ACCELERATING INNOVATION ... IN MEDICINE

CERN, Geneva
20th November 2014

Particles that fight cancer: The use of protons and carbon ions in cancer therapy

Roberto Orecchia
Chair of Radiation Oncology at the University of Milan
Scientific Director at European Institute of Oncology in Milan and at The National Centre of Oncological Hadrontherapy in Pavia

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

International Agency for Research on Cancer, Lyon, 2012

12.7 million new cases per year wordlwide

7.6 million deaths

63% of deaths in developing countries

Numbers of RT Treatments

30 years ago: less than 40% of patients with cancer

15 years ago: more than 50%

Today: about 65%

RT contributes towards 40% of curative treatment

Only 5% of the total cost of cancer care

The Future of Radiation Therapy……,

JCO 2010

Expected Patients from 2010 to 2020 (+ 22%)

Prostate + 35%

Stomach + 27%

Liver + 26%

Pancreas + 25%

Lung + 25%

Breast + 15%

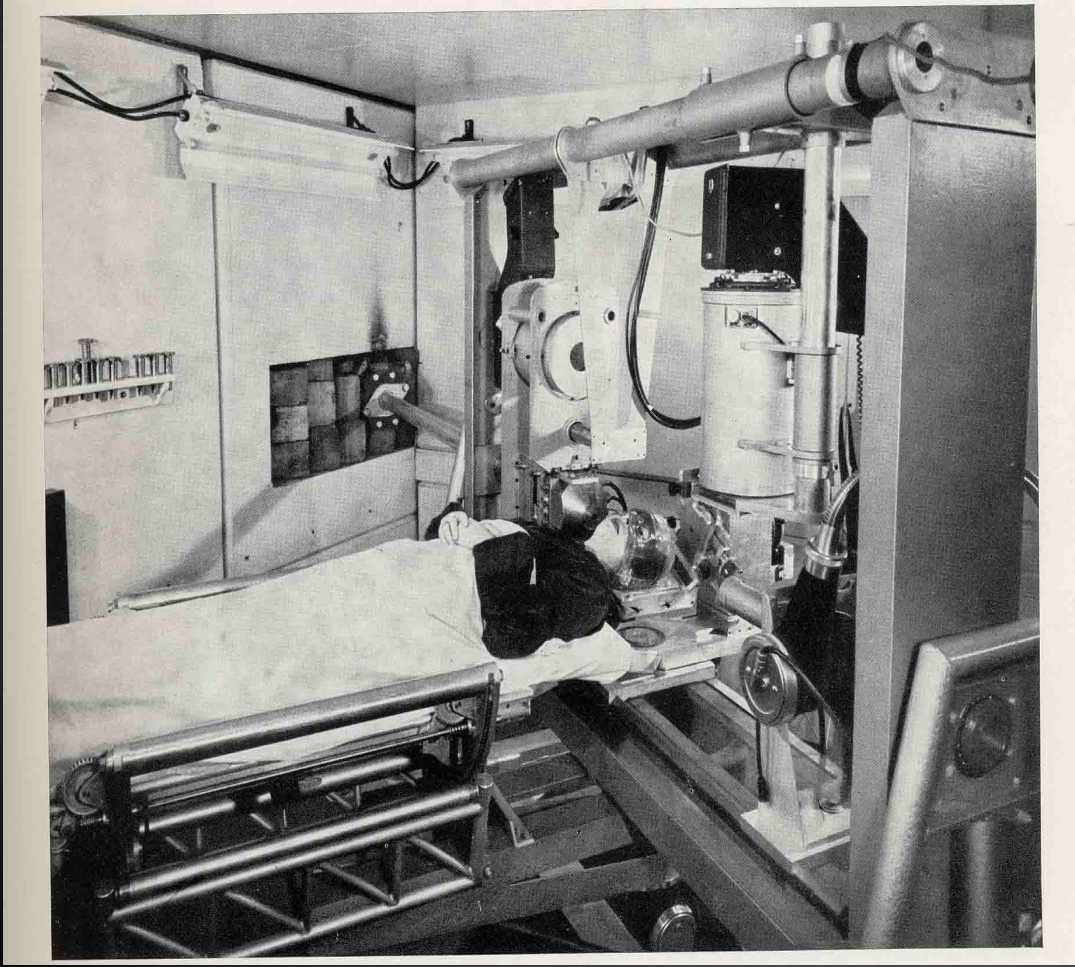
Improvment in Technology

Improvment in Dose Distribution

Coutard: daily fractions lasting 2-3 hours on regimen lasting 4-6 weeks

Baclesse: daily doses of 200R (1.8 Gy) given over 10 minutes using regimens of up to 4 months

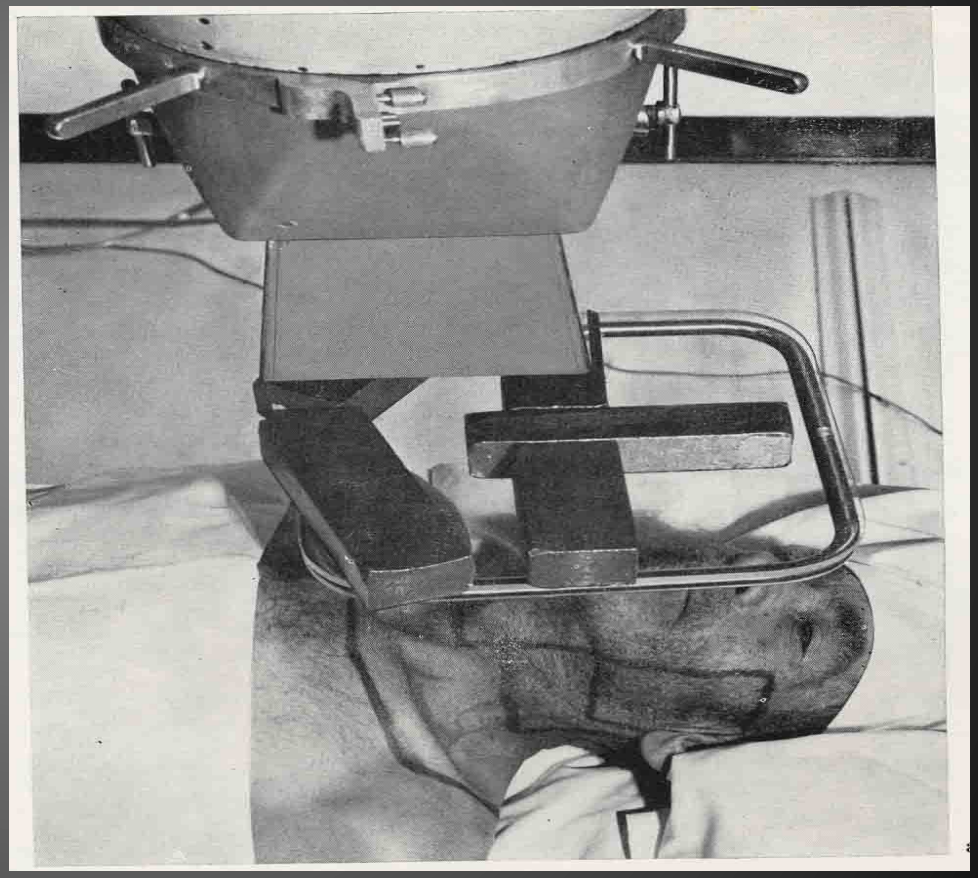
The Early 1920s



Once more reliable equipment became available, single fraction treatments were tried, with German speakers more in favour of massive single dose, **"Terapia Magna Sterilans"** and Francophones delivering **"Fractionated treatment"**

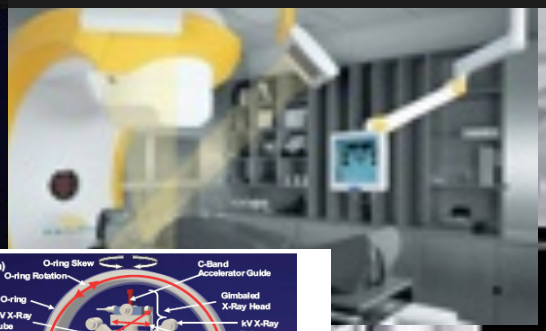
G Fletcher since1948

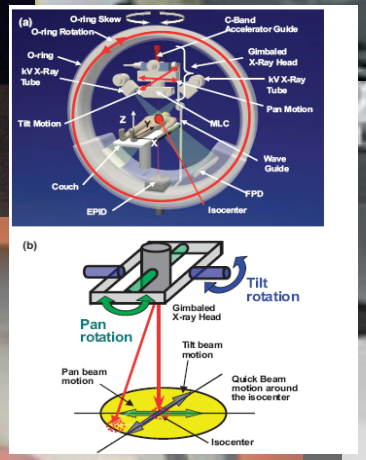
As a results of his influence and teaching there is a belief amongst radiation oncologists in the USA that to treat using fewer than 30 fractions is inherently dangerous

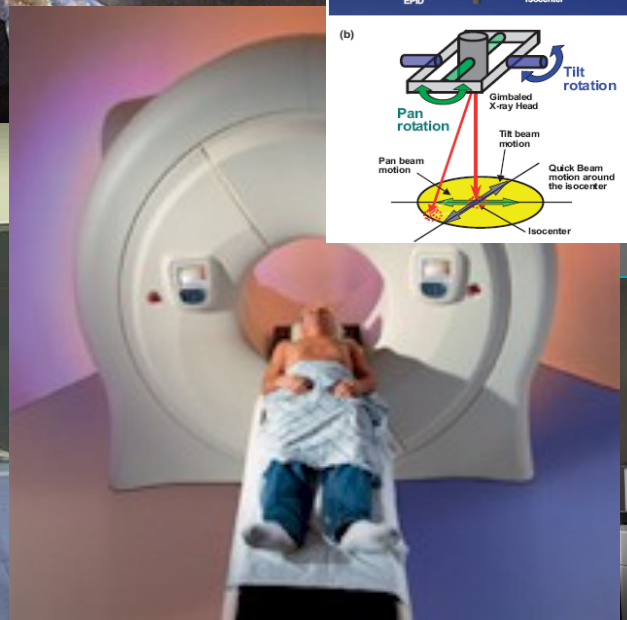


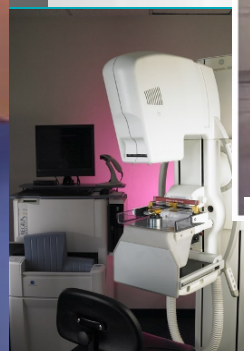

2000's
Tomotherapy
IMRT
ConeBeam CT
Respiratory
Management
VMAT
CyberKnife
IGRT
DART
Body
RadioSurgery
Trilogy
Etc...

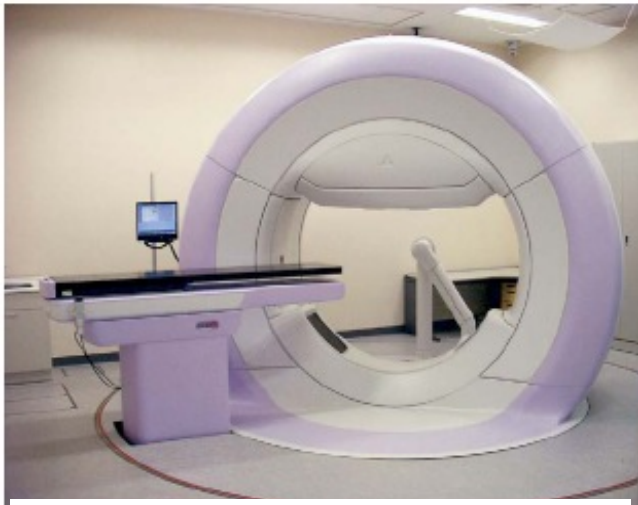
High Tecnology & IGRT/IMRT/SRT





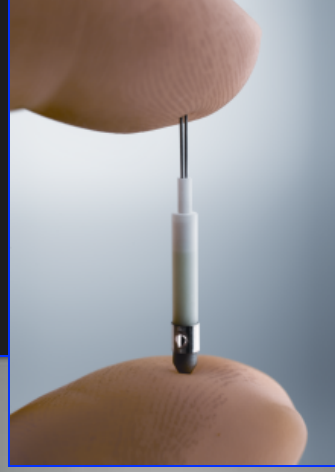


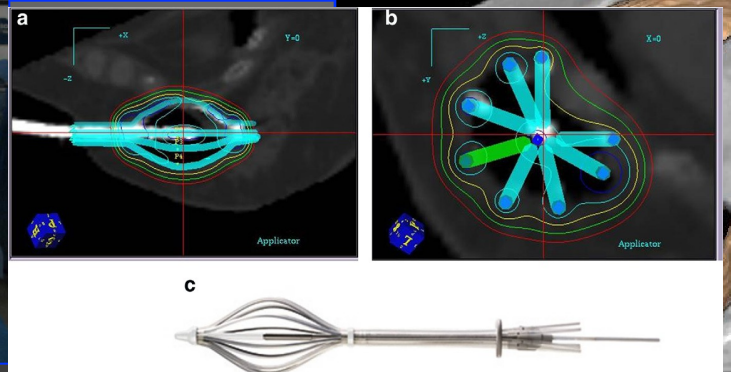


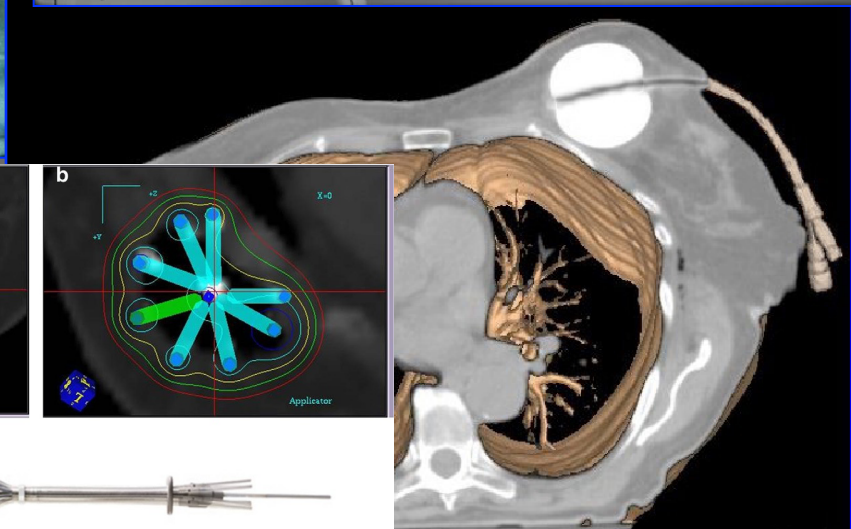


IEO
Arc Advanced Radiotherapy Center

High Tecnology & BRT







IEO
Arc Advanced Radiotherapy Center

Our goal ....

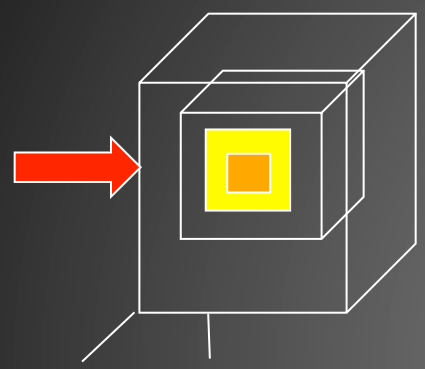
Dose Distibution ?

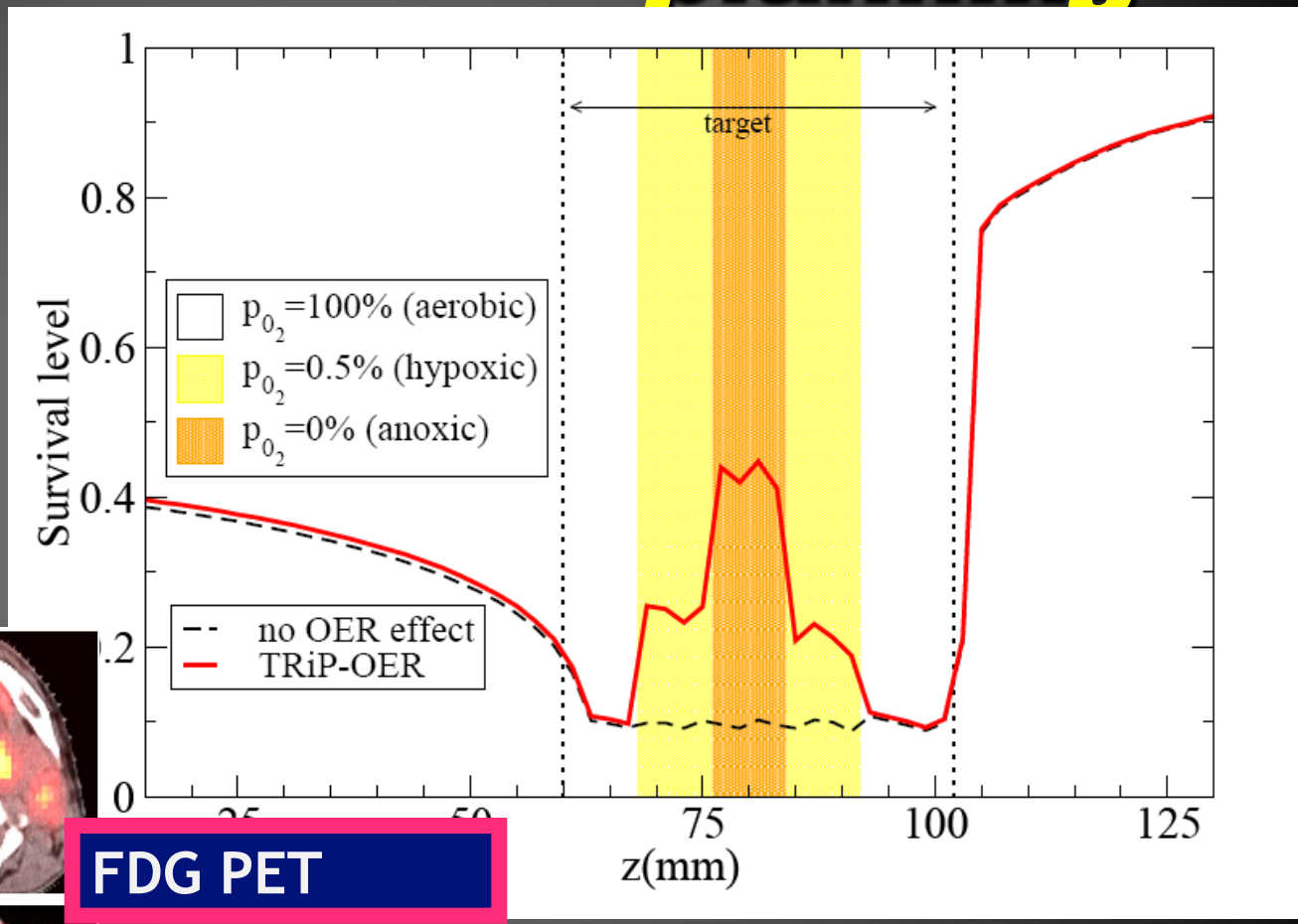
Is not a clinical issue

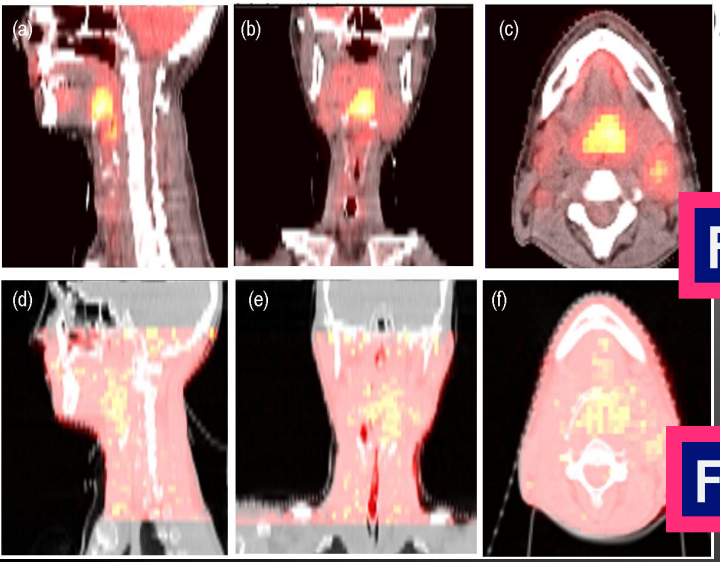
but

It's the condition necessary to improve clinical outcomes

Adaptive treatment planning







FDG PET

FMiso PET

Scifoni et al, GS Rep.2010
Santiago A. ULICE Rep 2011

Improved Dose Distribution

filrouge

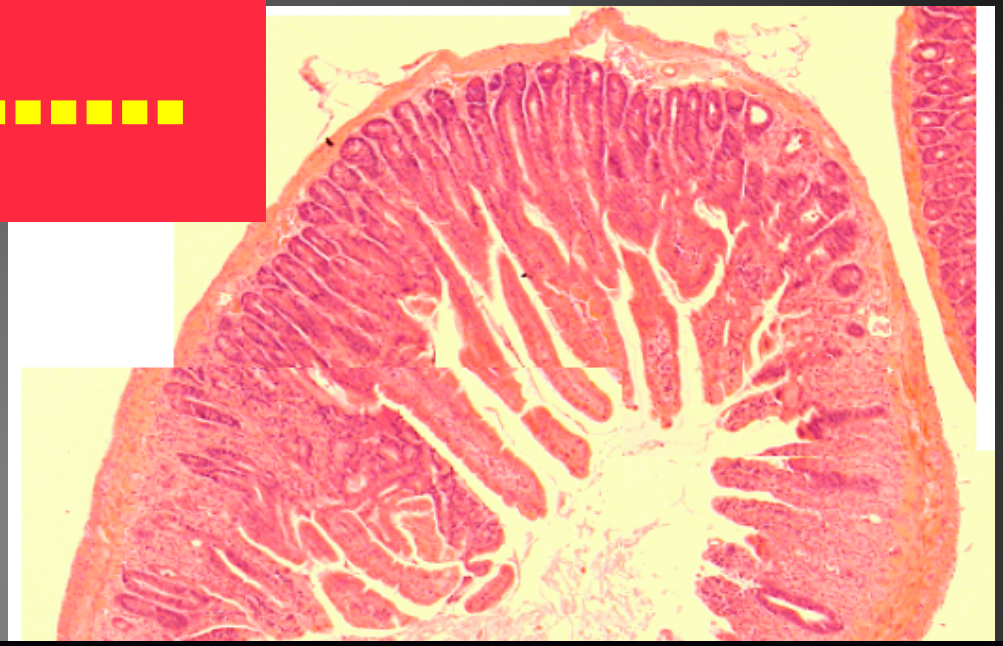
Technology

Smaller volume + Higher dose =

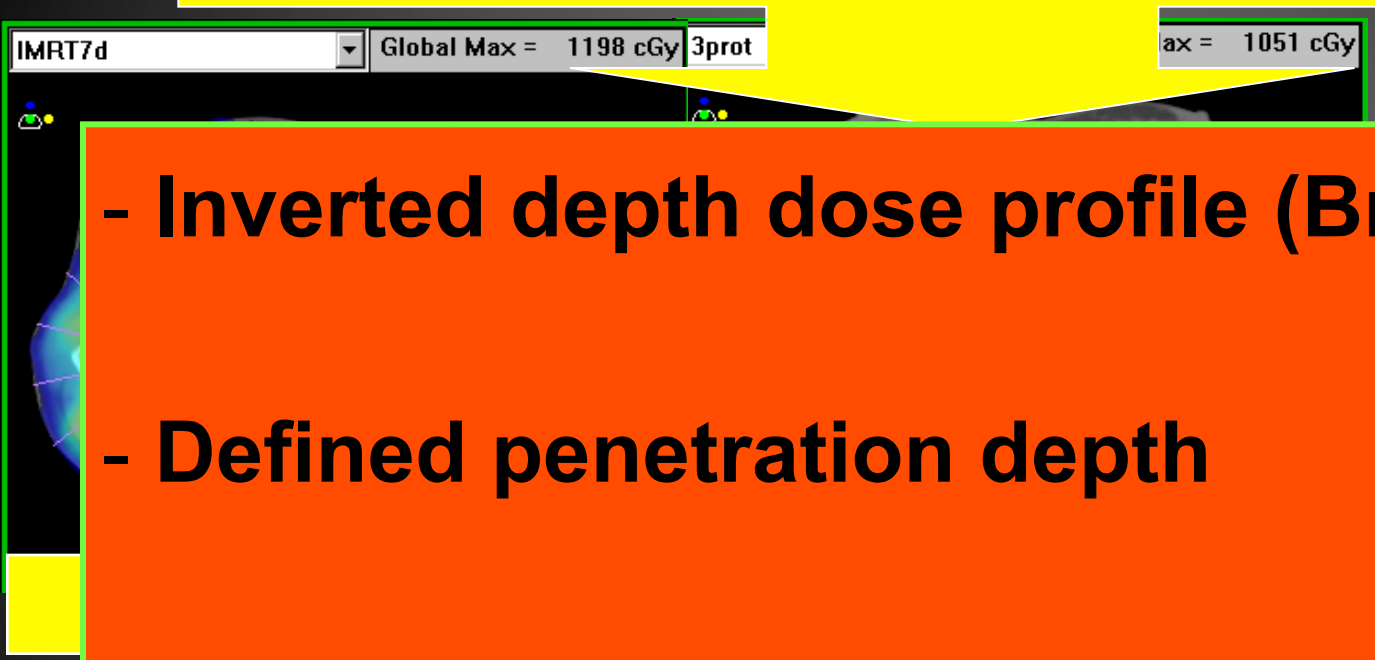
Inverse Square Law

- > LC & Survival
- < Toxicity
- Shorter treatment
-

Hadrons. A new dimension .....



Physical Selectivity



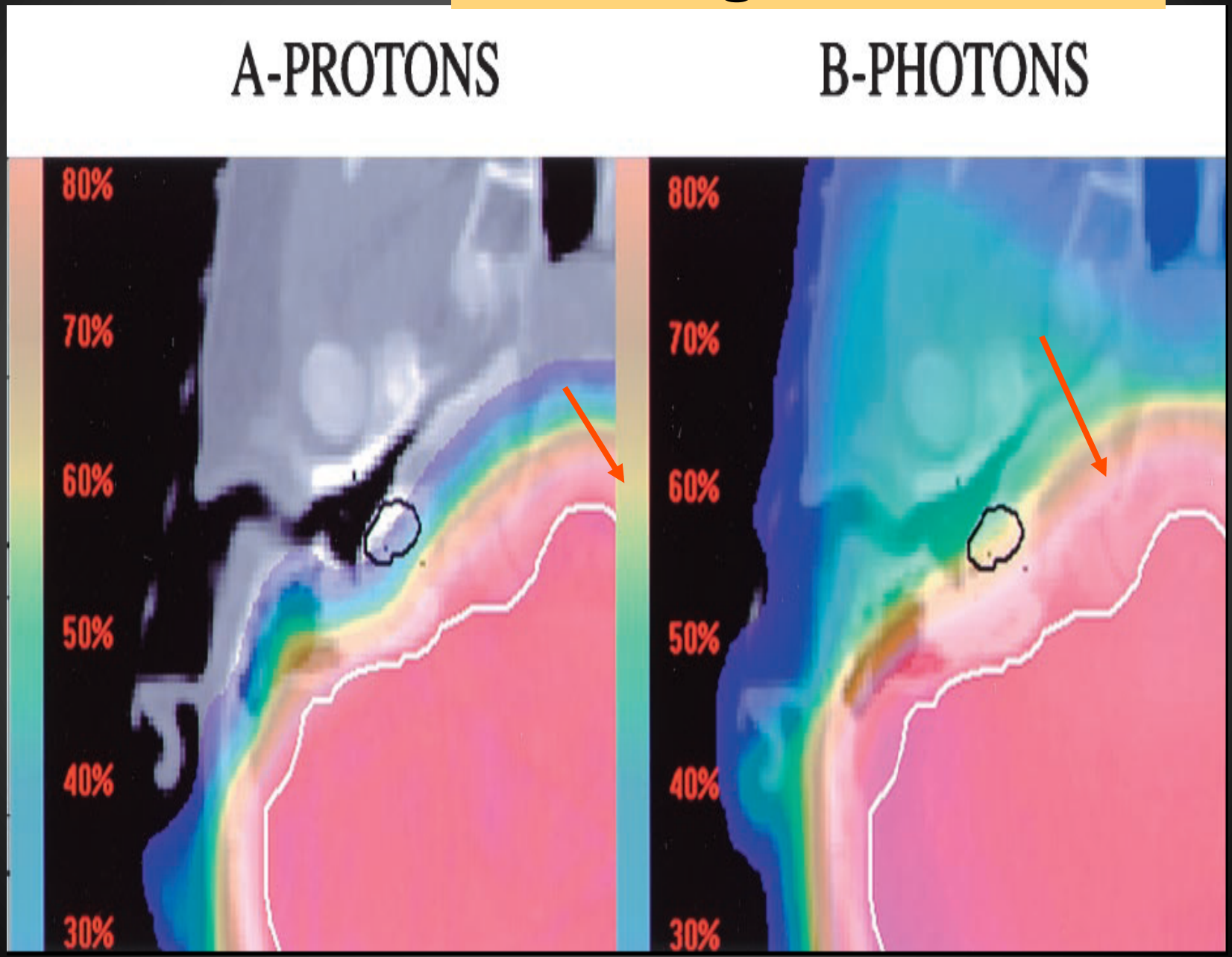
- Inverted depth dose profile (Bragg peak)

- Defined penetration depth

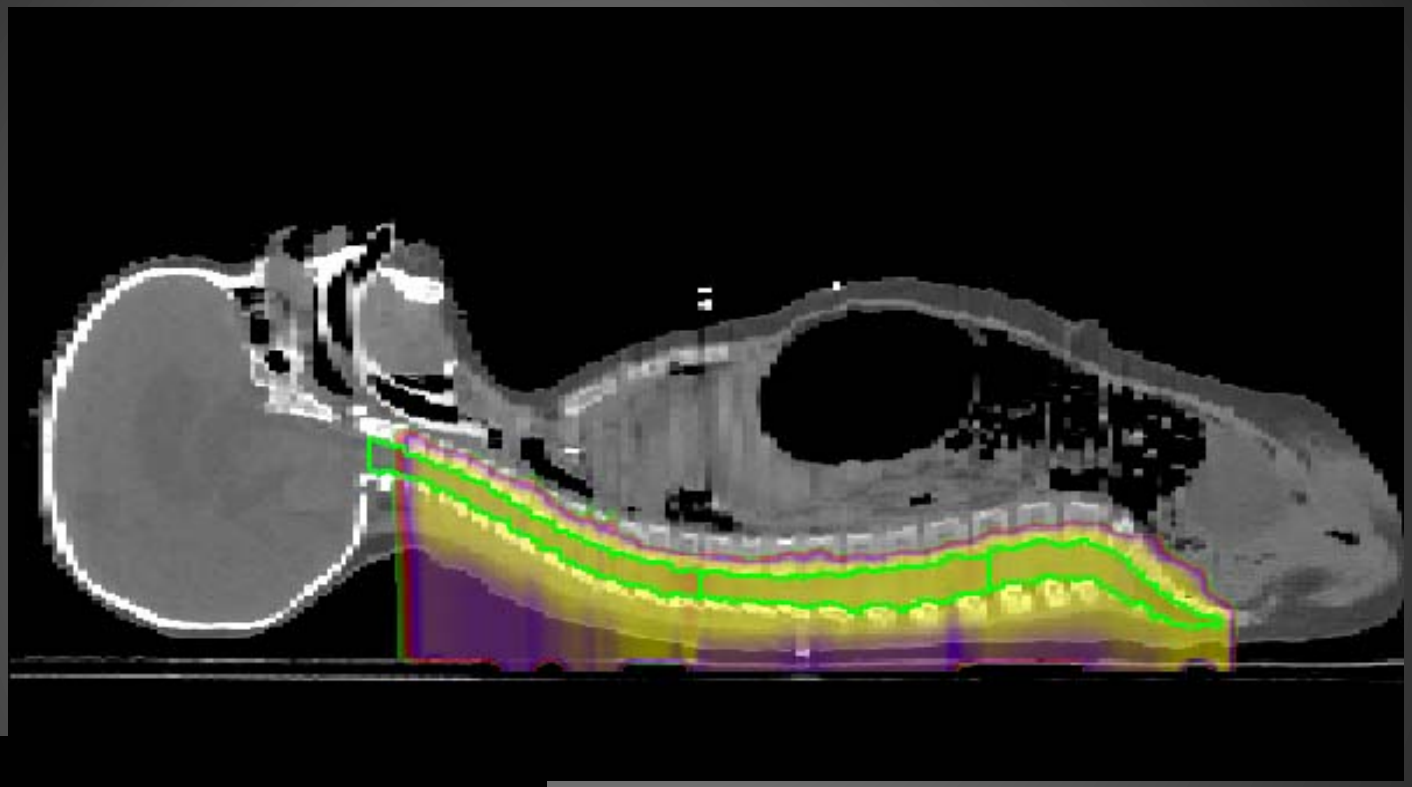
- Less lateral scattering ($_1H \neq C_{12}$)

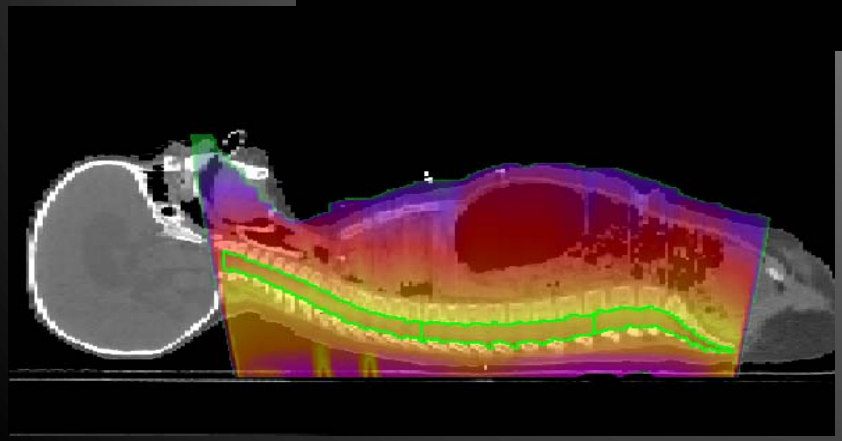
- Reduction of integral dose

Advantage of Hadrons



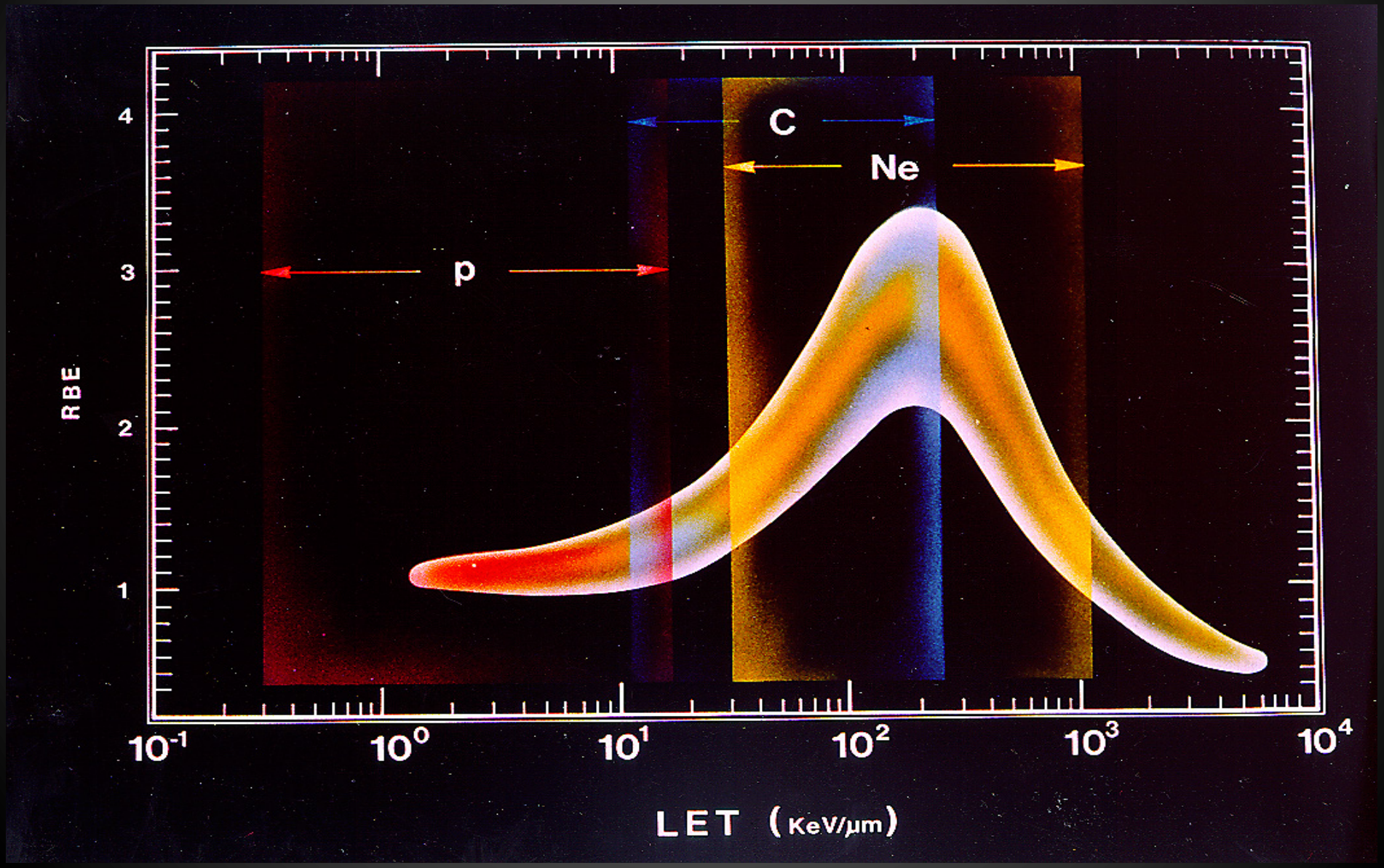
Protons in pediatric tumors





Protons

Radiobiology of particles



Which tumors might benefit of high LET particles?

Radioresistant for genetic alteration

- Up-regulated oncogenes
- Mutated tumor suppresor genes
- Dis-regulated apoptosis

Radioresistant for intratumoral micromilieau

- Deprivation of oxigen
- Up-regulated defense system
- High angiogenetic potential

Radioresistant for proliferation status

- High content of quiescent cell clones
- Slow proliferation activity

Some numbers .....

www.ptcog.psi.ch,

122,499 treated patients

-105,743 with p+, mainly in USA, 53,532

Loma Linda 17,829, Boston (NPTC) 7,345

- 13,119 with C-12, mainly in Japan, 10,993

Nirs (Chiba) 8,073, HIT (Heidelberg) 1,368

+ 46,000 in the past 5 years

≈ 10,000 patients per year

Some numbers .....

(www.ptcog.psi.ch)

42 centres with protons

(USA 14, Europe 12, Japan 8, ...)

6 centres with carbon ions

(Japan 3, Europe 2, China 1)

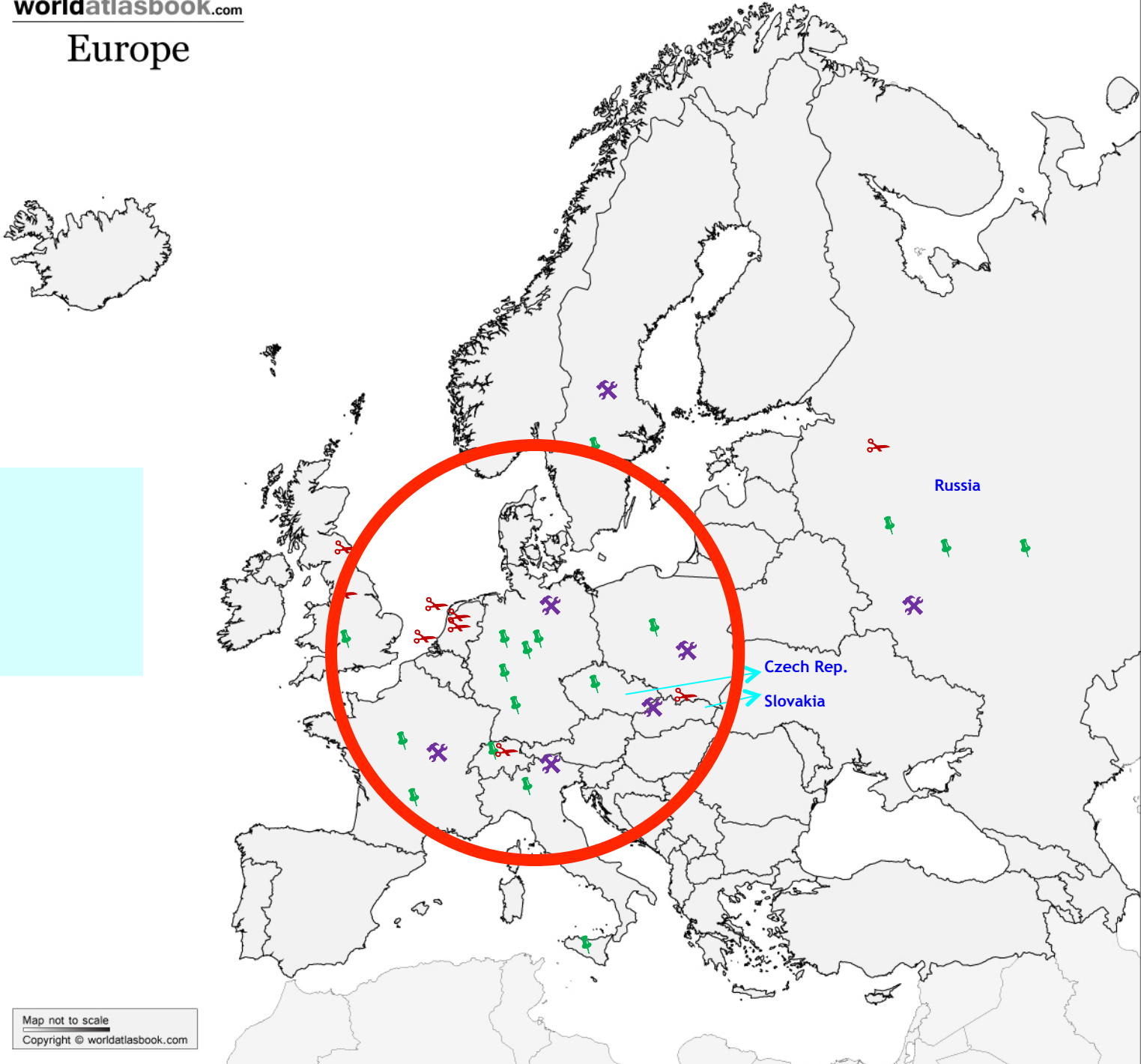
of these, 3 dual centres (p+ C-12)

27 new centres planned

Worldwide Access to Hadrons

worldatlasbook.com

Europe



under construction
in operation
in planning stage

Literature survey

In-silico studies

Cancer Registry

Standard

Indications

Recommends to treat

Improved

Local Control

Reduced

Side Effects

Reduced

Second Tumors

Recommends to investigate

Standard Indications

1% of RT

Eye, Pediatrics, Base of skull

Improved LC

3% of RT

Intracranial, H&N, Urologic, Lung, Sarcoma, Reirradiation

Reduced Side Effects

12% of RT

Intracranial, H&N, Urologic, Lung, Breast, GI, Lymphoma, Sarcoma, Gynecological

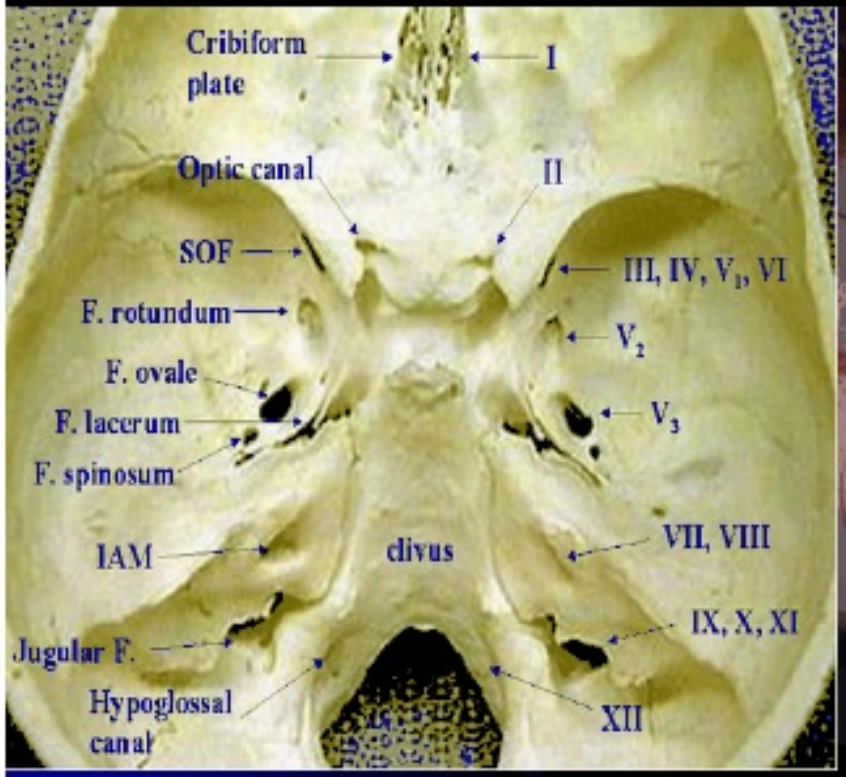
Reduced Second Tumors

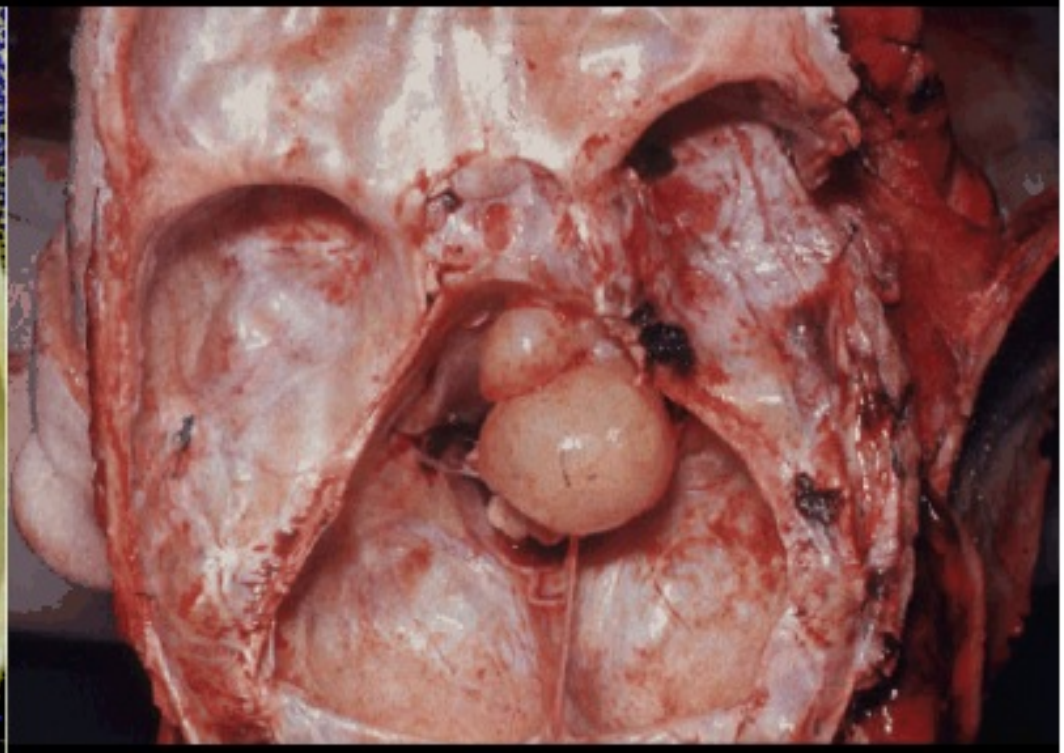
2% of RT

Breast, Lymphoma, Testis

Chordoma: Base of Skull

- Base of skull chordomas account for ~1/3 of chordomas

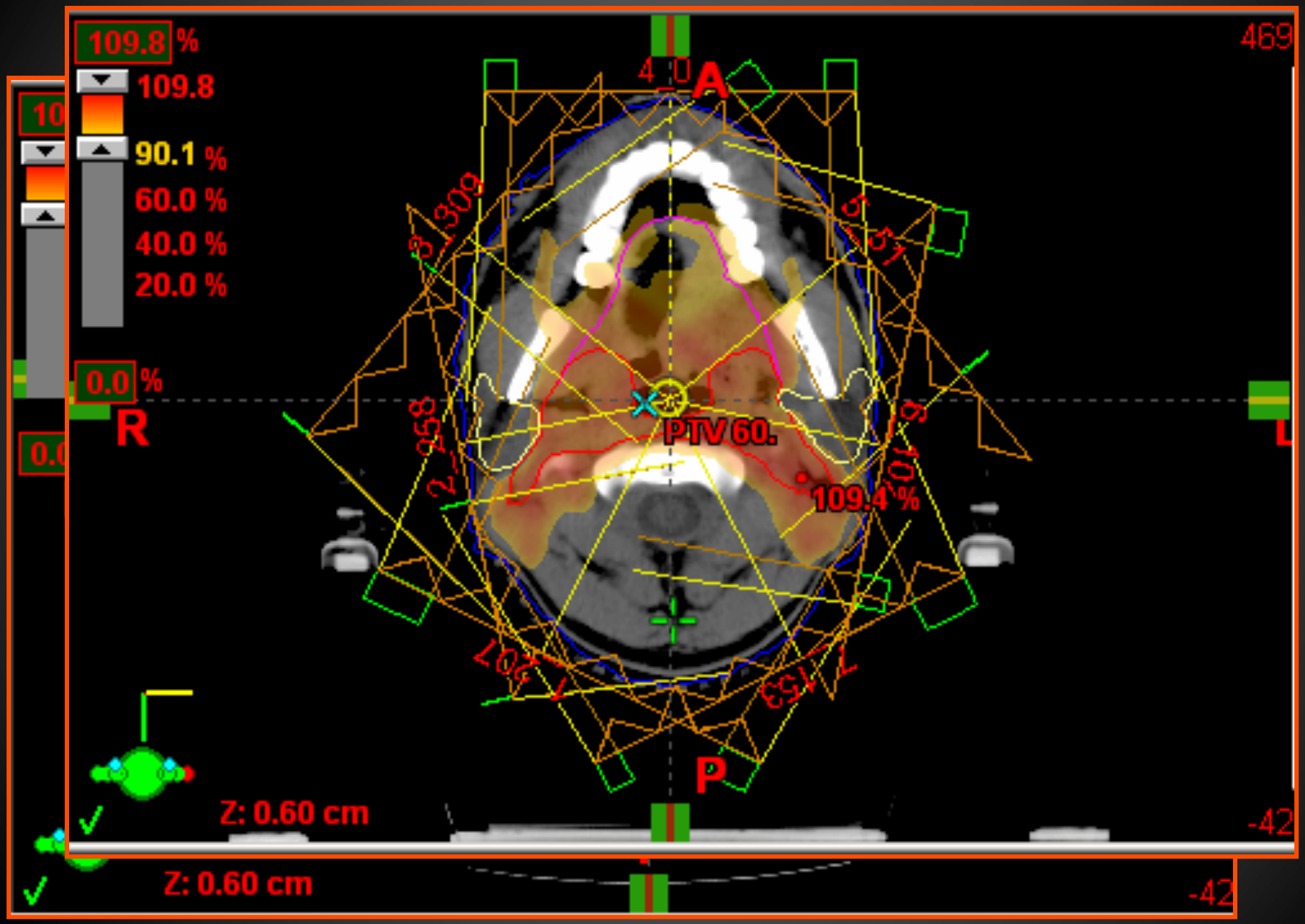




PT in Skull Base Chordomas and Chondrosarcomas

Reference	Institution	Pts	Histo-logy	RT	GTV	Dose , mean (CGE)	% LC	F-up (Months)
Hug et al, 1999	LLUMC	58	C (33) CS (25)	X+p	(9%): 0 to ≤15 mL (12%): >15 to ≤25 mL (79%): >25 Ml	71.9 (66.6-79.2)	3 yrs: 67 (C) 5 yrs: 59 5 yrs: 79 (CS)	33 (7-75)
Munzenrider et al, 1999	MGH	290 22	C	X+p	NA	72 (70 – 75.6)	5 yrs: 73 (C) 5 yrs: 98 (CS)	41 (1-254)
Igaki et al, 2004	Tsukuba	13		(8)		an 72.0 -95.0)	3 yrs: 67.1 (C) 5 yrs: 46.0	69.3 (14.6-123.4)
Noel et al, 2005	CPO	100	C	X+p	23 cm3 (1 - 125 cm3)	Median 67.0 (60.0-71.0)	2 yrs: 86 (C) 4 yrs: 53	31 (0-87)
Noel et al, 2004	CPO	26	Cs	X+p	NA	Median 67.0 (22-70)	3 yrs: 91 (CS)	34 (3-74)
Ares C et al, 2009	PSI	42	C (42) CS (22)	p	≤25 mL n=24 (C) , n= 15 (CS) > 25 mL n=18 (C) , n= 7 (CS)	73.5 for C (67-74) 68.4 for CS (63-74)	3yrs: 87 (C) 5yrs: 81 3 yrs: 94 (CS) 5 yrs: 94	38 (14-92)

5-y Local Control
Chordoma 59-81%
Chondrosarcoma 79-98%


109.8 %
109.8
90.1 %
60.0 %
40.0 %
20.0 %
0.0 %
R
A
P
L
PTV 60.
109.4 %
469
-42
Z: 0.60 cm
Z: 0.60 cm
-42

The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature

TA van de Water et al, The Oncologist, 2011, 16: 366-377

Groningen & Maastricht, The Netherlands

- 14 in silico planning comparative (ISPC) studies
- Protons have the potential for a significantly lower normal tissue dose, while keeping similar or better target coverage
- Probability of reducing >25% salivary flow with IMRT is 22% , and with IMPT 9%
- Probability of reducing grade 2-4 swallowing dysfunction is reduced by 8.8% with IMRT, and by 17.2% with IMPT

The results of these ISPC studies should be confirmed in properly designed clinical trials

fondazione CNAO

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 Milano n. 192
P.IVA n. 03491780965
Codice Fiscale n. 97301200156

Presented to:

- Italian Ministry of Health
- Lombardy Region

Main Tasks:

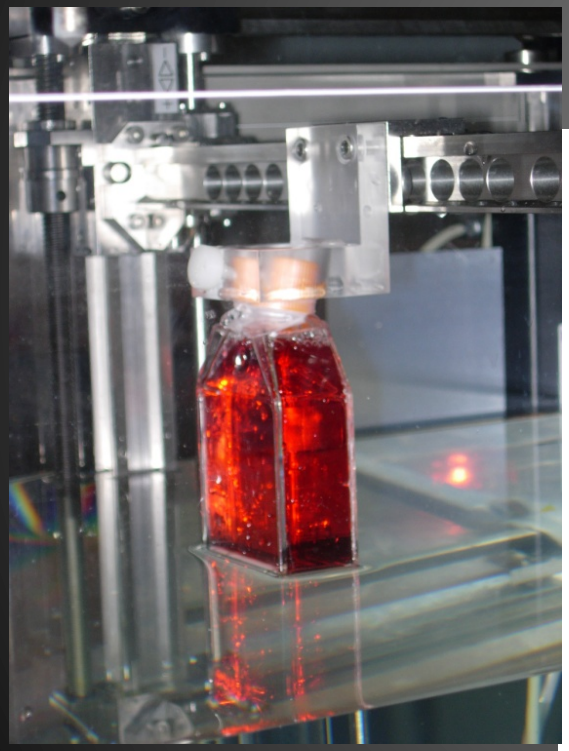
-Dosimetric characterization

-Radiobiological characterization

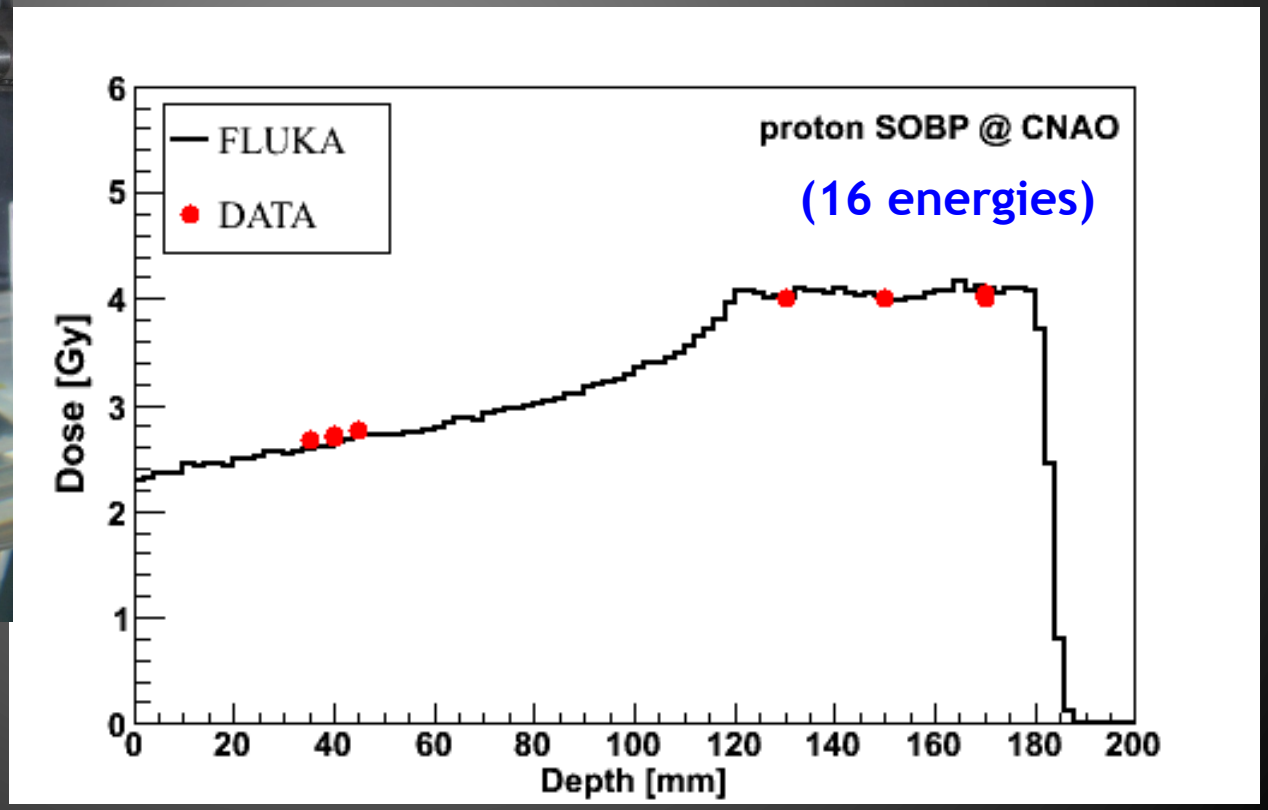
- Patient treatment

Proton Radiobiology

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

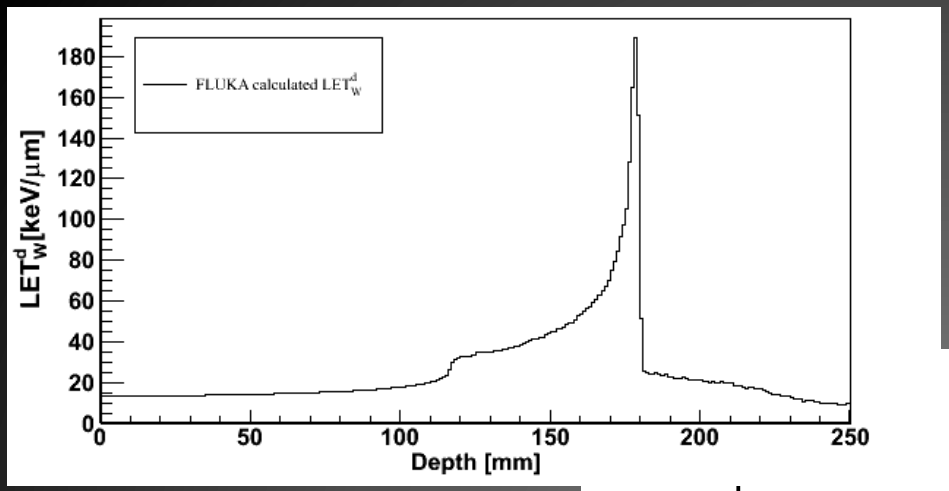


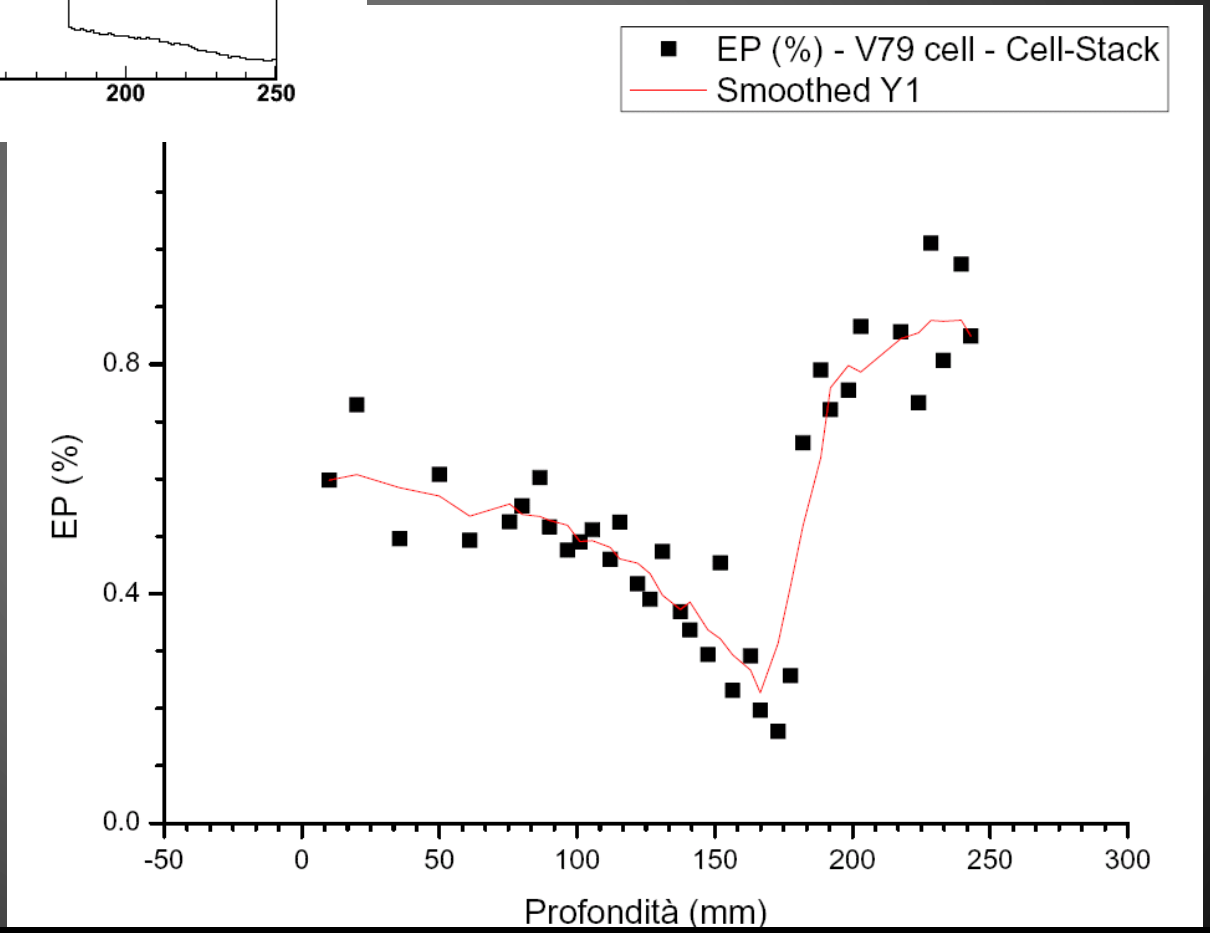
Field10x10 cm^2,
33x33 spots,
scanning step 3 mm



Cell Survival vs Depth

Dose uniformity





Carbon Ion Radiobiology

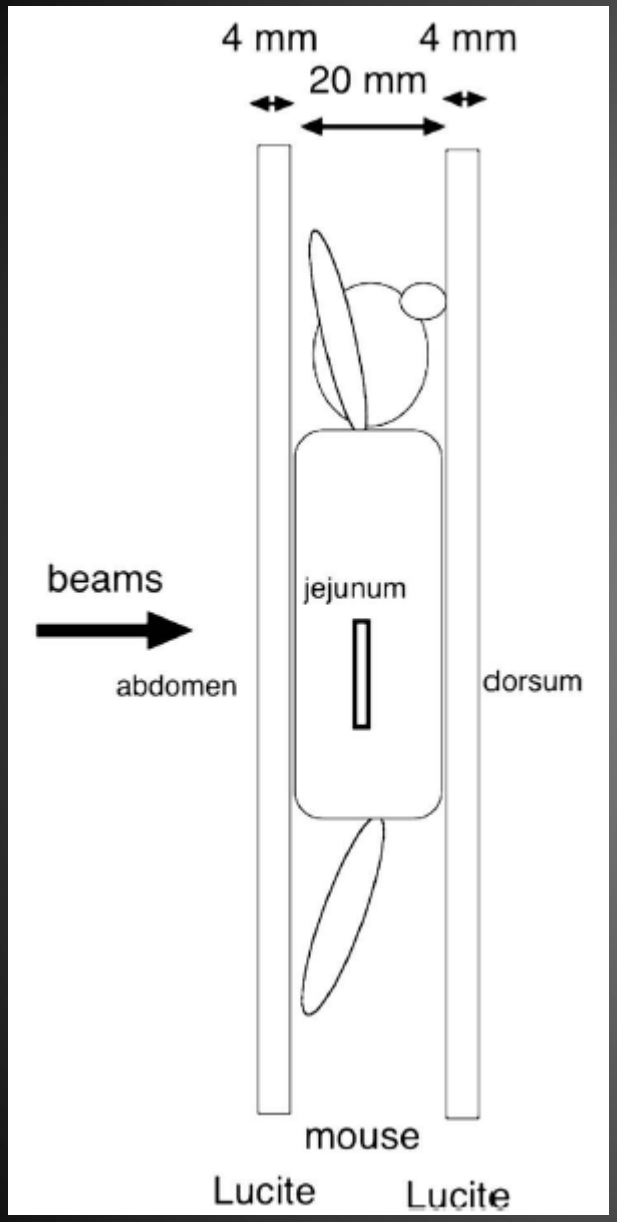
Group Leader:
Yoshiya Furusawa,
NIRS, Chiba

Carbon ions

Animals

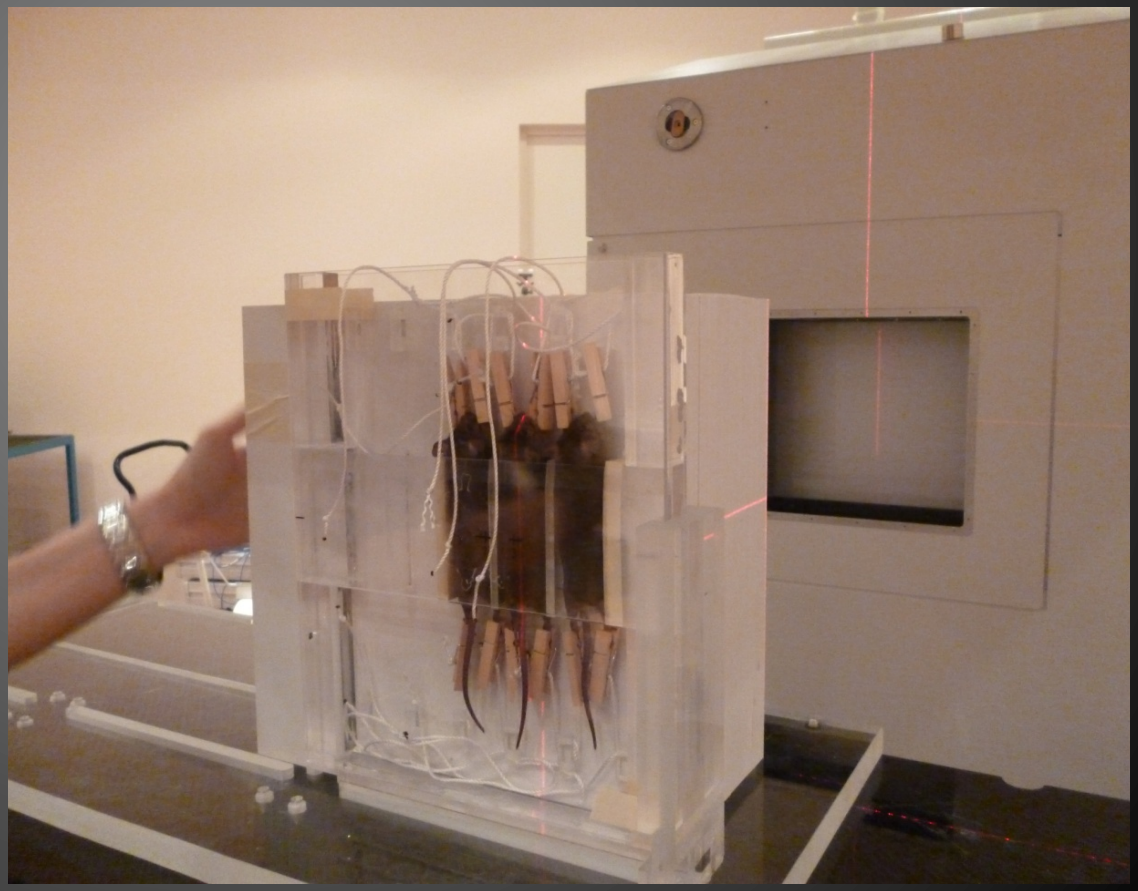
CNAO

Set-up

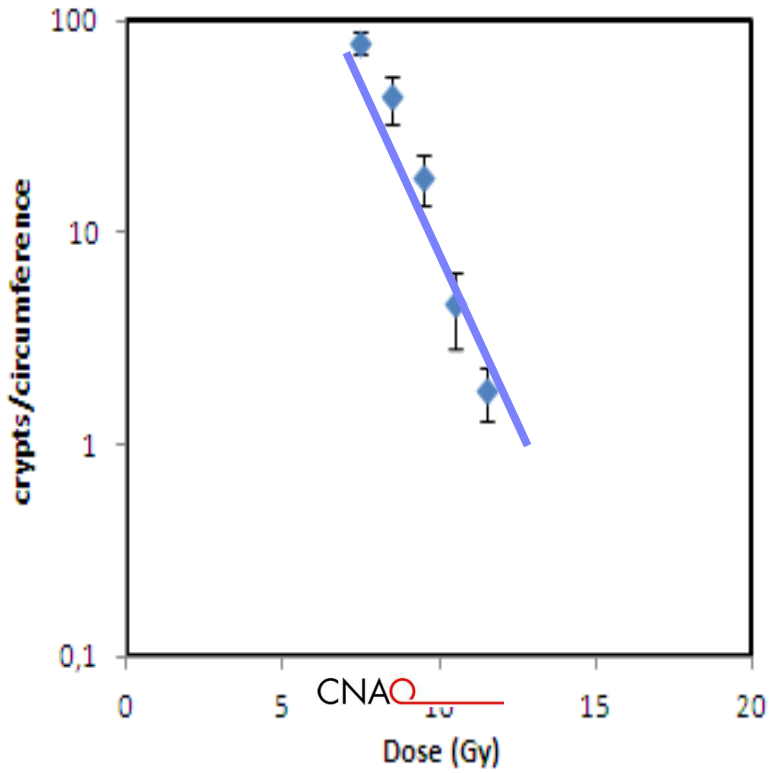


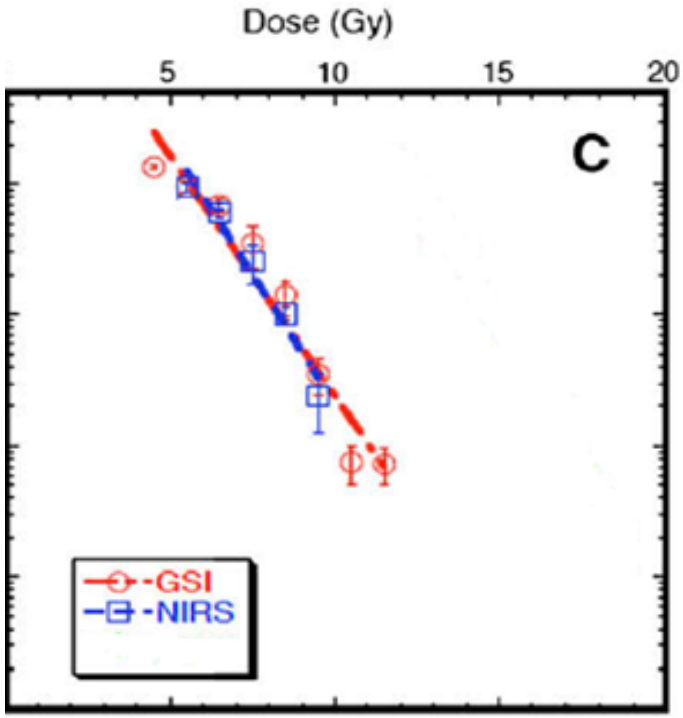
Horizontal beam, direction ventral - dorsal

3 animals per field



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.§

Experimental Activity

Between January 2012 and December 2013

147 patients have been treated in the framework of 23 clinical prospective phase II protocols.

With the aim to prove safety and effectiveness of CNAO Beam

CE label -> CNAO Sinchrotron

Patients in routine clinical practice since January 2014

2014 Clinical Activity: Total number of patients >350

- 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

Salivary gland tumors	34
Reirradiation of head and neck tumors	25
Mucosal melanoma	7
Chordoma	119
Chondrosarcoma	23
Sarcoma	32
Retreatment local recurrence rectal cancer	1
HCC	1
Local advanced pancreatic cancer	1

Adenoid Cystic Carcinoma 34 patients

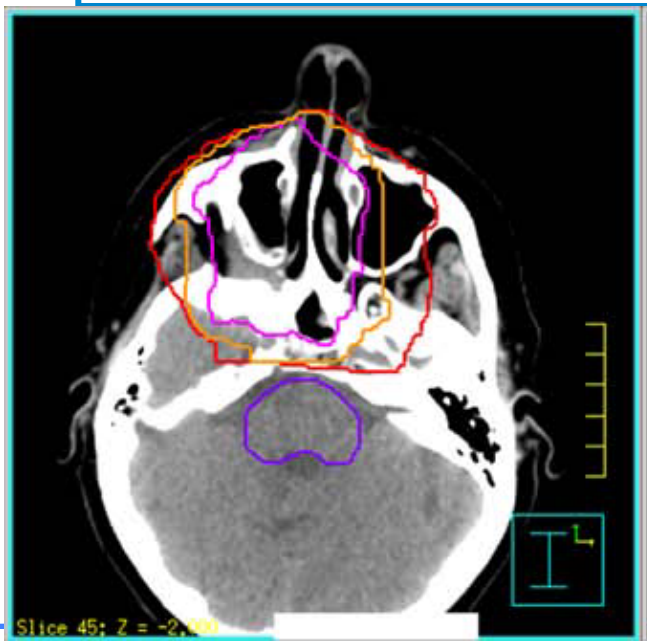
Pre-treatment Imaging

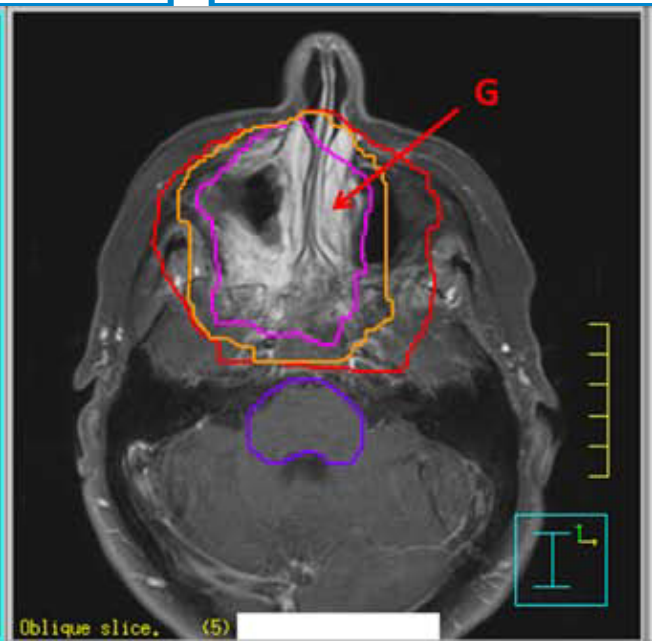
- CT
- MRI with contrast
- PET with C11 metionina

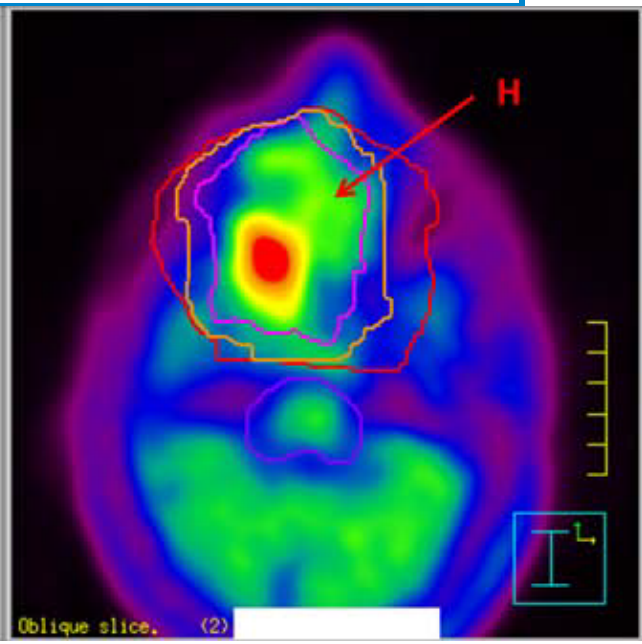
Prescription doses

- PTV1 Dose (low risk volume)
  38.7 Gy RBE /9 fractions
- PTV2 Dose (High risk volume)
  - 30.1 Gy RBE/ 7 fractions

  Total dose:68.8 Gy RBE/16 fractions







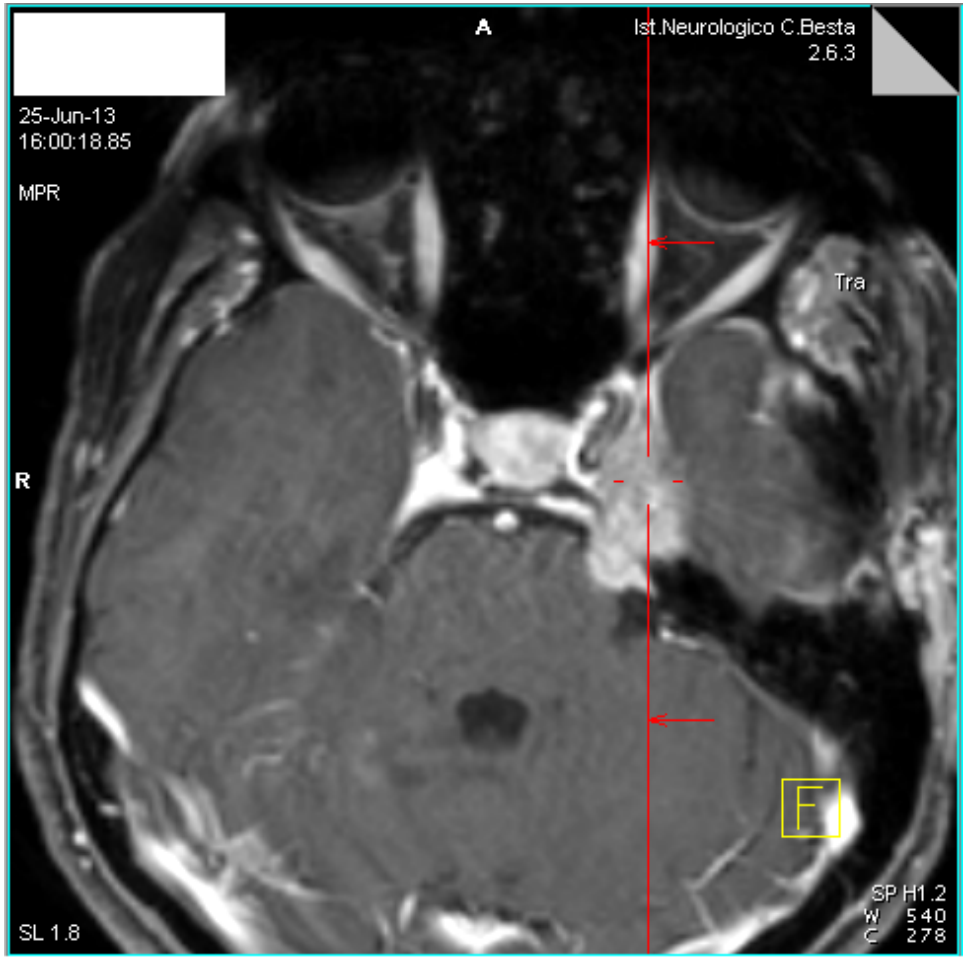
Clinical case

Pre- CIRT

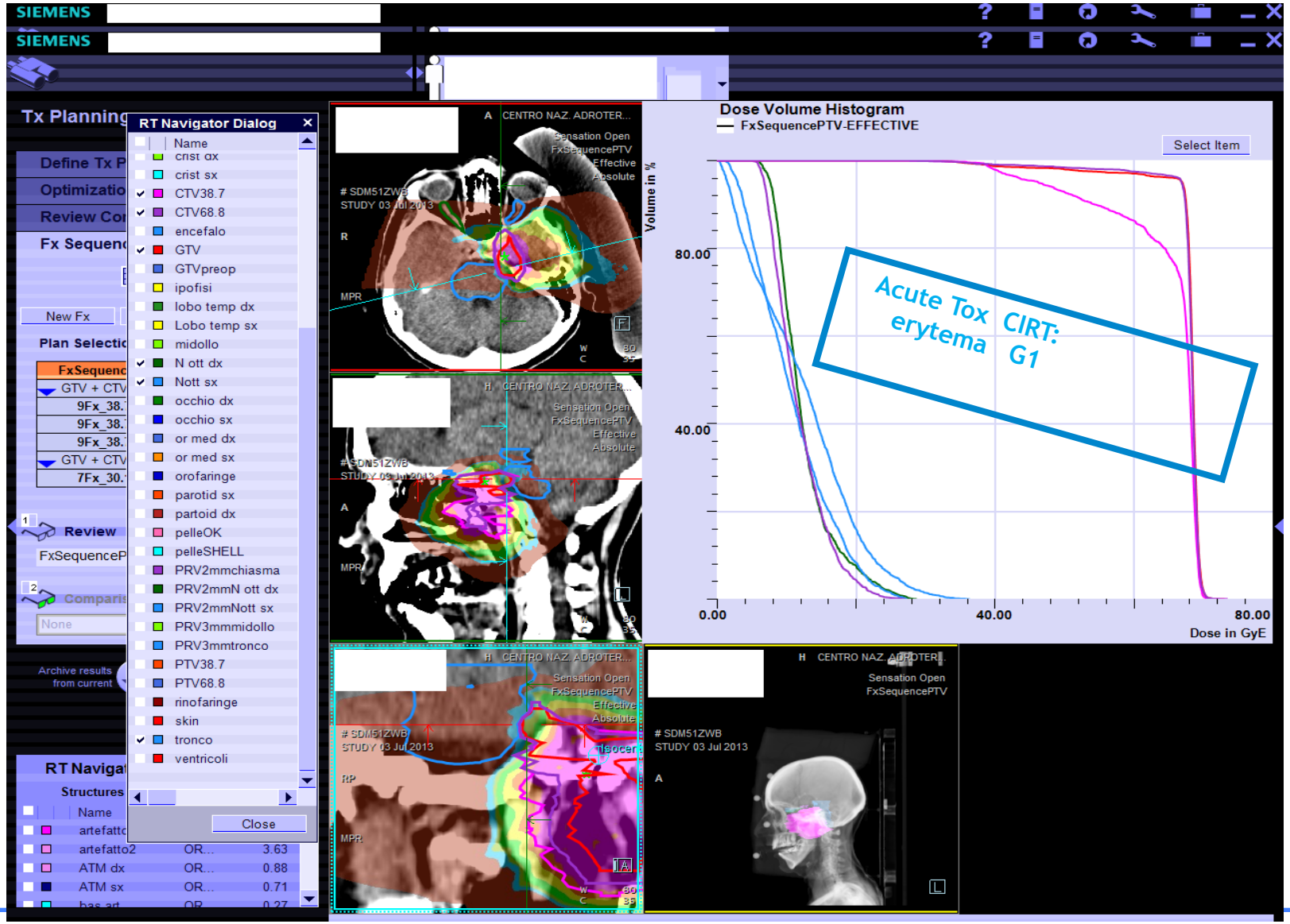
62 year old female

ACC left Meckel cave

21/05/2013 temporal craniotomy and biopsy



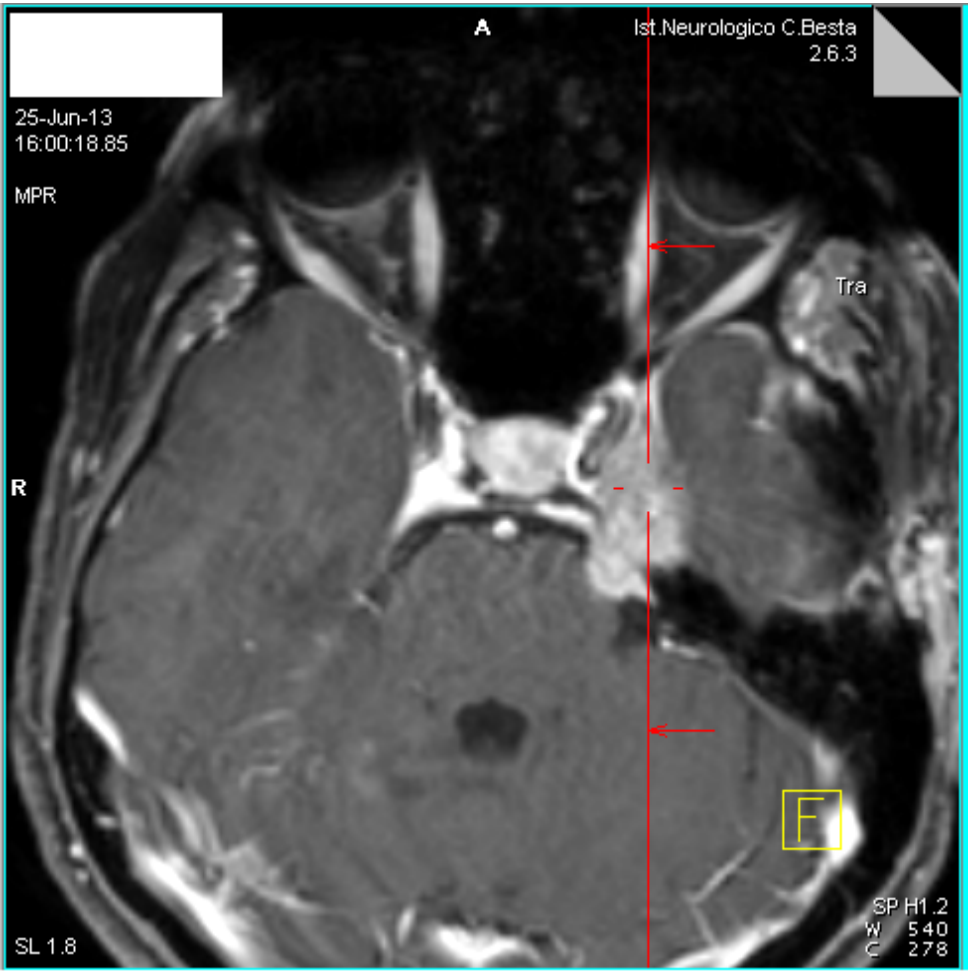
CIRT: 68.8 Gy(RBE) (4.3 Gy(RBE)/fraction, 16 fractions, 4 fractions/weekly

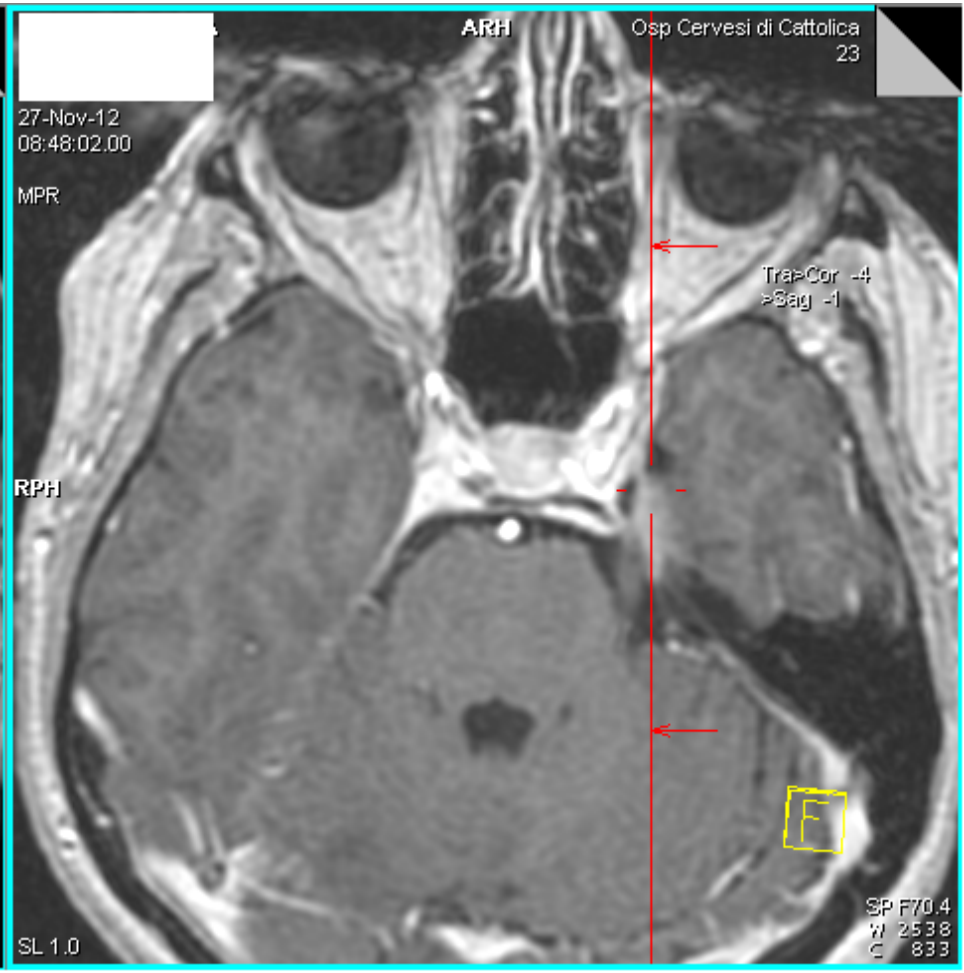


May 2014 (9 months)

Radiological control of disease confirmed by MRI.

Late Tox G0





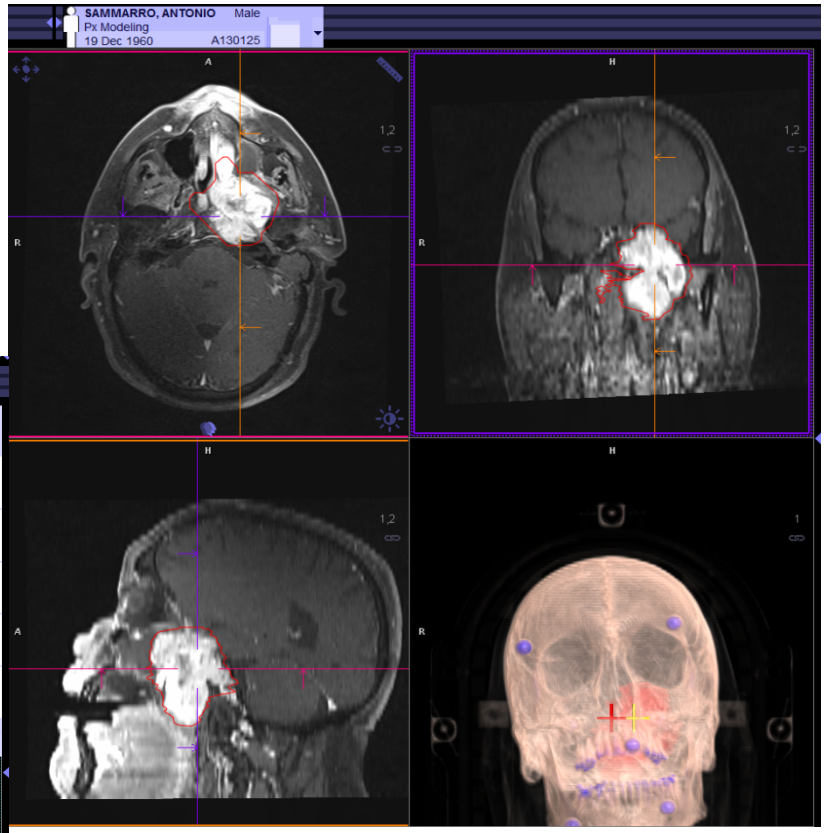
Clinical case

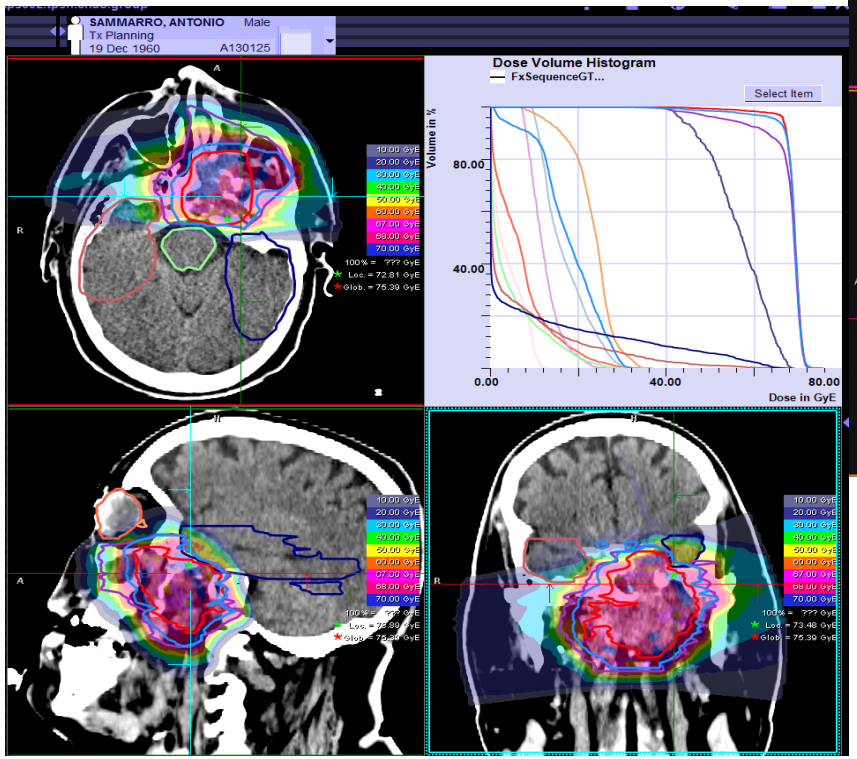
53 year old male

ACC in parafaringeal region with estention on clivus and petrous bone

07/2013 Nasopharinx biopsy: EI adenoideo cistic carcinoma

15/10/2013 -- 07/11/2013 CIRT 68.8 Gy [RBE]





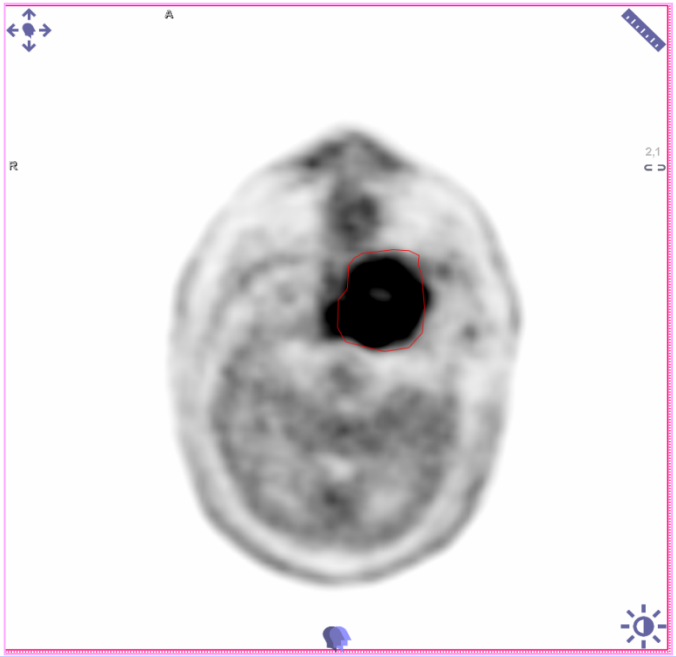
Toxicity at the end of CIRT: erythema G1, mucositis G1

Partial Remission and Acute Toxicity G0 after 3 months

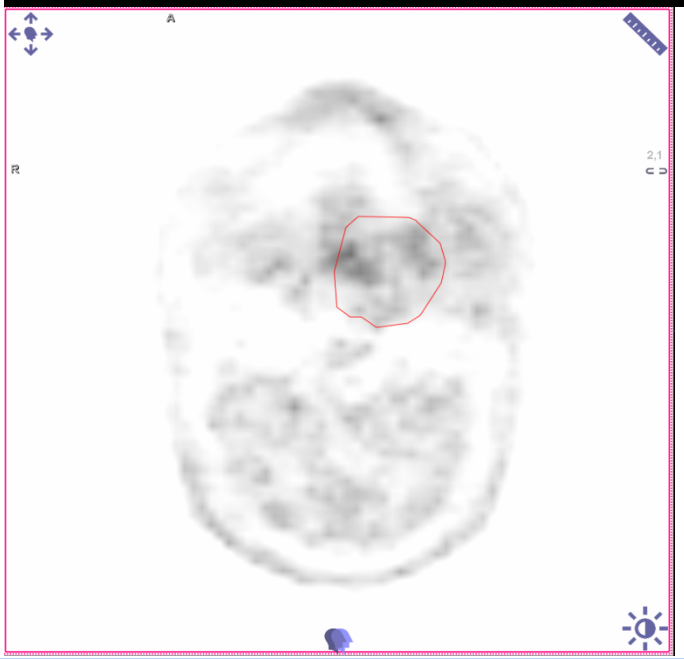
PET metionine: significant decrease in MET uptakafter 3 months

PET metionine at 6 months: negative

PET pre CIRT



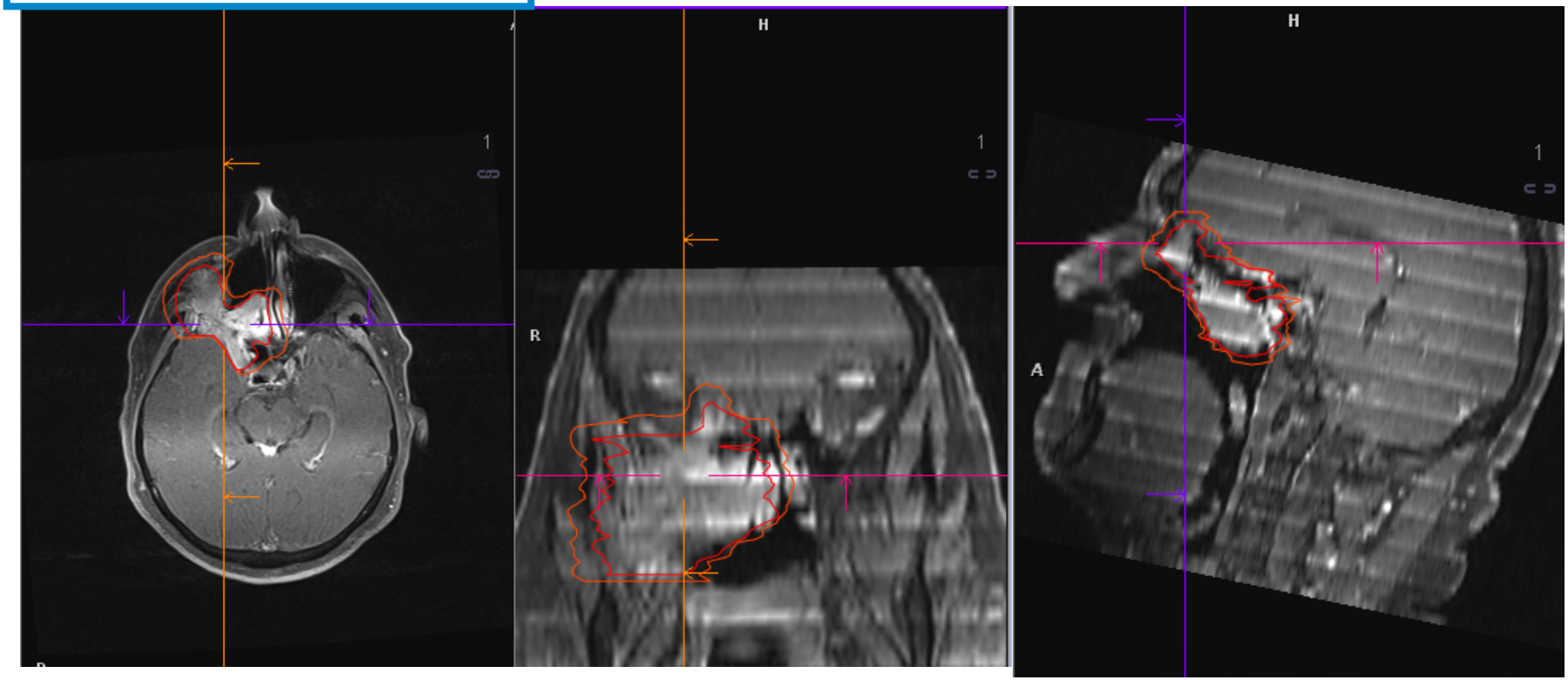
PET after 6 months



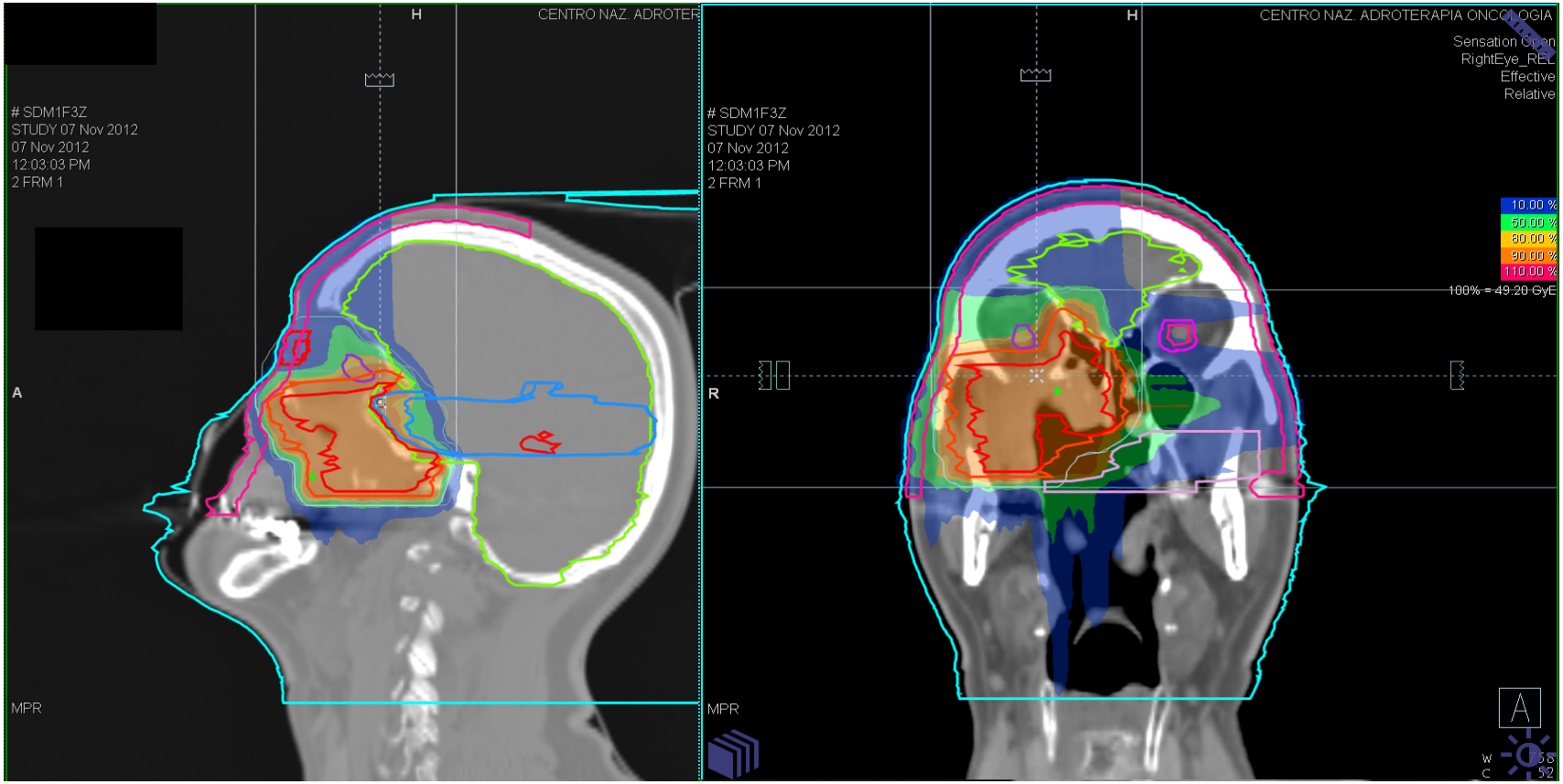
Salivary gland tumors	34
Reirradiation of head and neck tumors	25
Mucosal melanoma	7
Chordoma	119
Chondrosarcoma	23
Sarcoma	32
Retreatment local recurrence rectal cancer	1
HCC	1
Local advanced pancreatic cancer	1

Adenoid Cystic Carcinomas Reirradiation : 12 patients

Clinical case



- Recurrent ACC already treated by 60 Gy conventional RT and surgery in 1995



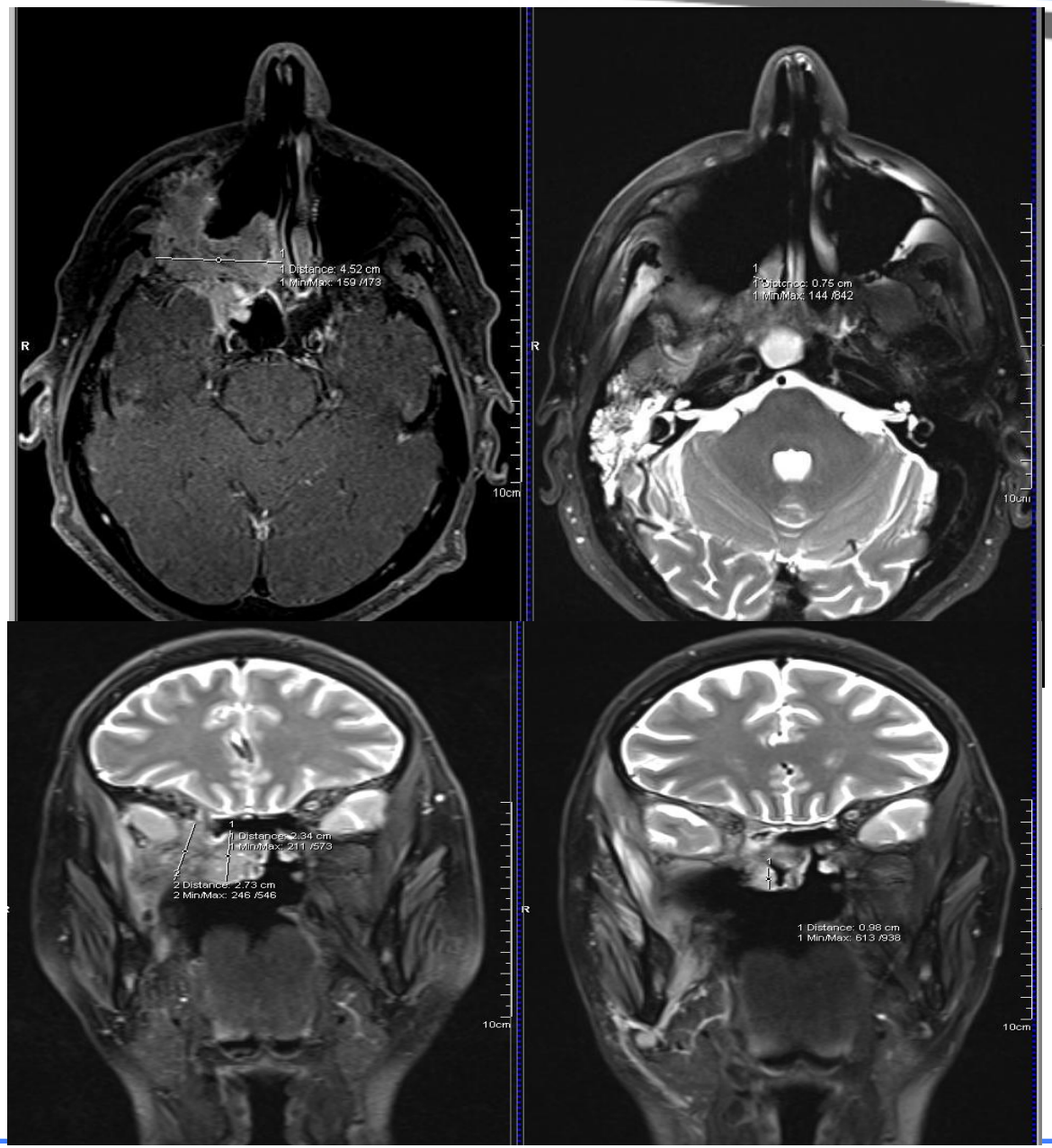
CIRT: 60 Gy E ; 15 fr; 4 Gy E /fr

Skin toxicity

End of treatment

4 months after

Before treatment



4 months after

Salivary gland tumors	34
Reirradiation of head and neck tumors	25
Mucosal melanoma	7
Chordoma	119
Chondrosarcoma	23
Sarcoma	32
Retreatment local recurrence rectal cancer	1
HCC	1
Local advanced pancreatic cancer	1

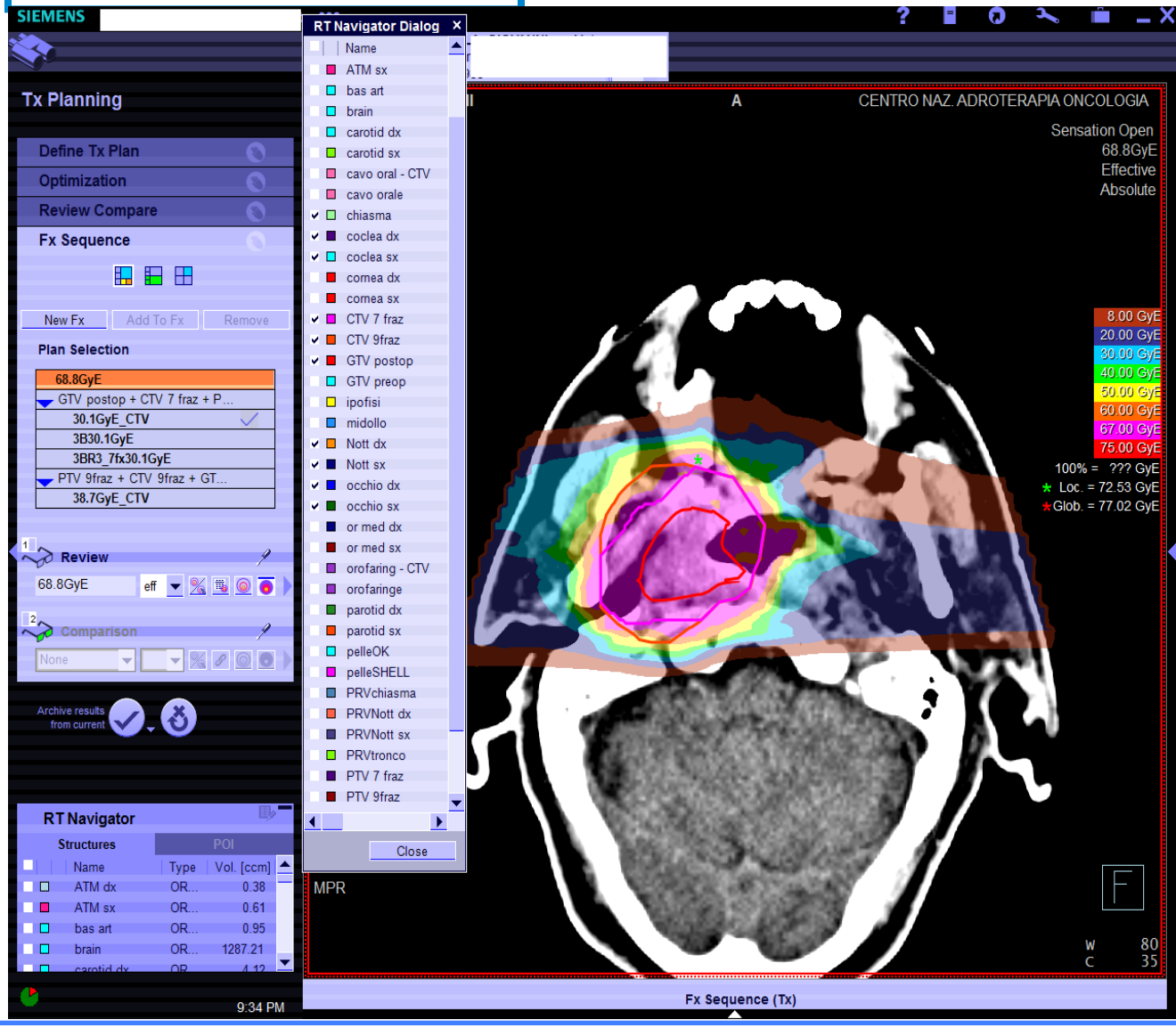
Clinical case

75 year old men

March 2013: endoscopic surgery R2

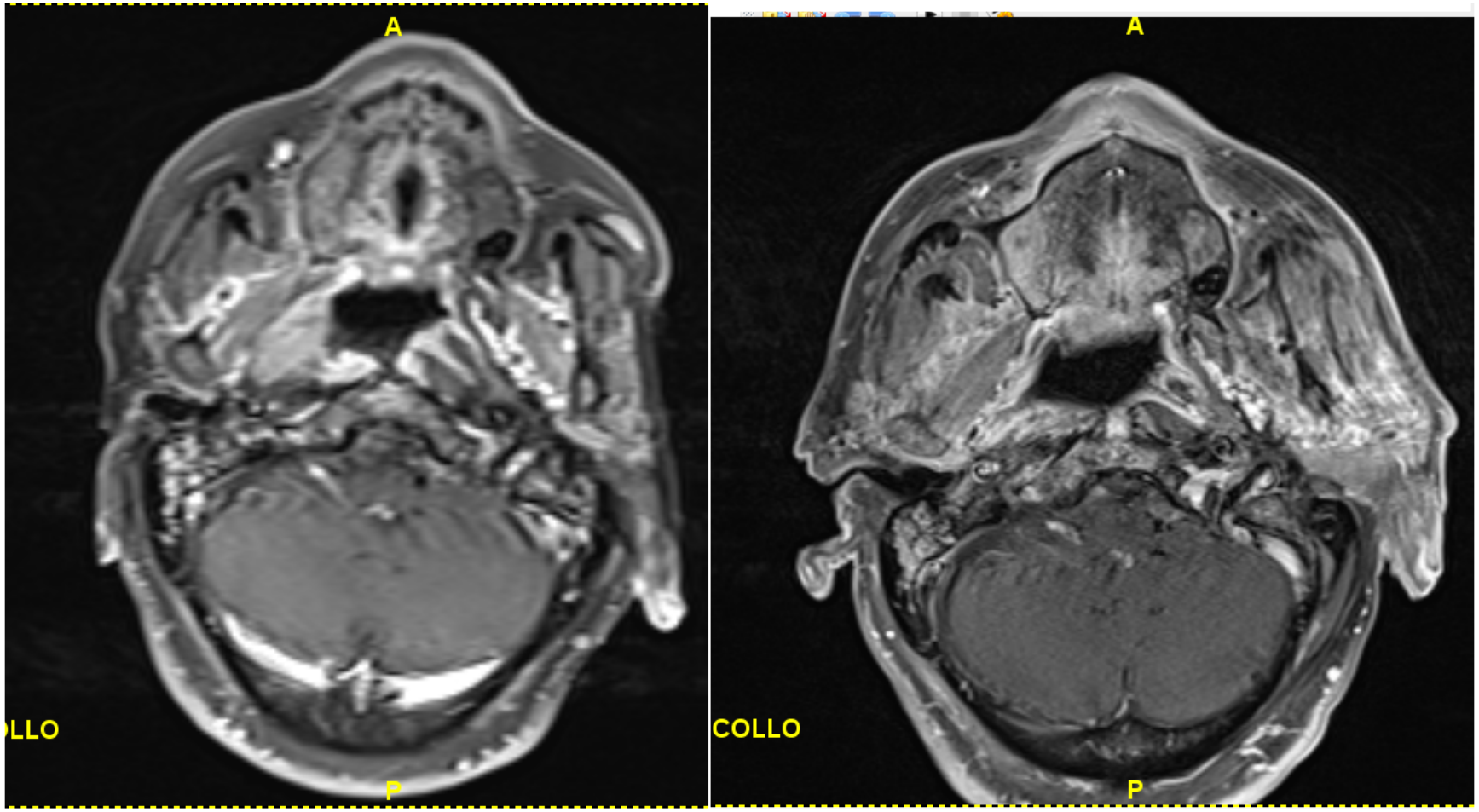
No CT for age and coomorbidity

CIRT :
68.8 Gy [RBE] / 16 fractions



April 2013 (pre-CIRT)

December 2013



FOLLOW-UP 9 AND 12 Months
tox G1 - CR

During CIRT

End of CIRT

Mucositis

Erytema

6 months

Salivary gland tumors	34
Reirradiation of head and neck tumors	25
Mucosal melanoma	7
Chordoma	119
Chondrosarcoma	23
Sarcoma	32
Retreatment local recurrence rectal cancer	1
HCC	1
Local advanced pancreatic cancer	1

toxicity

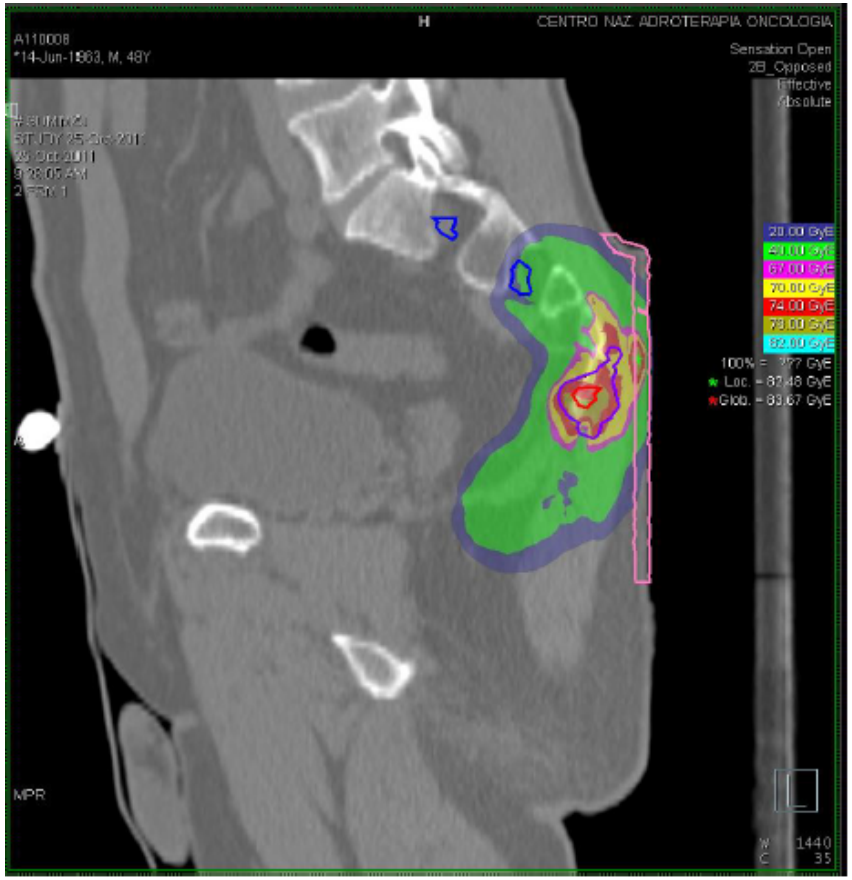
	Max during treat	End of treat	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
Pz	142	142	115	97	72	60	39	35	18	11
G0	38	48	69	56	40	36	22	17	10	5
G1	56	56	28	29	19	10	9	10	3	5
G2	46	37	18	12	12	12	5	7	1	-
G3	2*	1*	-	-		1**	4***	3***		-
G4	-	-	-	1	-	-	-	1++		

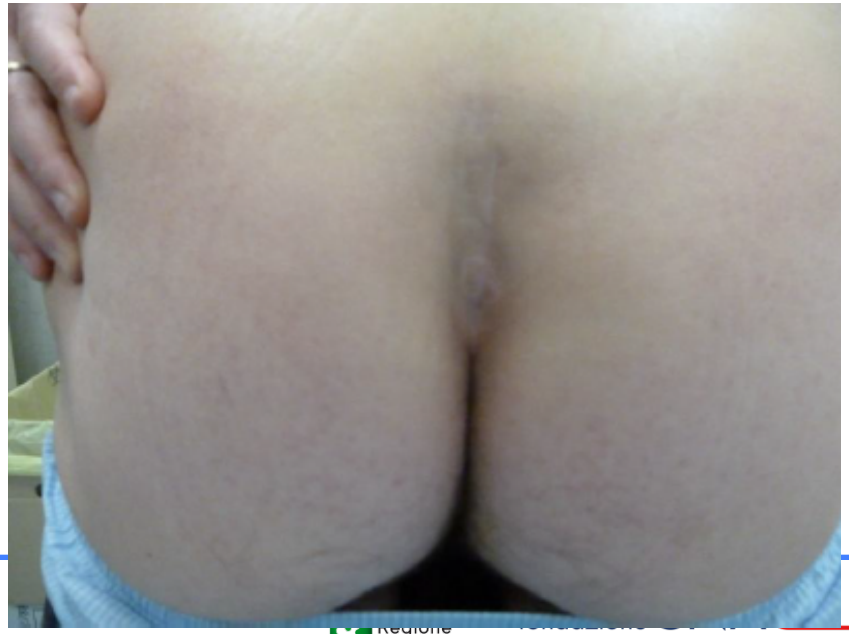
* Mucositis and Reactivation of herpes zooster infection responsive to antiviral drugs
** hearing impairment with acustic device
*** 2 hearing impairment 1 stroke 1 partial blindness
**** 1 blindness ++ 1 intestinal perforation

G1 Skin toxicity

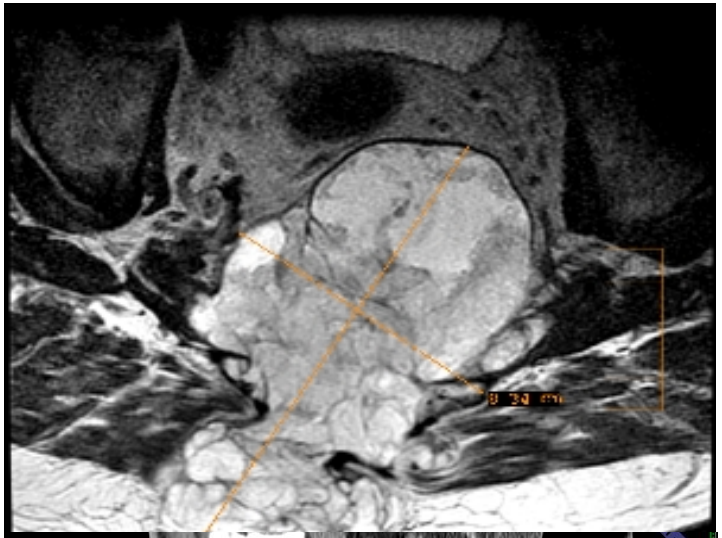
G2 Skin toxicity

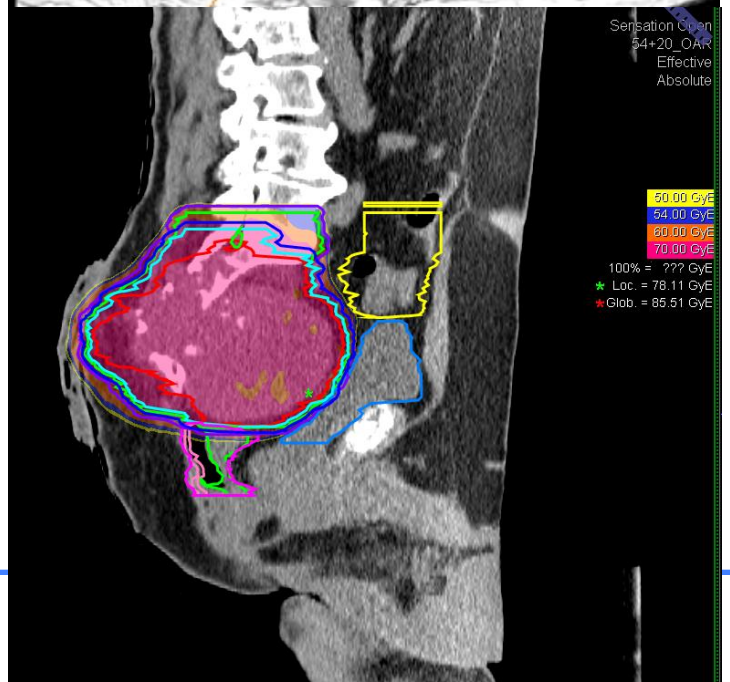
G2 Skin toxicity

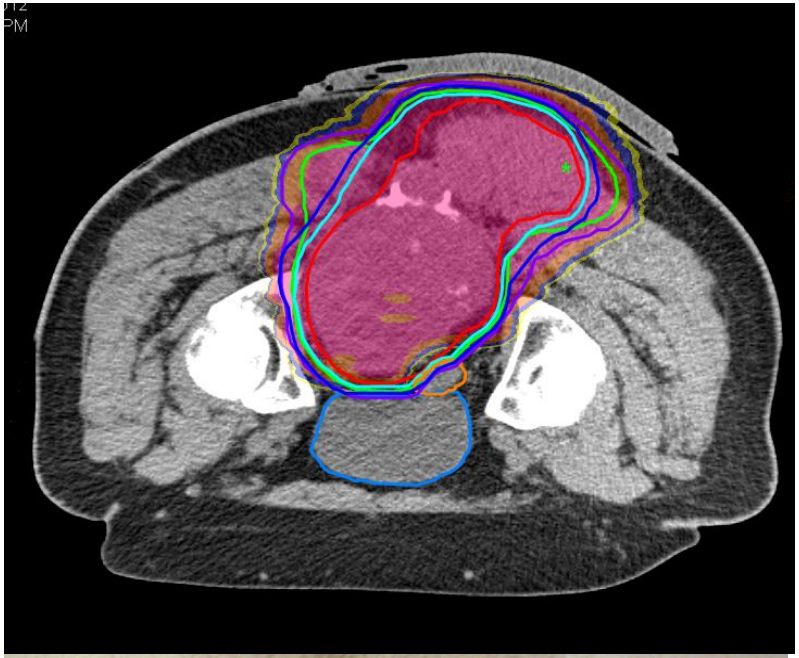




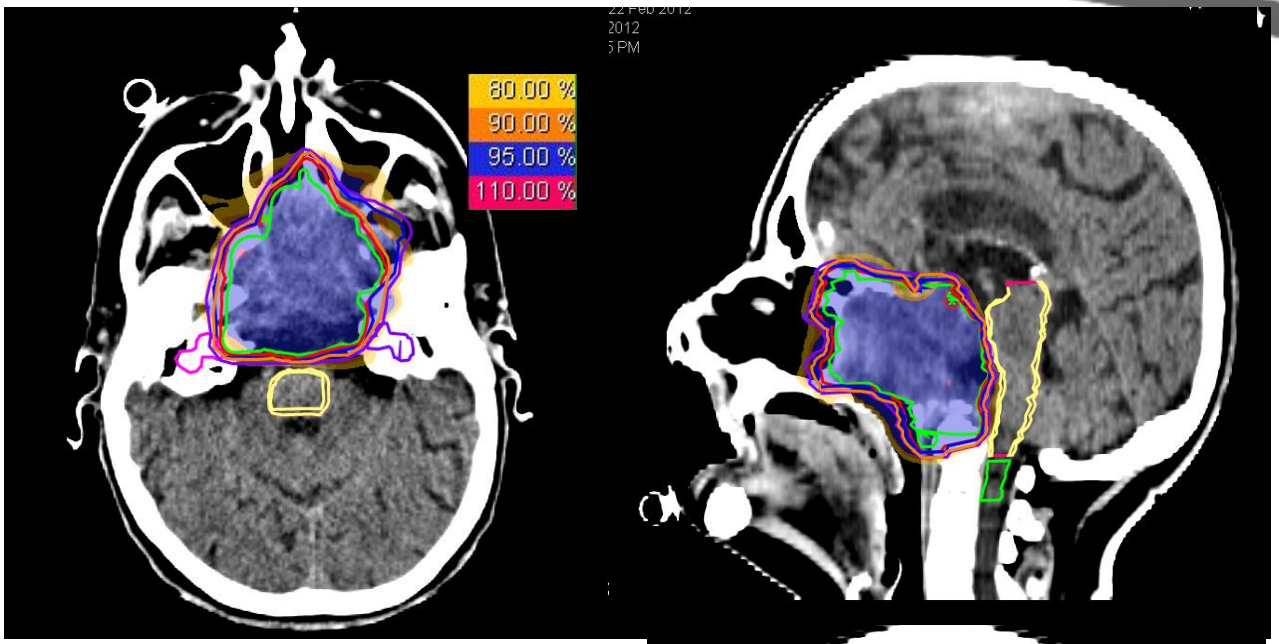
G2 Skin toxicity

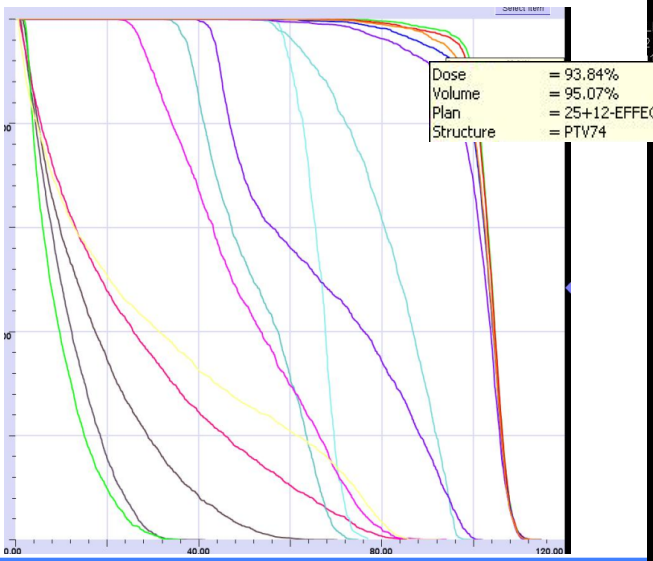


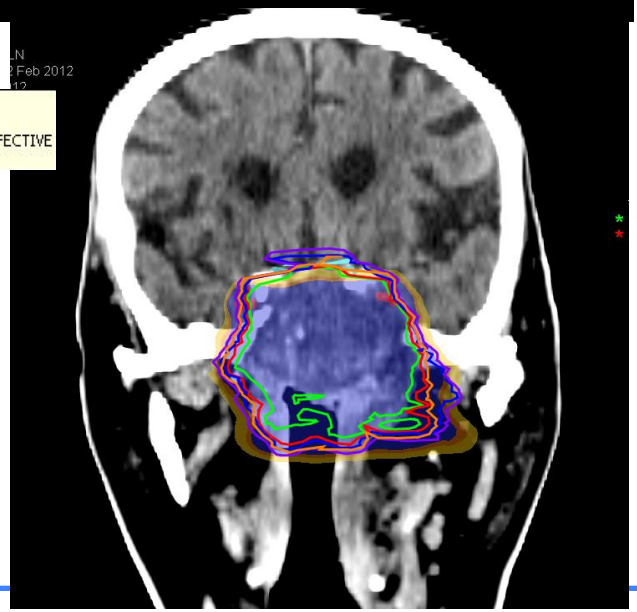




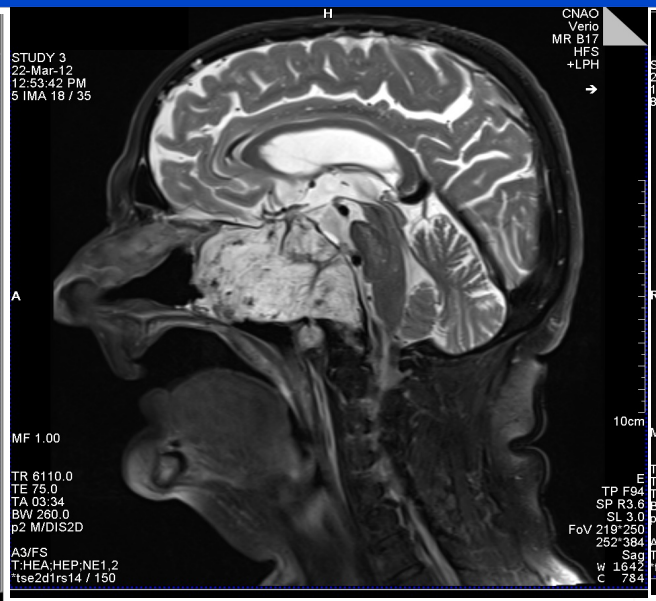
CLINICAL CASE

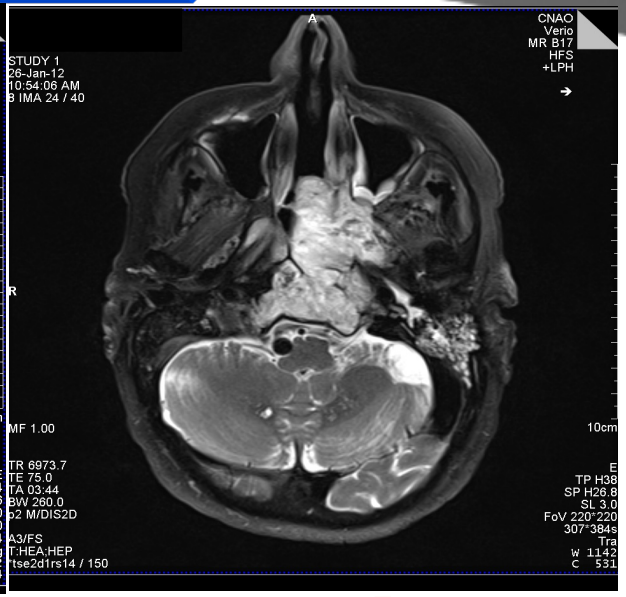




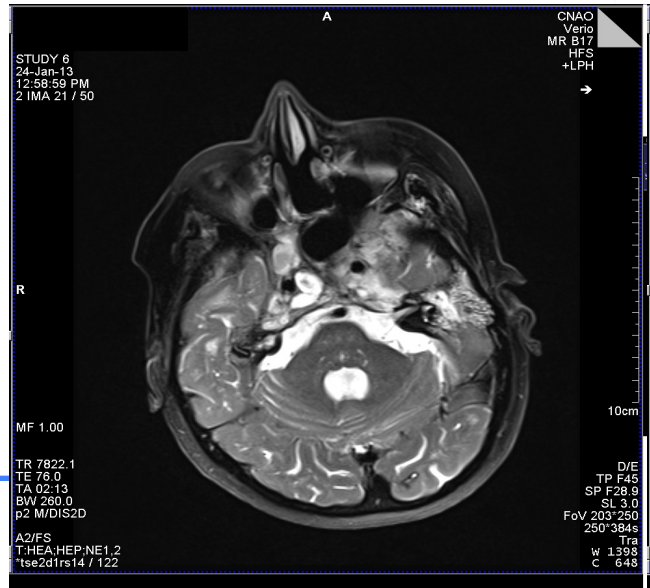


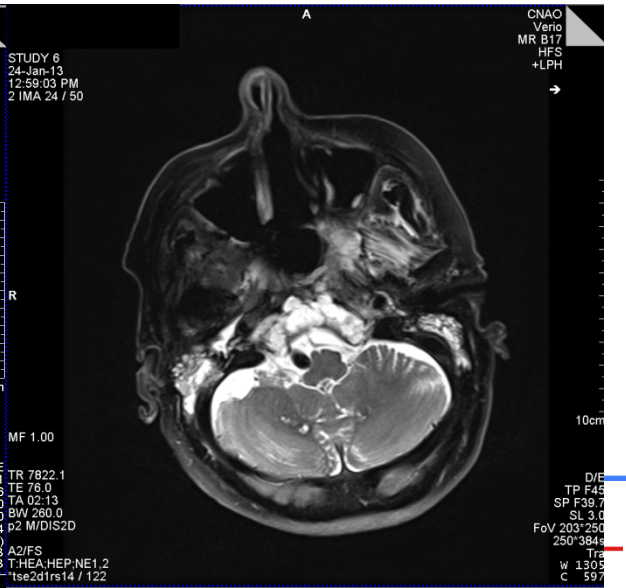
SKULL BASE CHORDOMA: Proton therapy



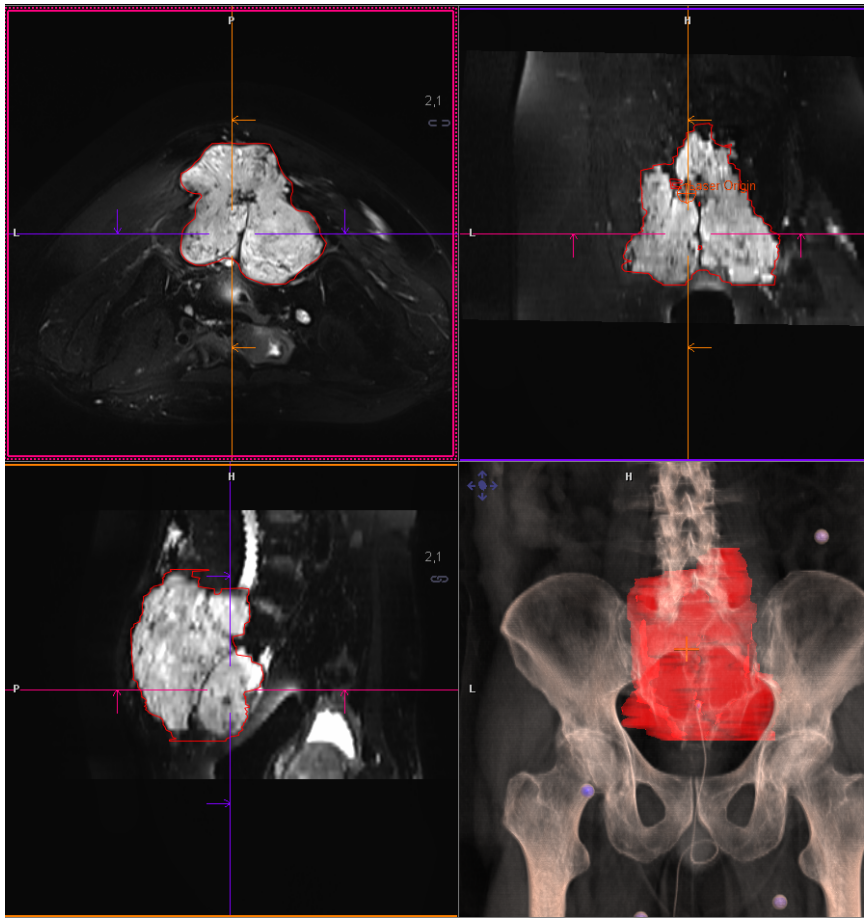


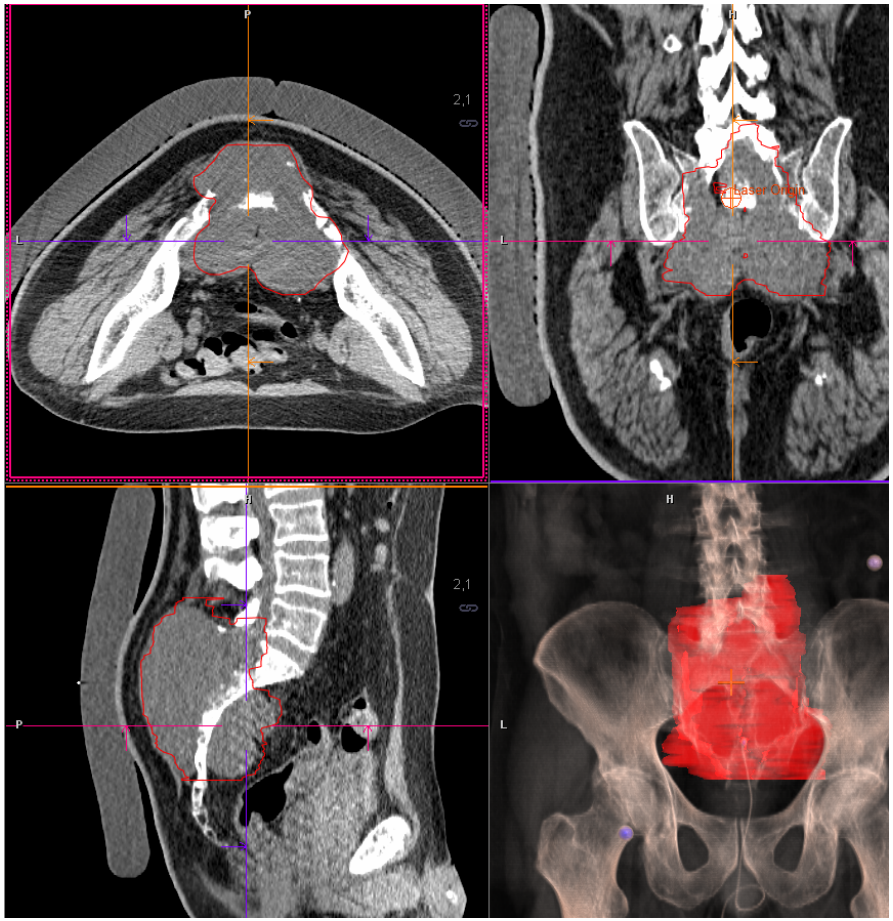
10 months F-up

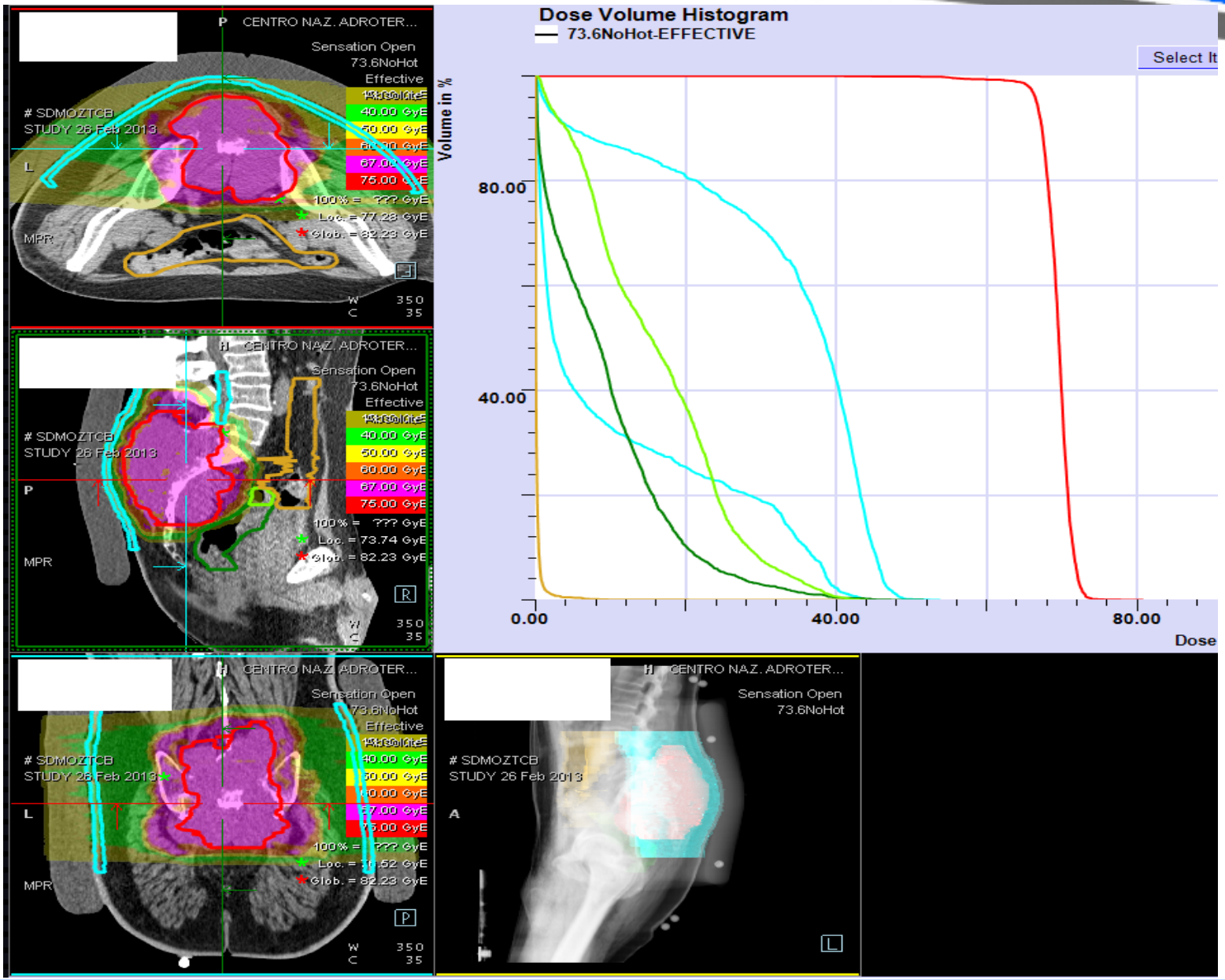




Sacral chordoma, male, 69 years old

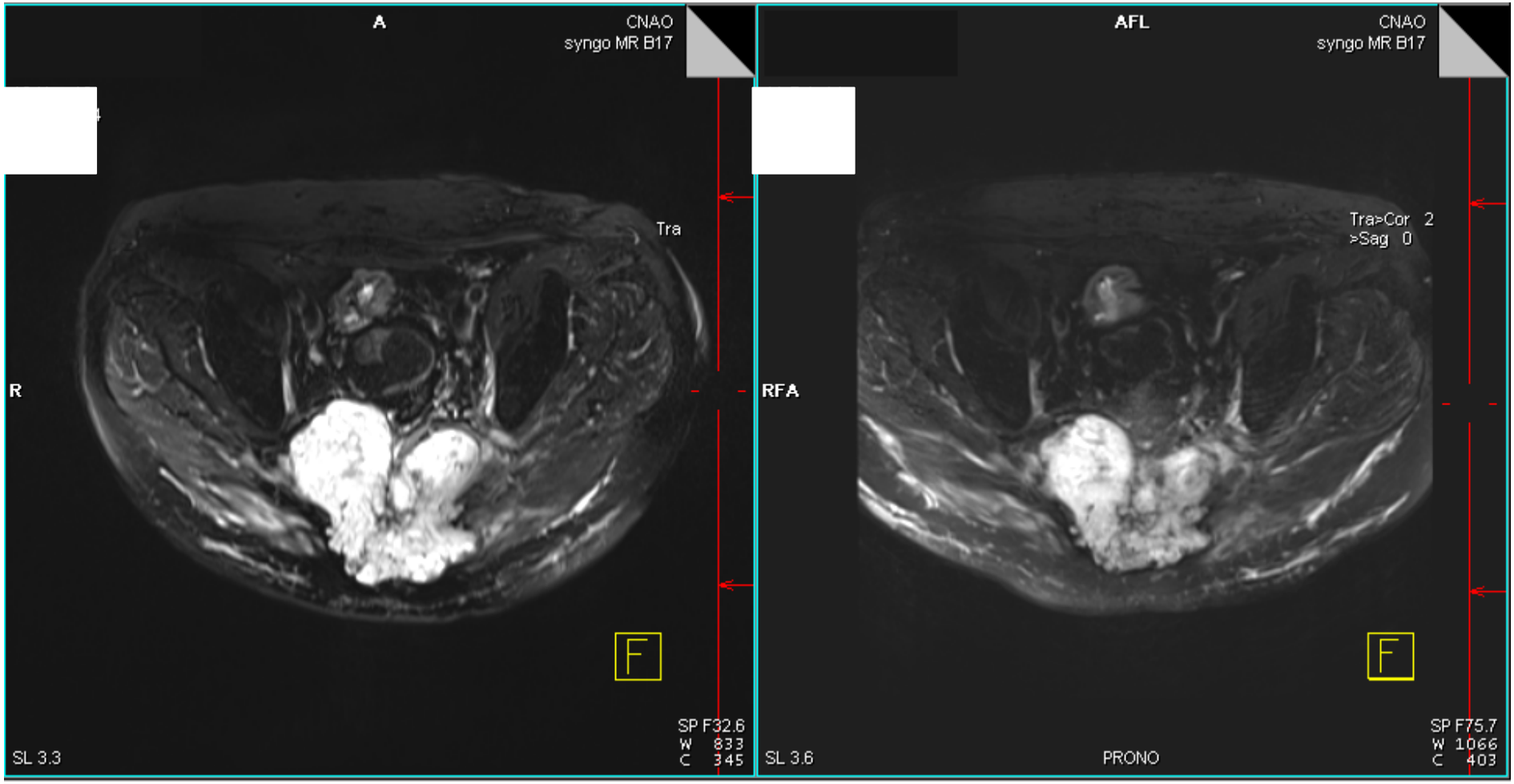





CENTRO NAZ. ADROTER...
Sensation Open
73.6NoHot
Effective
SDMOZTCB
STUDY 26 Feb 2013
40.00 GyE
50.00 GyE
60.00 GyE
67.00 GyE
75.00 GyE
100% = ??? GyE
Loc. = 77.28 GyE
Glob. = 82.23 GyE
MPR
W 350
C 35
Loc. = 73.74 GyE
Loc. = 70.52 GyE
Dose Volume Histogram
73.6NoHot-EFFECTIVE
Select It
Volume in %
80.00
40.00
0.00
40.00
80.00
Dose

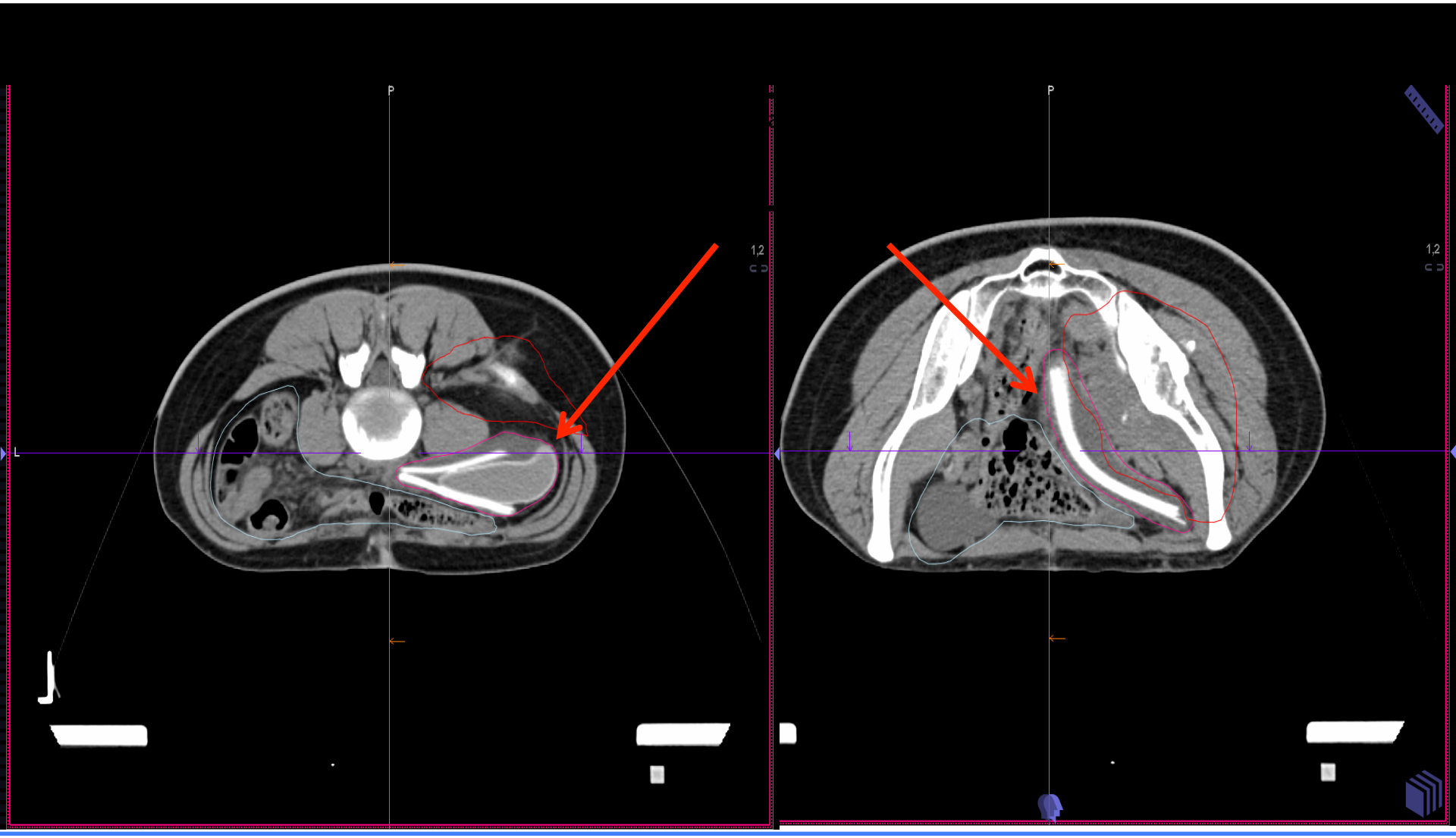
Before treatment

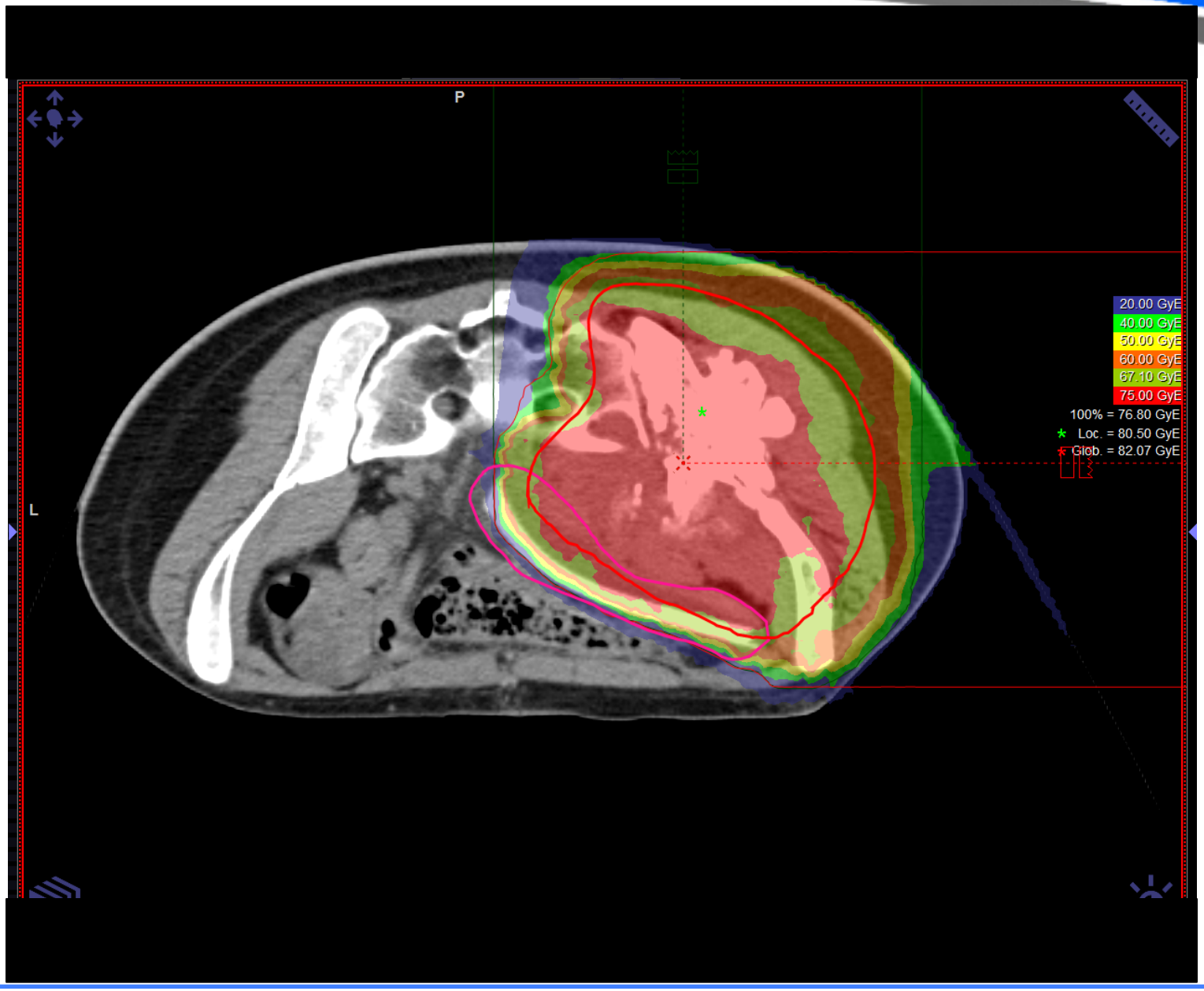
One year after treatment



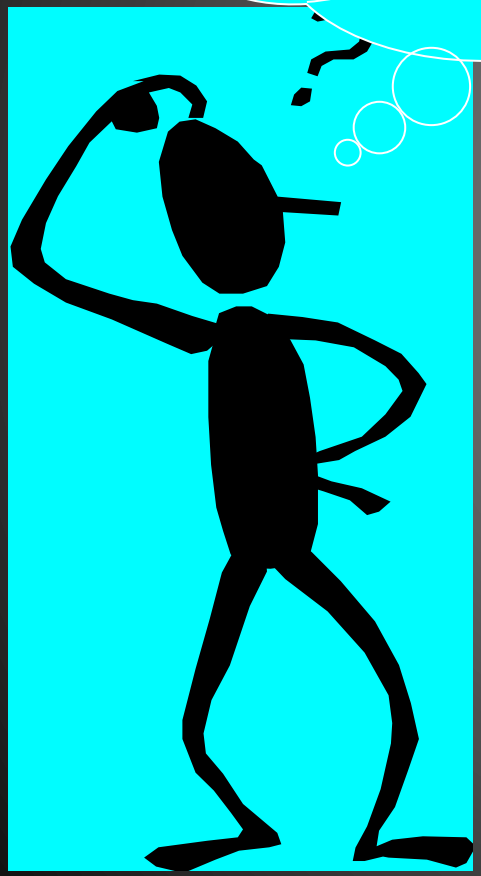
After one year hypoesthesia at the left foot: G1 toxicity, marked improvement in urinary and rectal continence, and pain, patient can sit and can walk for 15-20 minutes

Salivary gland tumors	34
Reirradiation of head and neck tumors	25
Mucosal melanoma	7
Chordoma	119
Chondrosarcoma	23
Sarcoma	32
Retreatment local recurrence rectal cancer	1
HCC	1
Local advanced pancreatic cancer	1


P
L
1,2
P
1,2


P
L
20.00 GyE
40.00 GyE
50.00 GyE
60.00 GyE
67.10 GyE
75.00 GyE
100% = 76.80 GyE
Loc. = 80.50 GyE
Glob. = 82.07 GyE

Yes, but how much does it cost?



High Tech

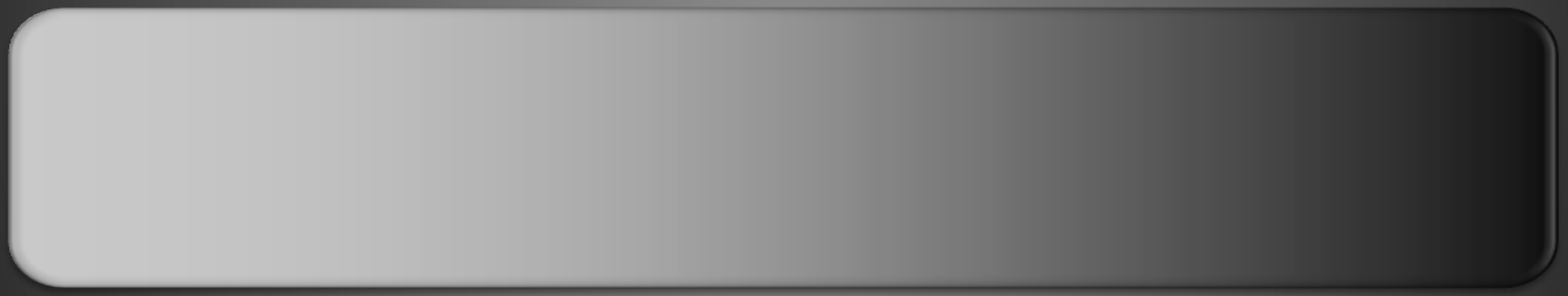
An Evidence-Based review of the role of Particle Therapy in the
of prostate canc

Improvment in Technology

filrouge

Improvment in Dose Distribution

The gray scale of appropriatness



Useless Unappropriate Appropriate Necessary

Patient
Treatment Plan Comparison
Photons vs Hadrons

NTCP
Small or absent

Photons

NTCP
Moderate or
questionable

Randomized Clinical Trial

NTCP
Major
in favour of P+

Hadrons

Technology Transfer in Clinics