The Status Report of CNAO

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Scientific Director at European Institute of Oncology in Milan and
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IEO
European Institute of Oncology

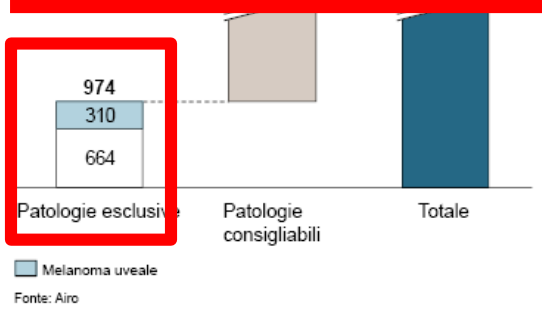
fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

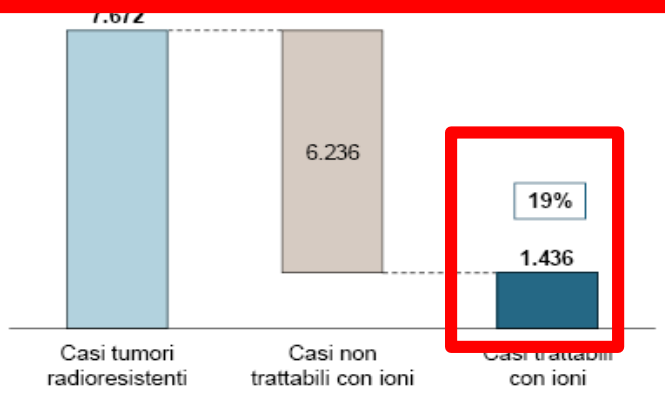

Bergamo
L O M B A R D
Legnano
Monza
Rho
Vigevano
S. Angelo Lodigiano
Oltrepò
IEO
Milan
CNAO
Pavia
Trentino Alto Adige
Lombardia
Friuli Venezia Giulia
Veneto
Emilia Romagna
Marche
Abruzzo
Molise
Puglia
Umbria
Lazio
Campania
Basilicata
Calabria
Sicilia
Liguria
Toscana

Italiy

Working Group 1998, 2003, 2008, 2009

2500 estimated new patients/year to be treated by hadrons





Fonte: Airo

essere adottate in quasi 20% dei casi di alcune categorie di tumori radioresistenti

- Le principali patologie neoplastiche trattabili con ioni sono: i tumori delle ghiandole salivari, i melanomi mucosi delle VADS, i adenocarcinomi dei seni paranasali, i sarcomi ossei e dei tessuti molli e i epatocarcinomi/tumori pancreatici e delle vie biliari
- Ad oggi l'applicazione della terapia a ioni Carbonio è piuttosto limitata, tuttavia in futuro si prevede una crescente estensione del campo di applicazione

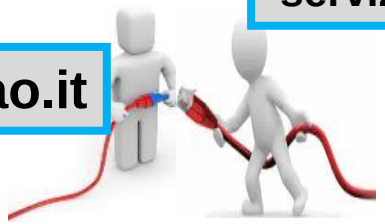
MIL-0101-08512-004-065-02

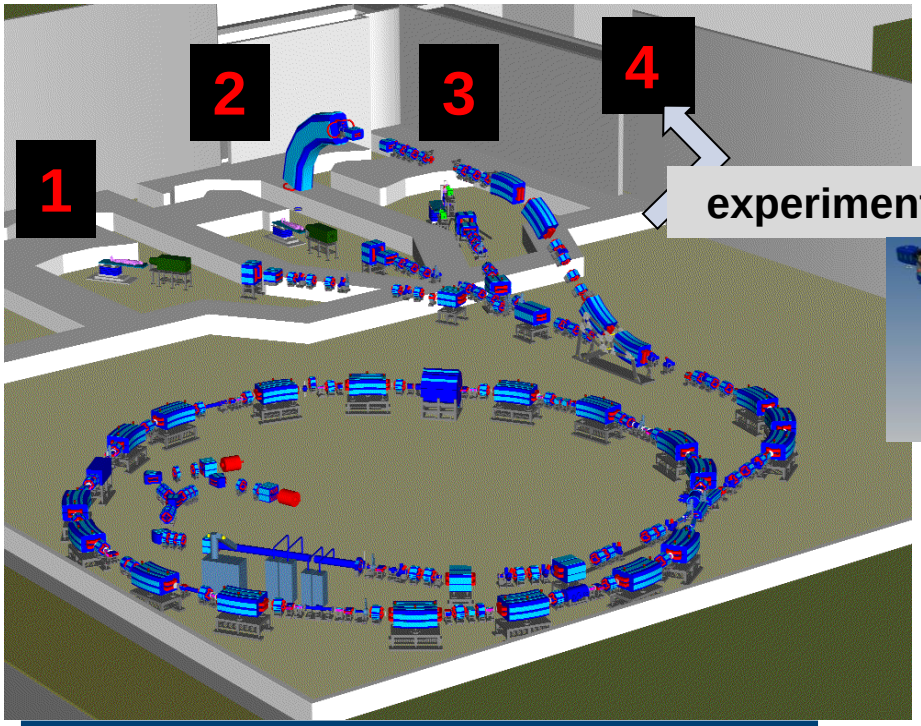
CNAO in Pavia

dual center
active scanning
Protons /Carbon Ions

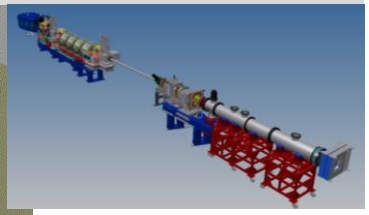
serviziomedico@cnao.it

http://folder.cnao.it



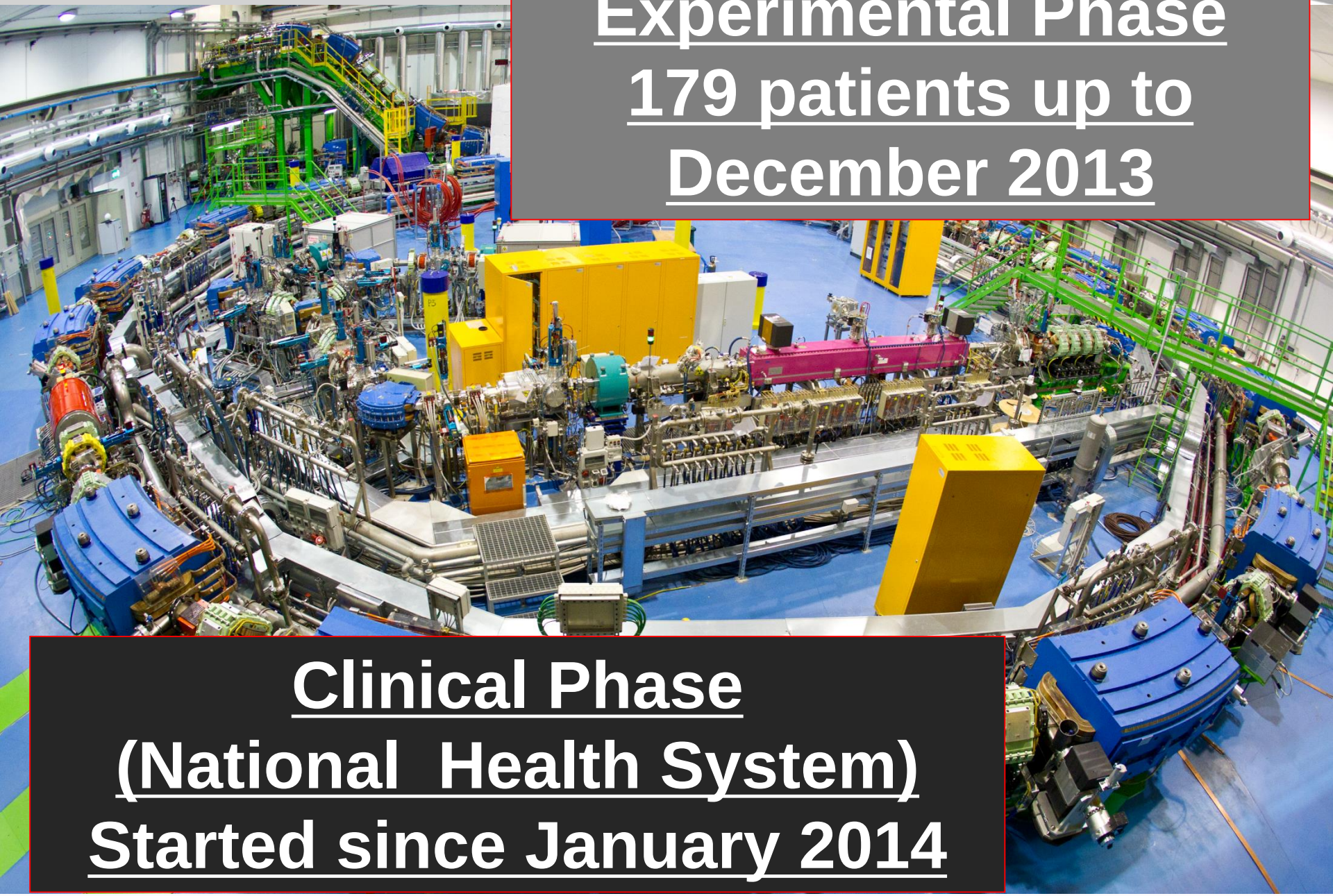


experimental room (2017)



in room 3D imaging

Synchrotron P-C 400 meV/*u*



Experimental Phase
179 patients up to December 2013

Clinical Phase
(National Health System)
Started since January 2014

fondazione CNAO

PROGETTO DI SPERIMENTAZIONE CLINICA

A CURA DI:

Erminio Borloni – Presidente
Roberto Orecchia – Direttore Scientifico
Sandro Rossi – Segretario Generale e Direttore Tecnico

IL CENTRO NAZIONALE DI ADROTERAPIA ONCOLOGICA

Strada Privata Campeggi – 27100 Pavia

Sedi: Via Caminadella, 16 - 20123 Milano
Iscrizione al Registro delle Persone Giuridiche della Prefettura di Mil...
P.IVA n. 03491780965
Codice Fiscale n. 97301200156

Presented to:

- Italian Ministry of Health
- Lombardy Region

Protons

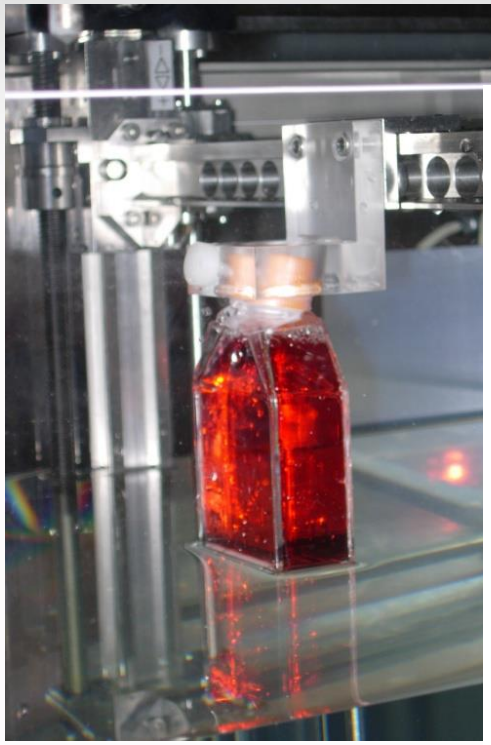
Carbon

Main Tasks:

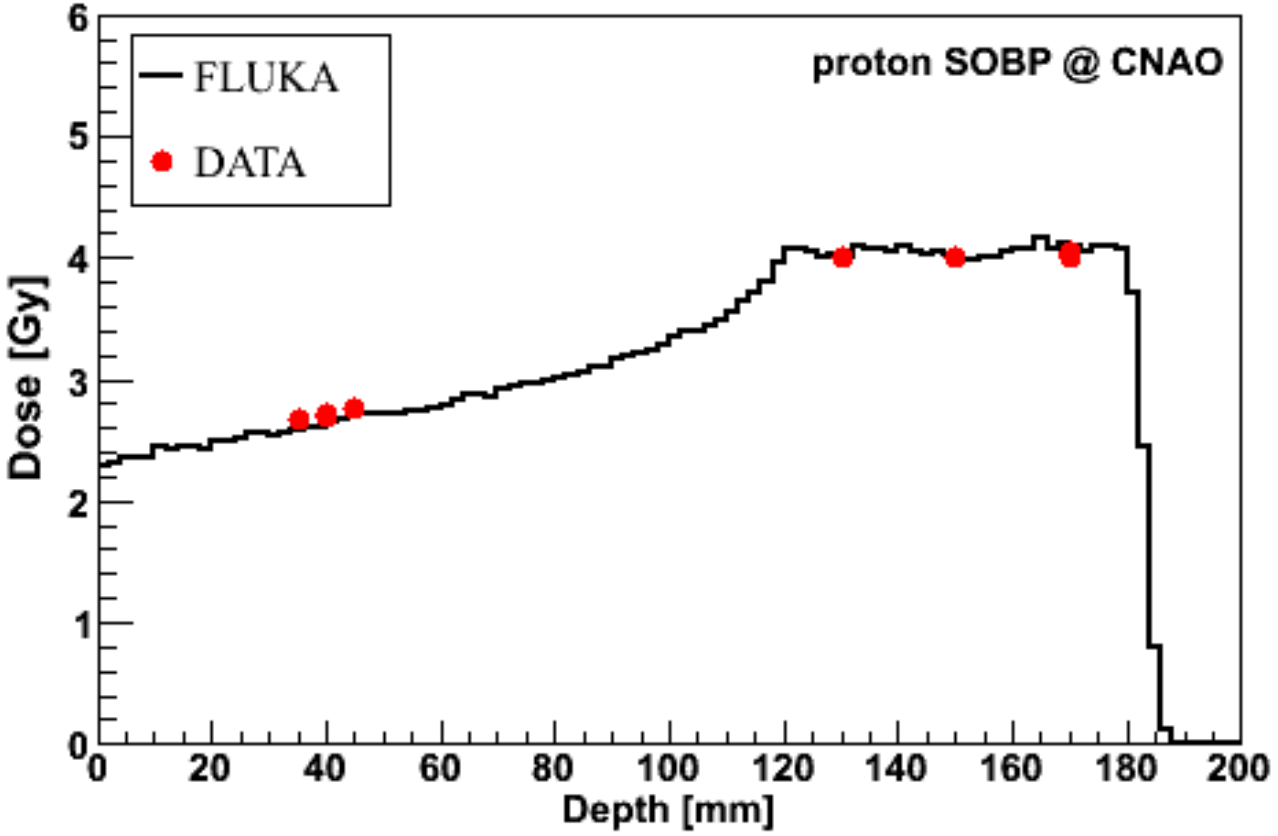
- Dosimetry characterisation
- Radiobiology characterisation
- Patient treatment

Proton Radiobiology

3 cell lines: HSG (human salivary gland tumour), T98G (human glioblastoma), V79 (Chinese hamster lung fibroblast)

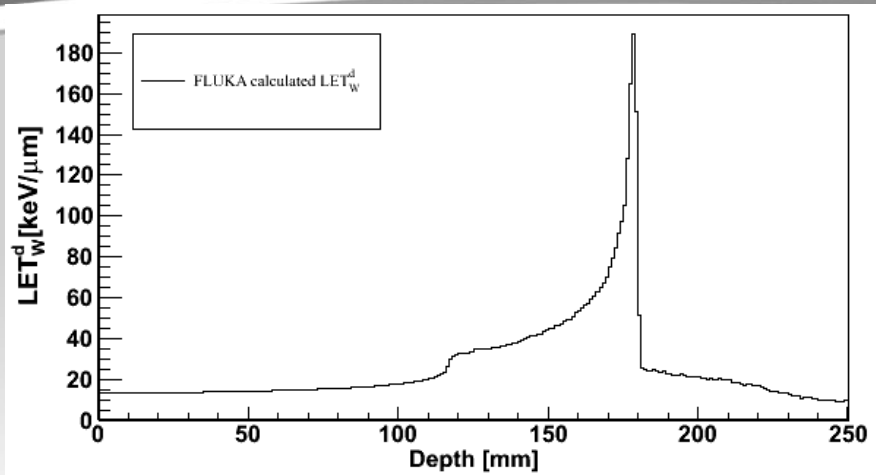


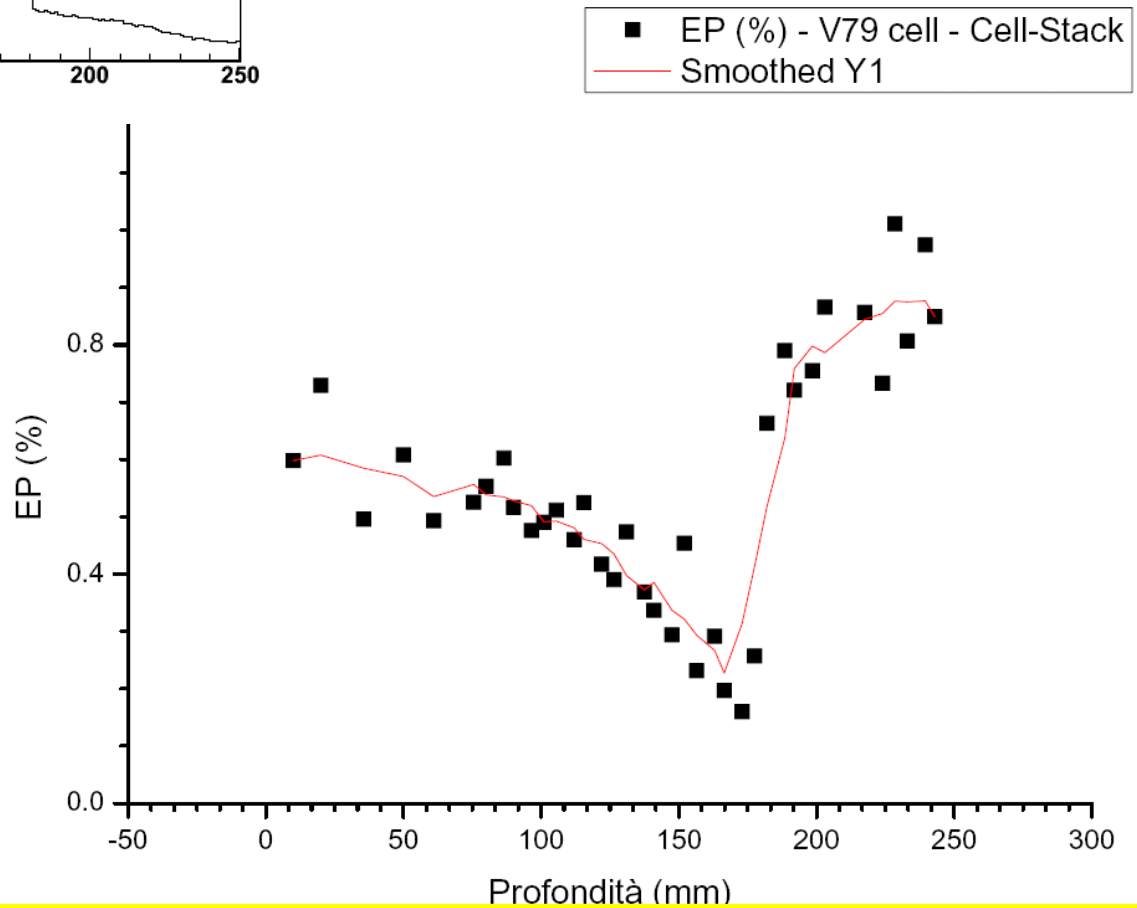
Field 10x10 cm², 33x33 spots, scanning step 3 mm



Cell Survival vs Depth

Dose uniformity



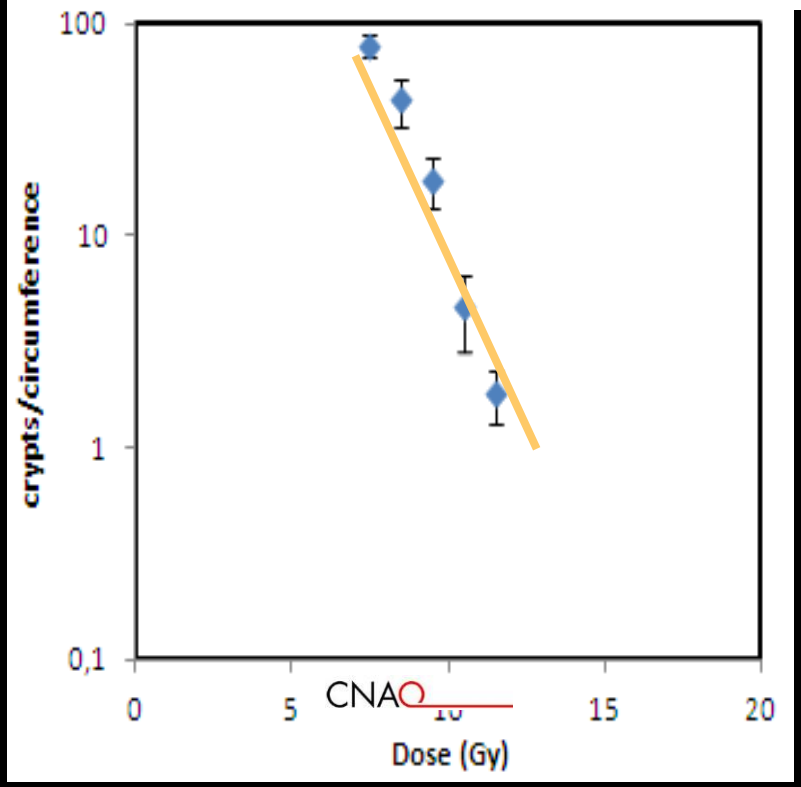


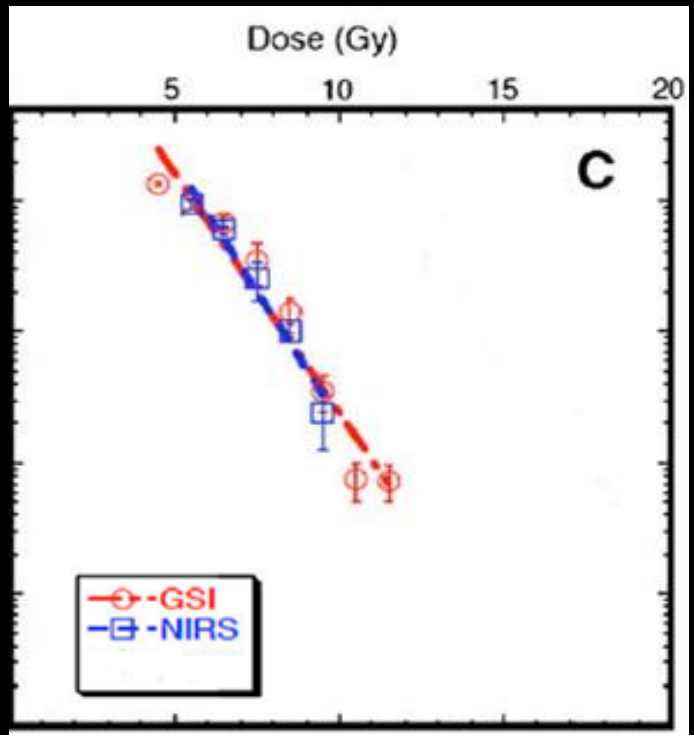
Carbon Ions Radiobiology

Group Leader:
Yoshiya Furusawa,
NIRS, Chiba

Carbon ions
Animals

Comparison of RBE results (CNAO vs GSI \ NIRS)





ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 5, pp. 1545–1551, 2009

0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.12.021

BIOLOGY CONTRIBUTION

COMPARISON OF BIOLOGICAL EFFECTIVENESS OF CARBON-ION BEAMS IN JAPAN AND GERMANY

Akiko Uzawa, M.Sc.,* Koichi Ando, D.M.Sc.,† Sachiko Koike, M.Sc.,* Yoshiya Furusawa, Ph.D.,* Yoshitaka Matsumoto, Ph.D.,* Nobuhiko Takai, Ph.D.,* Ryoichi Hirayama, Ph.D.,* Masahiko Watanabe, M.Sc.,* Michael Scholz, Ph.D.,‡ Thilo Elsässer, Ph.D.,‡ and Peter Peschke, Ph.D.§

2014 - 2015 Activity

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

Proton
Conventional fractionation
Patients: 107 (84, *)

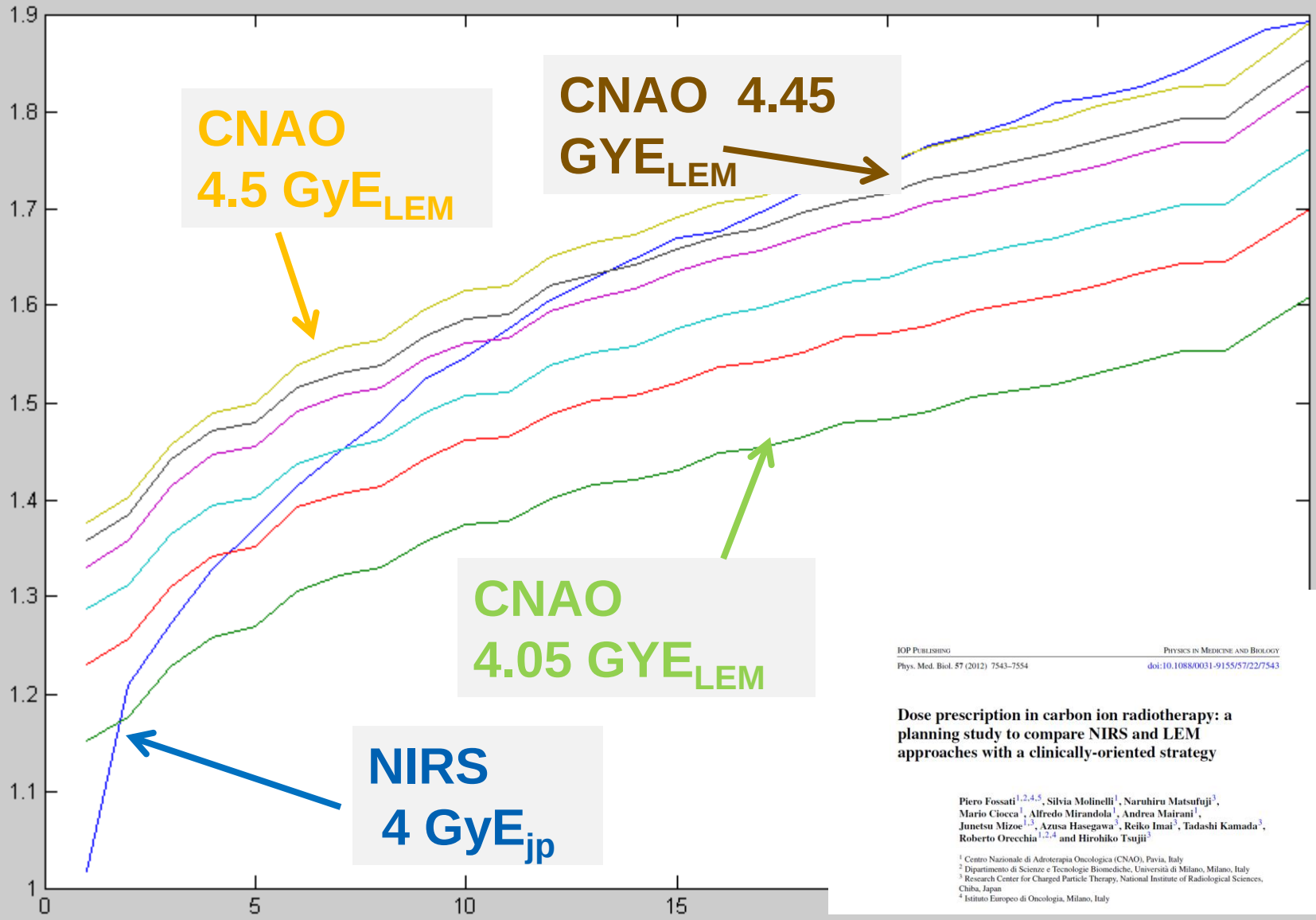
Carbon ion
NIRS fractionation
Patients: 446 (95, *)

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

- **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**

Physical dose in SOBP



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

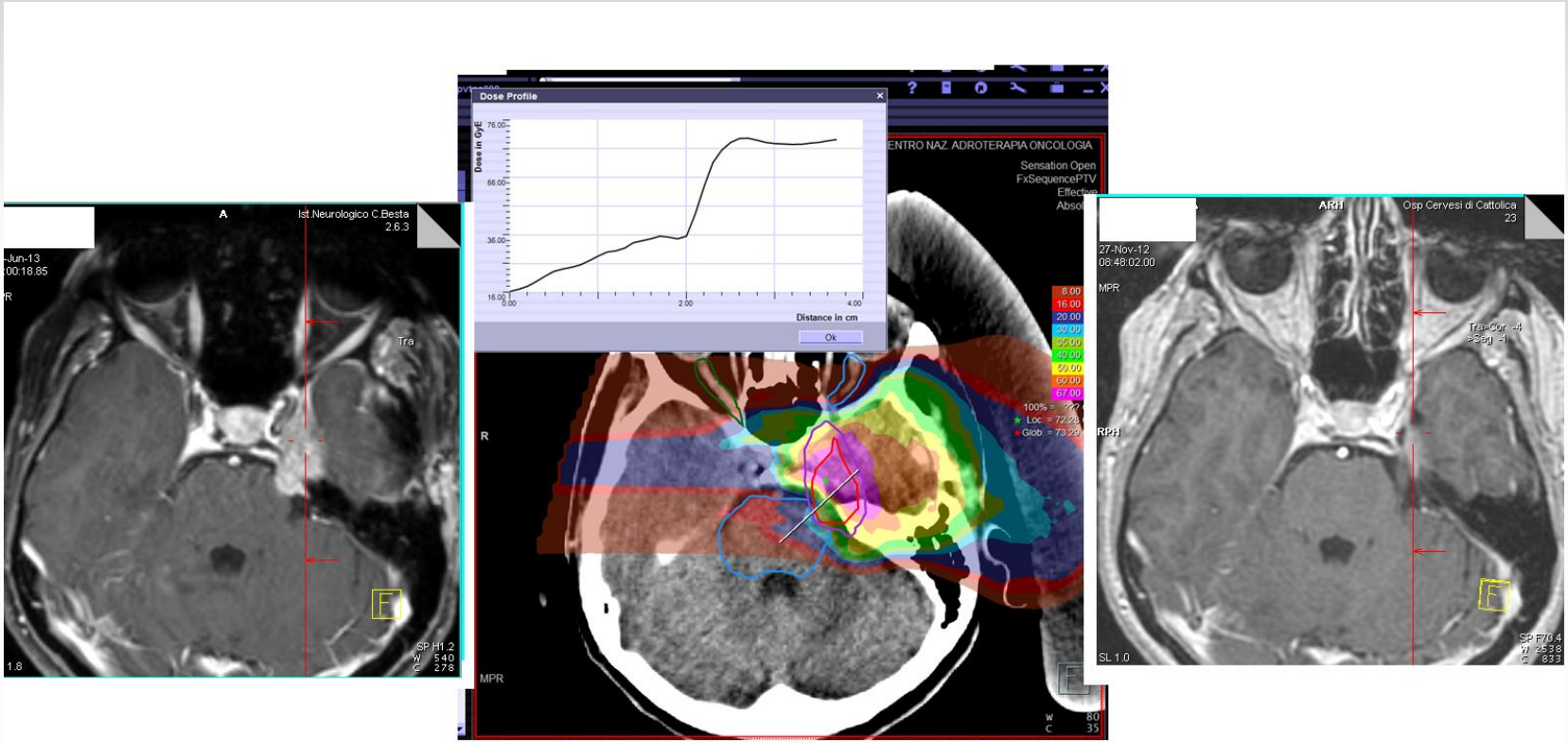
Piero Fossati[1,2,4,5], Silvia Molinelli[1], Naruhiru Matsufuji[3], Mario Ciocca[1], Alfredo Mirandola[1], Andrea Mairani[1], Junetsu Mizoe[1,3], Azusa Hasegawa[3], Reiko Imai[3], Tadashi Kamada[3], Roberto Orecchia[1,2,4] and Hirohiko Tsujii[3]

[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
[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

Local Control. ACC CNAO



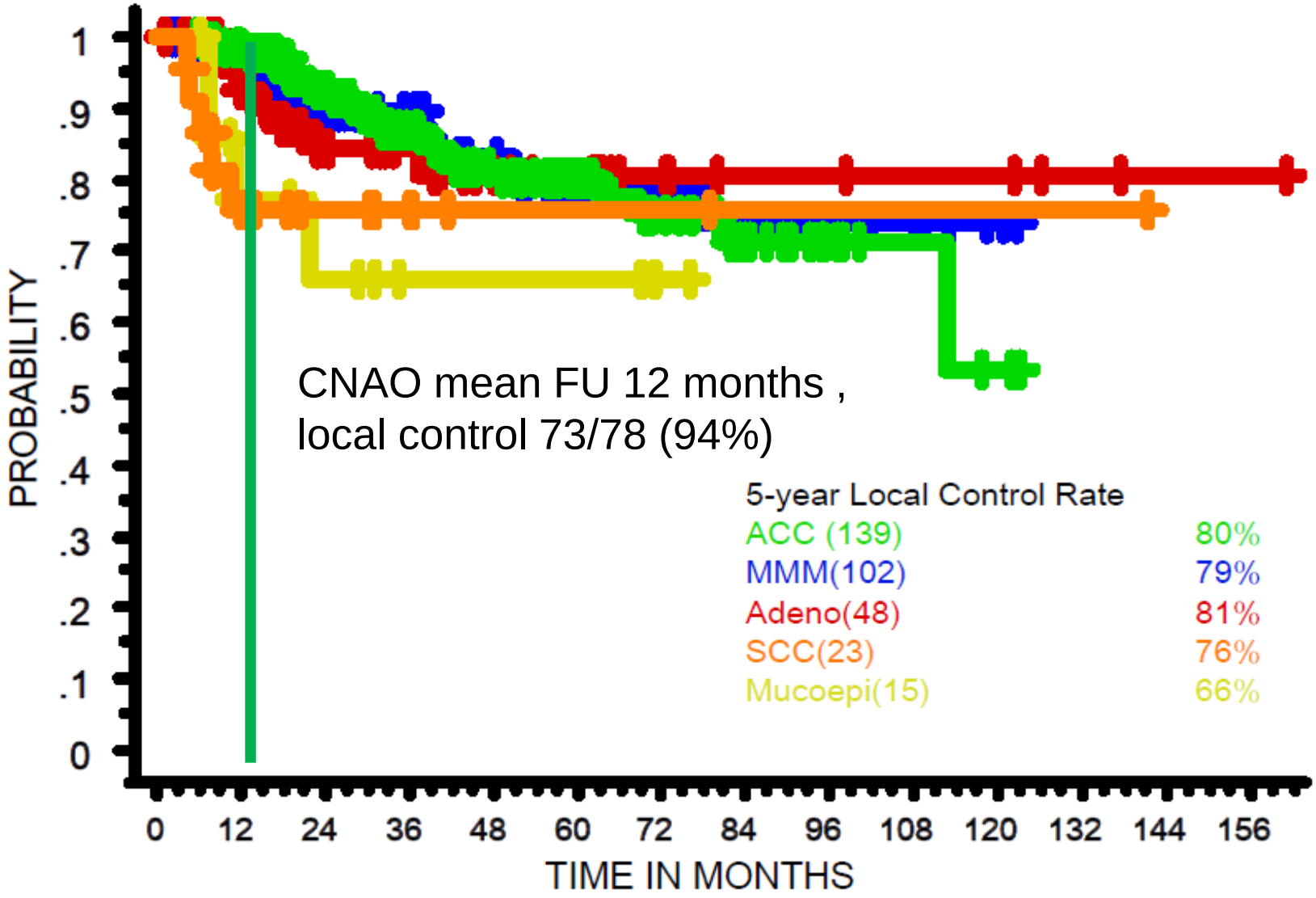
Before treatment

4.3 GyE x 16 fr = 68.8 GyE

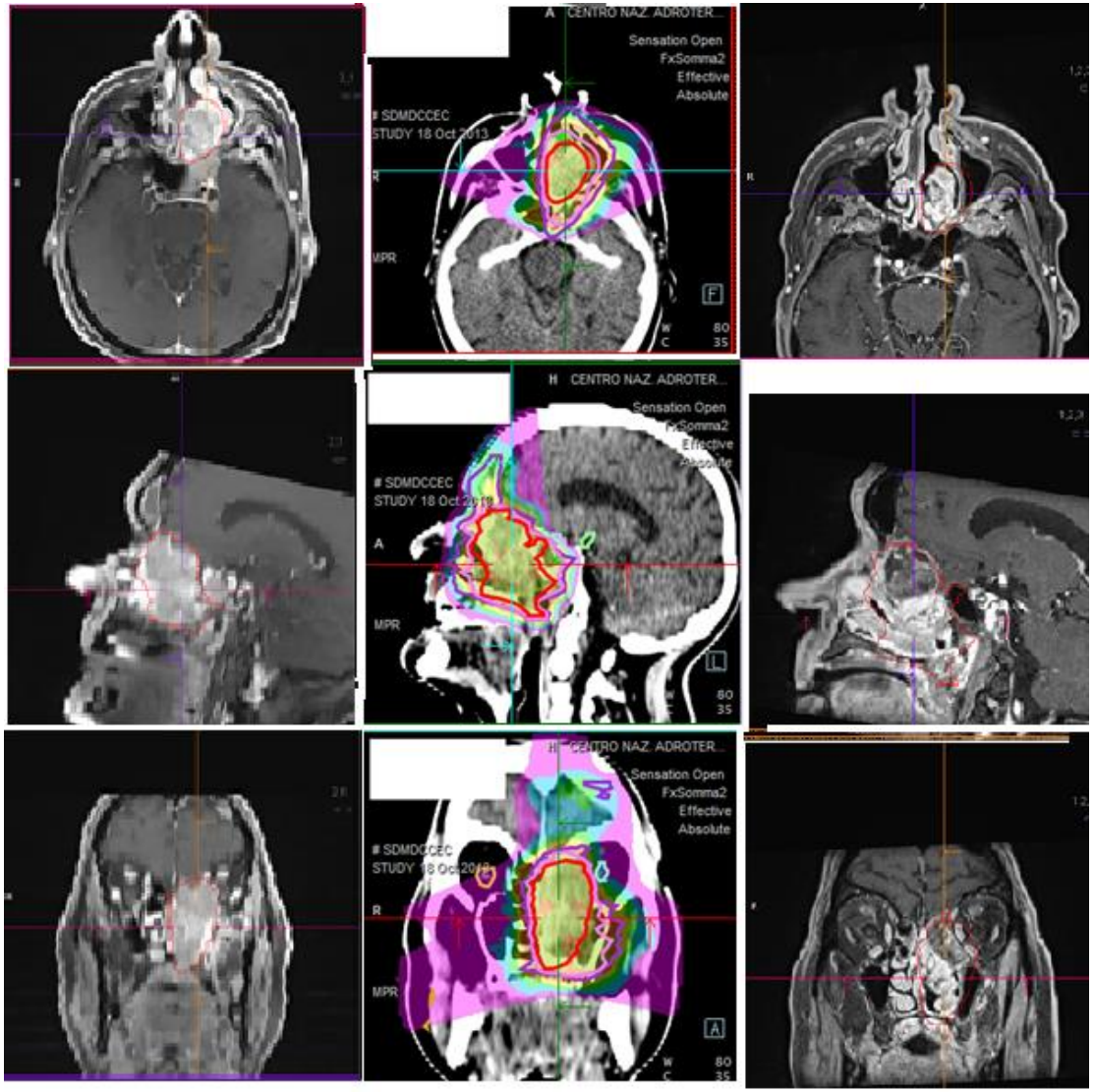
After 9 months

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

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



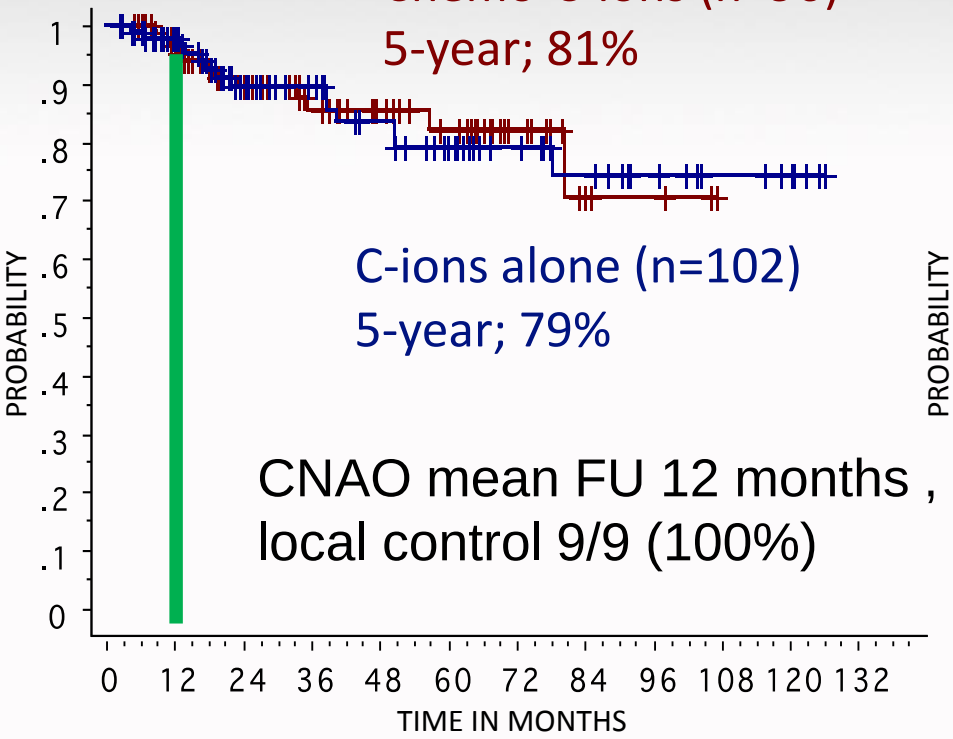
Local Control. MMM CNAO



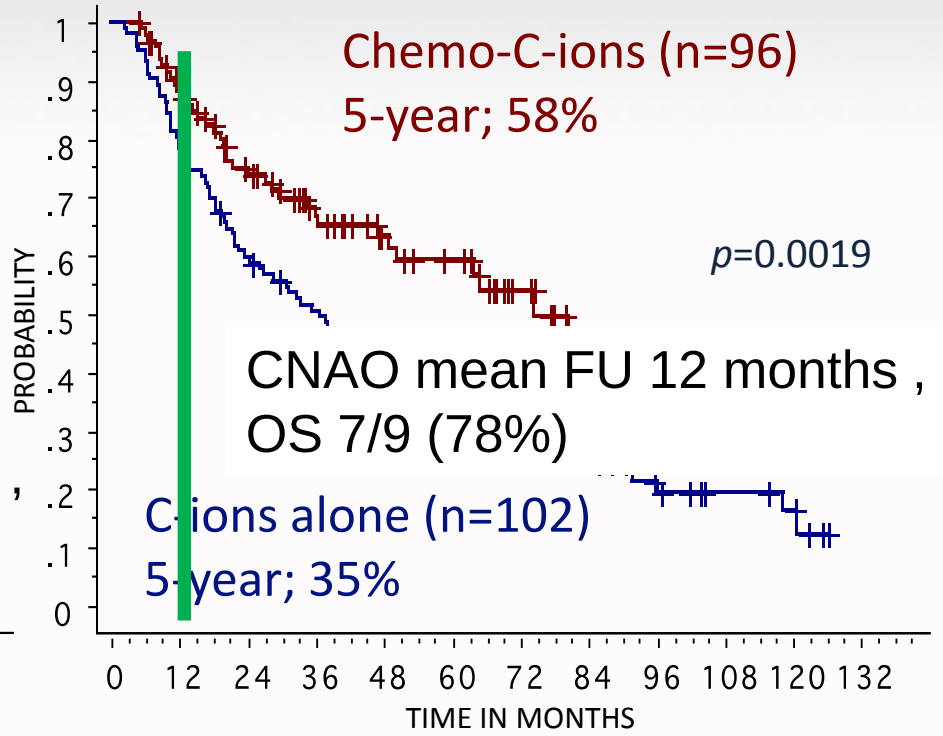
Carbon Ion Radiotherapy for Mucosal Malignant Melanomas

(Apr 97~Feb 11)

Local Control



Overall Survival



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

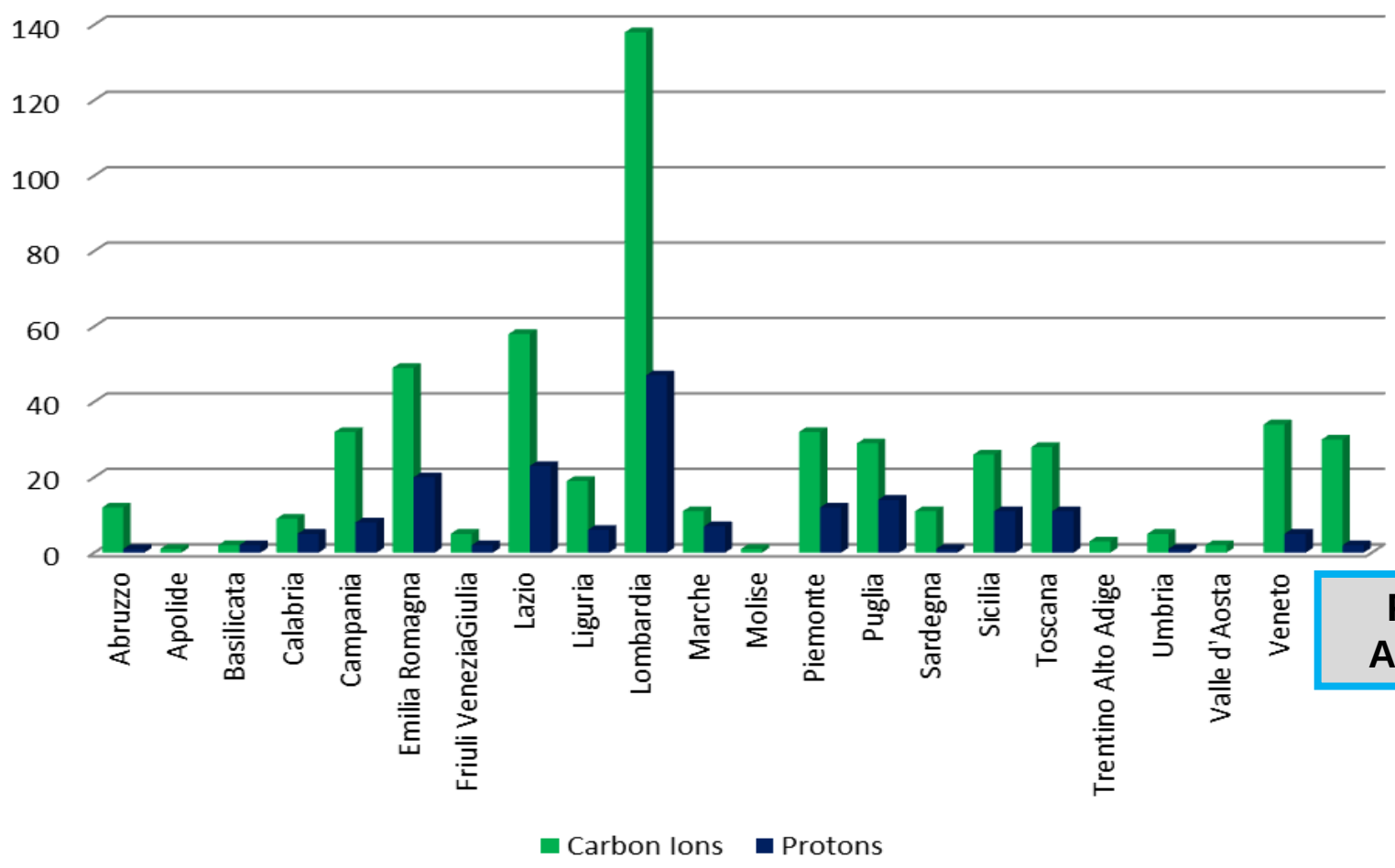
Patients: 446 (+ 95 *, total 541)

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

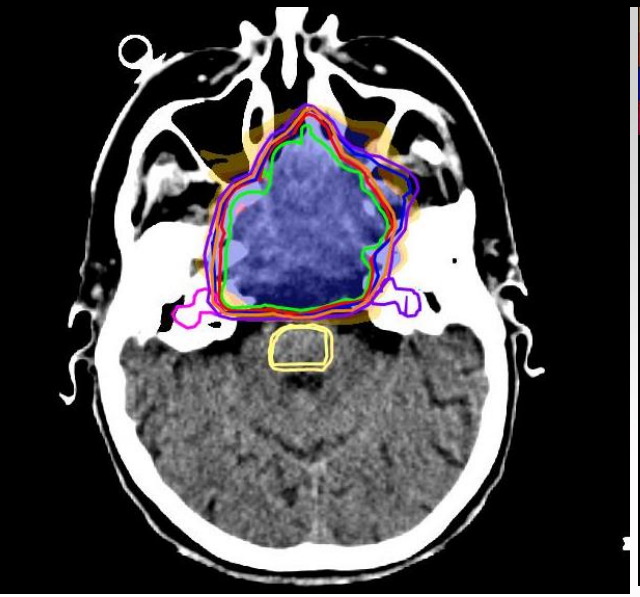
* Experimental phase

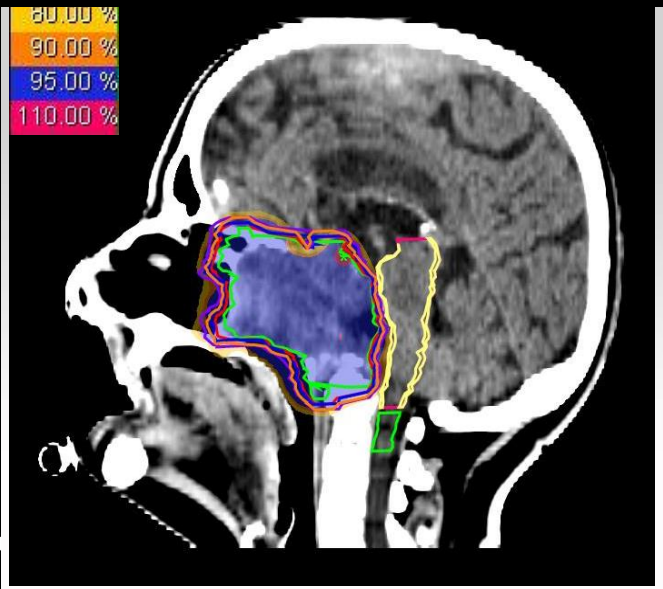
** Including chordoma & chondrosarcoma

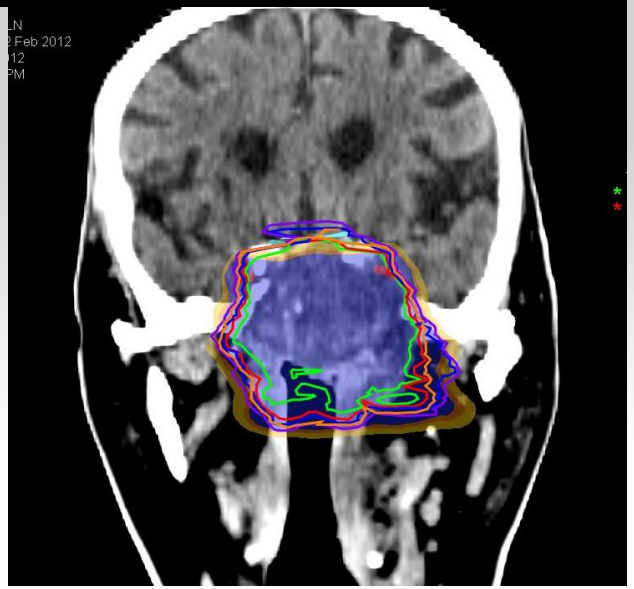
Referred new patients to CNAO by Italian Regions



Proton Therapy for Skull Base Chordoma



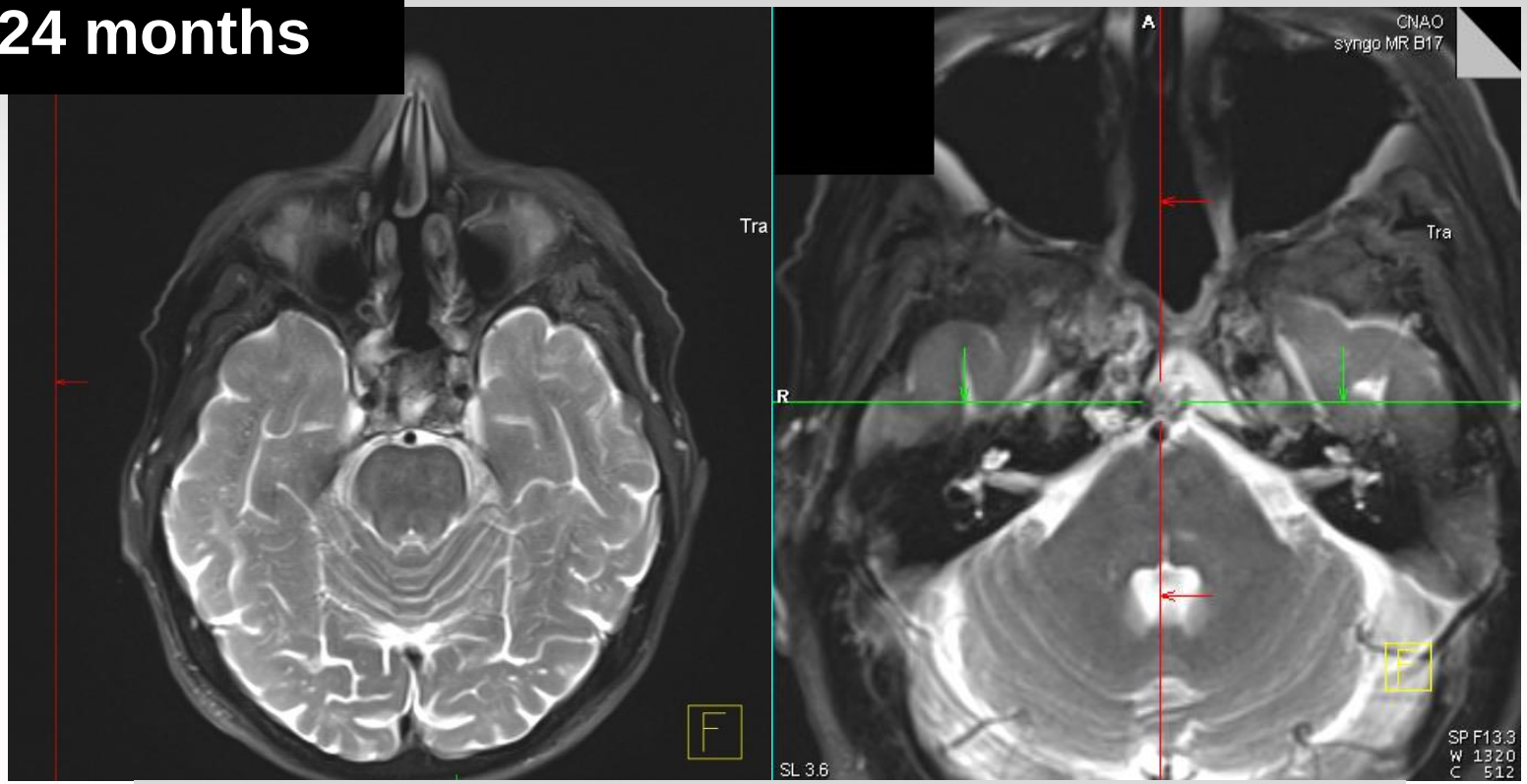




At 10 months

Proton Therapy for Skull Base Chordoma

At 24 months



Good condition, no symptoms.
Acute Toxicity scale CTCAE v4.0: G0
Late Toxicity scale CTCAE v4.0: G0

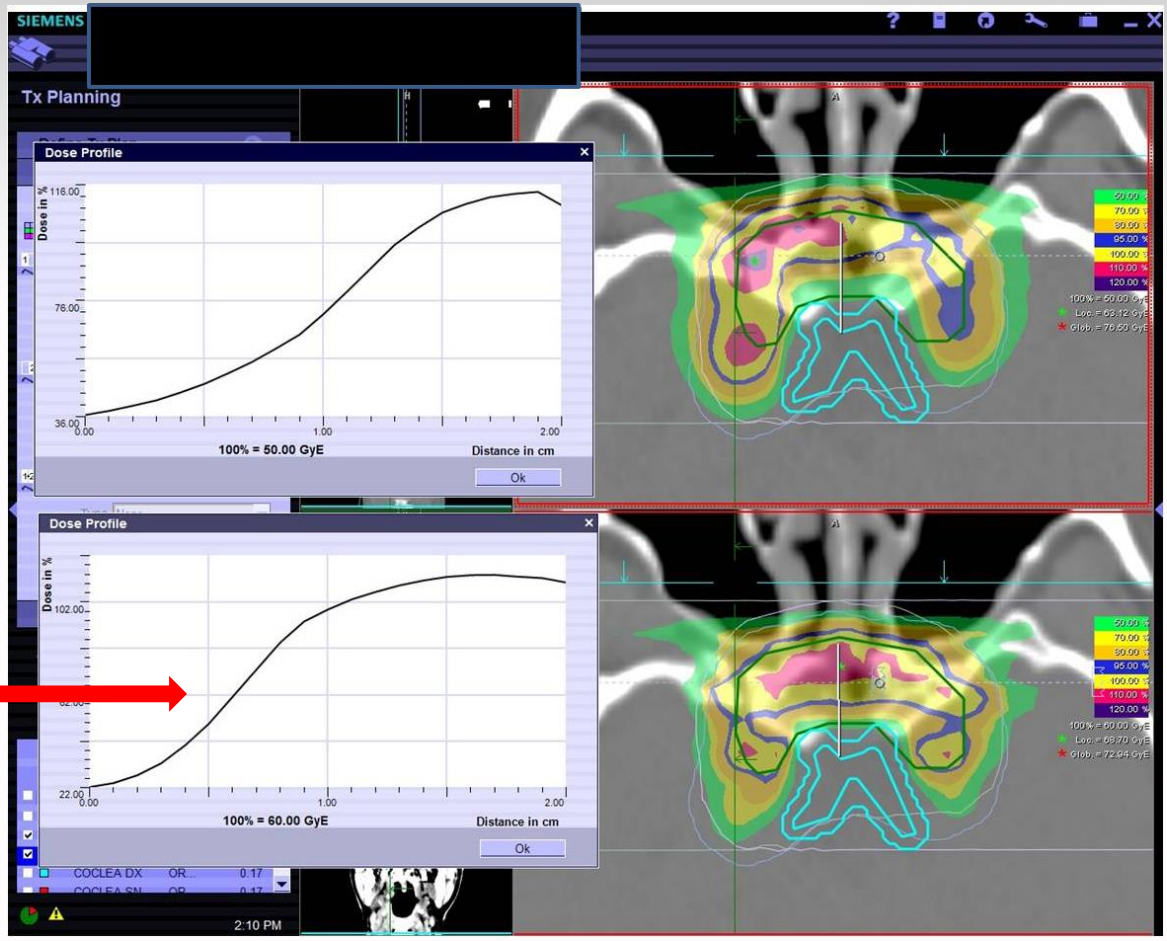
Proton - Carbon ions plans: Steep dose gradient

Proton plan

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

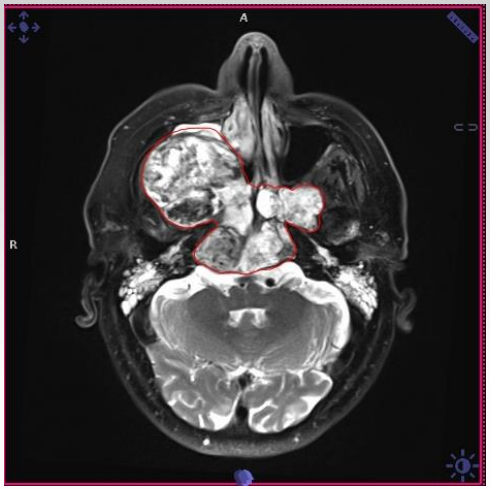
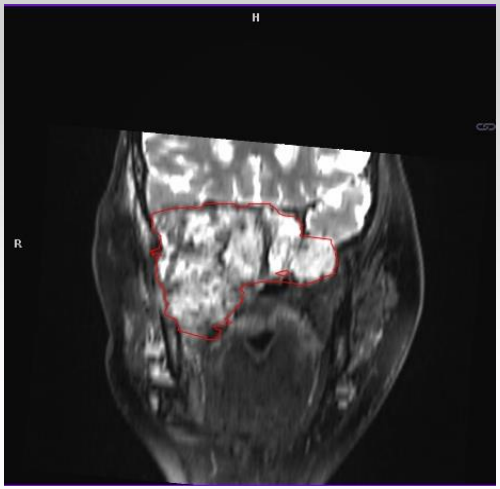
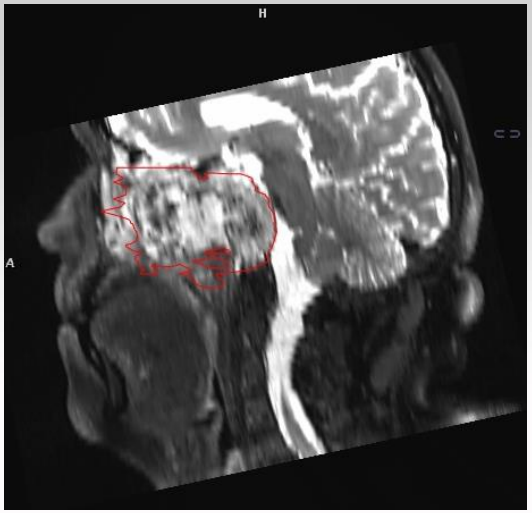
Carbon ions plan

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

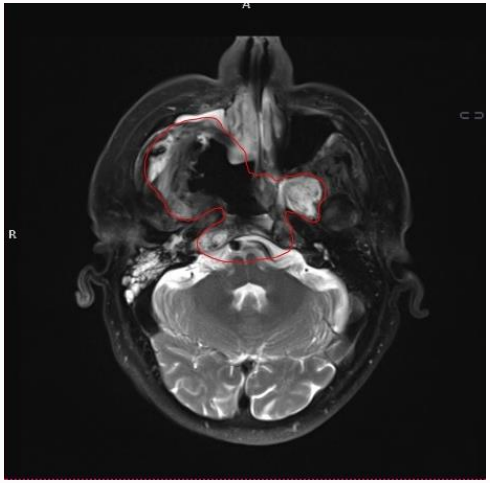
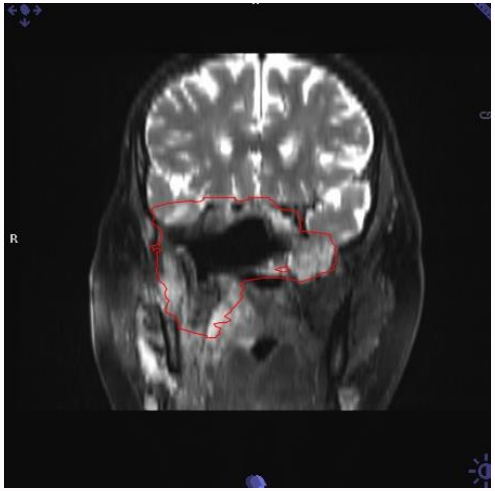
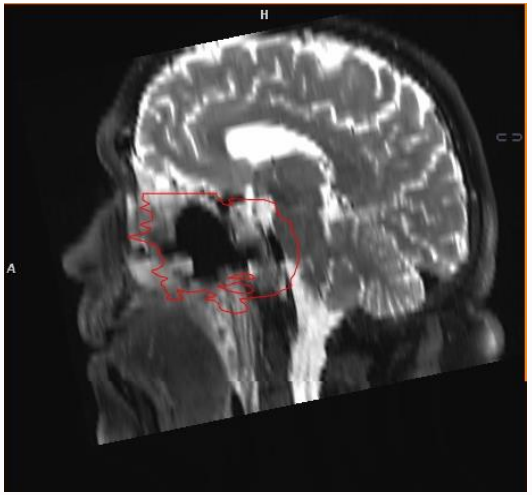


CIRT for Skull Base Chondrosarcoma

May 2014

January 2015

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

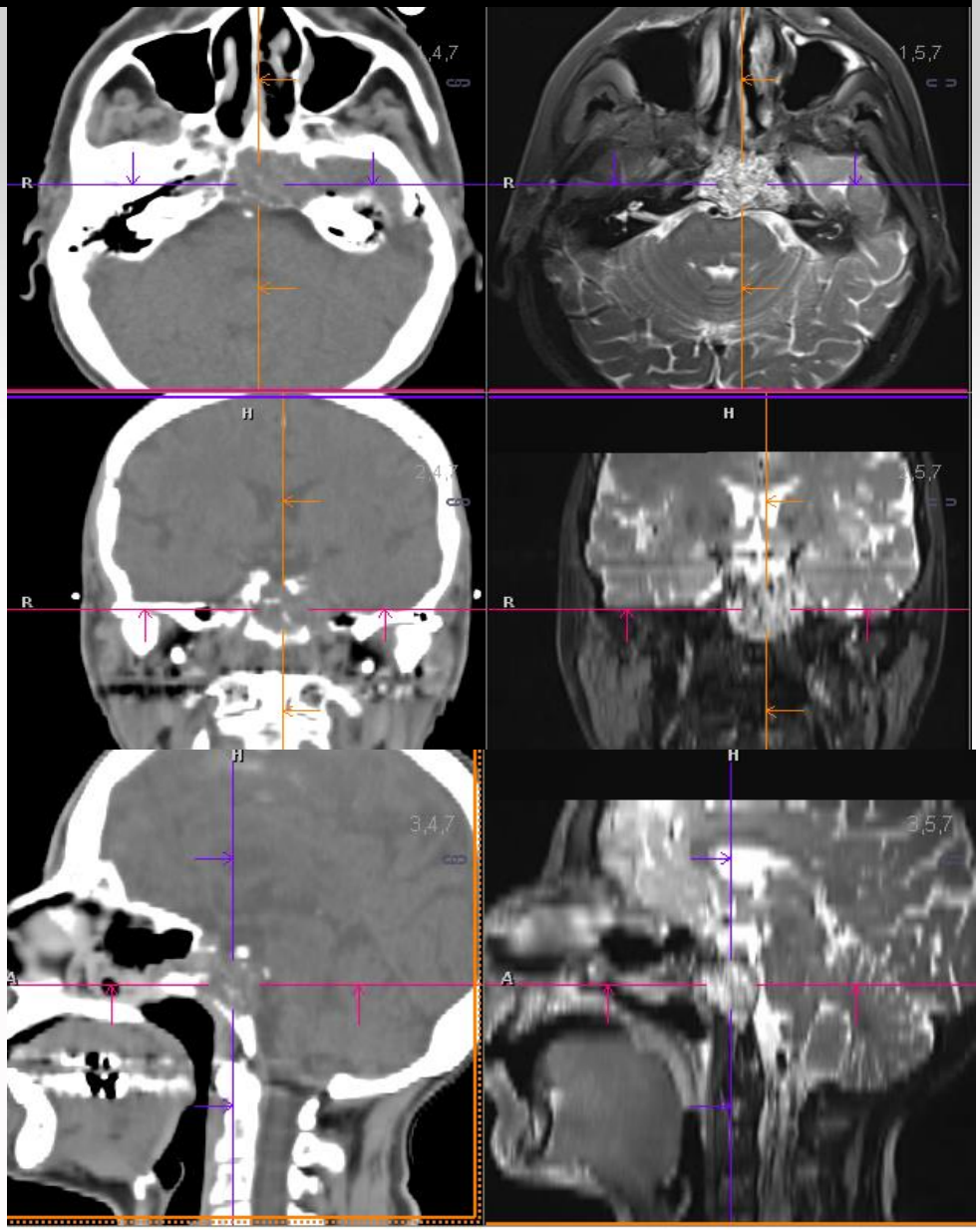
All local failures > brain stem compression / proximity

CIRT for Skull Base Chordoma

Female, 72 years old

24-05-2012 TC :
lesion of skull base region

14-06-2012 MRI :
solid lesion 39 x 37.4 x 36.4 mm with B S compression and invasion the sphenoid sinuses, the chiasm abutting the cavernous sinus

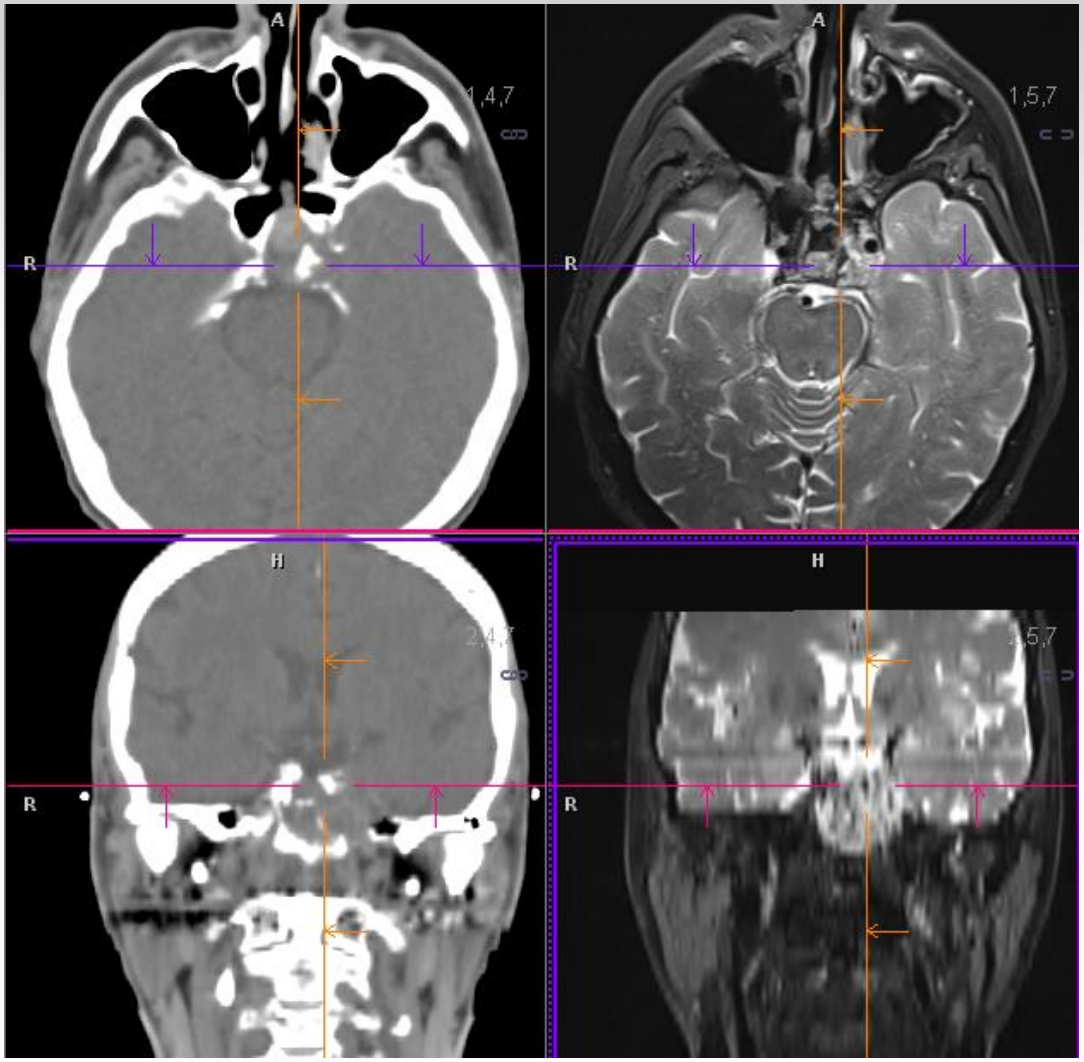


CIRT for Skull Base Chordoma

We ask for a new debulking surgery and decompression of the brain stem

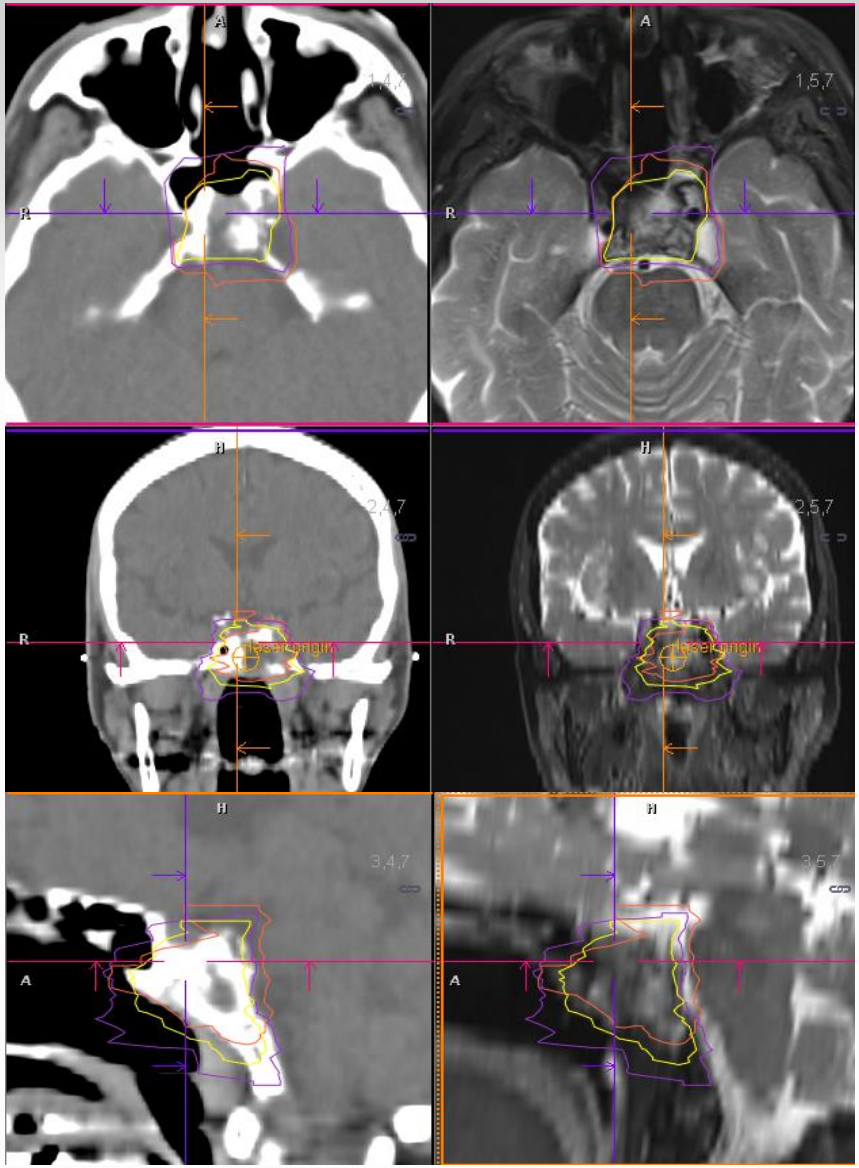
26-07-2012: trans-nasosphenoidal surgery

EI: Chordoma

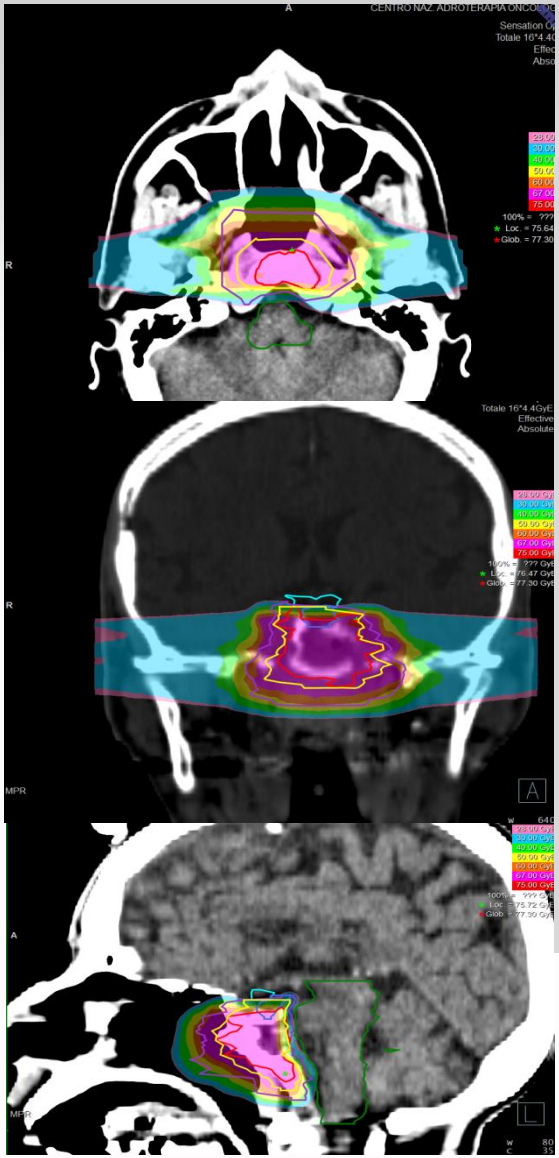


CIRT for Skull Base Chordoma

30/11/2012 Second surgery



18/02/2013- 14/03/2013



- **Carbon Ions (CIRT) IMPT**

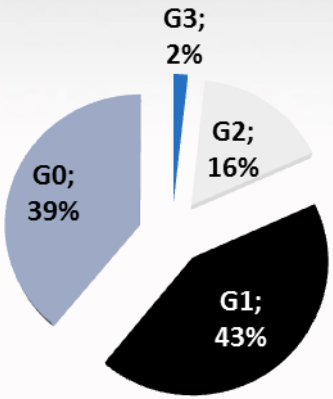
total dose 70.4 Gy

4.4 Gy/fraction

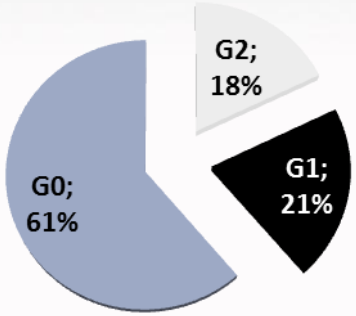
16 fractions,
4 fr/week

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

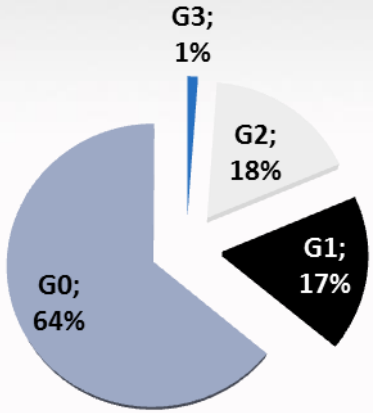
End of IMPT



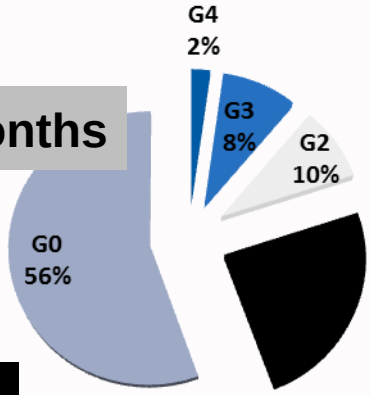
At 3 months



At 6 months



At 18 months



Late toxicity

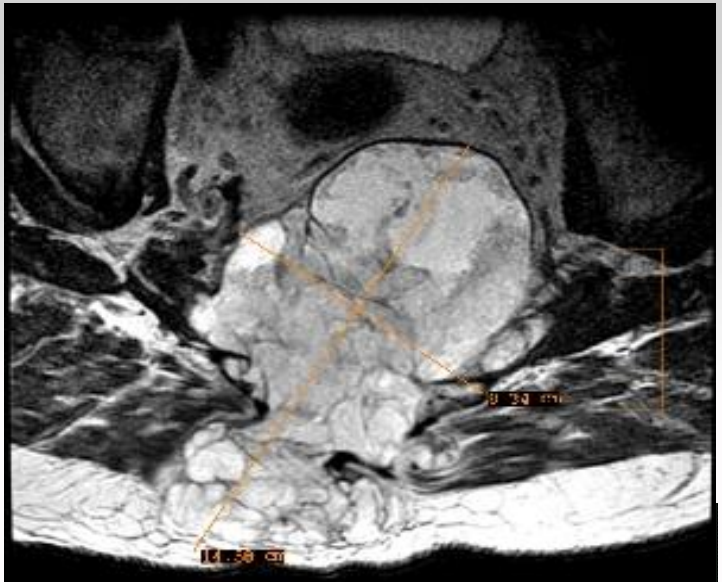
G4

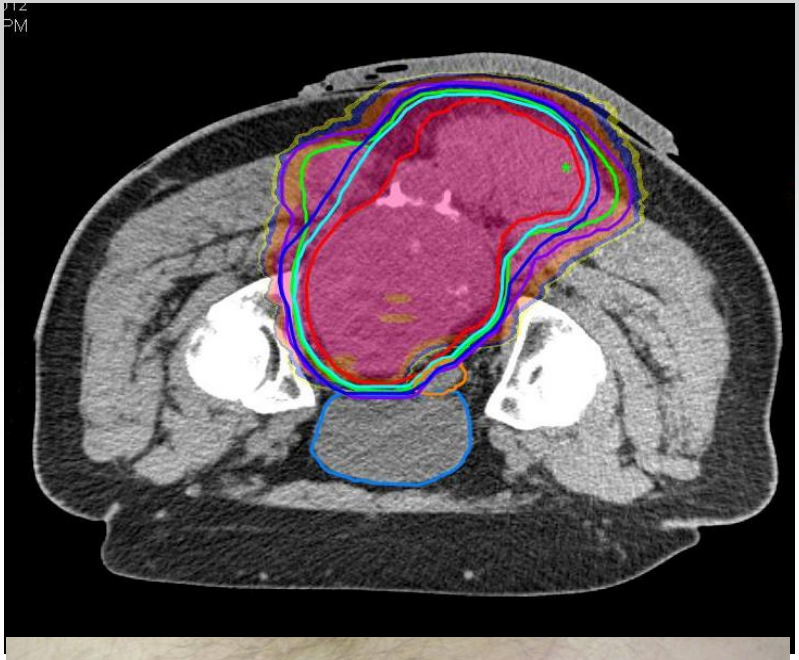
- 1 pt complete visual loss one side
- 1 pt Complete hearing loss

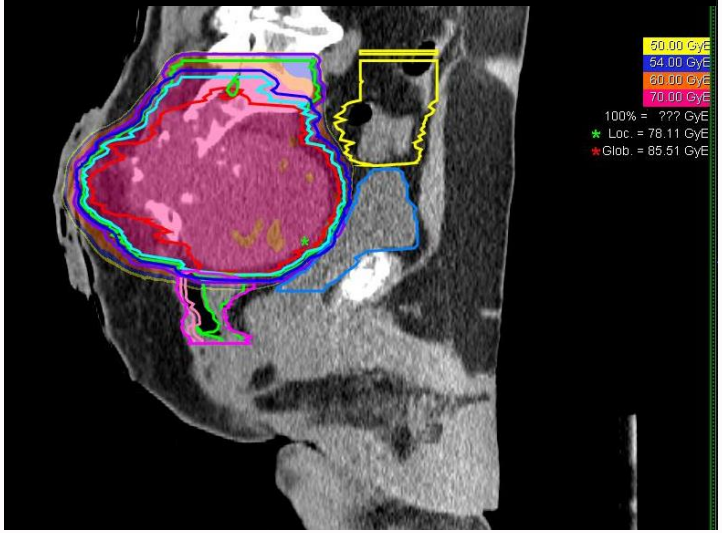
G3

- 1 Sympthomatic Brain necrosis
- 3 Hypopituitarism
- 2 Chronic middle ear infectious
- 2 visual field deficit

CIRT for Sacral Chordoma

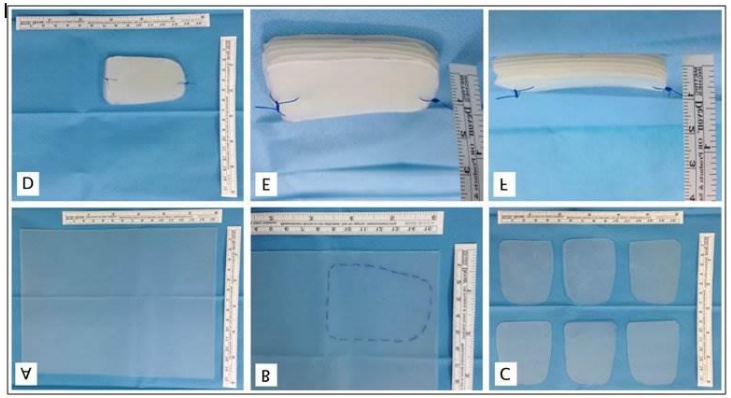


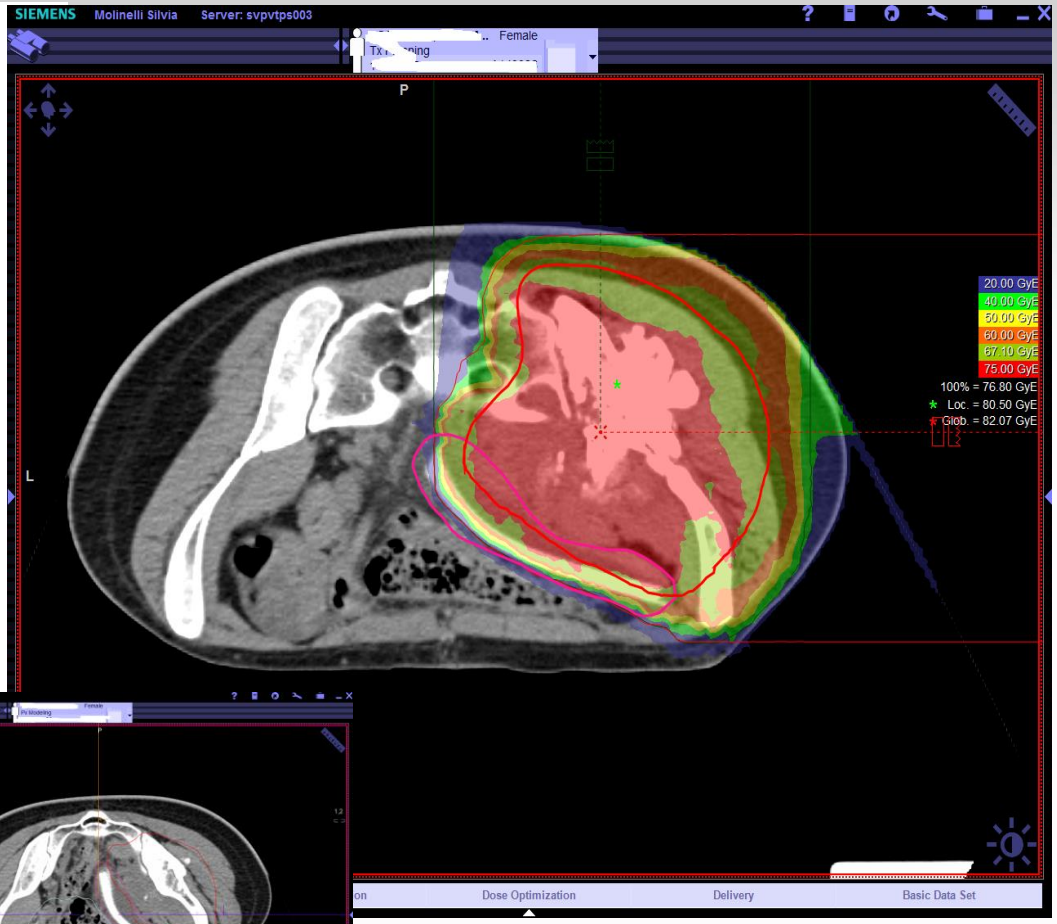


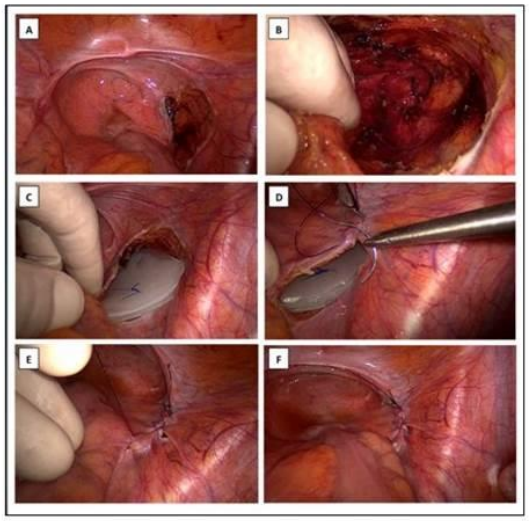


G2 skin toxicity

Surgical spacer placement

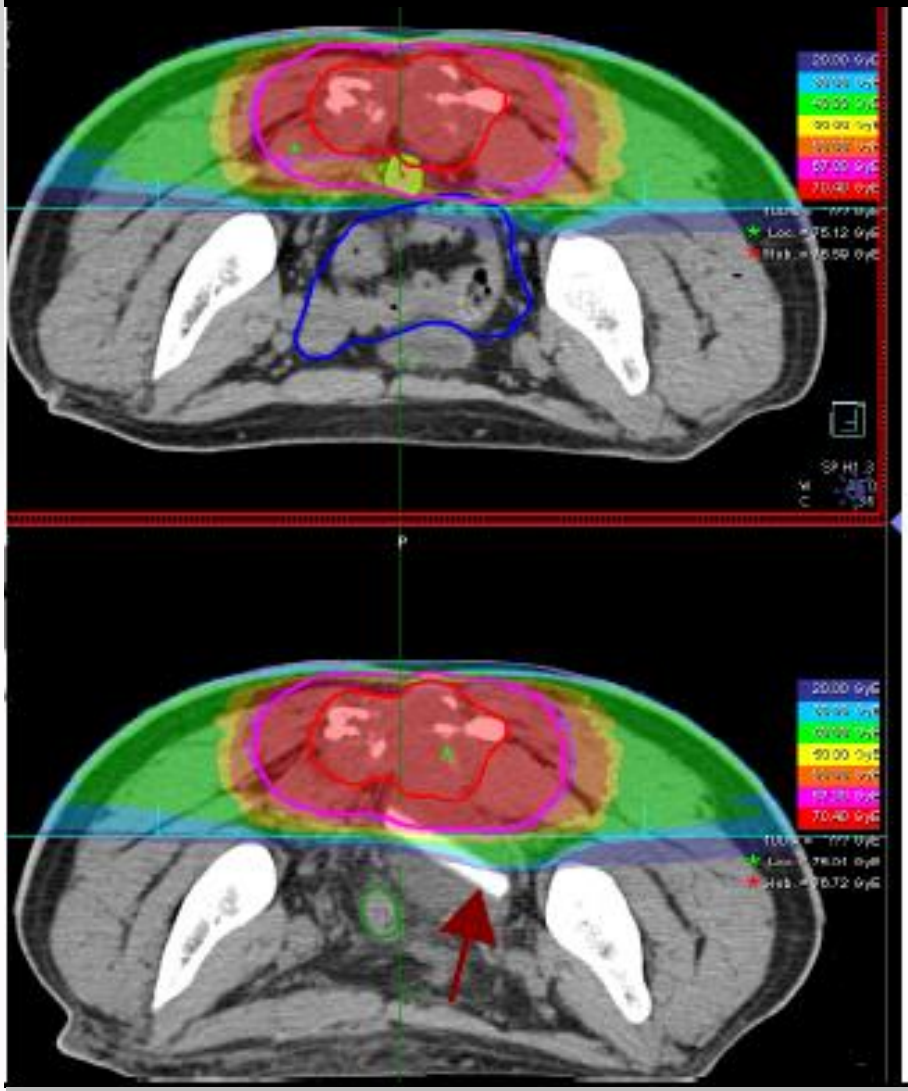


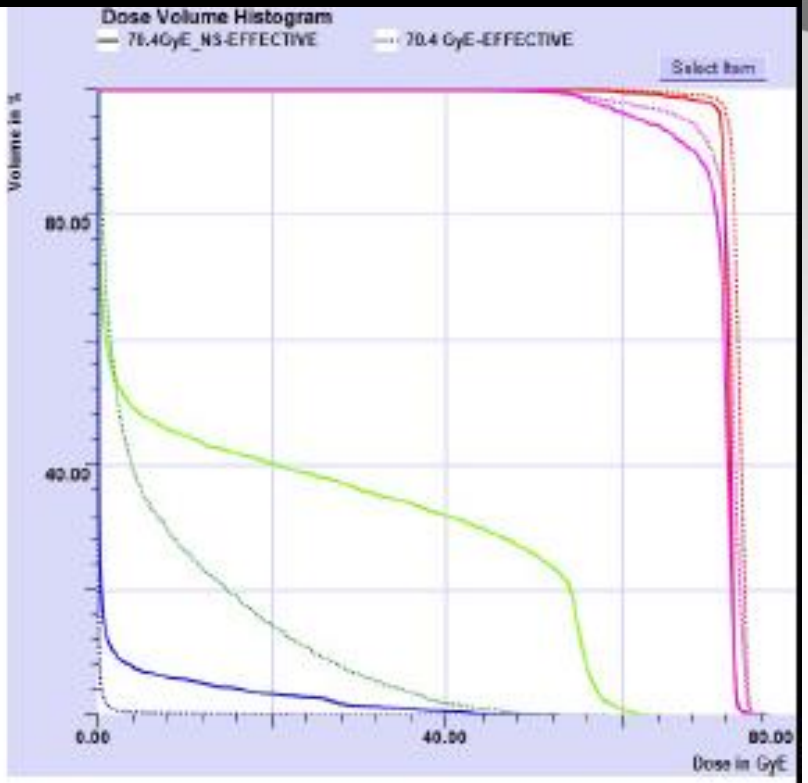




Silicon spacers
Width 5-6 mm

Surgical spacer placement

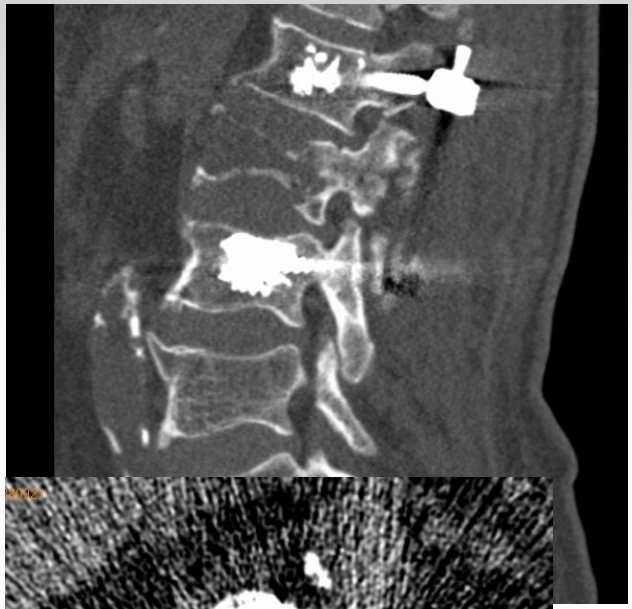




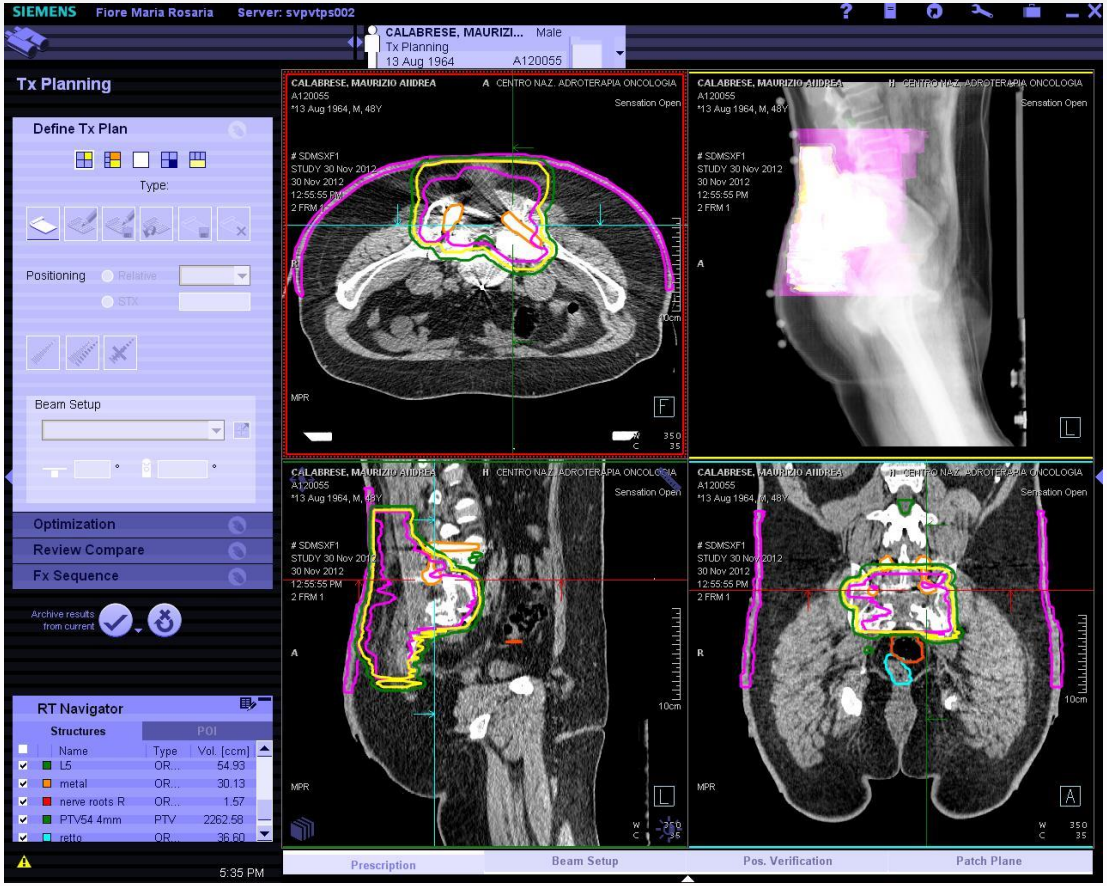
With spacer: dotted lines
W/out spacer: continous lines
Green lines: digestive tract

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

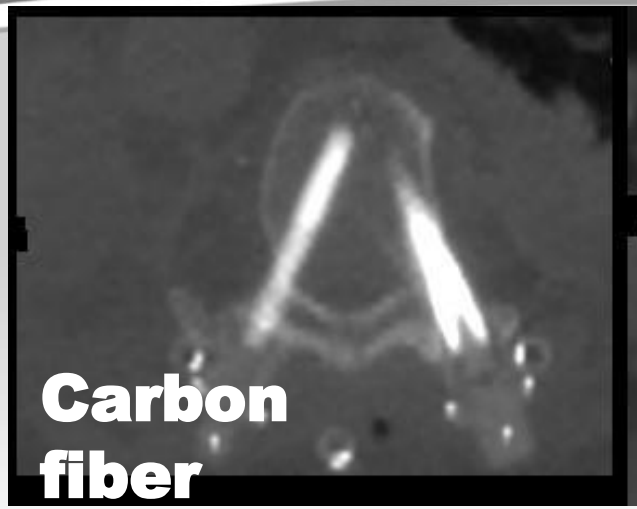
Artifacts

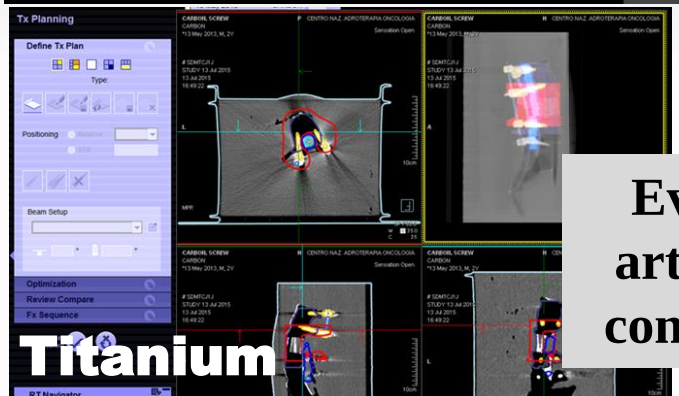


Uncertainties in the definition of volumes and greater uncertainty in the dose distribution

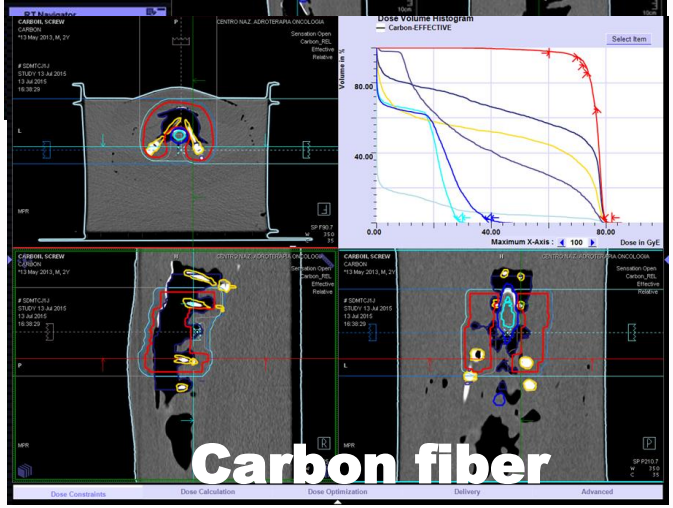


New implants in titanium/ carbon fiber

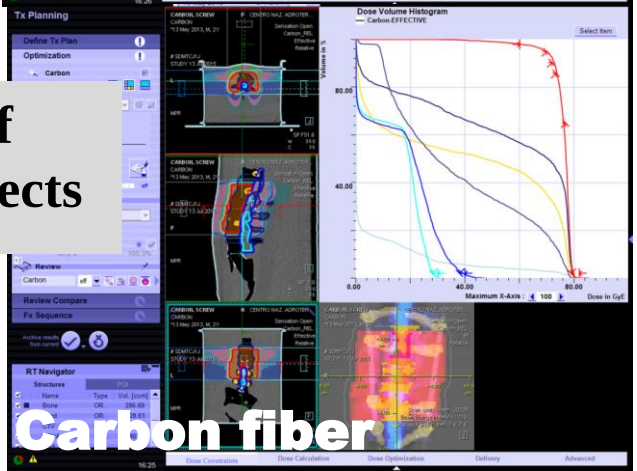




Evaluation of imaging artefacts and impact on contouring uncertainties



Evaluation of interference effects



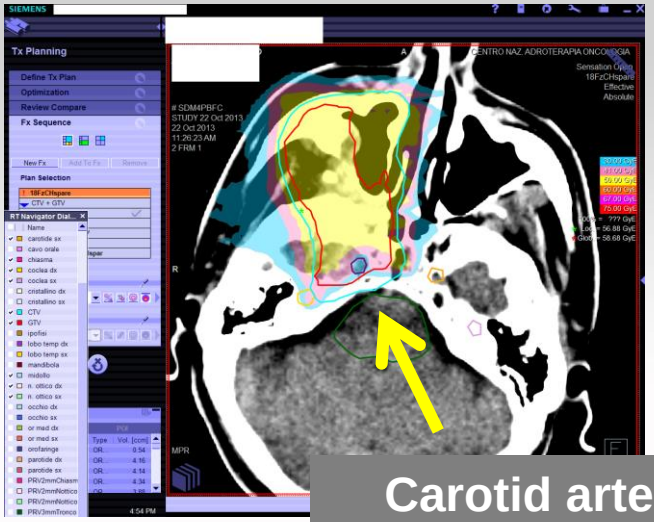
Reirradiation: 80 patients

- 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)

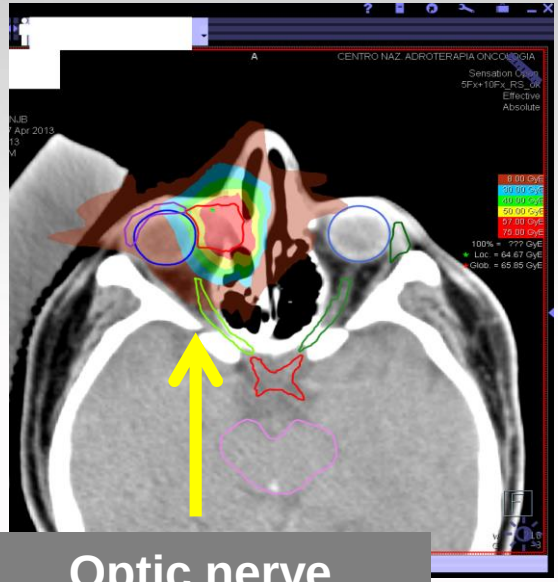
Mean time to reirradiation: 56 months (range 7 – 216 months)

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

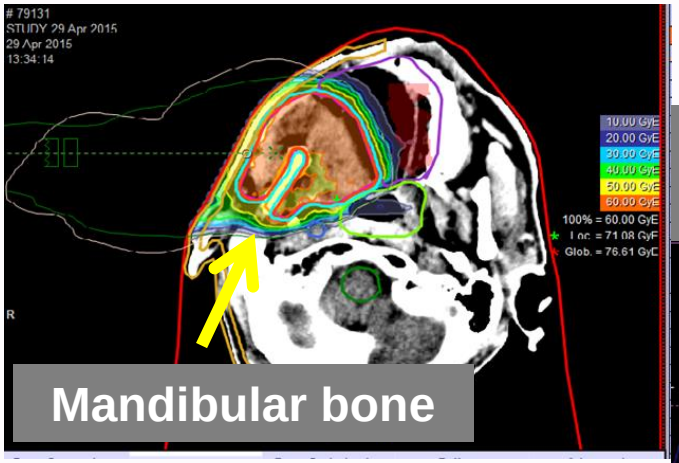
Main Goal: OARs Sparing



Carotid artery

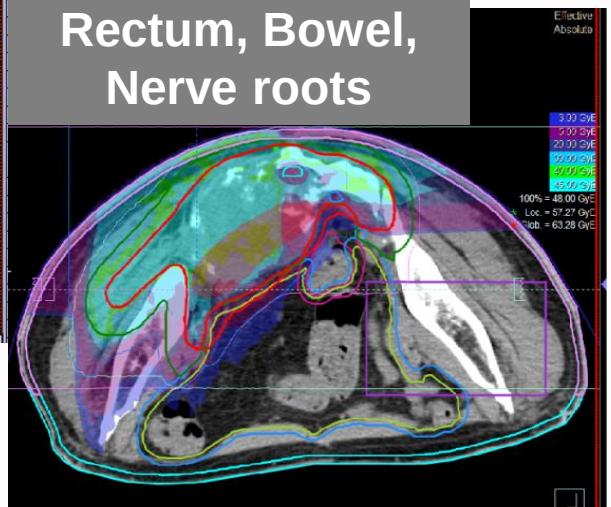


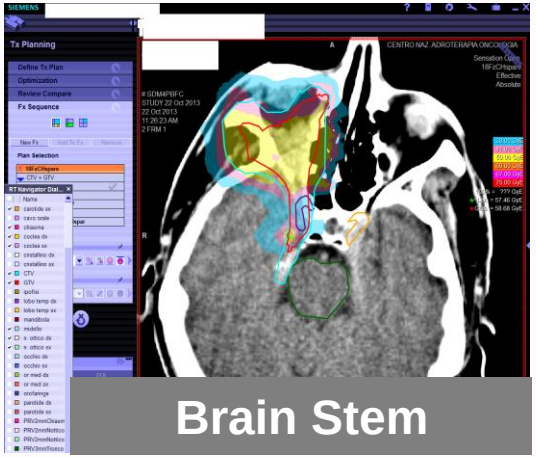
Optic nerve



Mandibular bone

Rectum, Bowel, Nerve roots

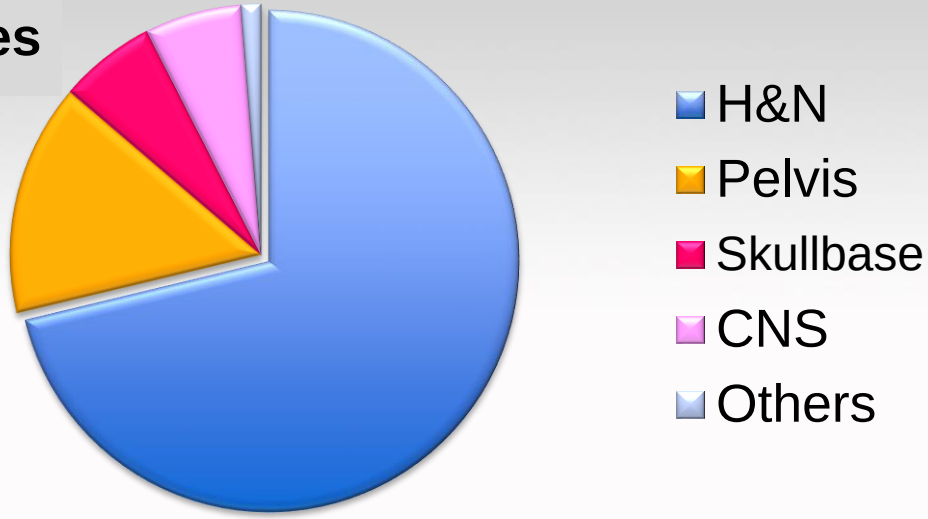




Brain Stem

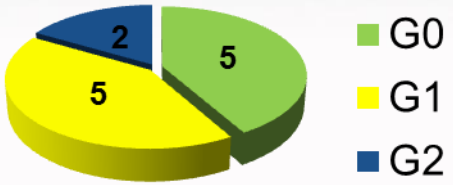
Reirradiation. Results

Cases

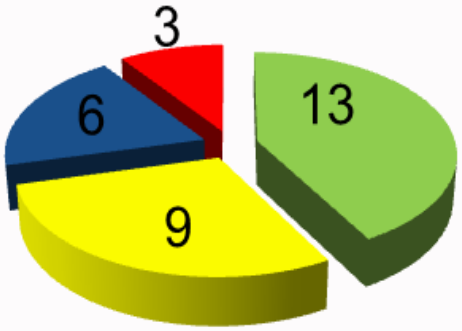


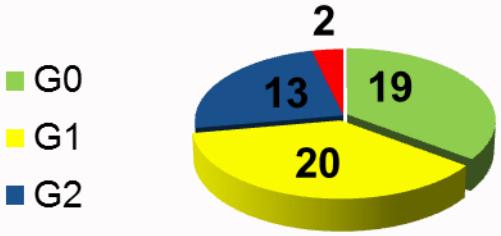
Acute toxicity

Pelvis



Late toxicity (overall)

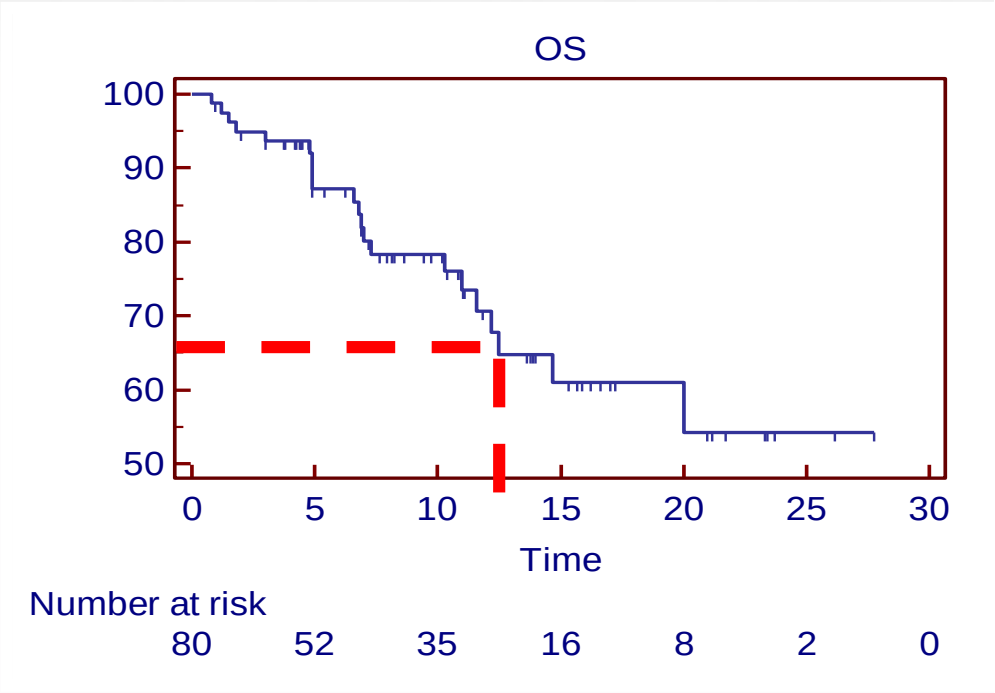




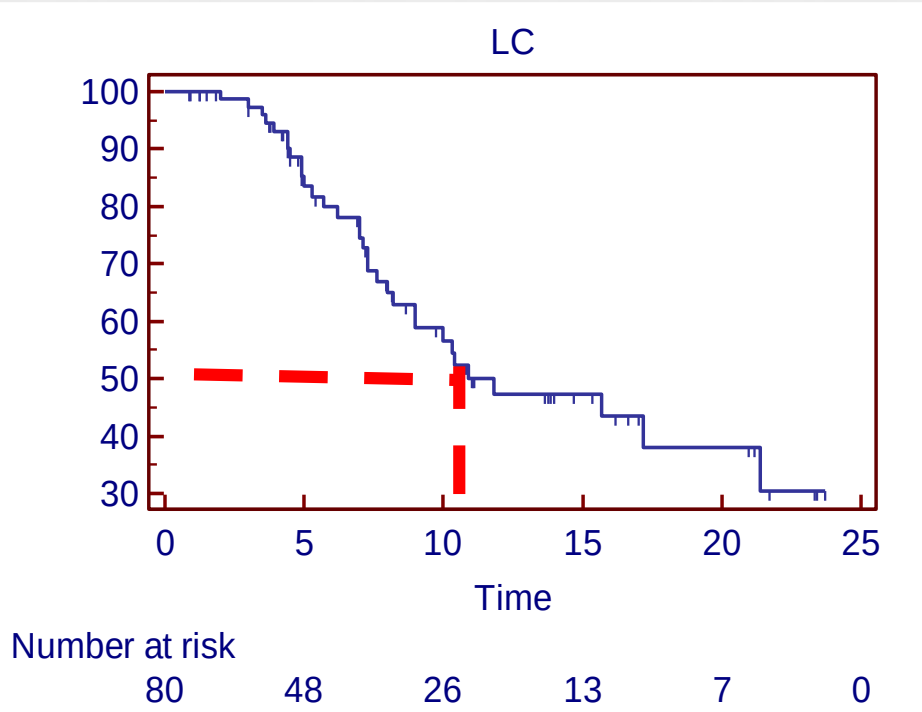
H & N

Reirradiation. Results

1y OS 65%



1y LC 50%



And in the next future .....

- Further improvement in NIRS/CNAO conversion RBE dose model
- Radiobiology
- Eye melanoma treatment
- Moving target treatment

Monte Carlo (MC) calculation

Case description				Absorbed Dose					RBE-weighted Dose			
					CTV $D_{abs\|50\%}$ ratio (%)					CTV $D_{RBE\|50\%}$ ratio (%)		
	Energy (MeV/u)	SOBP (mm)		D_{abs} (%)	MC&LEM I	CNAO A	CNAO B		D_{RBE} (%)	MC&LEM I	CNAO A	CNAO B
SOBP	290	60		0.2±0.2								
SOBP	400	70		1.7±0.1								
Prostate AdC (3.6 Gy $(RBE)_{NIRS}$	400	70		1.1±1.1	-1.3	-21.7	-3.2		14.8±2.6	14.5	0.3	15.6
	400	70		1.1±1.2	-0.6	-19.1	-2.5		15.6±2.4	14.8	0.3	15.6
Head (ACC) 4 Gy $(RBE)_{NIRS}$	290	80		2.4±5.5	-1.8	-13.2	0.0		11.7±2.7	12.0	2.0	12.2
Head (Sq CC) 4 Gy $(RBE)_{NIRS}$	290	70		2.4±2.8	-1.8	-14.7	-0.6		9.1±3.7	10.0	-0.5	9.5
Pancreas AdC (4.6 Gy $(RBE)_{NIRS}$	400	70		1.6±1.5	-2.0	-12.9	-5		5.9±2.5	5.2	0.0	4.3
	400	90		1.5±1.6	-2.4	-13.2	-3.9		7.8±1.0	5.9	0.0	4.3
	400	80		1.3±1.1	-2.5	-10.4	-4		6.5±2.8	4.8	0.7	5.0

NIRS beamline was simulated with a MC code. CT scan, structure set, plan and dose files of treatments at NIRS wre exported in DICOM format, for 3.6, 4, and 4.6 Gy (REB) per fraction nominal prescription dose. MC code was interfaced with LEM I to calculate, according different RBE models, the NIRS physical dose

Radiobiology activities

The main topics for the radiobiological research in CNAO comprise tissue, cell and molecular experimental activities aiming to investigate the mechanisms of response after particle irradiation.

- ✓**Mechanisms of radioresistance**
- ✓**Healthy tissues and microenvironment response**
- ✓**Effects of existing and/or new radiosensitising agents with high LET radiations**
- ✓**Low doses effects**
- ✓**…**

<u>Collaboration with INFN radiobiology groups</u>

(MI, NA, ISS, PV, Roma3, LNL) (continue…)

INFN-founded Research project 2015-2017

ETHICS

Pre-clinical experimental and theoretical studies to improve treatment and protection by charged particles

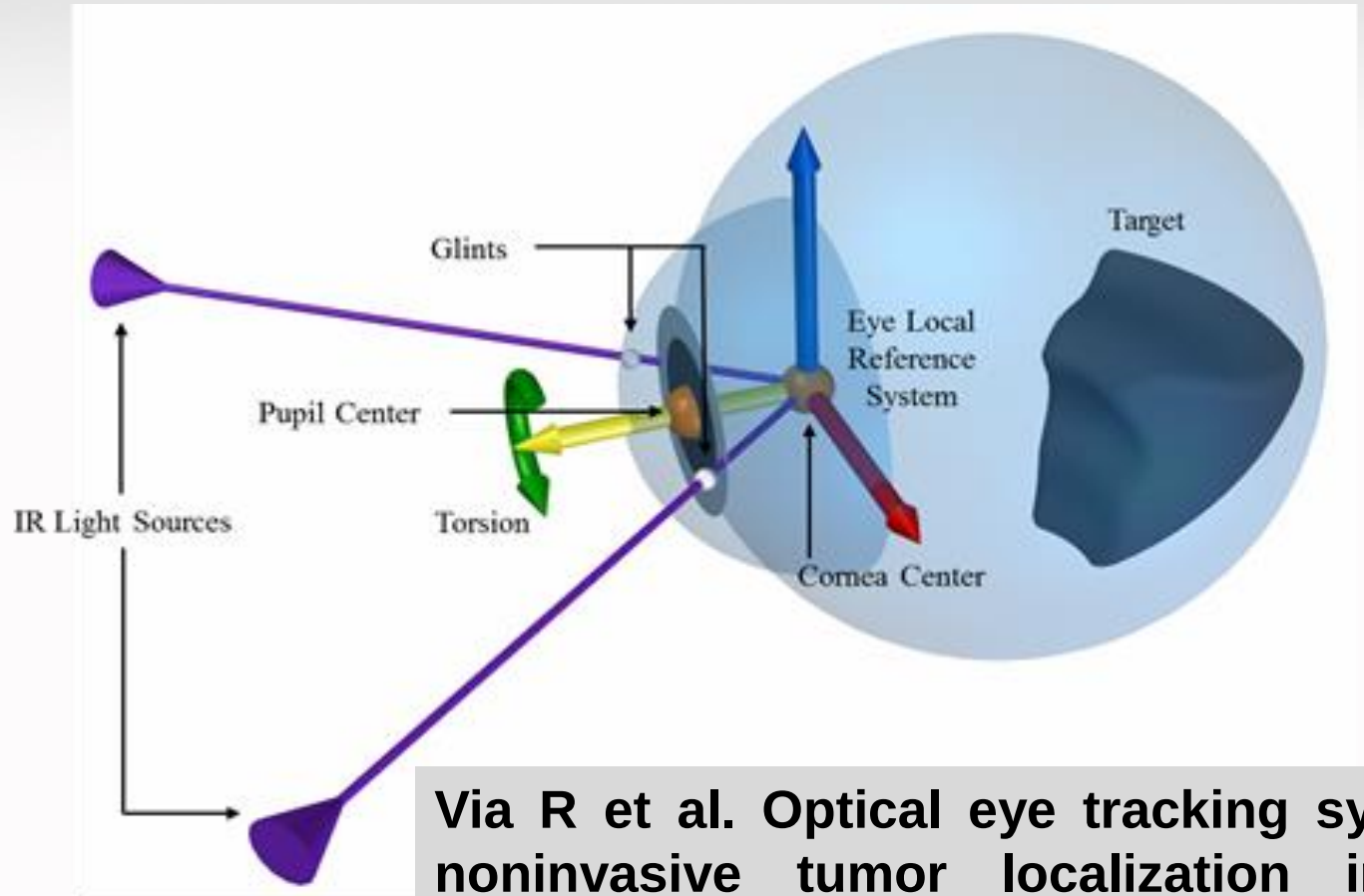
Understanding the underlying action mechanisms on normal cells by charged particles used in medicine to reduce the risks for human health

→ **The experimental activity of the CNAO Unit within the WP-1 will be dedicated to the evaluation of the effects of sublethal doses of different radiation qualities on the stroma mechanisms regulating cell adhesion and migration (risk of metastasis).**

→ ***Effects of paracrine diffusible factors secreted by fibroblasts irradiated with varying radiation quality on the adhesion, proliferation, migration and invasion of pancreatic cancer cells***

C Mosci et al. Proton beam radiotherapy of uveal melanoma: Italian patients treated in Nice, France.

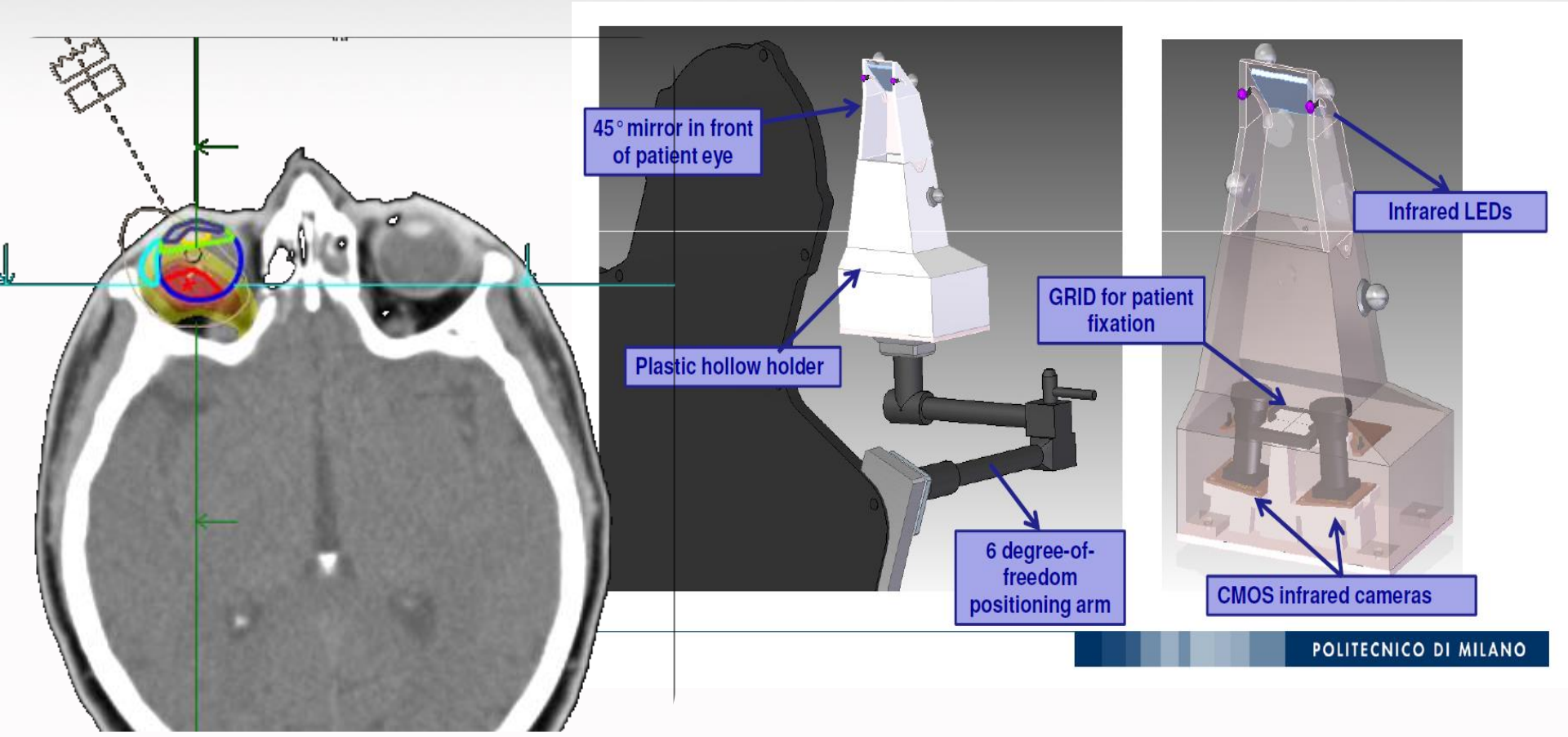
Eur J Ophthalmol 2009; 19(4): 654 - 660



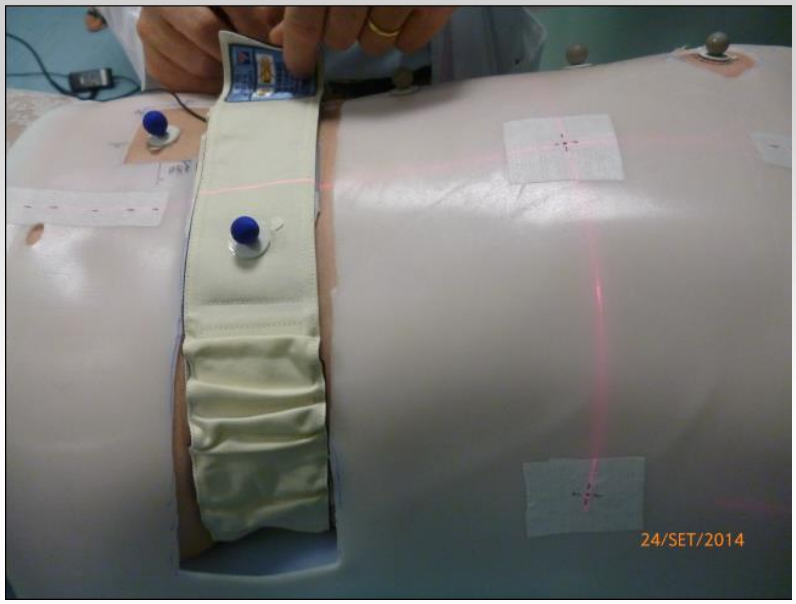
Schematic representation of the eye tracking method. The glints and the pupil center are recognized on the calibrated camera images and their 3D position is calculated through triangulation. The 3D cornea center is localized at the intersection of the virtual lines connecting each IR light sources and its respective glints. An eye local reference system is created starting from the optic axis that connects pupil and cornea centers. The assessed eye torsion is then taken into account by rotating the local axes around the optic axis. The coordinates of the target with respect to the eye local reference system are estimated during treatment planning.

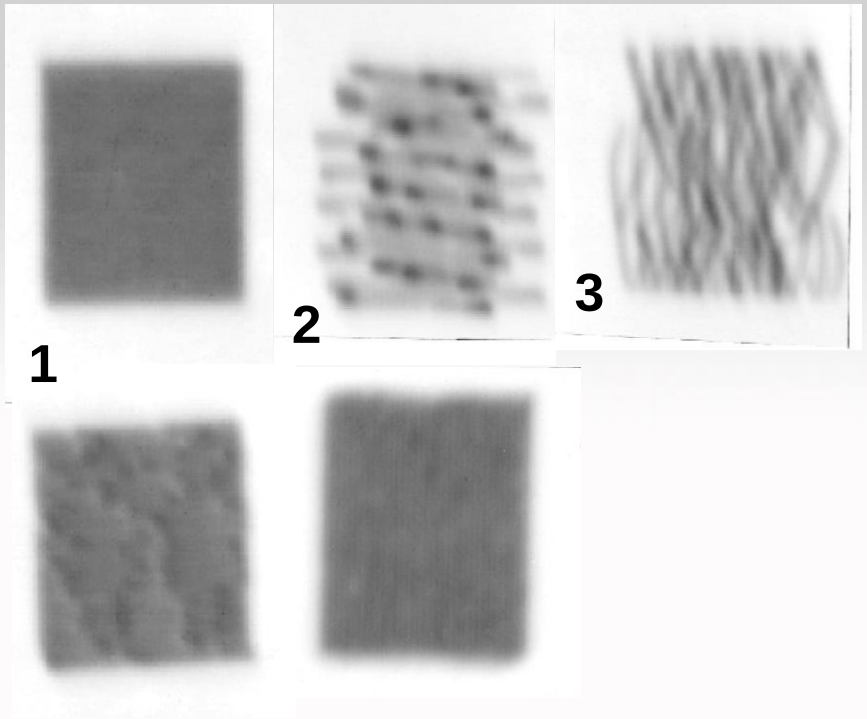
Via R et al. Optical eye tracking system for real-time noninvasive tumor localization in external beam radiotherapy. Med Phys 2015 May;42(5): 2194-202.

Non invasive eye tracking system for intraocular tumor localization in proton therapy treatment



4D Moving organs treatment

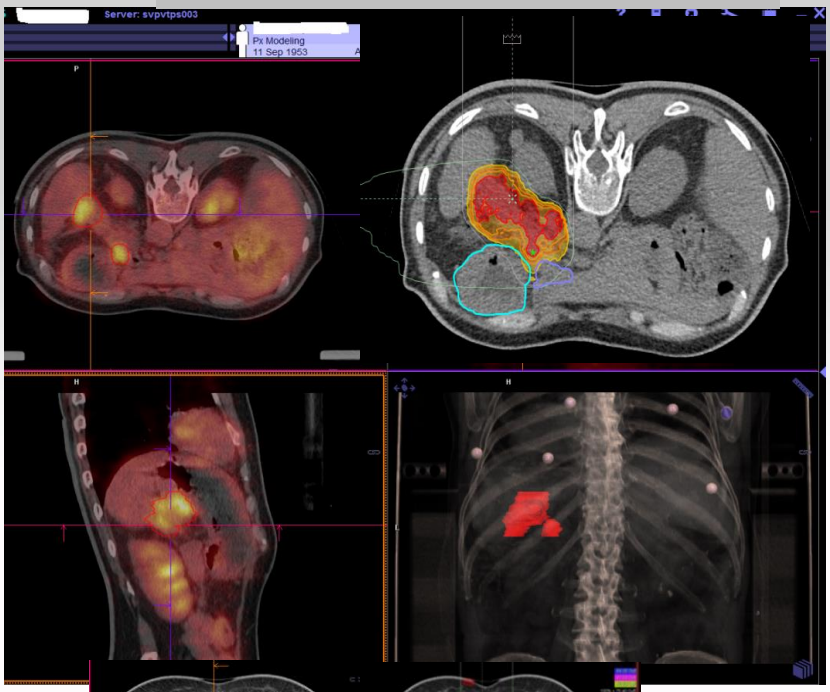




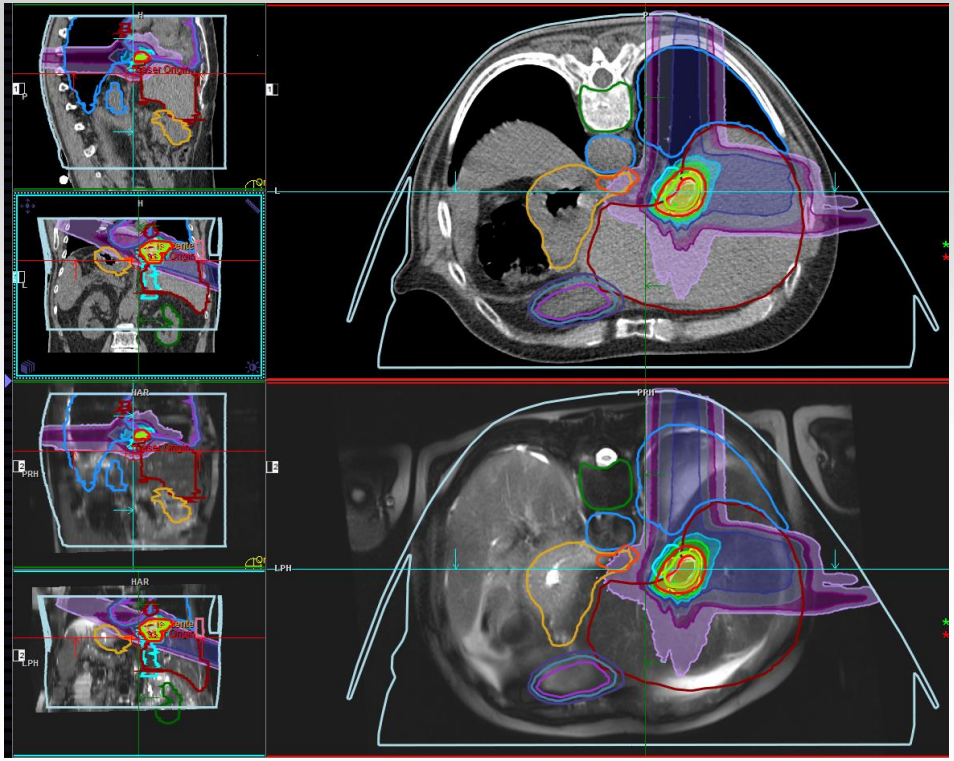
4 gating 5 rescanning

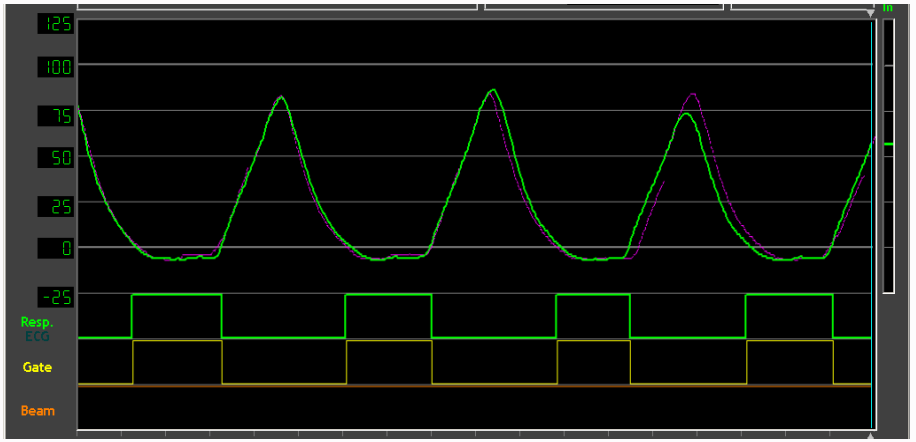
- Reducing respiratory motion (less than 5 mm) using thermo-plastic mask or compression band
- Multiple fields (2-3) and fractionated treatment
- Gating (reference phase: max expiratory. Anzai system and OTS) + rescanning (N = 5)

Pancreatic cancer

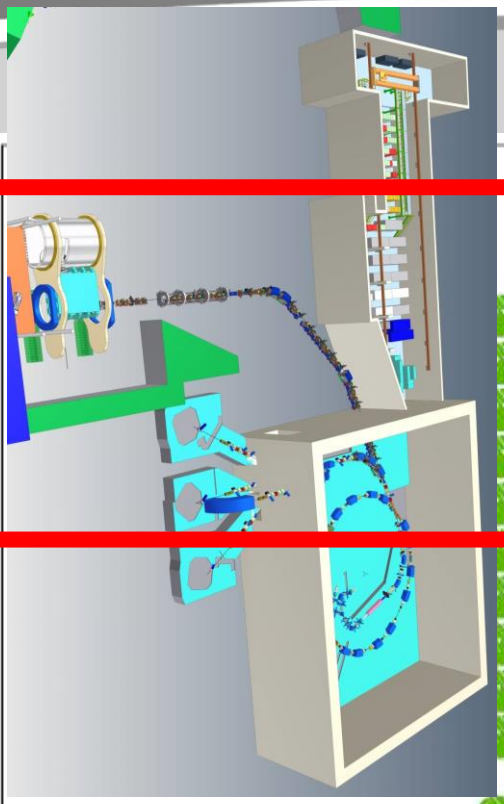


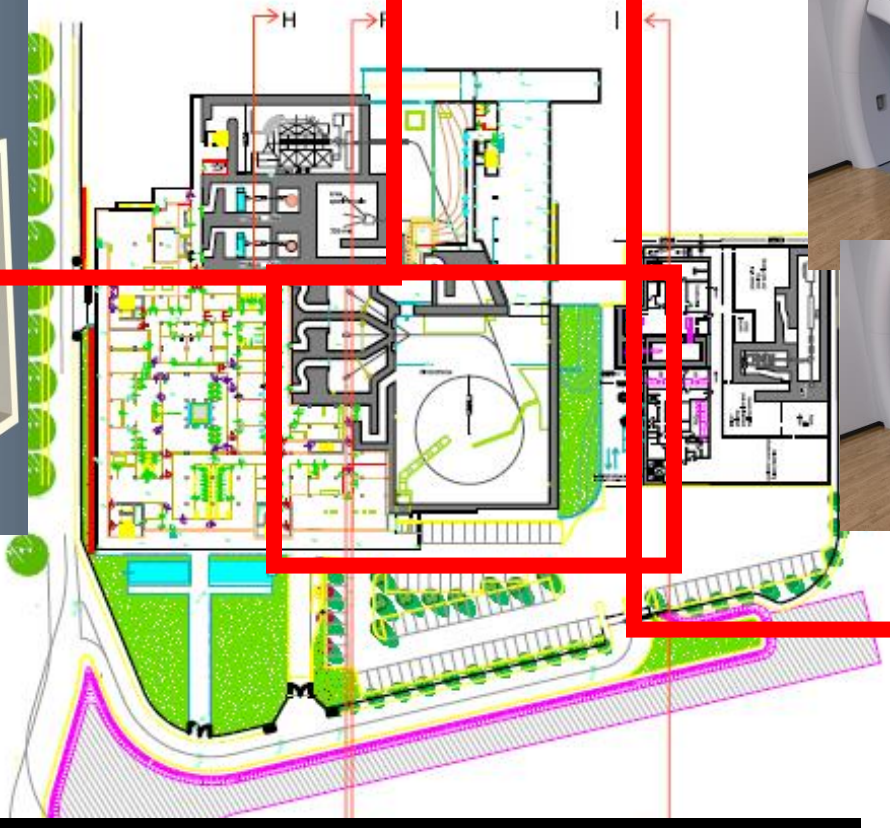
Liver cancer

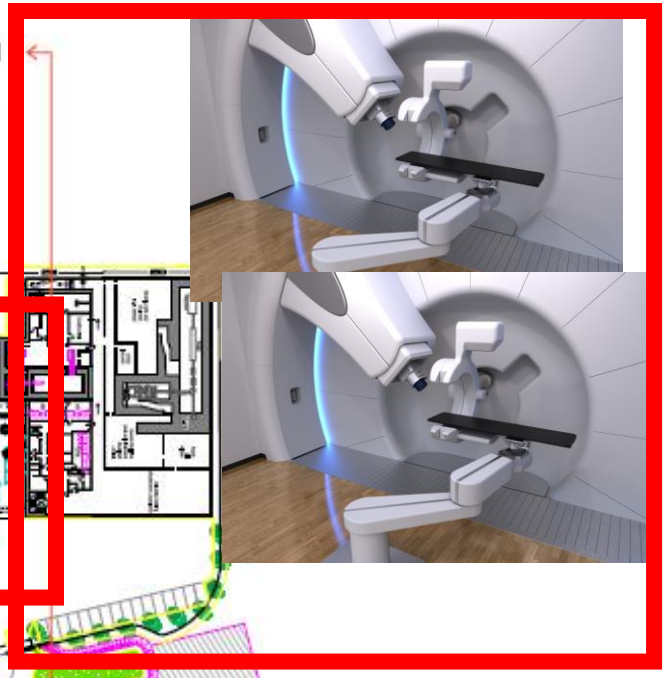




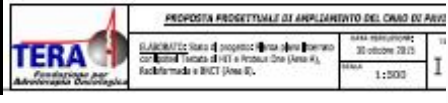
Angiosarcoma







A dream……,
but we are now working to realize



Thank you very much !!!!!!

And a happy New Year to all of you from the CNAO team