (35)	37 (29)	35 (27)
Total (374)	41 (11)	143 (38)	129 (35)	61 (16)

Acute Skin Toxicity at CNAO

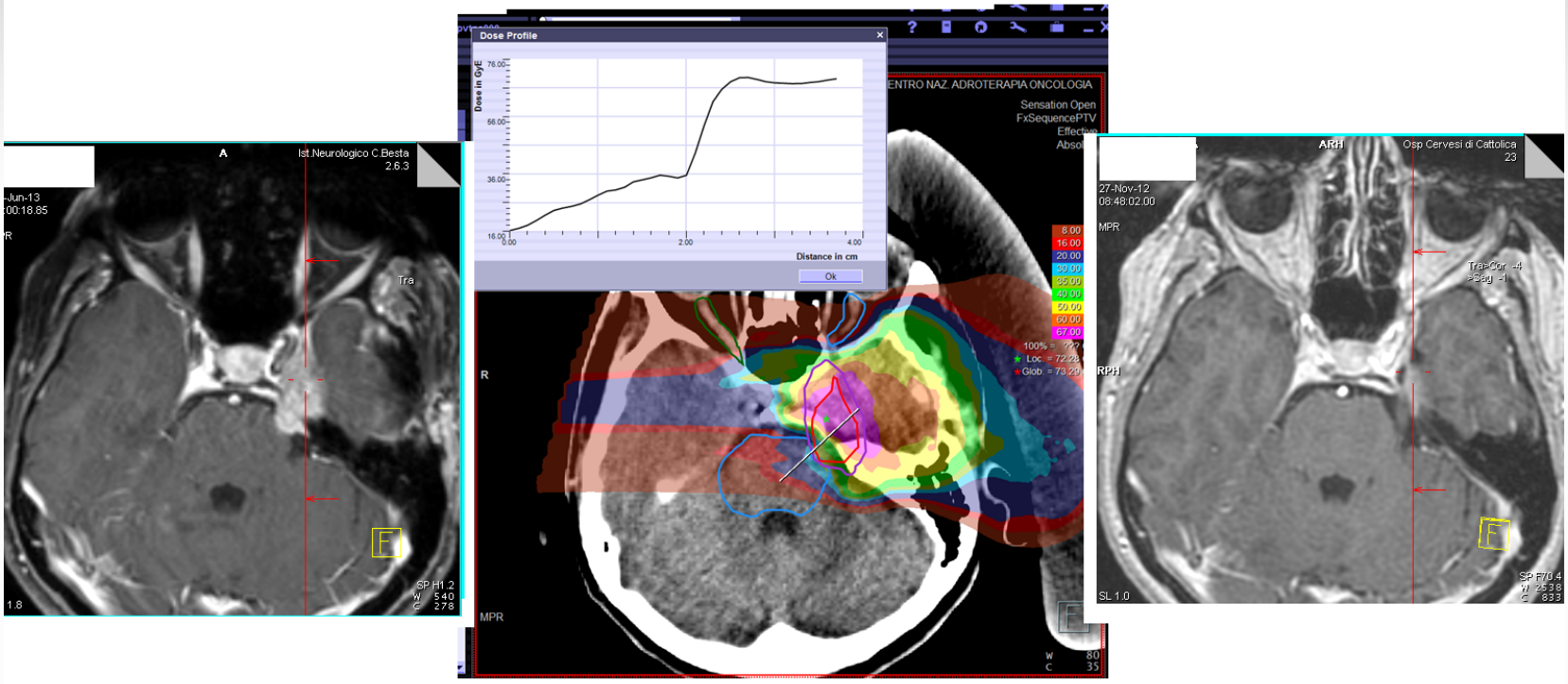
Grade 1: 90%
Grade 2: 10%
No Grade 3


DOSE002 : 78738ct31.ds01
3DWindow_popup
x 2.00
100
0
Polar
97.0
Azimuth
98.0
Compressed: 21:1

Local Control. ACC NIRS



Local Control. ACC CNAO



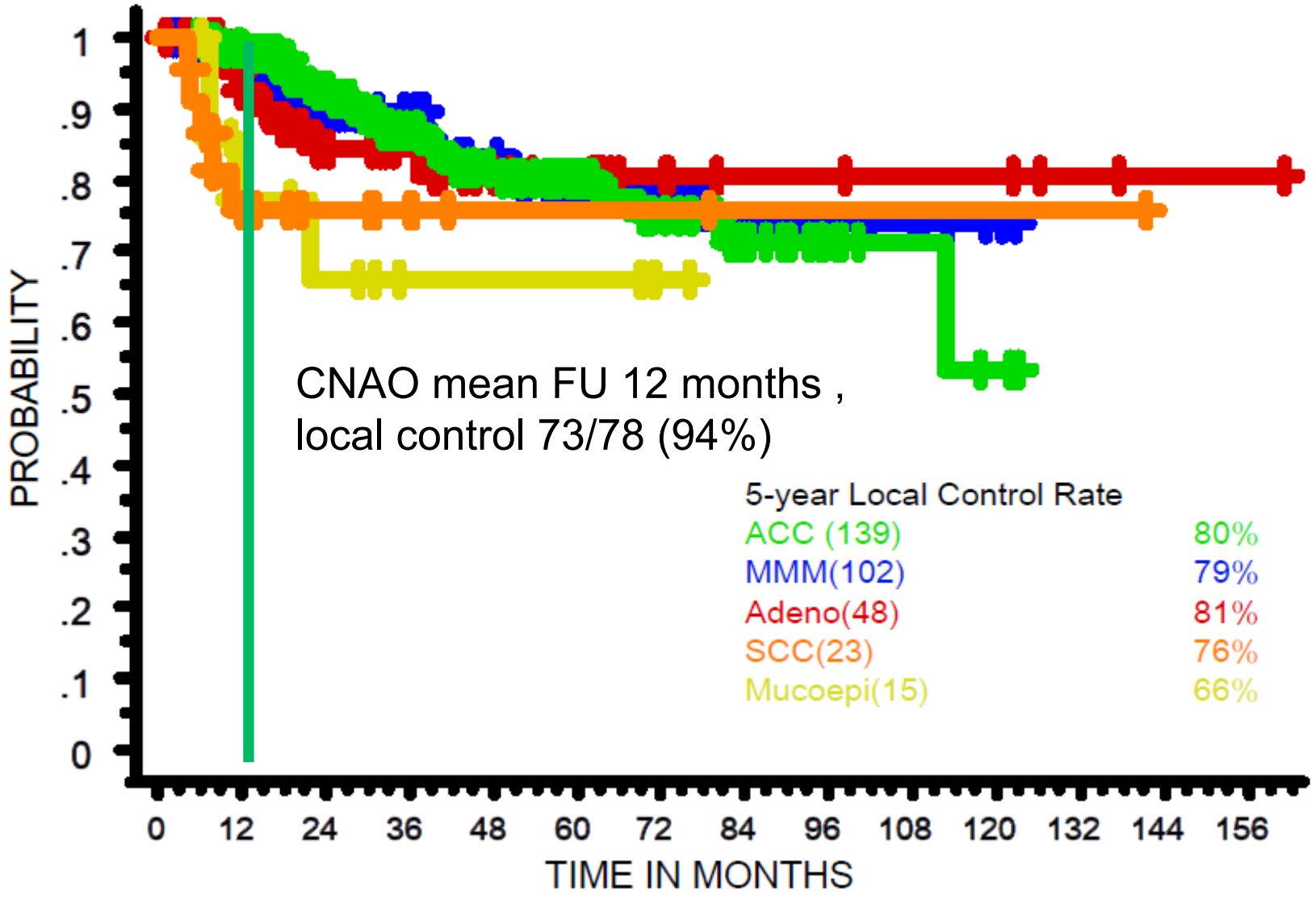
Before treatment

4.3 GyE x 16 fr= 68.8 GyE

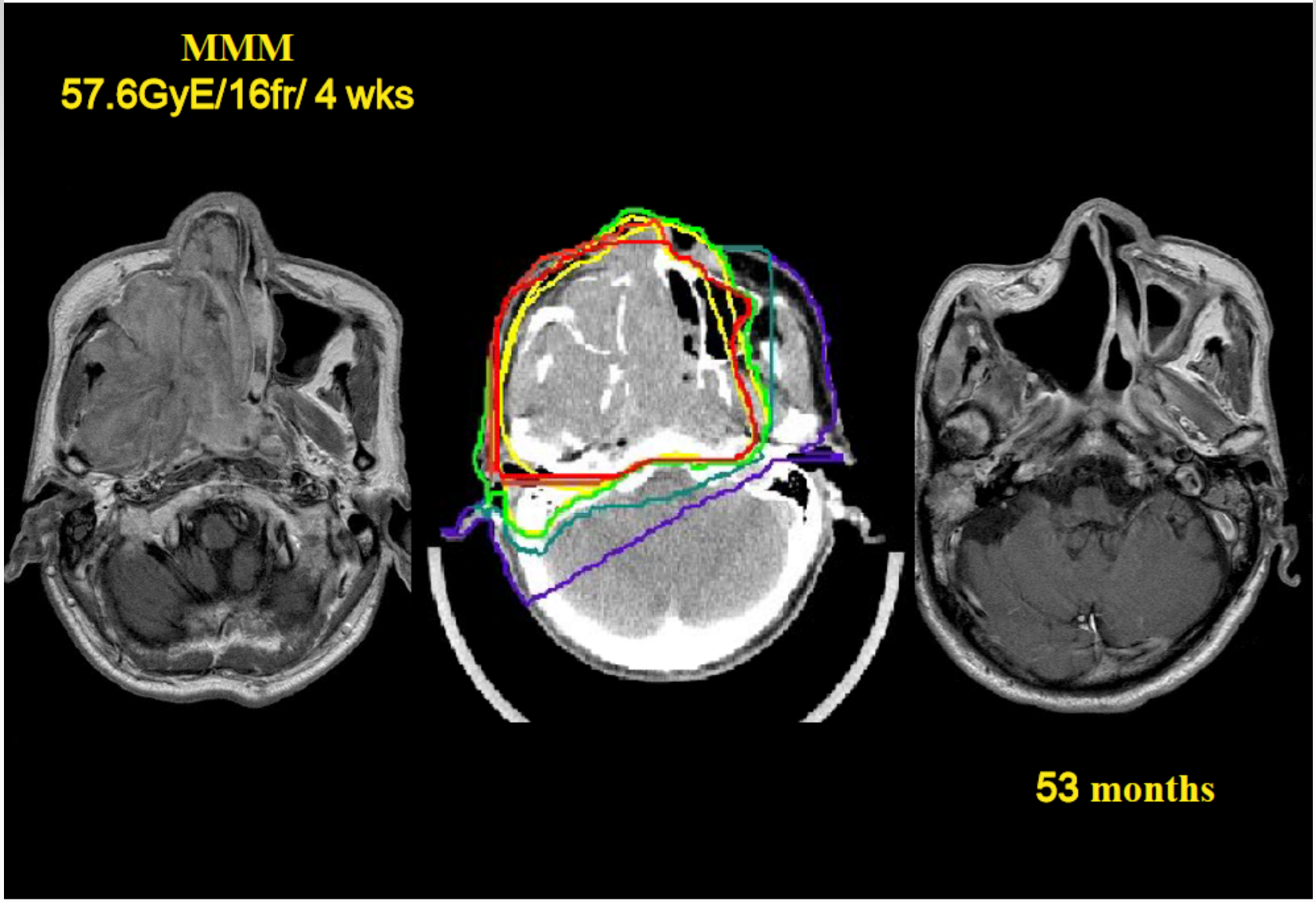
After 9 months

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

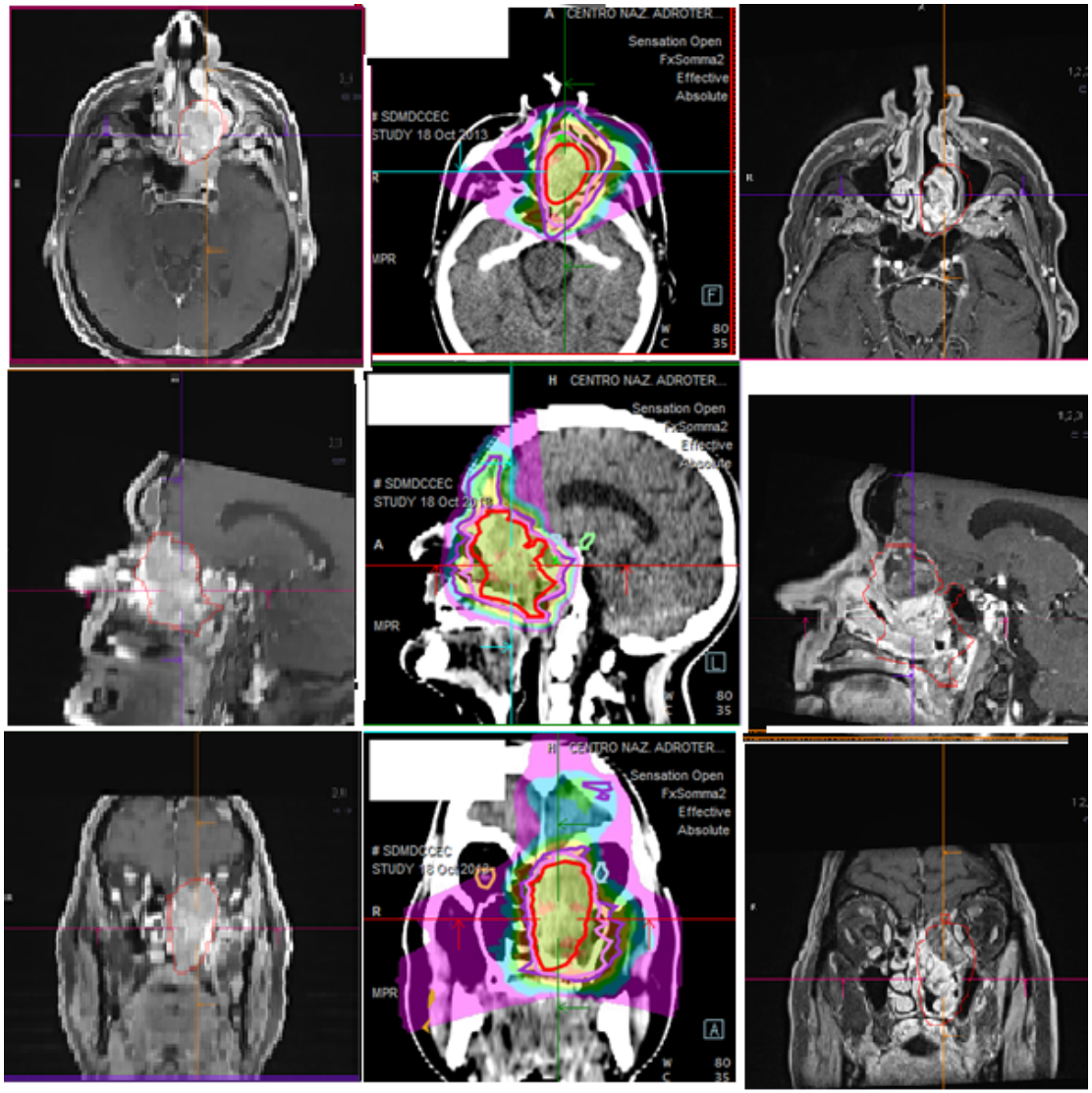
Local Control according to Histological Type (Apr 97~Aug 10)



Local Control. MMM NIRS

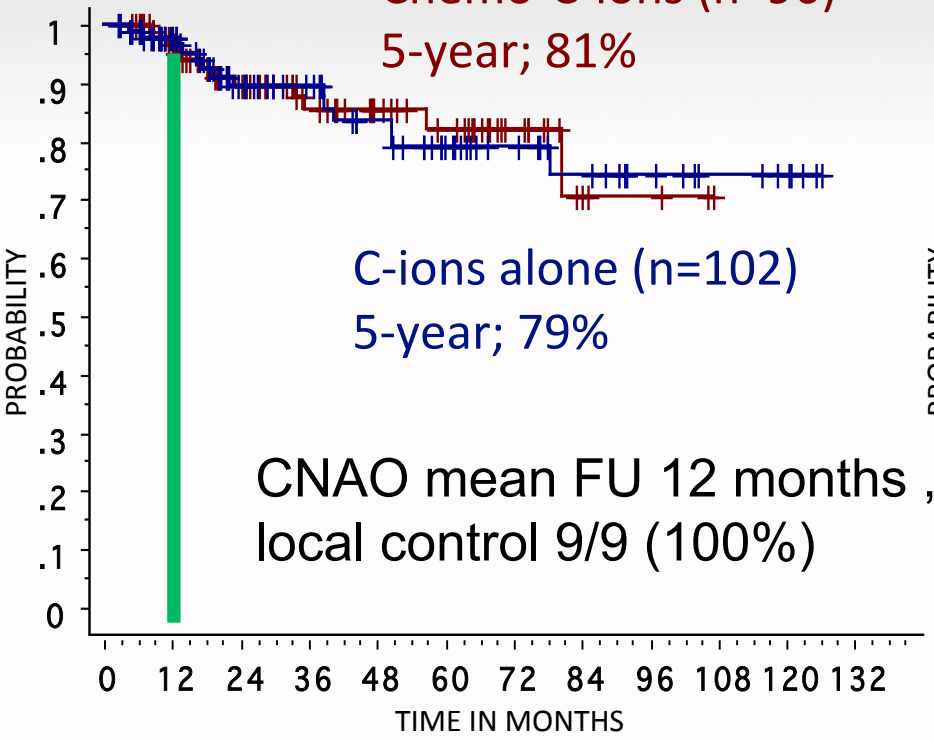


Local Control. MMM CNAO

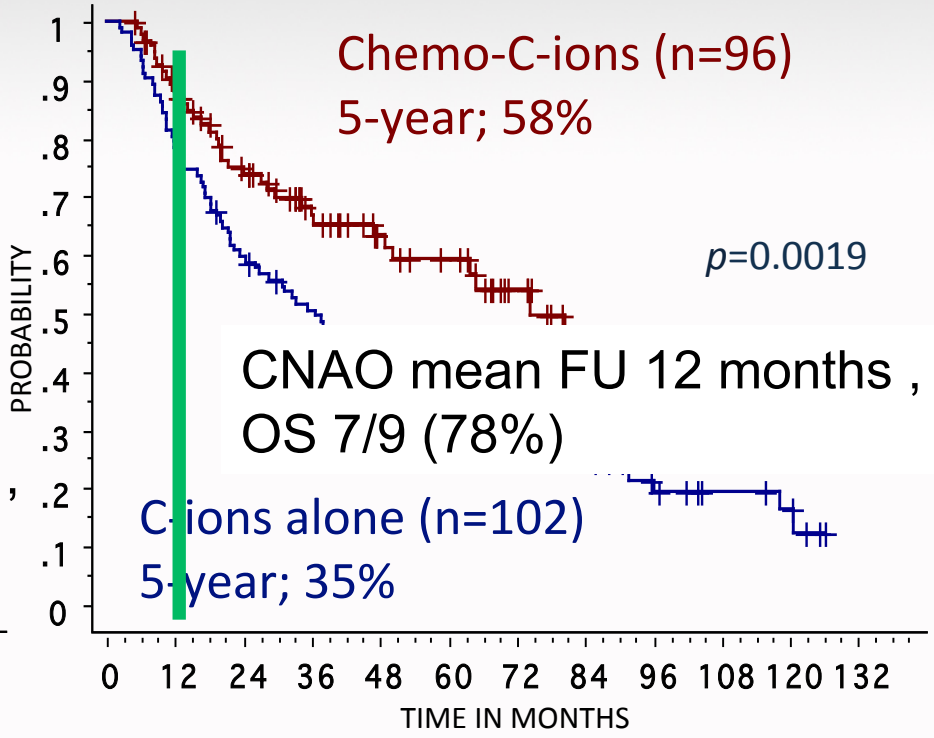


Carbon Ion Radiotherapy for Mucosal Malignant Melanomas

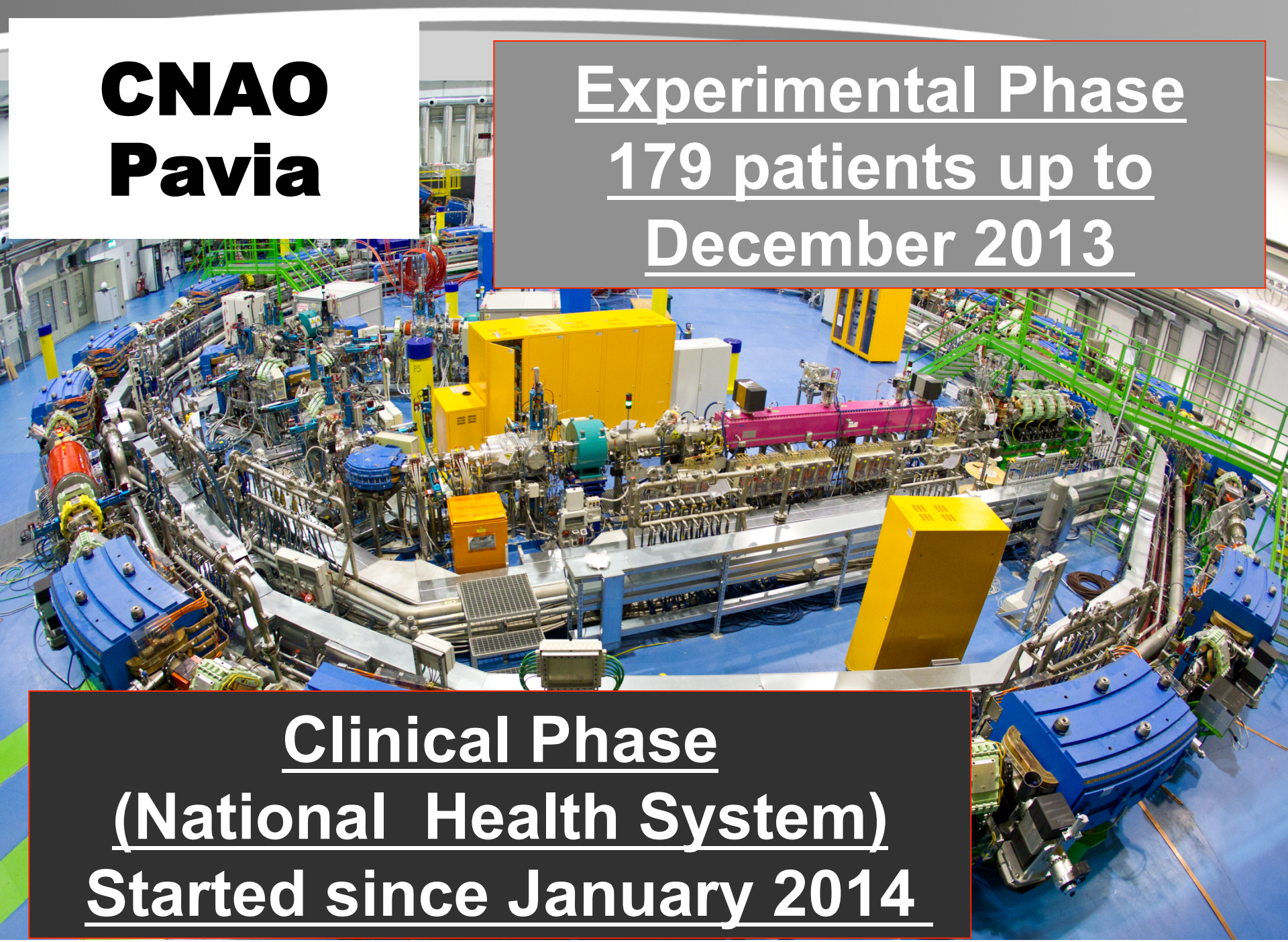
Local Control



Overall Survival



CNAO Pavia



Experimental Phase
179 patients up to December 2013

Clinical Phase (National Health System)
Started since January 2014

2014 - 2015 Activity

Patients: 553 (732, including the experimental phase *)

Proton
Conventional fractionation
Patients: 107 (84, *)

Carbon ion
NIRS fractionation
Patients: 446 (95, *)

Synchrotron Operation: H24, 7/7
Maintenance: 4/year - 5 days each (Thursday to Tuesday)
Treatments: Mon to Fri – 8:00 to 21:00
QA: Mon to Fri – 0:00 to 6:00
Beam time for research over week-ends

2014 - 2015 Protons

Patients: 107 (+ 84 *, total 191)

Chordoma & Chondrosarcoma: 27 (+ 44 *)
Meningiomas: 25
Brain: 12
Recurrent H&N: 19
H&N Boost (mixed IMRT): 22
Other: 4

* Treated in the experimental phase

2014 - 2015 Carbon Ions

Patients: 446 (+ 95 *, total 541)

Bone & Soft Tissue Sarcoma **: 191 (+ 30*)
Salivary Glands: 113 (+ 19 *)
Mucosal Melanoma: 12
Recurrent H&N: 80
Primary H&N: 16
Pancreas / Liver: 11 / 4
Recurrent Rectum: 8
Other: 4

* Experimental phase

** Including chordoma & chondrosarcoma

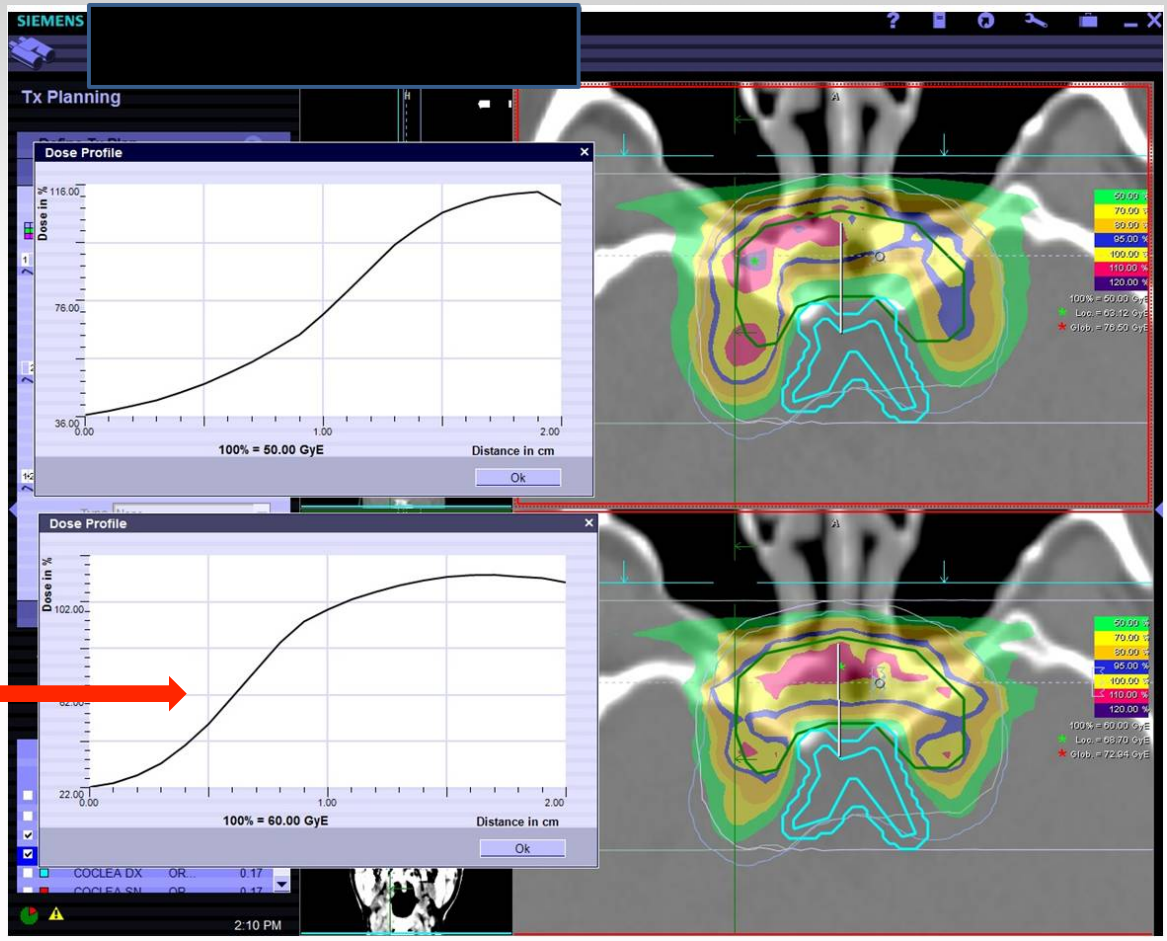
Proton - Carbon ions plans: Steep dose gradient

Proton plan

At 1 cm the dose falls down from 76% to 36%

Carbon ions plan

At 1 cm the dose falls down from 102% to 22%

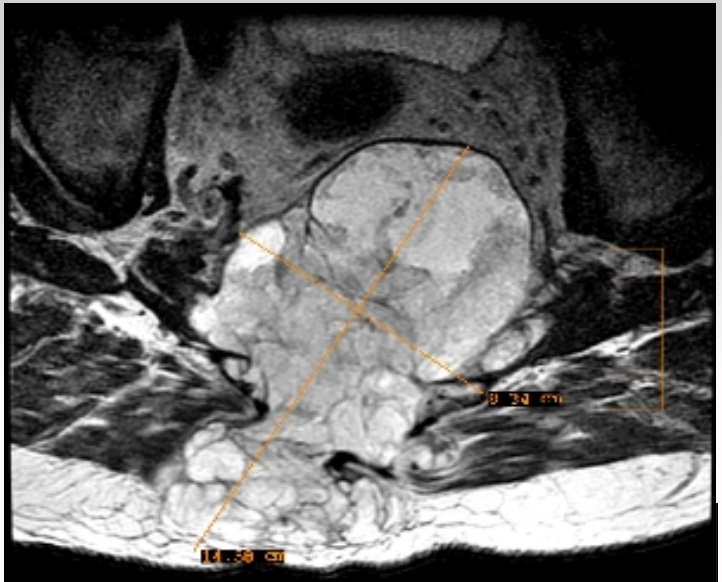


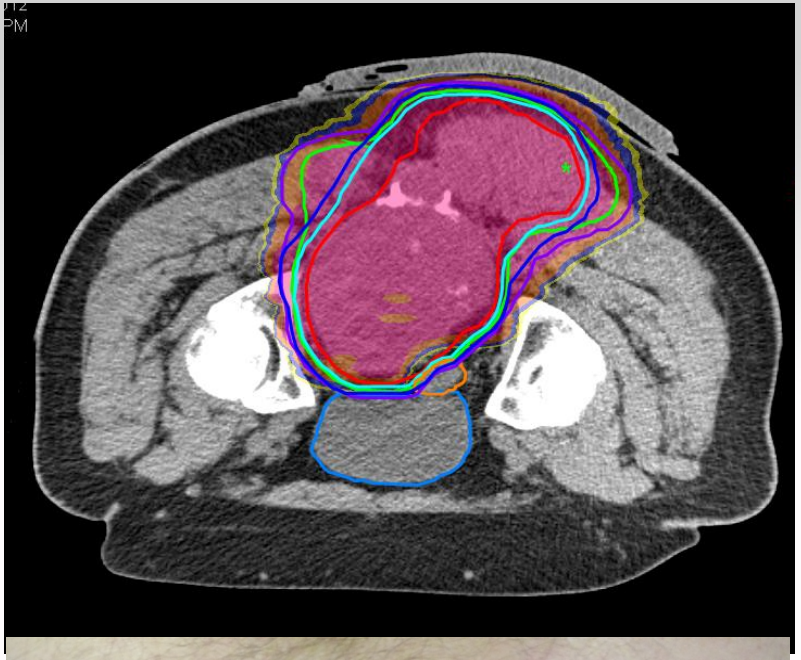
Particle Radiation Therapy for Tumors of the Skull Base at CNAO 2011-2015

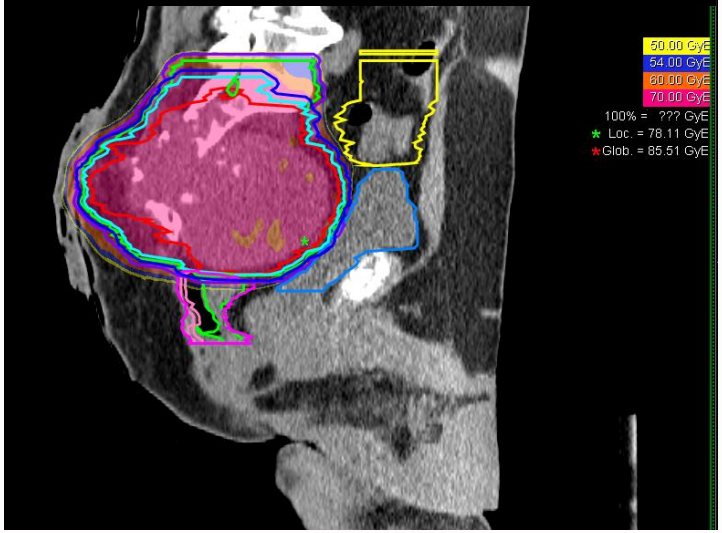
	Tot	PT	CIRT	Mean FU (months)	Local Failure	Local Control %
Chordoma	88	43	45	20	7	92
Chondrosarcoma	23	10	13	22	1	95.6

All local failures > brain stem compression / proximity

CIRT for Sacral Chordoma

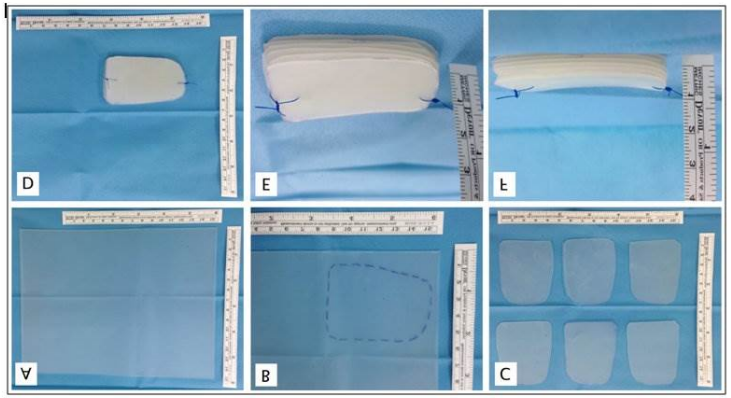


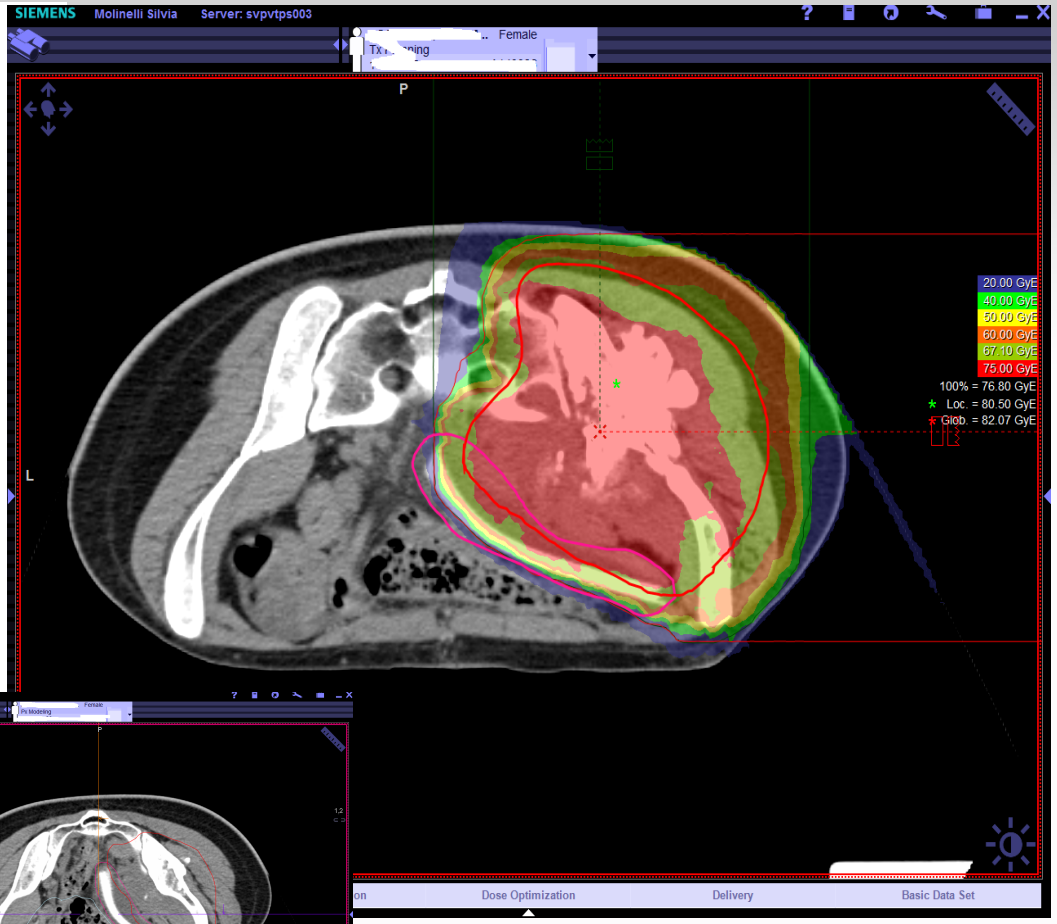


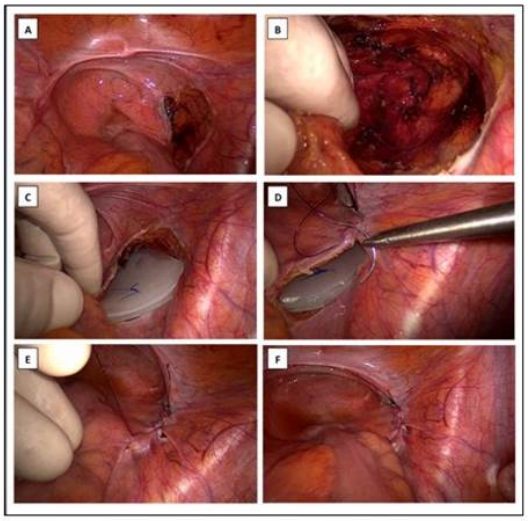


G2 skin toxicity

Surgical spacer placement

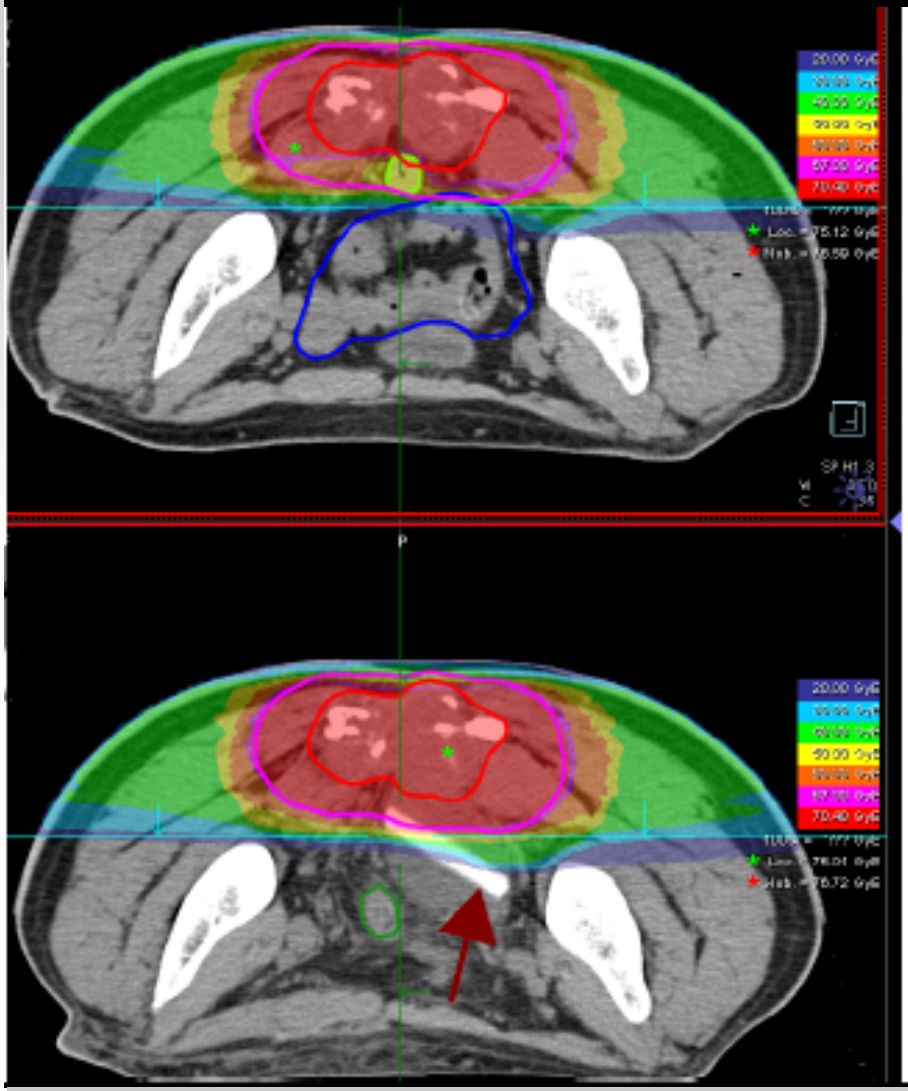


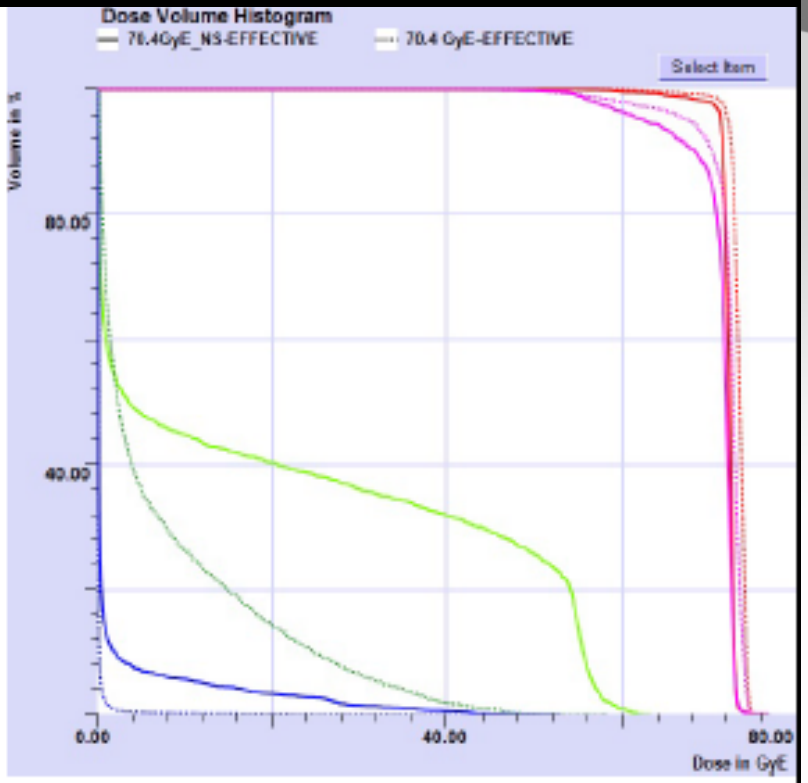




Silicon spacers
Width 5-6 mm

Surgical spacer placement

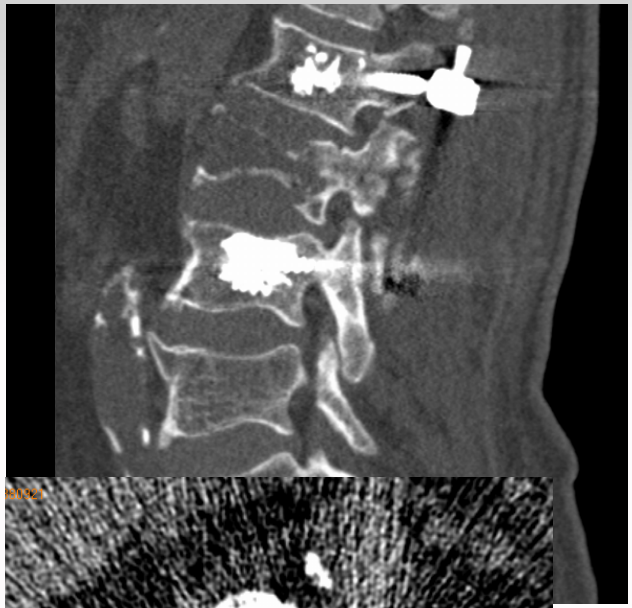




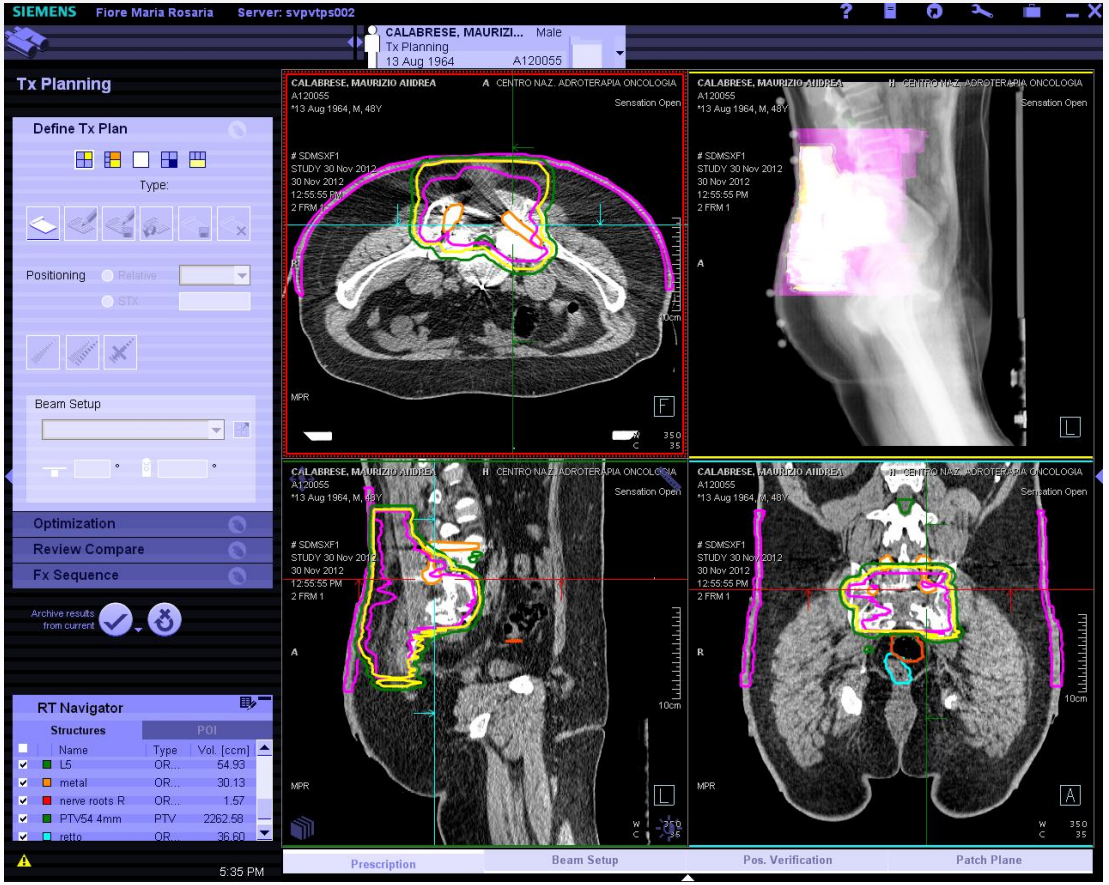
With spacer: dotted lines
W/out spacer: continous lines
Green lines: digestive tract

Plan comparison study on different CT from the same patient selected for spacer positionnig

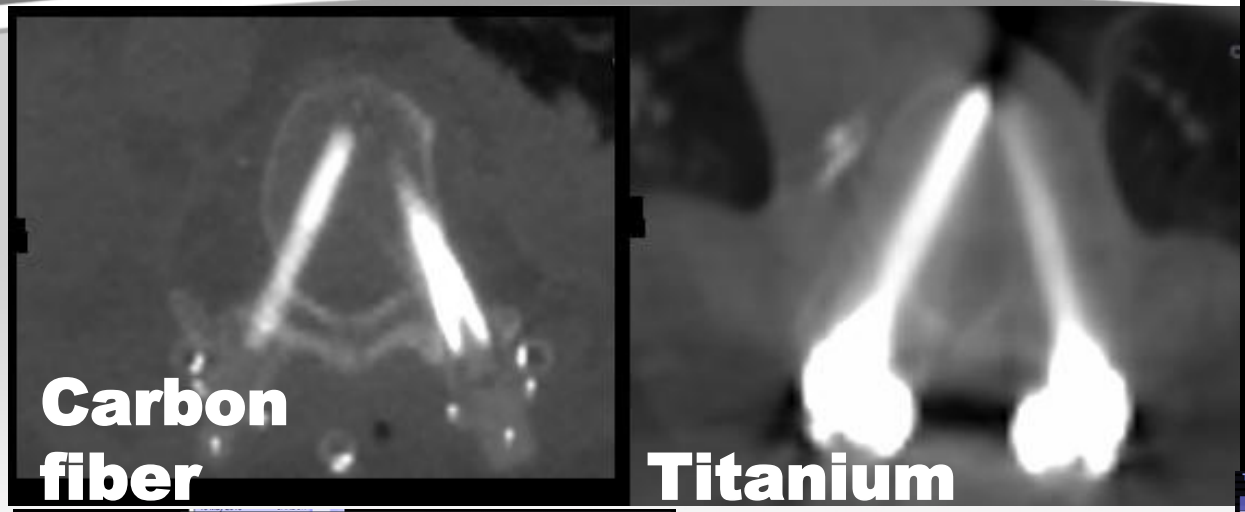
Artifacts

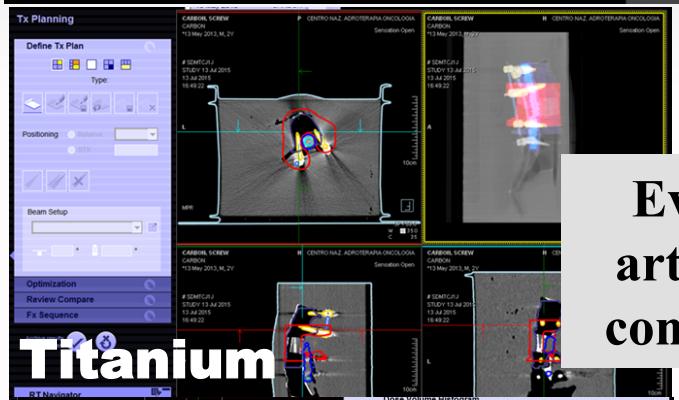


Uncertainties in the definition of volumes and greater uncertainty in the dose distribution

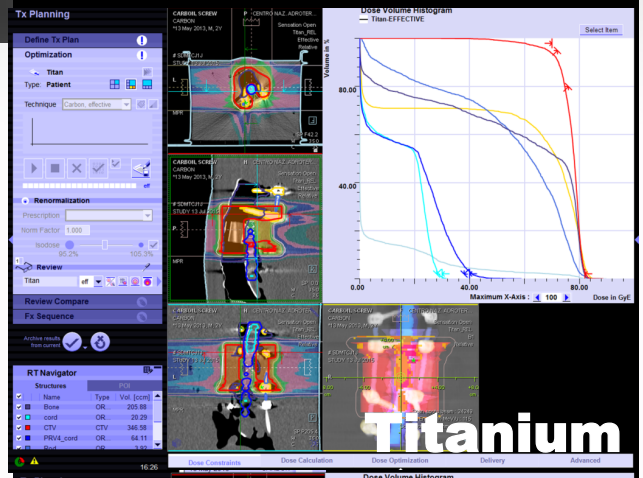


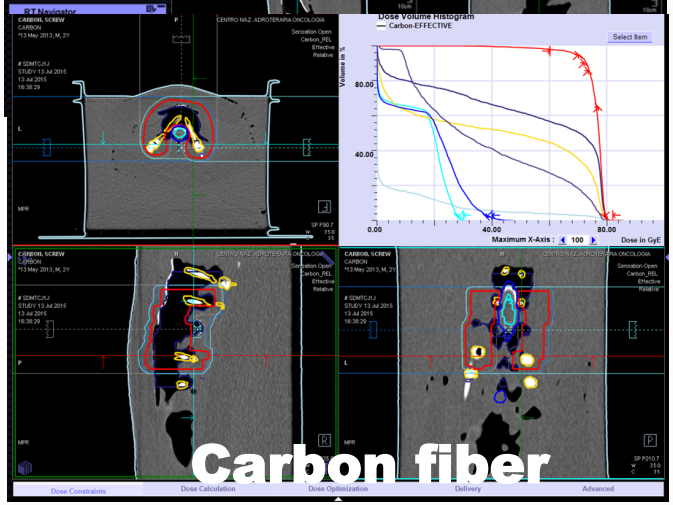
New implants in titanium/ carbon fiber



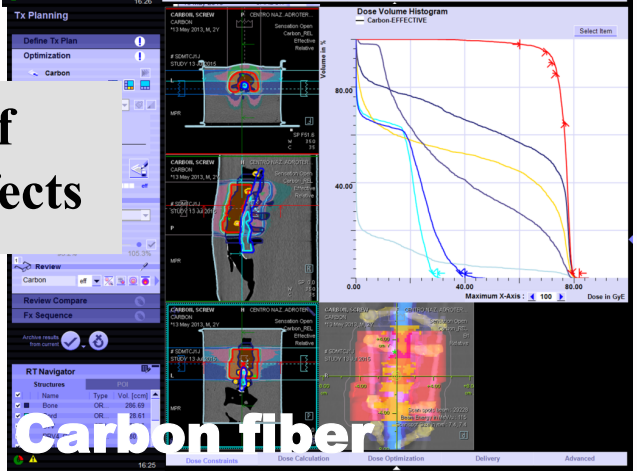


Evaluation of imaging artefacts and impact on contouring uncertainties





Evaluation of interference effects



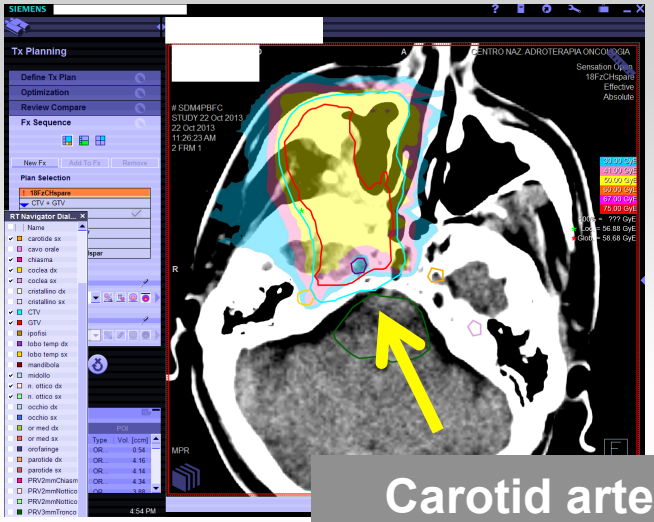
Reirradiation: 80 patients

- 70 pts Conventional Fractionation: mean dose 61 Gy (45 – 76 Gy)
- 6 pts Hypo Fractionation (3 Gyx10 fr or 12 Gyx4 fr)
- 4 pts receved two previus courses of radiotherapy (CF + HF)

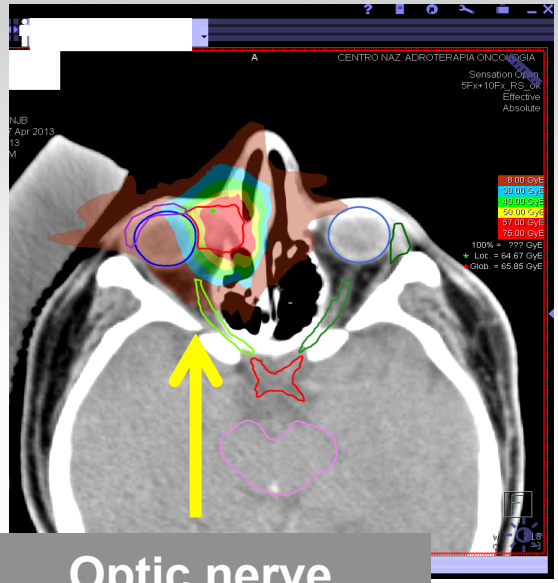
Mean time to reirradiation: 56 months (range 7 – 216 months)

Particle radiotherapy		
	Carbon Ions (72 pts)	Protons (8 pts)
Total Dose	Mean 53 Gy RBE (range 12–74 Gyeq)	Mean 58 Gy RBE (range 50–70 Gyeq)
Dose per Fraction	2.5 – 4.8 Gy RBE	2 Gy RBE

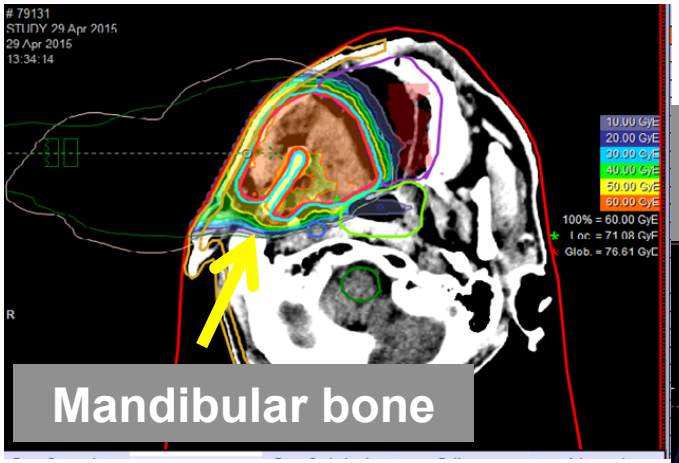
Main Goal: OARs Sparing



Carotid artery

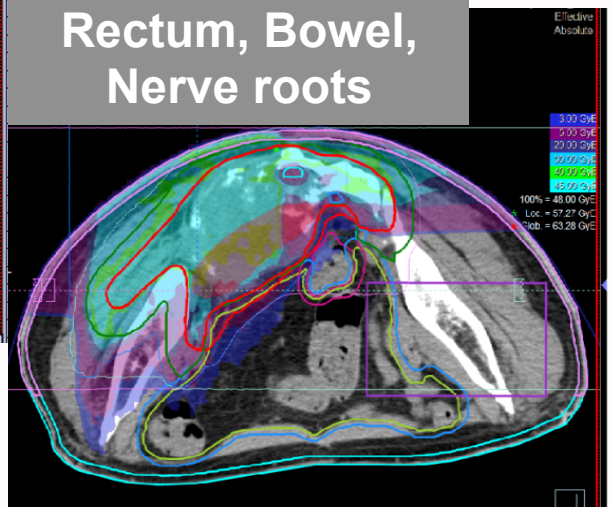


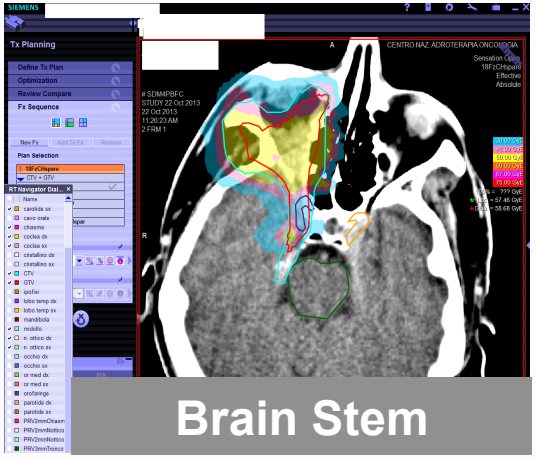
Optic nerve



Mandibular bone

Rectum, Bowel, Nerve roots

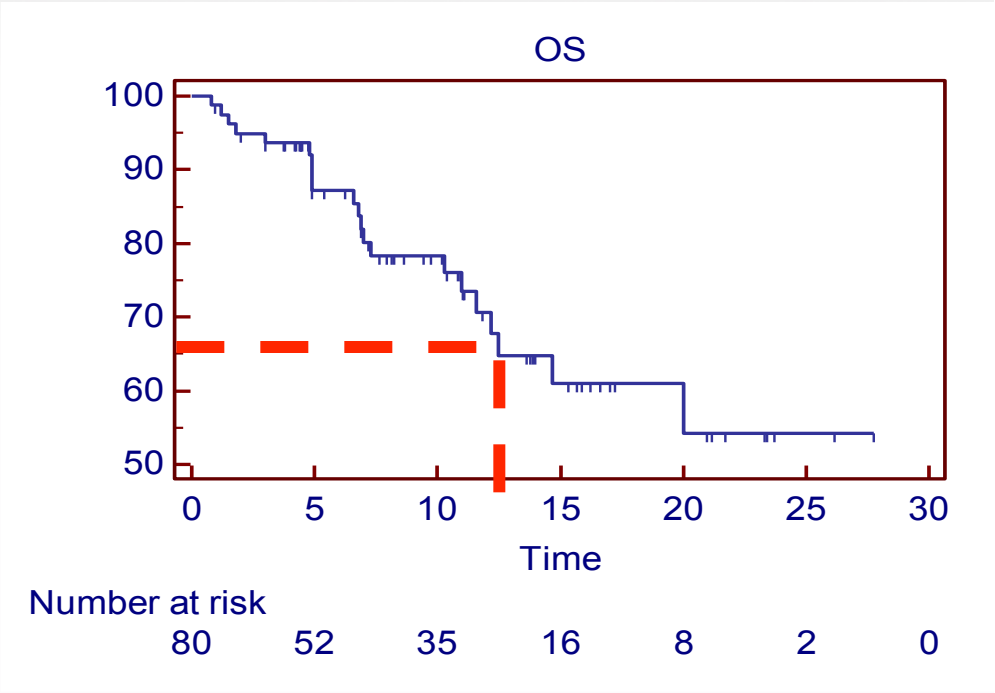




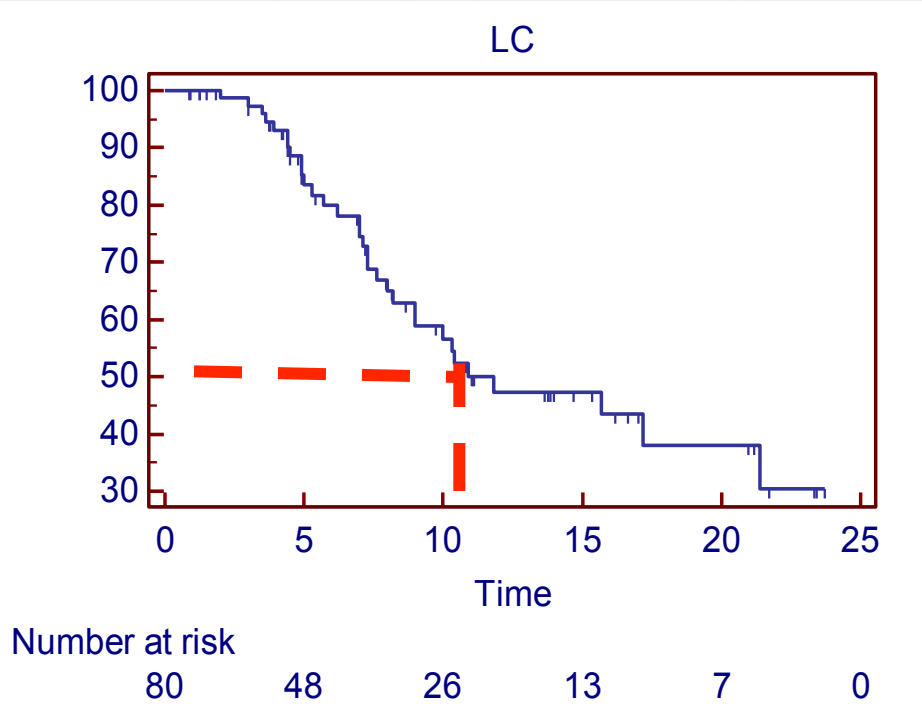
Brain Stem

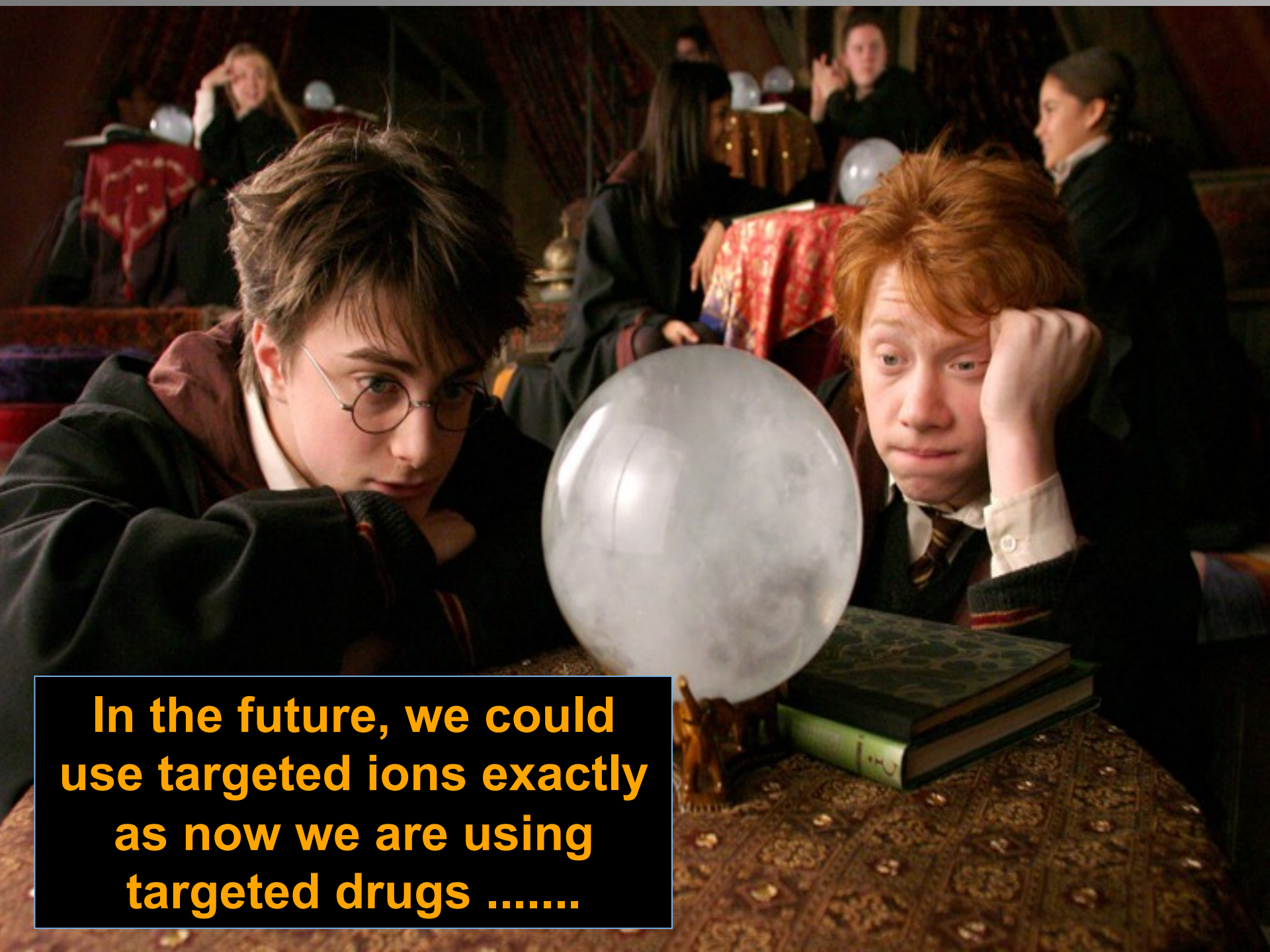
Reirradiation. Results

1y OS 65%

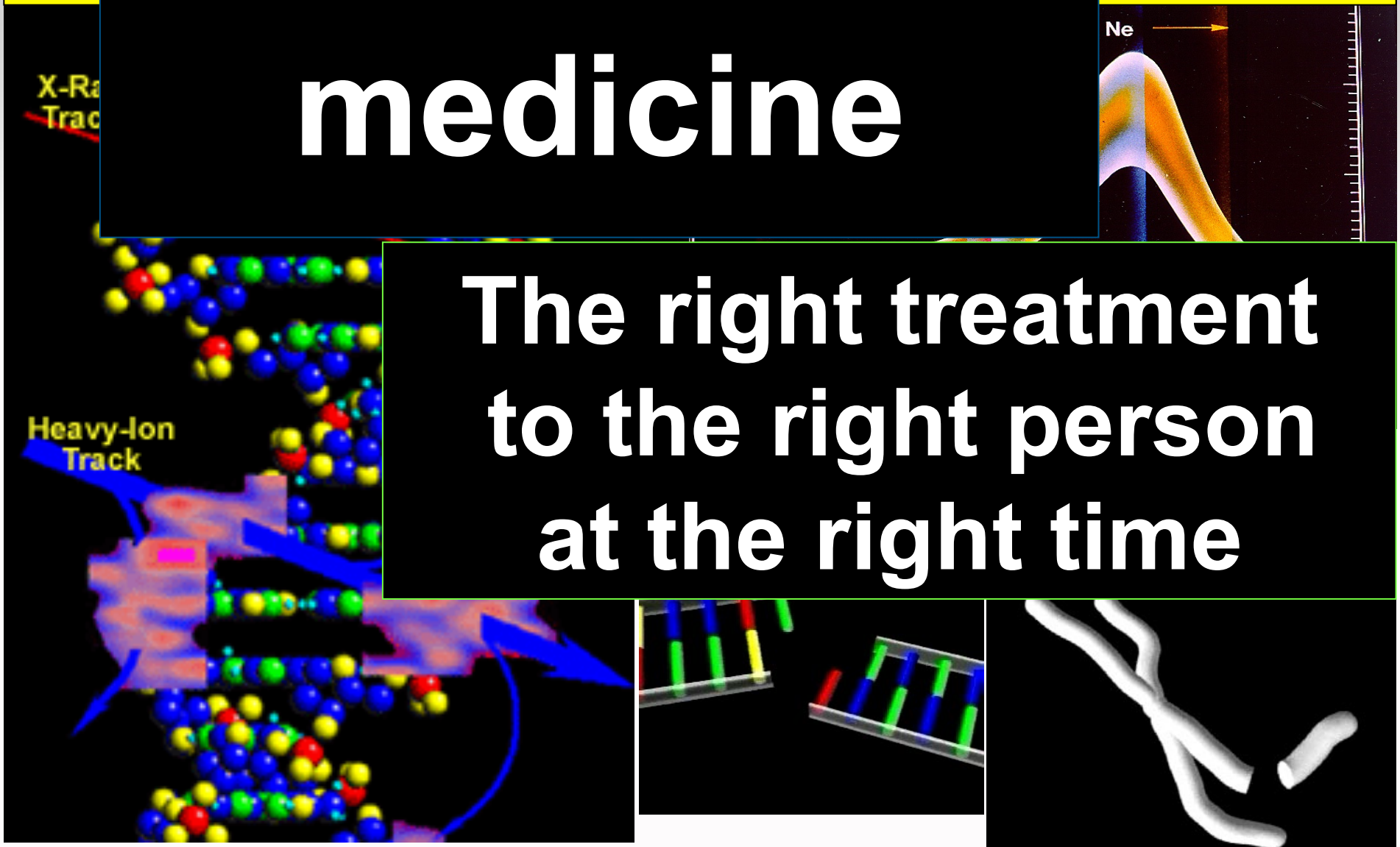


1y LC 50%



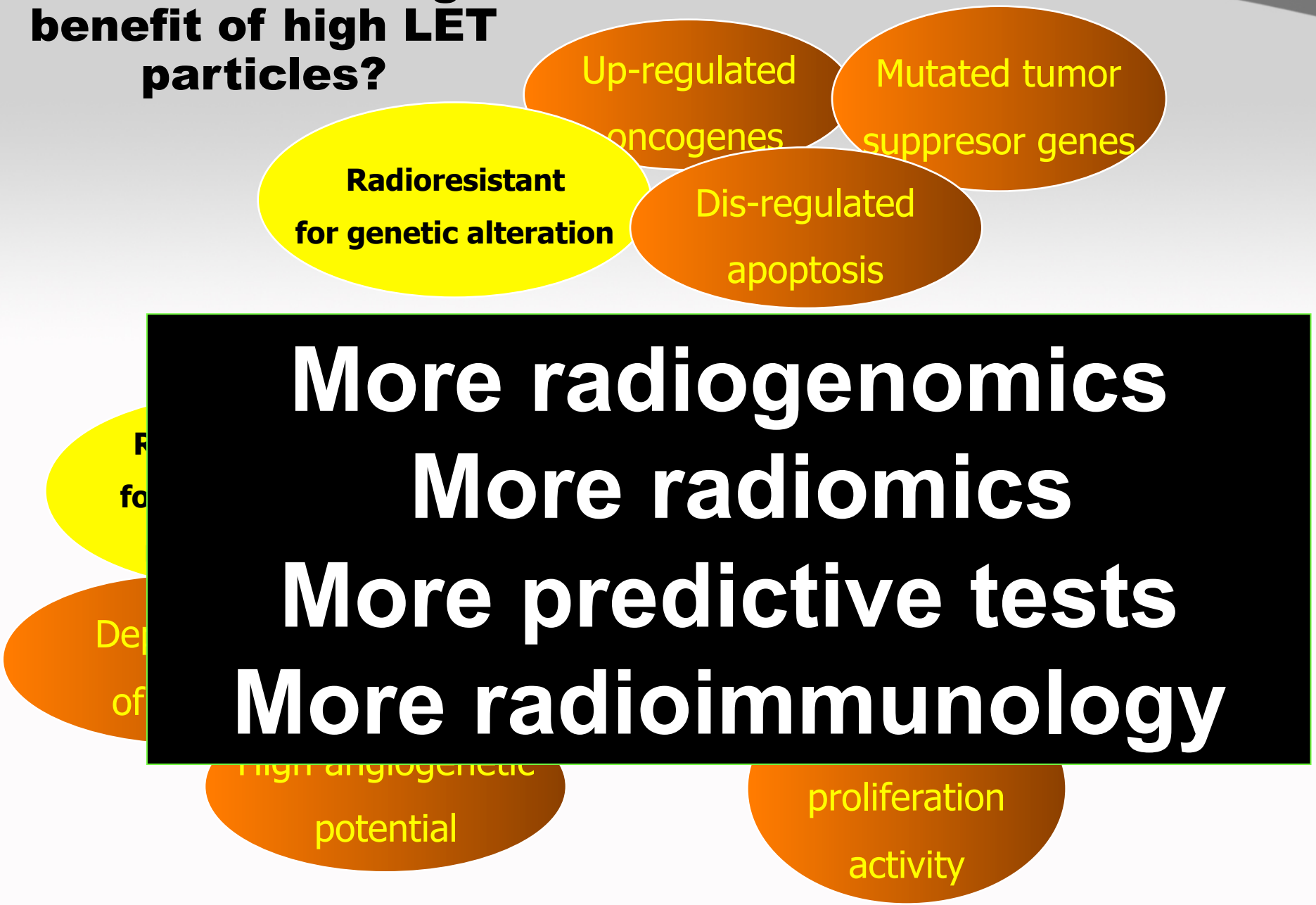

In the future, we could use targeted ions exactly as now we are using targeted drugs .....

Personalised medicine



The right treatment to the right person at the right time

Which tumors might benefit of high LET particles?



Thank you very much !!!!!!

to All of You
from the CNAO team