Adroterapia

Un pò di tutto...
o di tutto un pò...

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XXI Congresso Nazionale AIRO
20 Novembre 2011

fondazioneCNAO

Adroterapia

dal 1993 .....

Prima:

radioterapia con particelle pesanti,
terapia con particelle,
neutrontherapy,

protontherapy ....

Adroterapia:

Un pò di storia ...

Neutroni

- **Anni 30': primi trattamenti a Berkeley**
  (Zirkle RE, Am J Cancer, 1935)

- **10 anni dopo vengono riferiti gravi effetti collaterali**
  (Stone RS, Am J Roentgenol, 1948)

- **Ripresa all'Hammersmith di Londra**
  (Catterall M, Br Med J, 1975)

Experience w/h fast neutrons

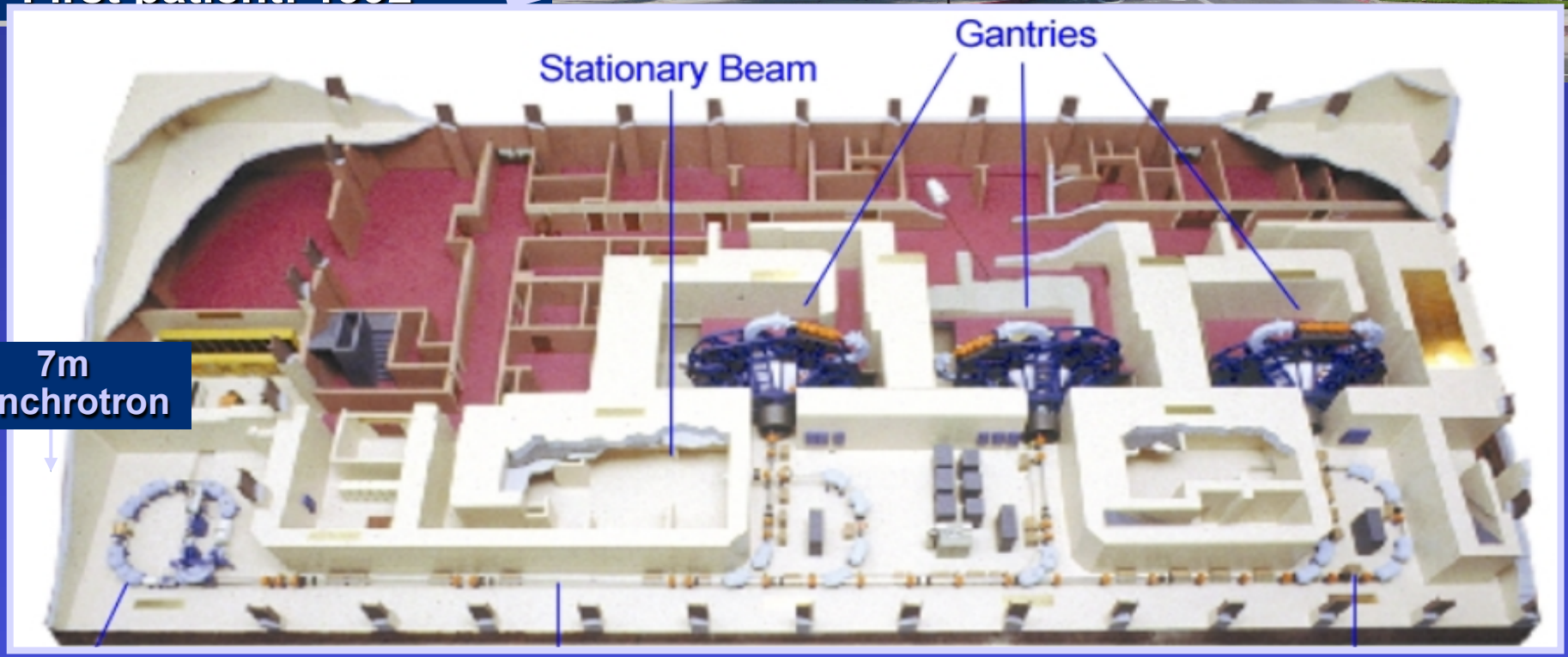
- Soft tissue and bone sarcomas
  (slowly growing/well differentiated)
- Chondrosarcomas
- Melanomas (inoperable/recurrent)
- Salivary glands tumours
- Paranasal sinuses
- Prostatic adenocarcinomas
  (locally extended/well differentiated)

BNCT

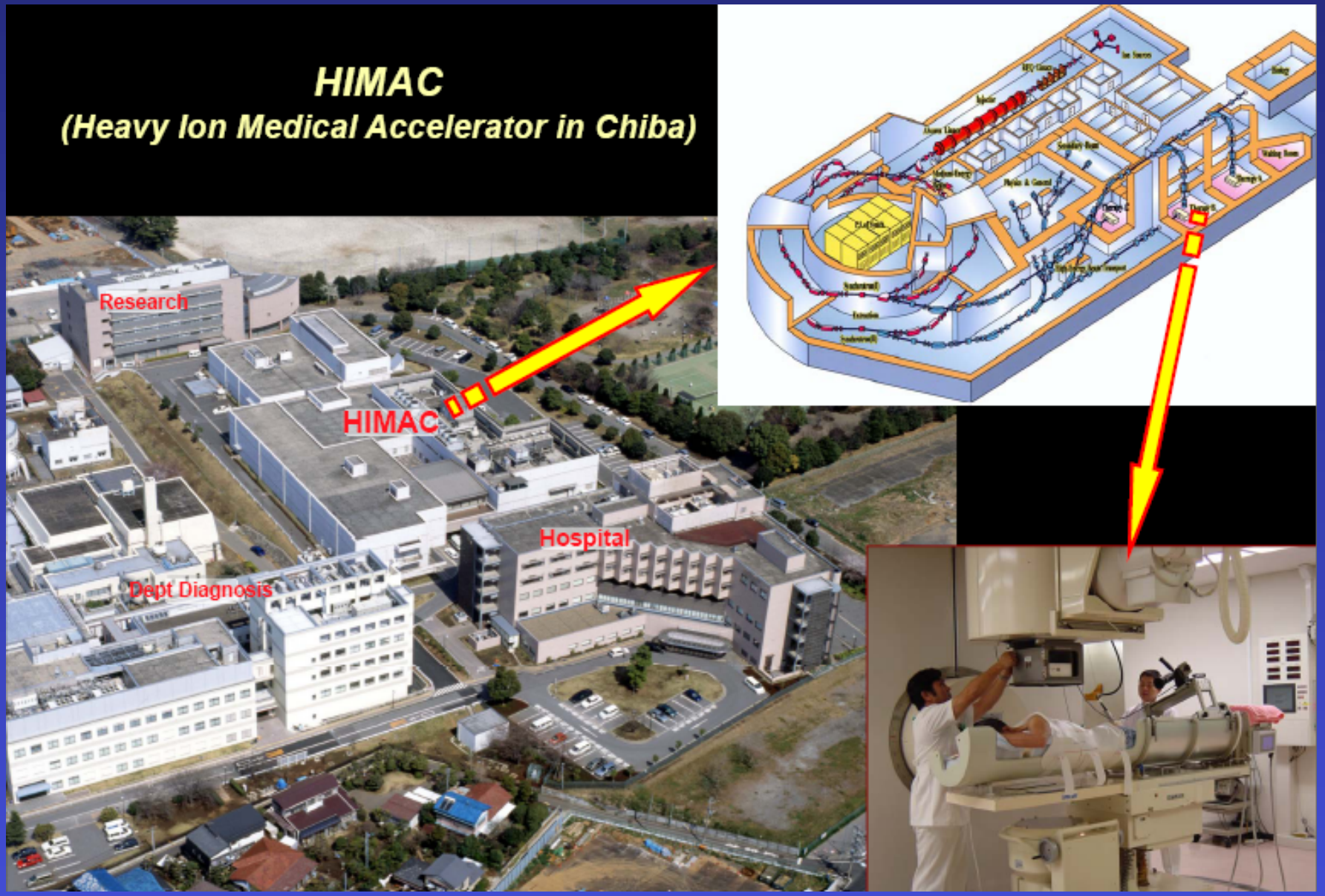
- **Proposta negli Anni 30’** (Zirkle RE, Am J Cancer, 1935)
- **Tra il 1951 e il ‘61 in USA per tumori cerebrali** (Sweet W RS, NEJM, 1951)
- **Dal 1968 in Giappone con teca cranica aperta** (Hatanaka H, Nucl Sel Appl, 1991)
- **“Concerted Action” della UE al High Flux Reactor di Petten**

Protoni

- First hospital-based proton-therapy centre
- First patient: 1992



Ioni


HIMAC
(Heavy Ion Medical Accelerator in Chiba)
Research
HIMAC
Hospital
Dept Diagnosis

Experience with light ions at LBL

1314 patients treated from 1975 to 1992

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

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

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)

Helium & Neon ions

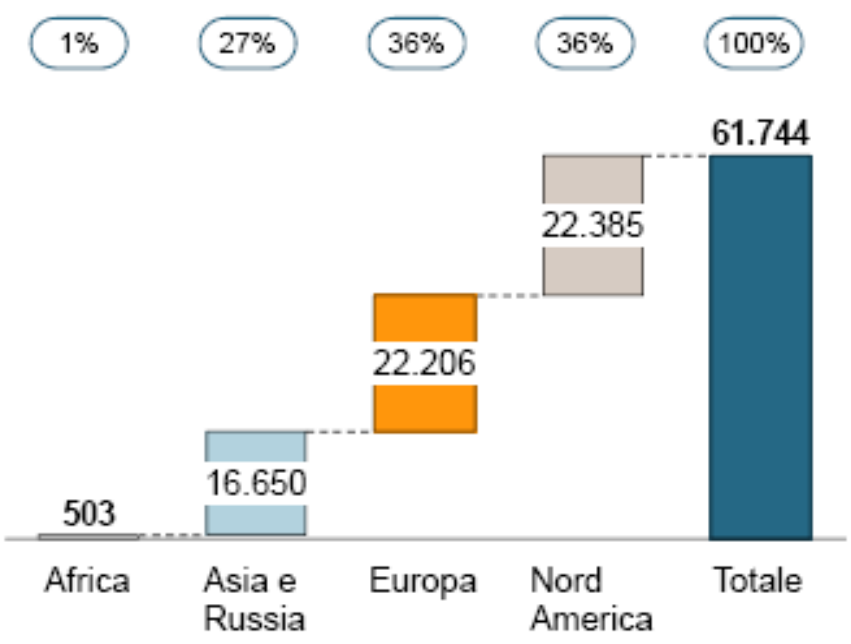
Tumor site	Local control rate with :		
	Helium ions	Neon ions	Conventional Treatment
Salivary gland		80 % (10 pts)	28 % (188 pts)[a]
Nasopharynx Paranasal Sinus	53% (13 pts)	63% (21 pts)	21% (97 pts) (UCSF)
Sarcoma	65% (17 pts)	45% (24 pts)	28% [a]
Prostate		100 % (9 pts)	60-70 % [a]
Lung		39% (18 pts)	22-40% (UCSF)
Brain/glioblastoma (median survival		17 months (13 pts)	9-12 months (UCSF, RTOG,NCOG)

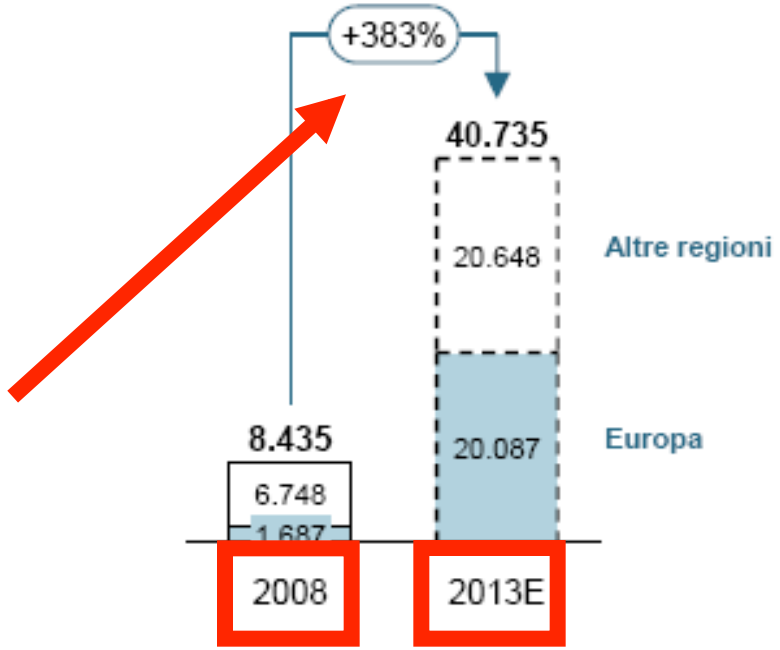
BEVALAC complex

(SuperHILac linear accelerator + Bevatron)

Development of Hadrontherapy

Up to day, more than 60.000 patients have been treated. This number is expected to be strongly increased

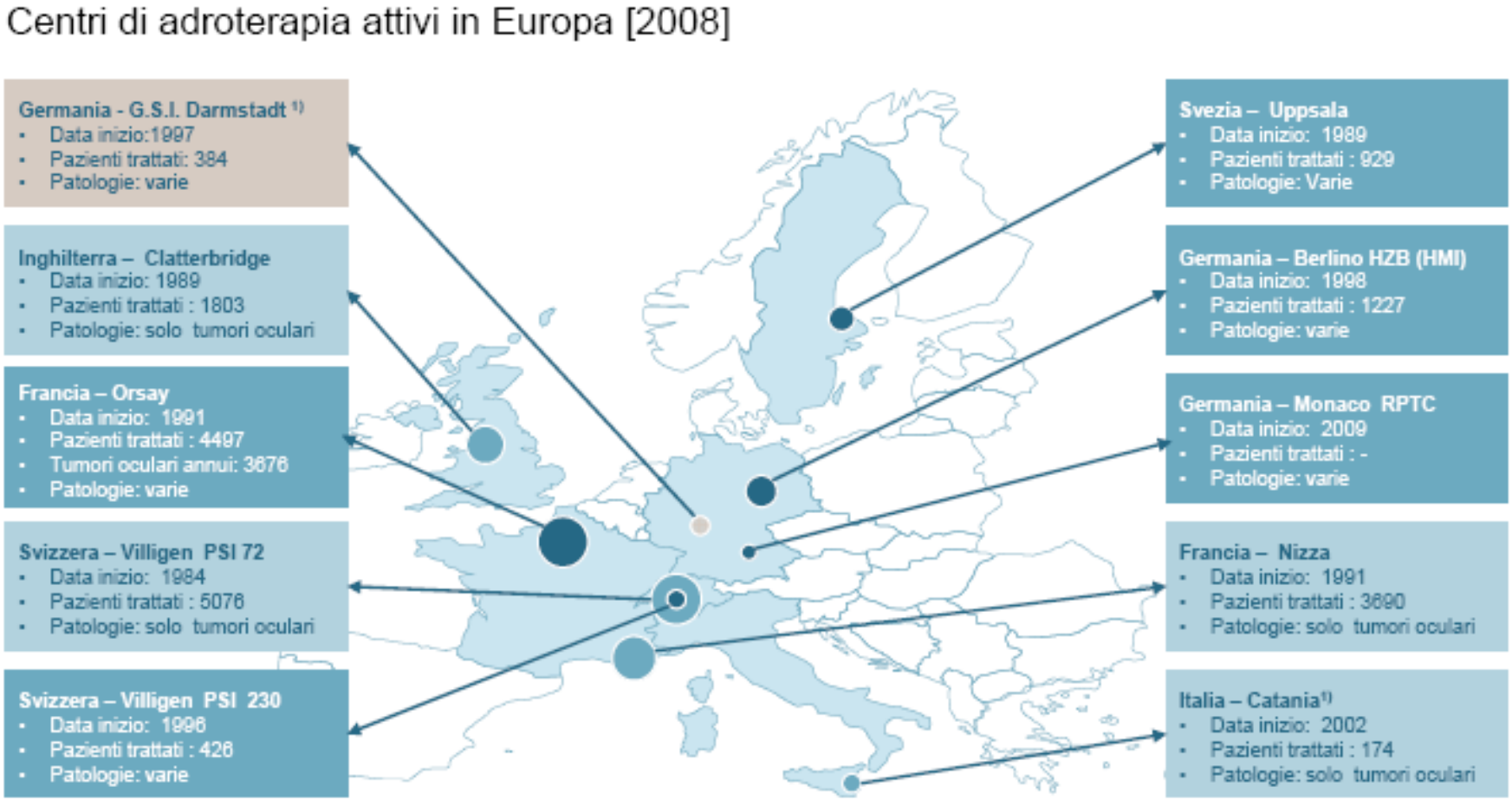




1) Stima al 2013 effettuata considerando una media di 400 pazienti/anno per sala di trattamento

Fonte: PTCOG (Particle Therapy Co-Operative Group)

10 centers of hadrontherapy, 9 with protons are currently working in Europe



In the next 4 years other 14 centers will be opened. Five will offer both proton and C-ion therapy

Nuovi Centri di Adroterapia

A Germania e Austria

- Germania, Koeln:
  - Inizio: n.d.
  - # di sale: 5
- Germania, Essen:
  - Inizio:2010
  - # di sale: 4
- Germania, Heidelberg:
  - Inizio: 2010
  - # di sale: 3
- Germania, Marburg:
  - Inizio: 2010
  - # di sale: 4
- Germania, Kiel :
  - Inizio: 2012
  - # di sale: 3
- Austria, Wiene:
  - Inizio: 2013
  - # di sale: 3

B Europa dell'Est

- Slovacchia, Bratislava:
  - Inizio probabile: 2010
  - # di sale:1
- Slovacchia, Ruzomberok:
  - Inizio: 2010
  - # di sale: 1
- Russia, Protvino:
  - Inizio: 2010
  - # di sale: 1
- Svezia, Uppsala:
  - Inizio probabile 2012
  - # di sale: 2

C Italia

- Italia, Pavia:
  - Inizio probabile: 2010
  - # di sale: 3-4
- Italia, Trento:
  - Inizio probabile: 2011
  - # di sale: 2

D Francia e Svizzera

- Francia, Orsay:
  - Inizio: 2010
  - # di sale: 3
- Svizzera, Villigen:
  - Inizio: 2009
  - # di sale: 1+2

1) Le date di Inizio indicate sono quelle presenti sul sito del *Particle Therapy Co-Operative Group*, presumibilmente l'apertura dei centri sarà spostata di qualche anno

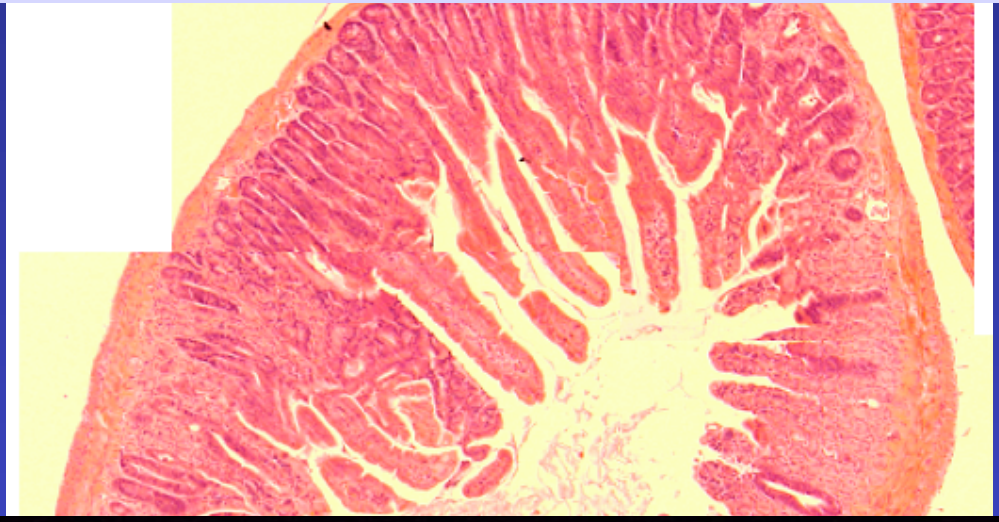
MIL-0101-08512-004-065-01

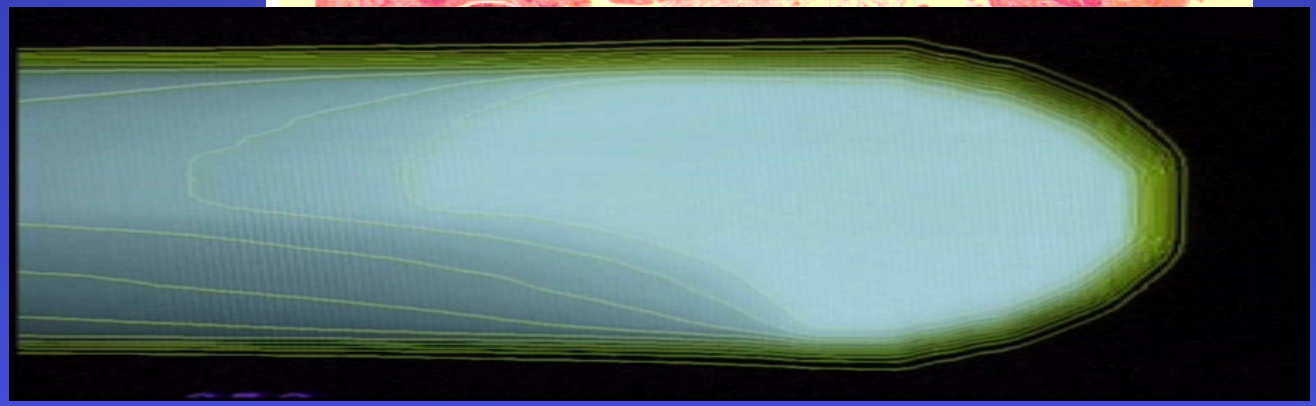
Adroterapia:

Un pò di razionali ...

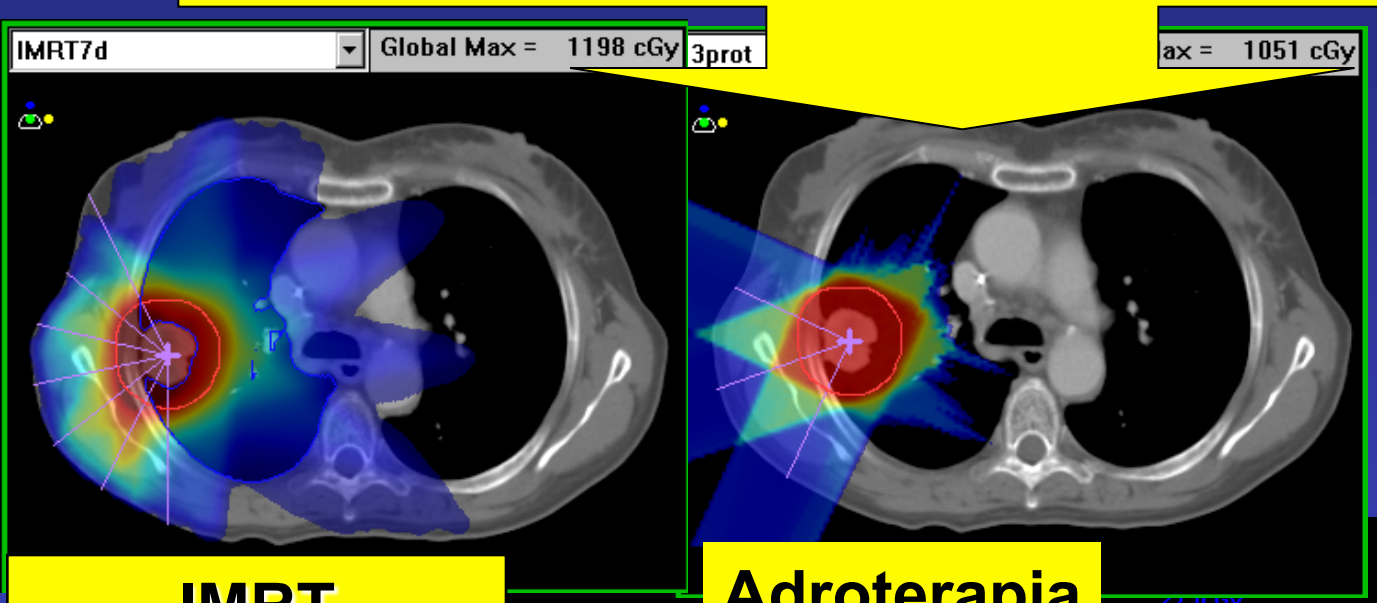

Il nostro obiettivo
.....

Una nuova dimensione .....



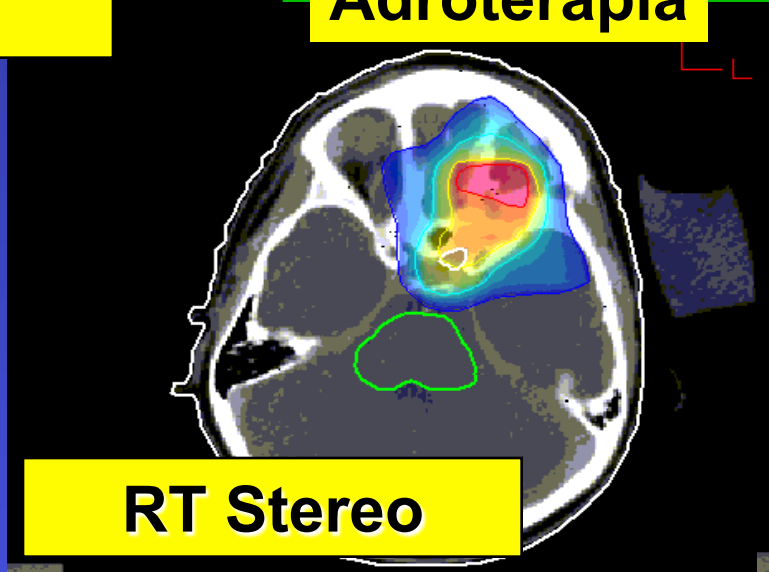


Physical Selectivity

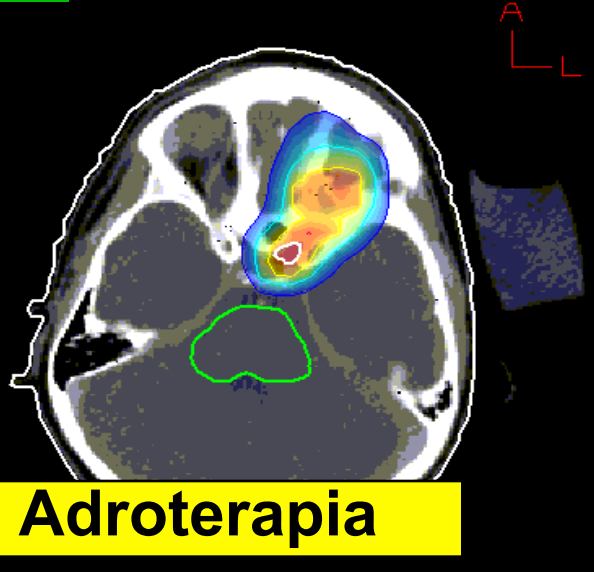


IMRT

Adroterapia

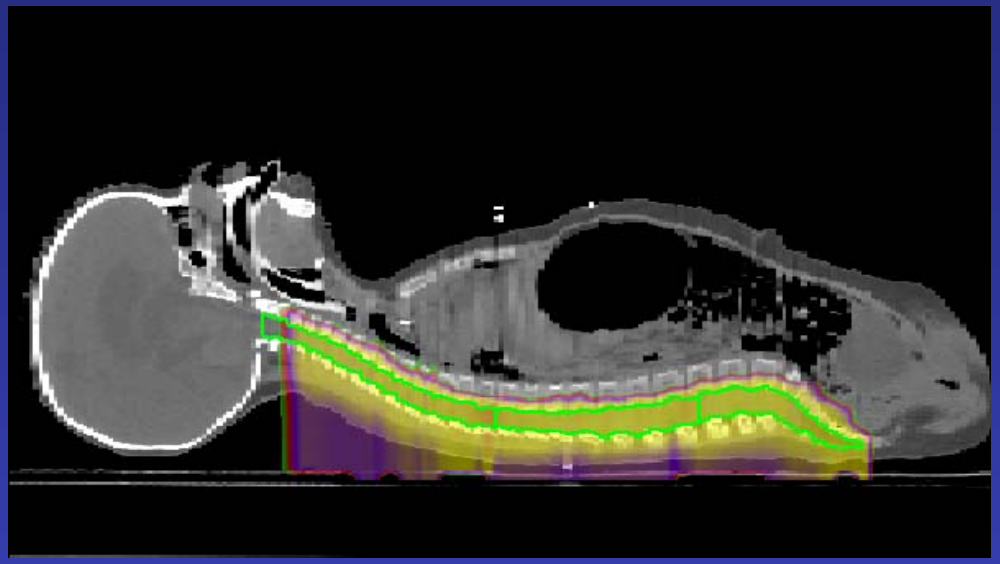


RT Stereo

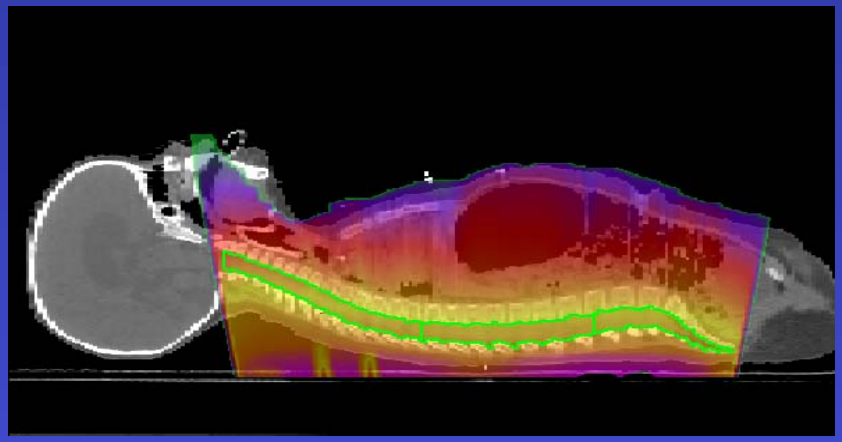


Adroterapia

Protons in pediatric tumors



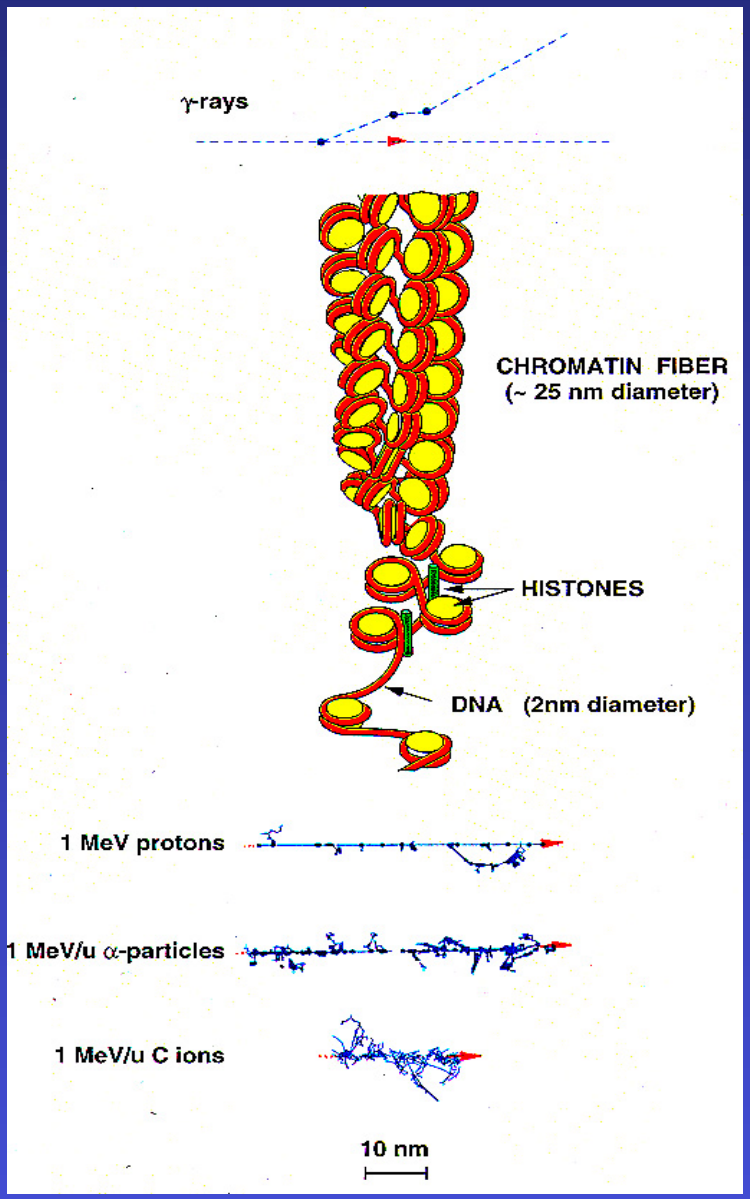
Protons

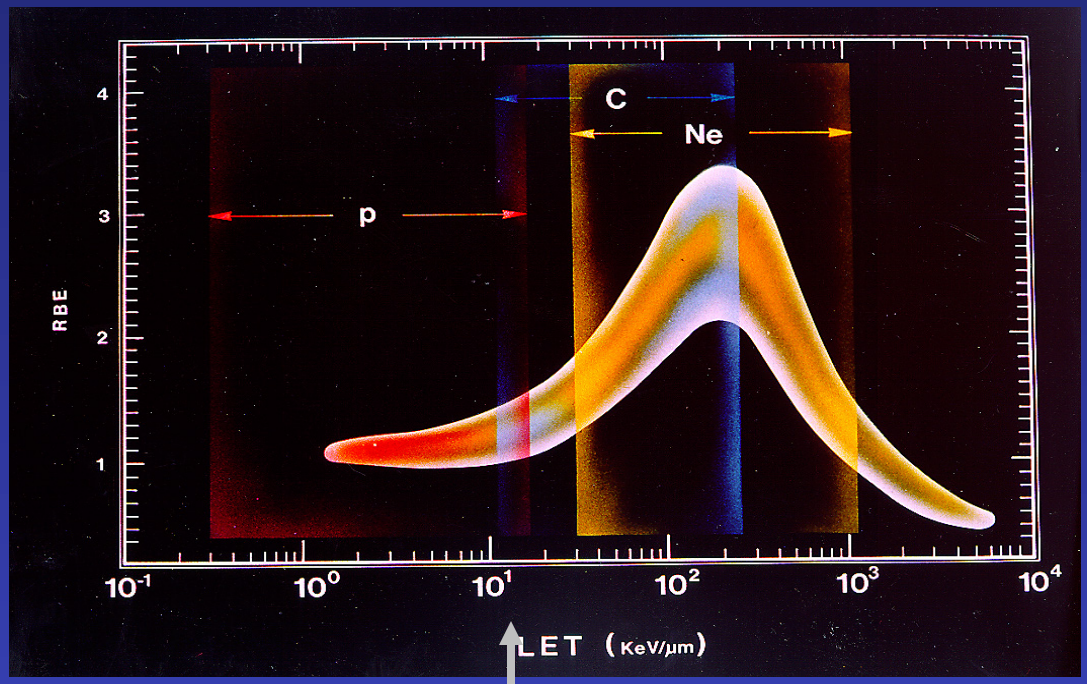


Photons

	X-ray	IMRT	Proton
CTV	90%	90%	90%
Heart	18.2	17.4	0.1
Right lung	3.5	21.9	0.1
Esophagous	11.9	32.1	10.2
Stomach	3.7	20.6	0.1
Right kidney	3.3	29.8	0.1
Transvers colon	2.6	18.0	0.1

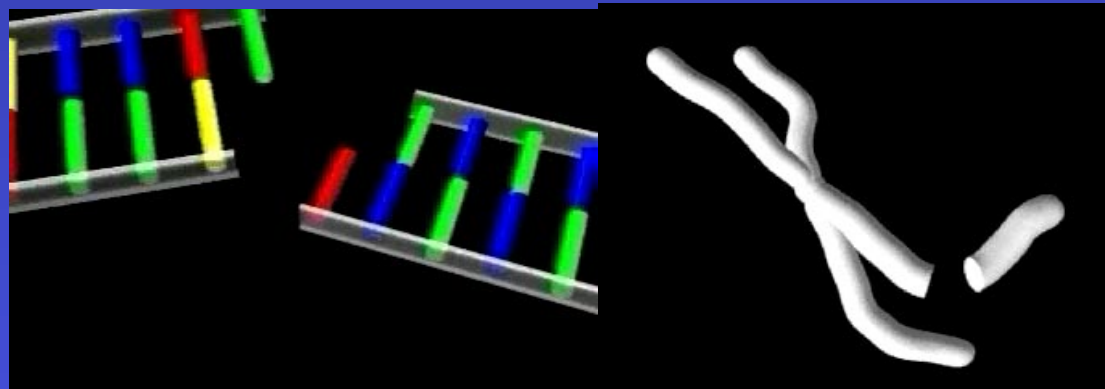
Biological Selectivity





10 – 20 keV/μm = 100 – 200 MeV/cm =

20 – 40 eV/(2 nm)

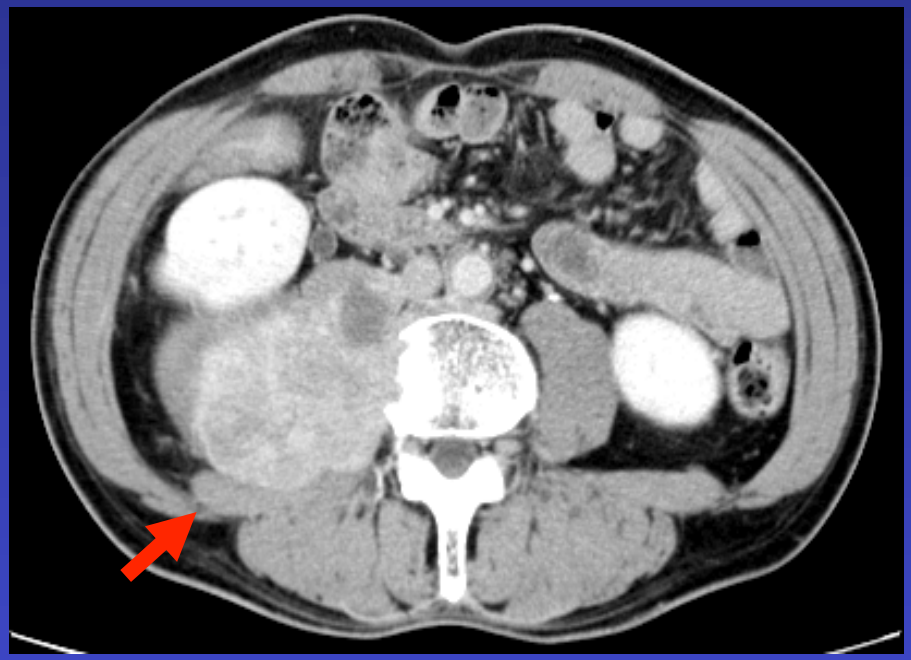


High – LET particles

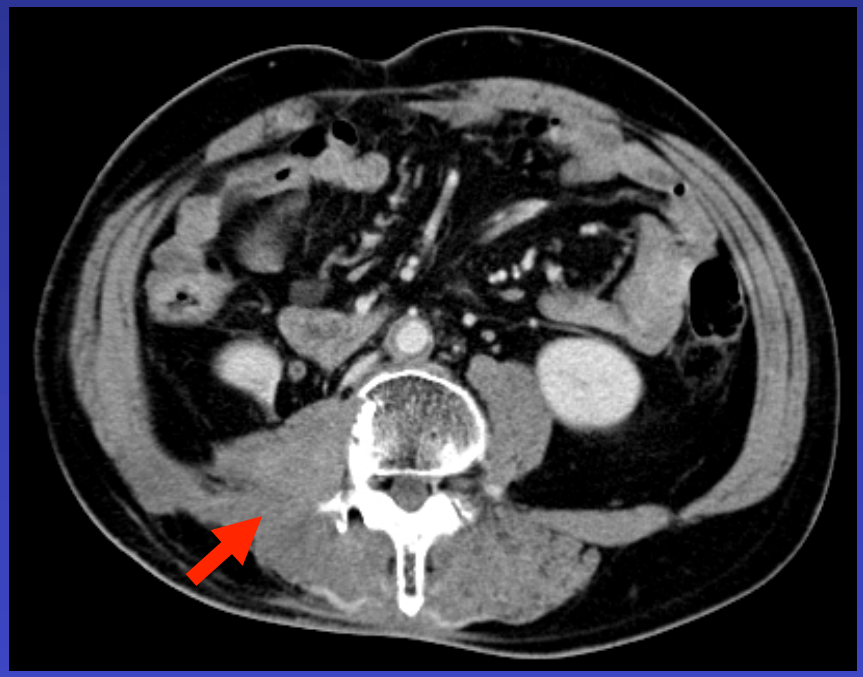
- Not related to OER
- No
- No
- ……

Suitable for “radioresistant” tumours

Retro-peritoneal rhabdomyosarcoma



Before



After 5 years

Adroterapia:

Un pò di radiobiologia ...

Caratterizzazione radiobiologica dei fasci di adroni

- Considerato un determinato effetto biologico (*end point*: morte cellulare, induzione di mutazioni geniche, aberrazioni cromosomiche…)
- Scelta una radiazione di riferimento (RX da tubo radiogeno di 250kV$_p$, Rγ del ^{60}Co)

RBE: rapporto tra l'effetto indotto dalla radiazione in esame e quello indotto dalla radiazione di riferimento a parità di dose assorbita.

Nel caso della sopravvivenza cellulare:

$$R.B.E. = \left(\frac{SF_{RX}}{SF_r} \right)_{D=2Gy}$$

(iso-dose)

Caratterizzazione radiobiologica dei fasci di adroni

Stima dell'RBE

Generalmente si utilizza l'RBE10: l'RBE definito al 10% di sopravvivenza:

$RBE10 = (D10_{RX} / D10_{ione})_{SF=10\%}$

In alternativa all'RBE10, si può valutare e utilizzare l'RBE50, ovvero l'RBE calcolato al 50% di sopravvivenza

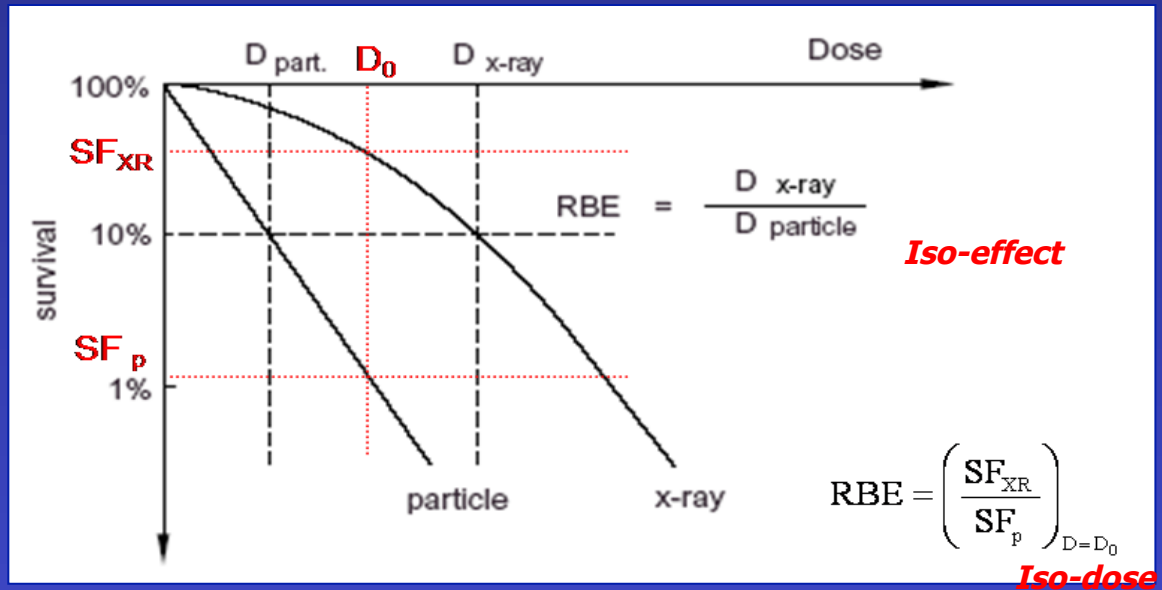
oppure

l'RBE2Gy calcolato al livello di dose D = 2 Gy, corrispondente alla dose per frazionamento utilizzata nei trattamenti radioterapici:

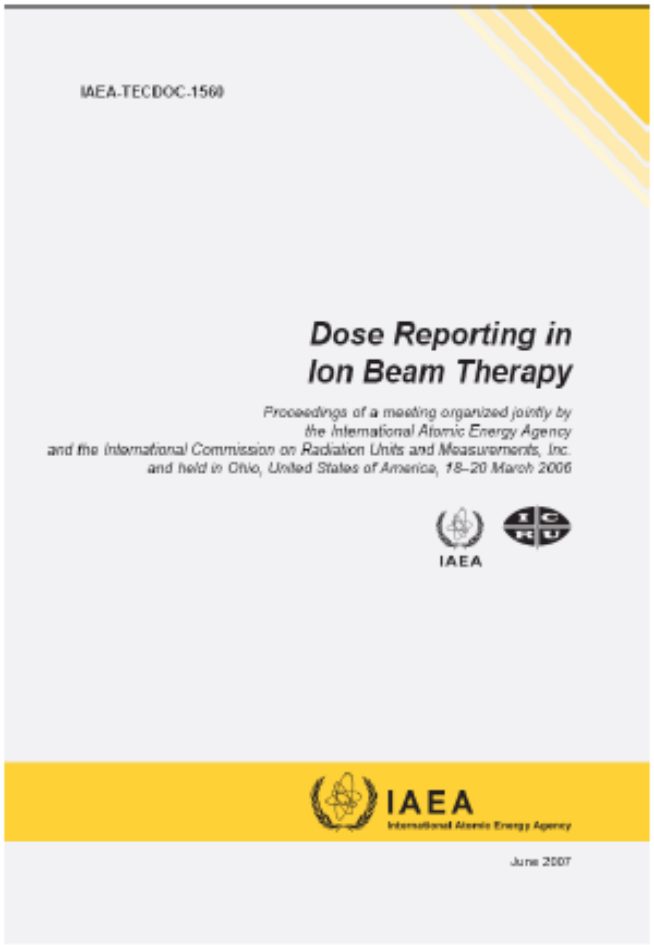
$RBE_{2Gy} = (SF_{RX} / SF_{ione})_{D = 2\ Gy}$

Caratterizzazione radiobiologica dei fasci di adroni

- Protoni (60-250 MeV):
  RBE assunto di 1.1
  -Caratterizzazione in vitro



- Ioni carbonio (120-400 MeV/n):
  RBE variabile
  - Caratterizzazione in vitro e in vivo



of experiment, i.e. "*preclinical*" experiments, need to be performed. The latter experiments have only reference to RBE determinations and aim at the clinical application of the new beams in safe and optimal conditions. Preclinical experiments are particularly important in high-LET radiation beams (e.g. fast neutrons, carbon ions) as RBE values are high (2–5) and do vary widely with dose and biological effect. Moreover, RBEs of these beams depend significantly on both the energy and the mode of production of the beams and on depth (especially for carbon ions). However, preclinical experiments are also necessary in clinical protons beams (which exhibit low RBE values in the range 1.10–1.15) as the latter RBEs are still high in comparison with the dose accuracy needed in radiation-therapy (±4.5% [2]).

Sperimentazione CNAO

Caratterizzazione Radiobiologica dei fasci di protoni

Valutazione dello RBE *in-vitro* dei protoni in funzione della profondità *(in acqua)* lungo la curva di Bragg *(Plateau e SOBP, Spread Out Bragg Peak)*

1. Misura delle curve di sopravvivenza cellulare a seguito di irraggiamento con protoni
2. Misura delle curve di sopravvivenza cellulare a seguito di irraggiamento con radiazione di riferimento (Raggi-X o gamma)
3. Stima dello RBE

Material and Methods

Cells are plated in appropriate samples (flasks and/or especially designed dishes) and irradiated as cell monolayer

A number of sample are irradiated in 3 (for protons) or 5 (for carbon ions) position along the plateau and the SOBP

Cells are irradiated at 5 to 7 different doses, in the dose range 0 – 8 Gy, depending on the cell line radiosensitivity

Clonogenic cell survival curves are measured

Three independent experiments are performed to evaluated the fitting curve parameters (a; b) by using the L-Q relation $SF = \exp(-aD-bD^2)$ or linear one $SF = \exp(-aD)$ and then the RBE:

Iso-effect

$RBE10 = (D10_{Rg} / D10_{ione})_{SF=10\%}$

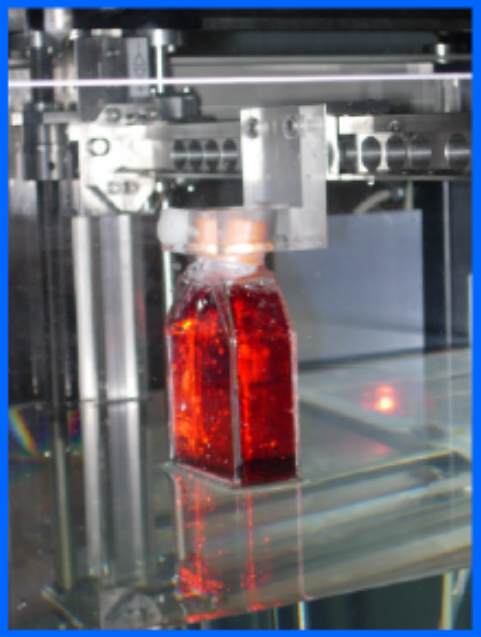
$RBE50 = (D50_{Rg} / D50_{ione})_{SF=50\%}$

Iso-dose

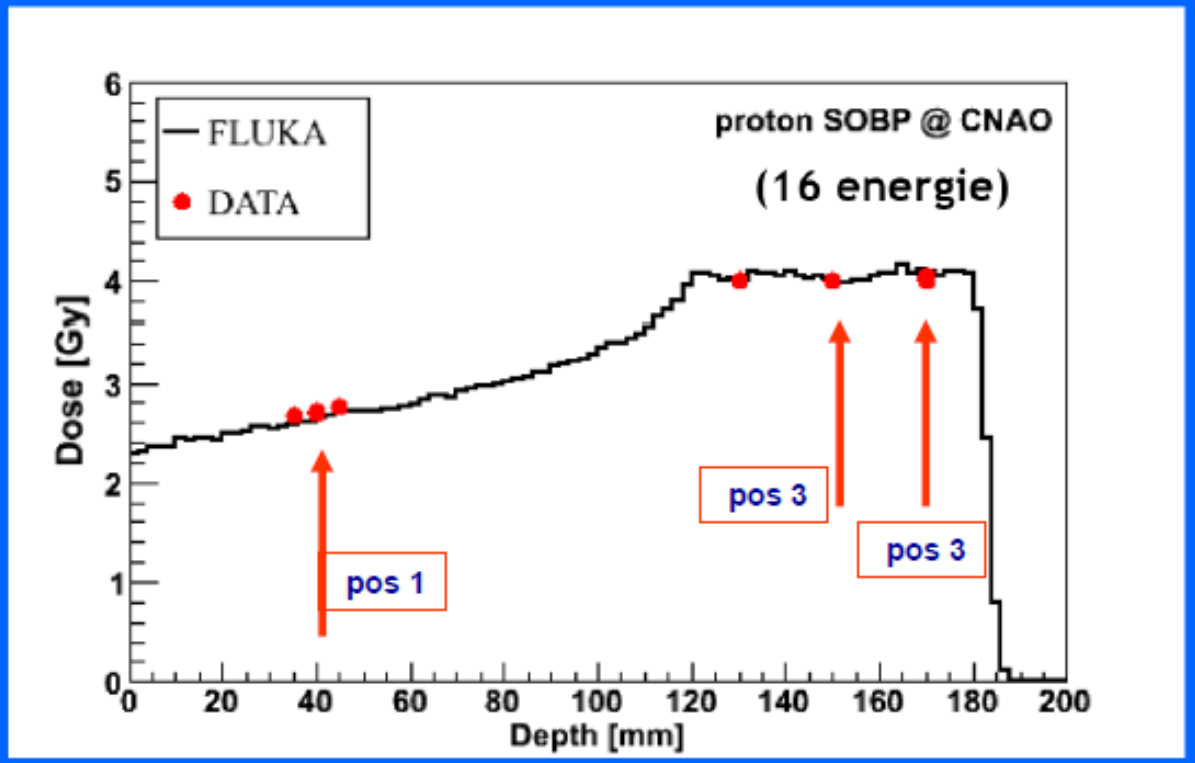
$RBE2Gy = (SF_{Rg} / SF_{ione})_{D=2Gy}$

Sperimentazione CNAO

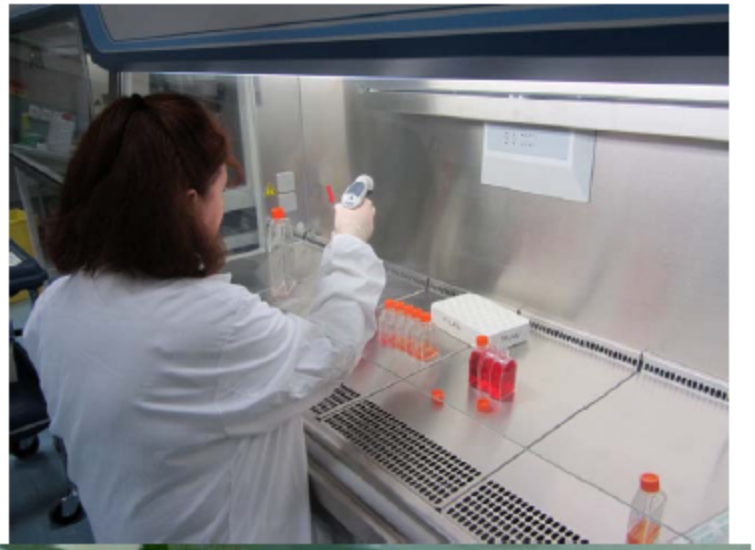
Irraggiamento con Protoni - CNAO



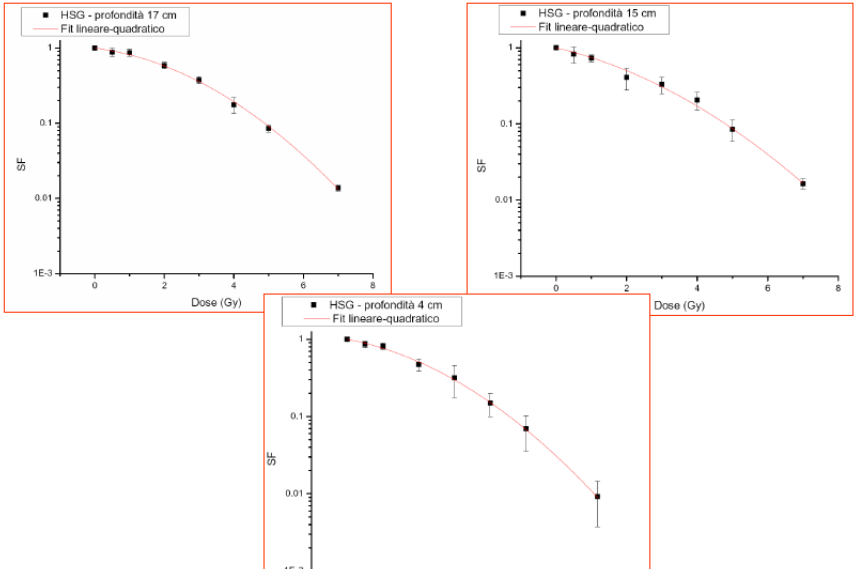
Campo 10x10 cm², 33x33 spot, step scansione 3 mm)



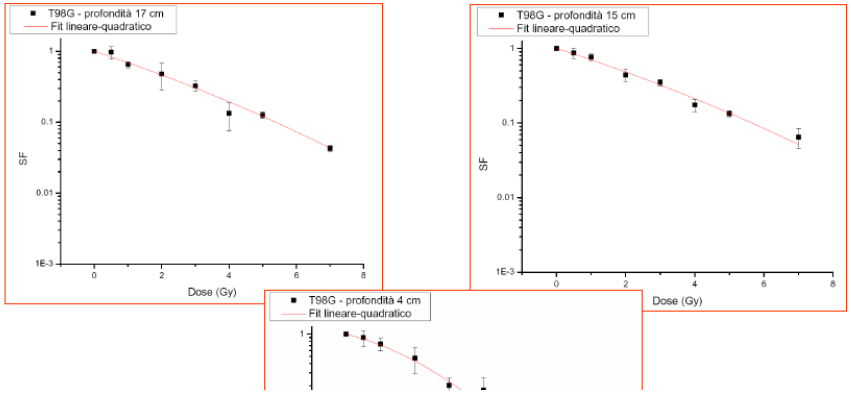
Laboratorio Radiobiologia - CNAO



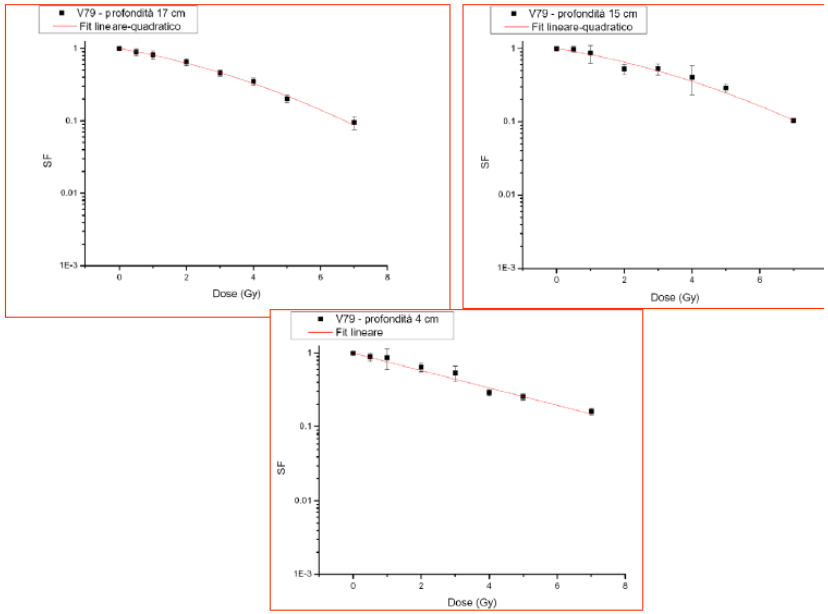
Curve di Sopravvivenza – Protoni: cellule HSG



Curve di Sopravvivenza – Protoni: cellule T98G



Curve di Sopravvivenza – Protoni: cellule V79



Radiazione di Riferimento: RX_INT 6MV

HSG					
RX INT			Rg Cs-137		
α (Gy^{-1}) β (Gy^{-2})	SF_{2Gy}	$D_{SF10\%}$ (Gy)	α (Gy^{-1}) β (Gy^{-2})	SF_{2Gy}	$D_{SF10\%}$ (Gy)
0.30±0.03 0.035±0.005	0.46	4.8	0.17±0.01 0.052±0.003	0.58	5.2

T98G					
RX INT			Rg Cs-137		
α (Gy^{-1}) β (Gy^{-2})	SF_{2Gy}	$D_{SF10\%}$ (Gy)	α (Gy^{-1}) β (Gy^{-2})	SF_{2Gy}	$D_{SF10\%}$ (Gy)
0.22±0.08 0.04±0.02	0.55	5.3	0.16±0.03 0.047±0.005	0.60	5.5

V79					
RX INT			Rg Cs-137		
α (Gy^{-1}) β (Gy^{-2})	SF_{2Gy}	$D_{SF10\%}$ (Gy)	α (Gy^{-1}) β (Gy^{-2})	SF_{2Gy}	$D_{SF10\%}$ (Gy)
0.09±0.02 0.030±0.004	0.74	7.4	0.13±0.02 0.029±0.003	0.69	7.0

Dati LNL

Stima RBE – Protoni CNAO

HSG	RBE protoni CNAO (rispetto RX INT)		RBE protoni CNAO (rispetto Rg Cs-137)	
	RBE_{2Gy} 0.46/SFp	RBE_{10} 4.8/D10p	RBE_{2Gy} 0.58/SFp	RBE_{10} 5.2 /D10p
P 4 cm	0.92	1.06	1.16	1.15
P 15 cm	0.94	1.02	1.18	1.11
P 17 cm	0.81	0.98	1.02	1.06

T98G	RBE protoni CNAO (rispetto RX INT)		RBE protoni CNAO (rispetto Rg Cs-137)	
	RBE_{2Gy} 0.55/SFp	RBE_{10} 5.3/D10p	RBE_{2Gy} 0.60/SFp	RBE_{10} 5.5/D10p
P 4 cm	1.27	1.32	1.39	1.37
P 15 cm	1.17	0.95	1.28	0.98
P 17 cm	1.22	0.98	1.33	1.02

V79	RBE protoni CNAO (rispetto RX INT)		RBE protoni CNAO (rispetto Rg Cs-137)	
	RBE_{2Gy} 0.74/SFp	RBE_{10} 7.4/D10p	RBE_{2Gy} 0.69/SFp	RBE_{10} 7 /D10p
P 4 cm	1.27	0.89	1.18	0.84
P 15 cm	1.14	1.06	1.06	1.00
P 17 cm	1.19	1.10	1.11	1.04

C-12. Mice crypt survival assay

ELSEVIER

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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

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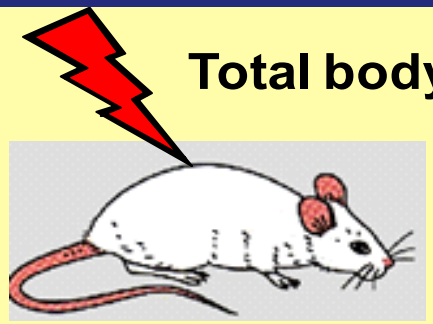
CNAO

Mice crypt survival assay



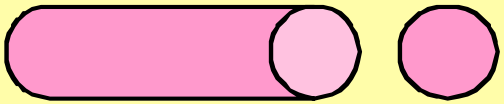
Total body irradiation
8-18 GyE

•topi femmina strain C3H/He
di 10–12 settimane acquistate
dalla Charles Rivers Company

3.5 days

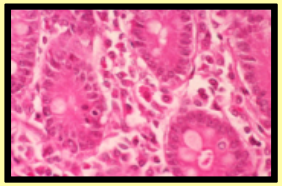
sacrifice

Gut Cross sections

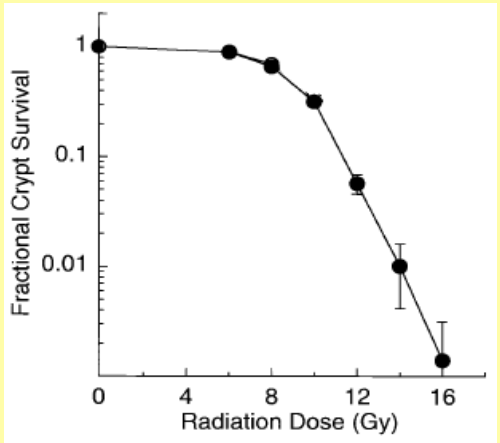


Microtome 4 µm sections

Histology



Counting

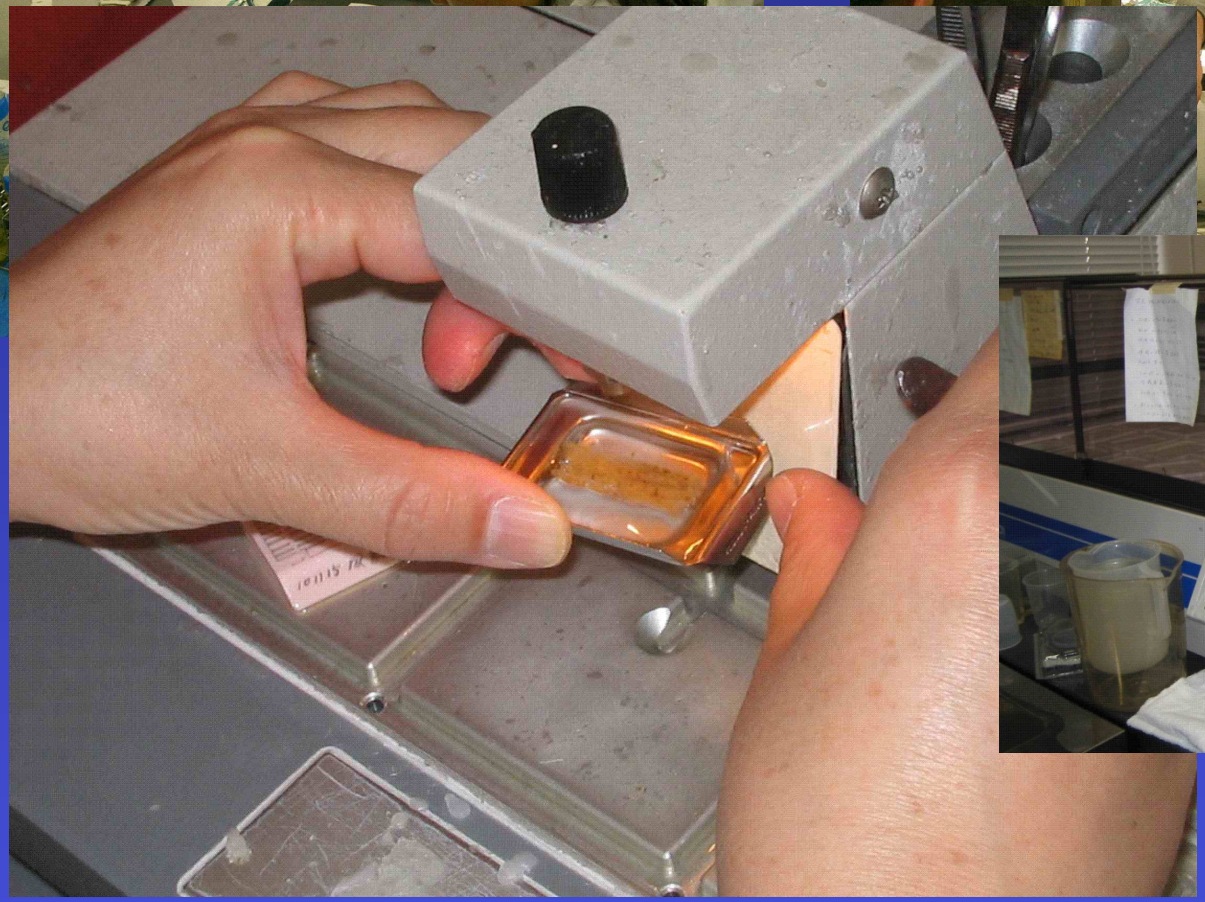


CNAO

Mice crypt survival assay

CNAO

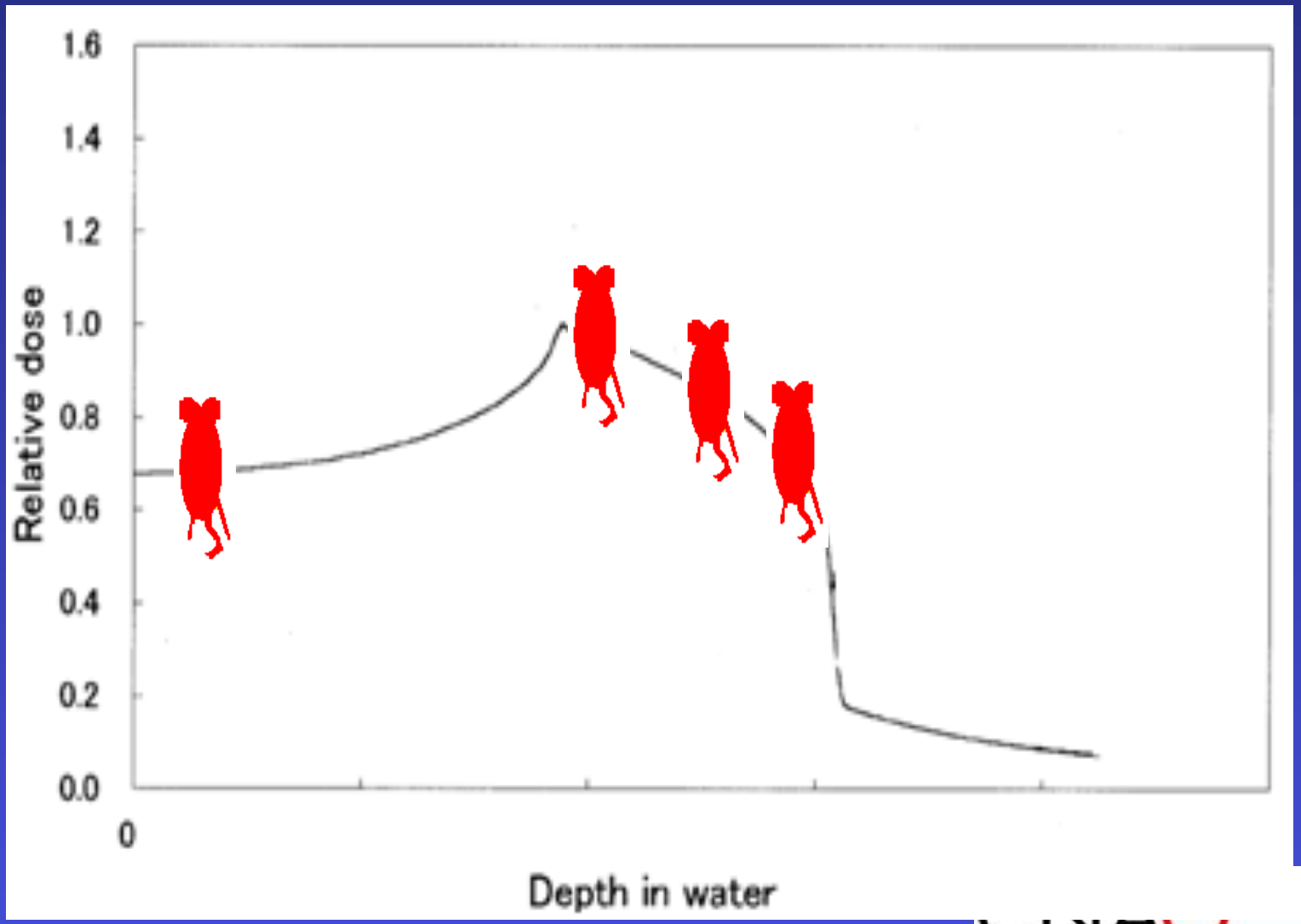
Mice crypt survival assay



CNAO

Mice crypt survival assay

Mice crypt survival assay
Risultati novembre 2010



Carbon ions (120-400 MeV/n)

Prescription of biological dose

- LEM (Local Effect Model)

- NIRS Model

NIRS – CNAO Collaboration

Prescription doses (GyE) (16 fractions, 4 fractions per week)								
Indication	NIRS dose	CNAO dose						
		Opposed ports		Orthogonal ports		Single port		
		q.e.		q.e.		q.e.		MC
		Cubes	Spheres	Cubes	Spheres	Cubes	Spheres	
Head and neck non mesenchymal cancer	3.6	4.2	4.15	4.2	4.15	4.2	4.15	4.19
Skull base chordoma and chondrosarcoma	3.8	4.35	4.3	4.35	4.3	4.35	4.3	4.33
Head and neck non mesenchymal cancer	4	4.5	4.4	4.5	4.45	4.5	4.45	4.47
Spinal chordoma and chondrosarcoma	4.2	4.65	4.6	4.7	4.6	4.7	4.6	4.64
Head and neck sarcoma	4.4	4.8	4.7	4.8	4.7	4.8	4.7	4.75
Bone and soft tissue sarcoma	4.4	4.8	4.75	4.8	4.75	4.8	4.75	4.78

Rat spinal chord tolerance

RADIATION TOLERANCE OF THE RAT SPINAL CORD AFTER 6 AND 18 FRACTIONS OF PHOTONS AND CARBON IONS: EXPERIMENTAL RESULTS AND CLINICAL IMPLICATIONS

CHRISTIAN P. KARGER, PH.D.,* PETER PESCHKE, PH.D.,† RITA SANCHEZ-BRANDELIK, PH.D.,‡ MICHAEL SCHOLZ, PH.D.,§ AND JÜRGEN DEBUS, M.D., PH.D.¶

Departments of *Medical Physics in Radiation Oncology; †Clinical Cooperation Unit Radiation Oncology; ‡Central Animal Laboratory, German Cancer Research Center (DKFZ), Heidelberg, Germany; §Department of Biophysics, Gesellschaft für Schwerionenforschung (GSI), Darmstadt, Germany; ¶Department of Clinical Radiology, University of Heidelberg, Heidelberg, Germany

Radiation Tolerance of the Rat Spinal Cord after Single and Split Doses of Photons and Carbon Ions[1]

Jürgen Debus,[a,d] Michael Scholz,[c] Thomas Haberer,[d] Peter Peschke,[d,2] Oliver Jäkel,[b] Christian P. Karger[b] and Michael Wannenmacher[a]

[a] Department of Clinical Radiology, University of Heidelberg, Germany; [b] Department of Medical Physics, German Cancer Research Center (DKFZ), Heidelberg, Germany; [c] Department of Biophysics, Gesellschaft für Schwerionenforschung, Darmstadt, Germany; and [d] Department of Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

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Rat spinal chord tolerance

Experimental Design

Biological Endpoint:

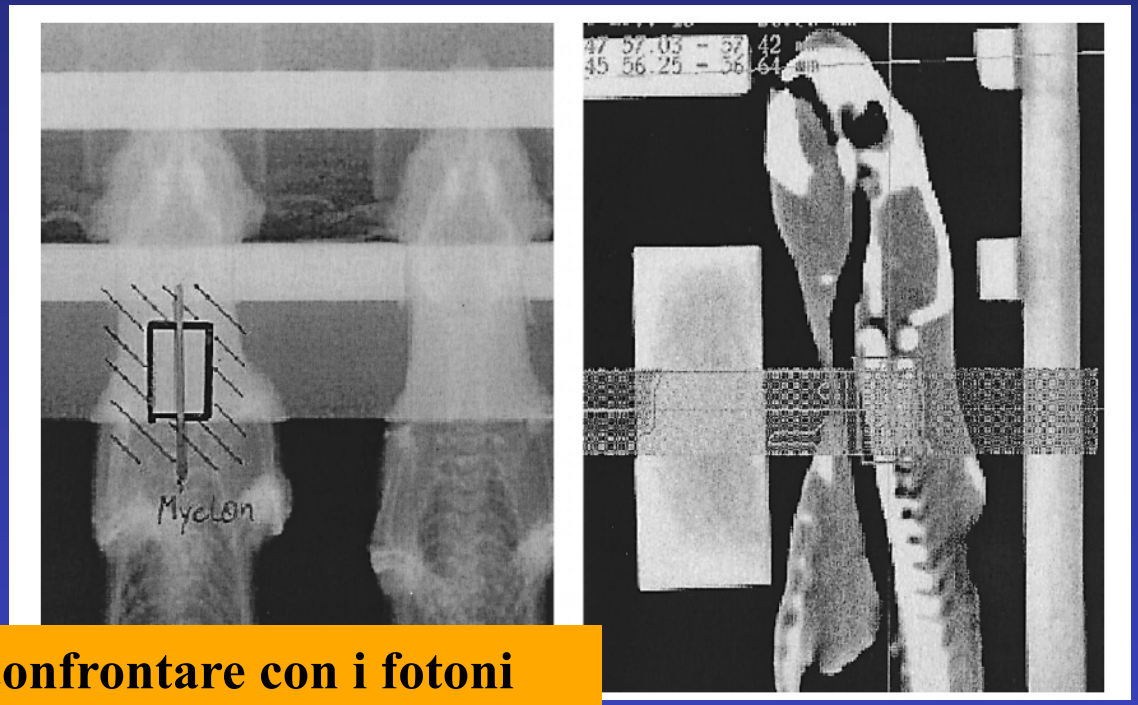
Paresis [Classification according to Ruifrook et al. 1994]

- **Latency**
- **Damage probability**
  related to dose and dose/fraction

Grade II locomotion disorders of extremities, limping

CNAO

Rat spinal chord tolerance



- Ingresso e centro SOBP da confrontare con i fotoni
- 150 ratti (10 controllo, 50 plateau. 50 centro SOBP) con 5 diverse dosi totali
- Follow-up necessario: 10 mesi
- Curve dose-risposta e calcolo ED50 per RBE

CNAO

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Biology Contribution

Carbon Ion Irradiation Inhibits Glioma Cell Migration Through Downregulation of Integrin Expression

Stefan Rieken, M.D.,* Daniel Habermehl, M.D.,* Lena Wuerth, B.T.A.,* Stephan Brons, Ph.D.,† Angela Mohr, M.D.,* Katja Lindel, M.D.,* Klaus Weber, Ph.D.,* Thomas Haberer, Ph.D.,† Jürgen Debus, M.D., Ph.D.,* and Stephanie E. Combs, M.D.*

*Department of Radiation Oncology, University Hospital of Heidelberg, Heidelberg, Germany; and †Heavy Ion Therapy Center, University Hospital of Heidelberg, Heidelberg, Germany

Purpose: To investigate the effect of carbon ion irradiation on glioma cell migration.

Methods and Materials: U87 and Ln229 glioma cells were irradiated with photons and carbon ions. Migration was analyzed 24 h after irradiation. Fluorescence-activated cell sorting analysis was performed in order to quantify surface expression of integrins.

Results: Single photon doses of 2 Gy and 10 Gy enhanced $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin expression and caused tumor cell hypermigration on both vitronectin (Vn) and fibronectin (Fn). Compared to integrin expression in unirradiated cells, carbon ion irradiation caused decreased integrin expression and inhibited cell migration on both Vn and Fn.

Conclusion: Photon radiotherapy (RT) enhances the risk of tumor cell migration and subsequently promotes locoregional spread via photon induction of integrin expression. In contrast to photon RT, carbon ion RT causes decreased integrin expression and suppresses glioma cell migration on both Vn and Fn, thus promising improved local control.

Keywords: Glioma, Integrin, Migration, Particle therapy, Radiotherapy

Adroterapia:

Un po’ di clinica …

Alternative all'EBM

Basis of clinical practice

Basis for clinical decisions	Marker	Measuring device	Unit of measurement
Evidence	[illegible]	Meta-analysis	Odds ratio
Eminence	Radiance of white hair	Luminometer	[illegible]
Vehemence	Level of stridency	Audiometer	Decibels
Eloquence (or elegance)	[illegible]	Teflometer	[illegible]
Providence	Level of religious fervour	Sextant to measure angl[illegible]	piety
Diffidence	Level of gloom	Nihilometer	Sighs
Nervousness	[illegible]	Every[illegible]	[illegible]
Confidence*	Bravado	Swea[illegible]	[illegible]

*Applies only to surgeons.

Eminence

Vehemence

Diffidence

Eloquence

Providence

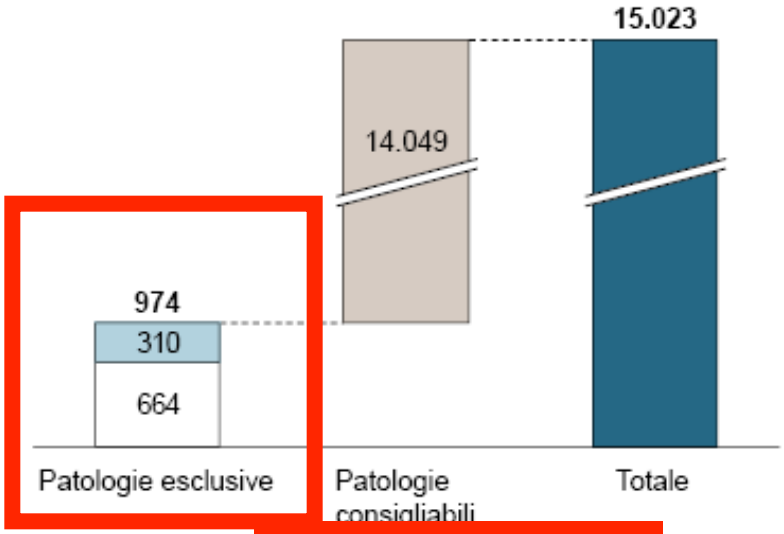
Nervousness

Confidence

Working Group 2003, 2008, 2009

Estimated 15.000 new eligible patients in Italy

for protons (2008)



High priority

- Le principali patologie esclusive sono il melanoma uveale (corrispondendi al 47% delle patologie elettive), i cordomi della base cranica e della colonna vertebrale, i condrosarcomi dell'estremità cefalica e del tronco, i meningiomi della base cranica, i tumori paraspinali, gli schwannomi dei nervi cranici, gli adenomi ipofisari e i tumori solidi pediatrici
- Le principali patologie consigliabili, su cui risulta particolarmente vantaggioso ,sono i tumori alla prostata, al pancreas, ai polmoni e al fegato
- In futuro si prevede una crescente estensione del campo di applicazione della terapia a protoni ad altre patologie anche non oncologiche

PT in Skull Base Chordomas and Chondrosarcomas

Ref	Institution	Pts	Histo	RT	GTV	Dose , mean (CGE)	% LC	Fu (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**	290 229	C CS	X+p	NA	72 (70 – 75.6)	5 yrs: 73 **(C)** 5 yrs: 98 **(CS)**	41 (1-254)
Igaki et al, 2004	**Tsukuba**	13	C	X+p (5) P only (8)	33.7 mL (3.3–88.4)	Median 72.0 (63.0 -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)

Protontherapy for Atypical and Malignant Meningiomas

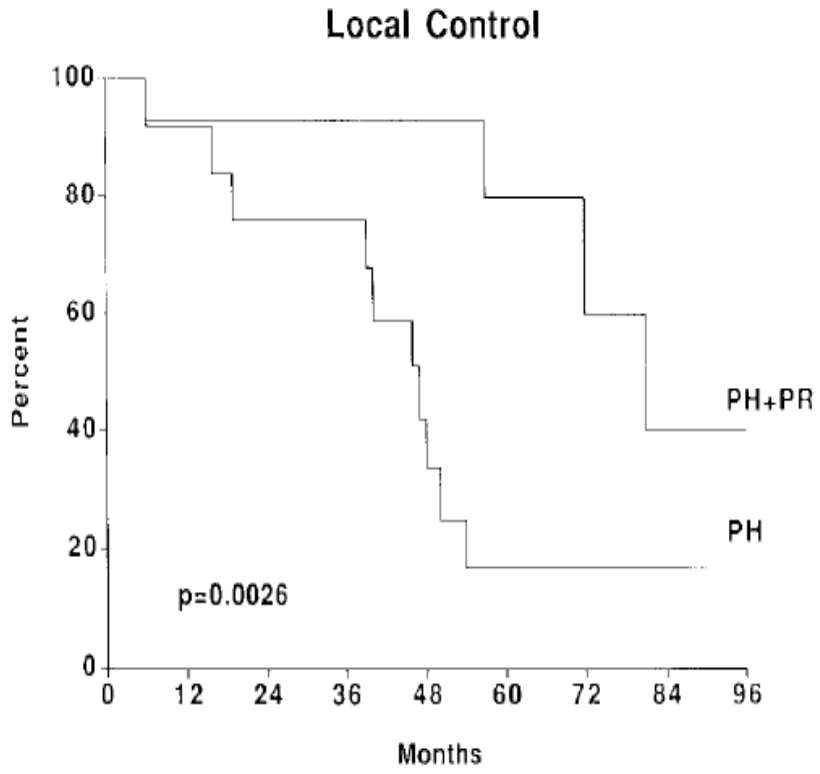


Figure 2. Actuarial local control of 28 patients with atypical or malignant meningioma treated either with photon radiation only (PH) or combined photon and proton RT (PH + PR).

IMPROVED L C with

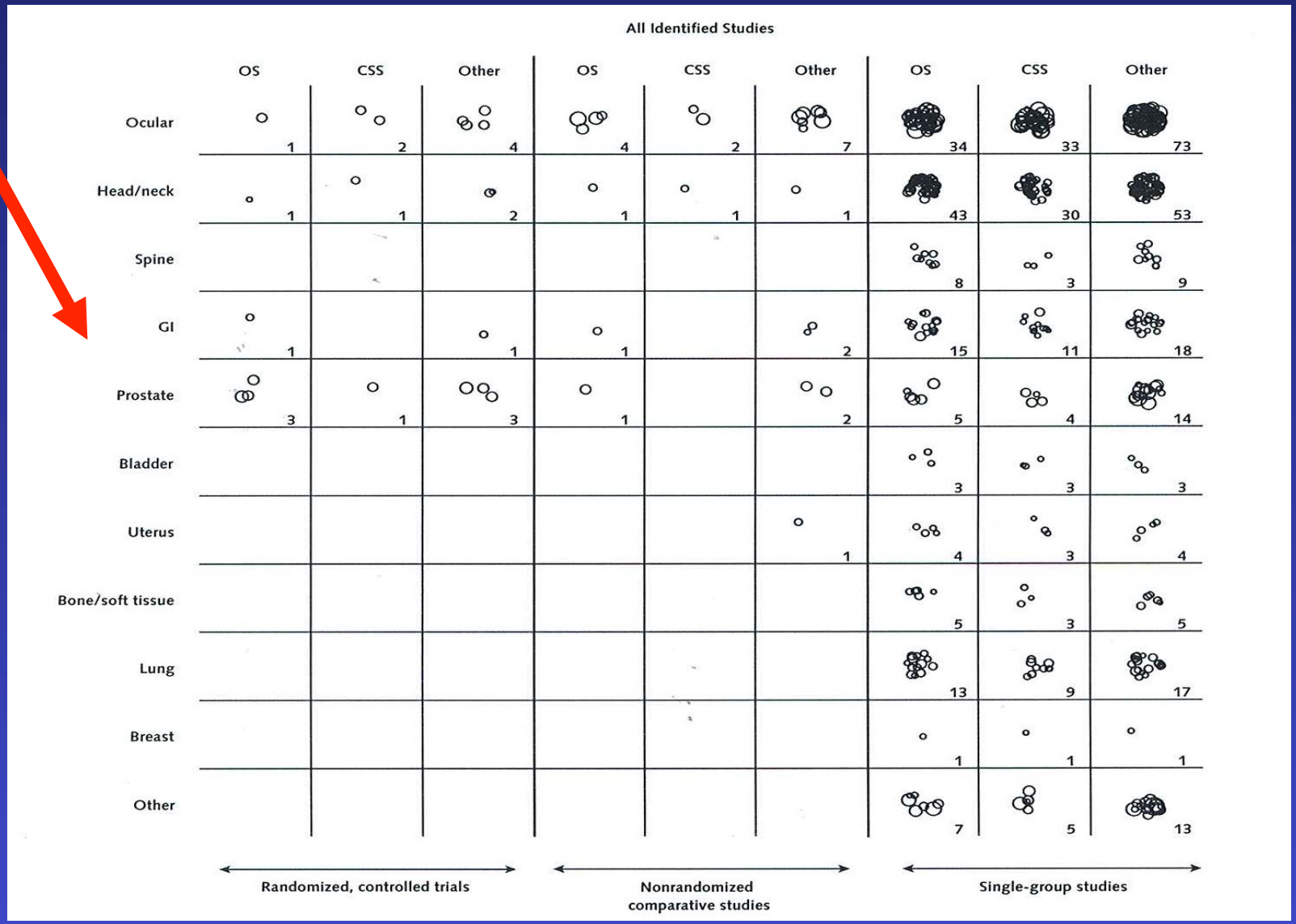
Proton-Photon: 80% at 5 yrs

Vs

Photon only: 17 % at 5 yrs

(p=0.008)

Hug E, J Neuro-Oncol ,2000



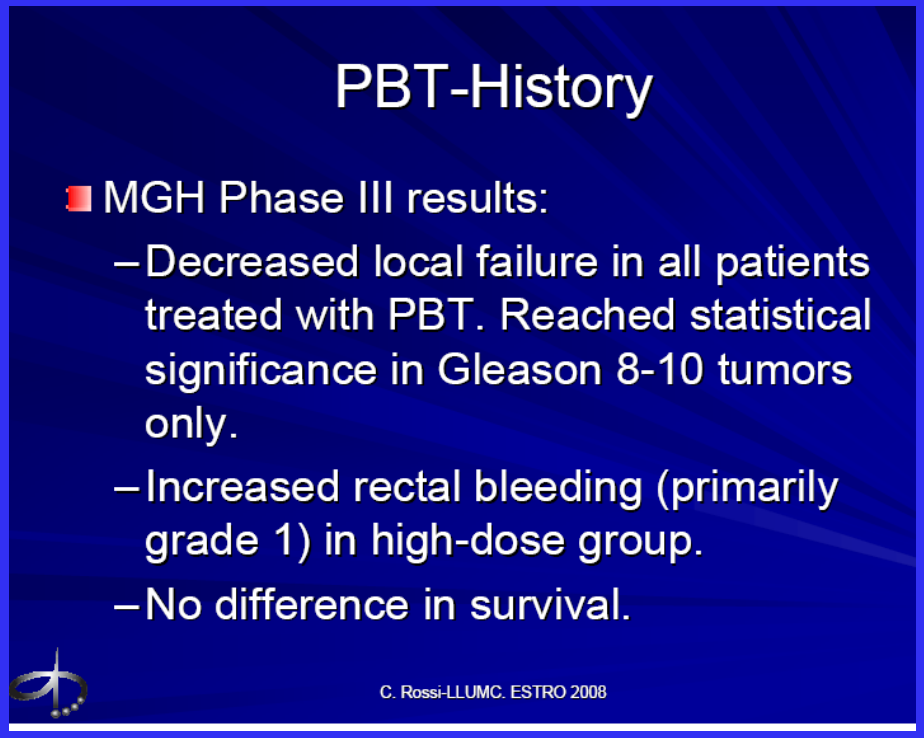
Terasawa T et al. Systematic review: Charged-Particle Radiation Therapy for Cancer Ann Intern Med 2009; 151: 556-65

1982-1995, T3-T4, 67.2 Gy vs 75.6 Gy

Shipley, IJROBP, 1995

MGH

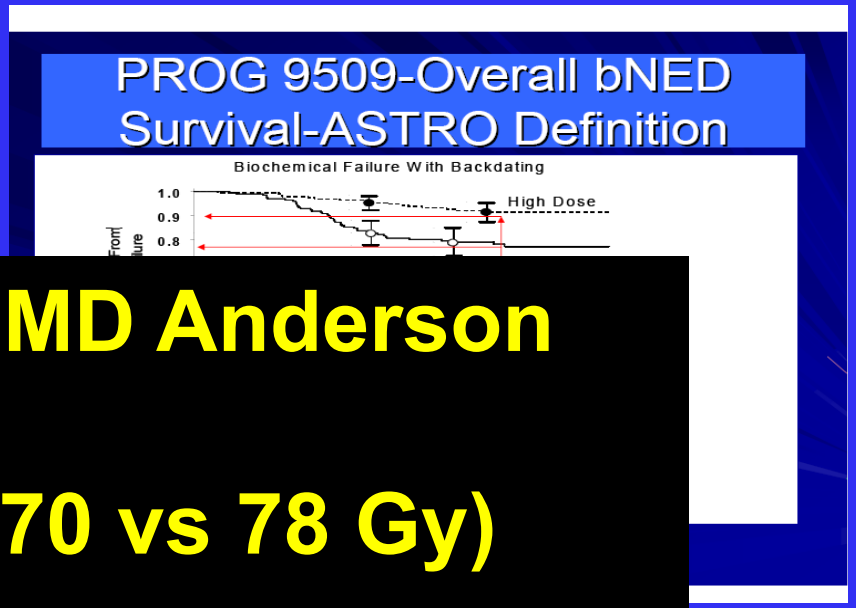
Boston



First Phase III randomized trial

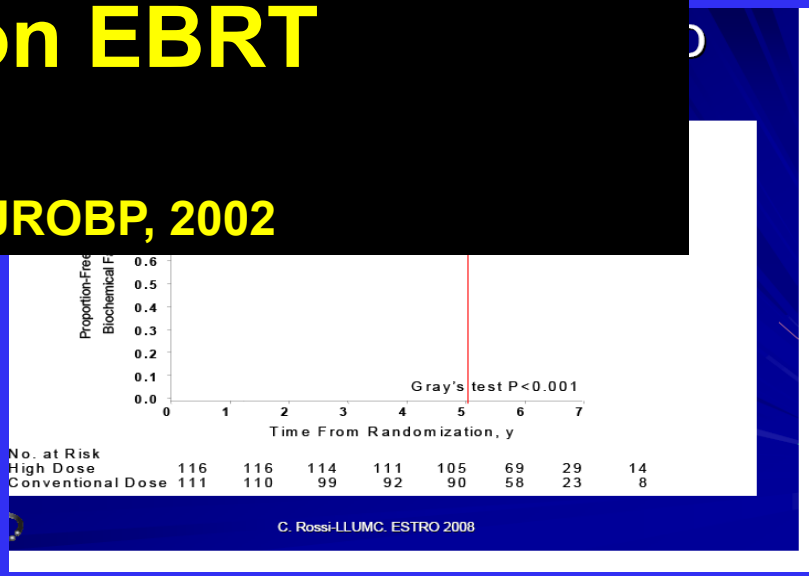
MGH & LLUMC

392 patients with early-stage



Same results of MD Anderson phase III trial (70 vs 78 Gy) with photon EBRT

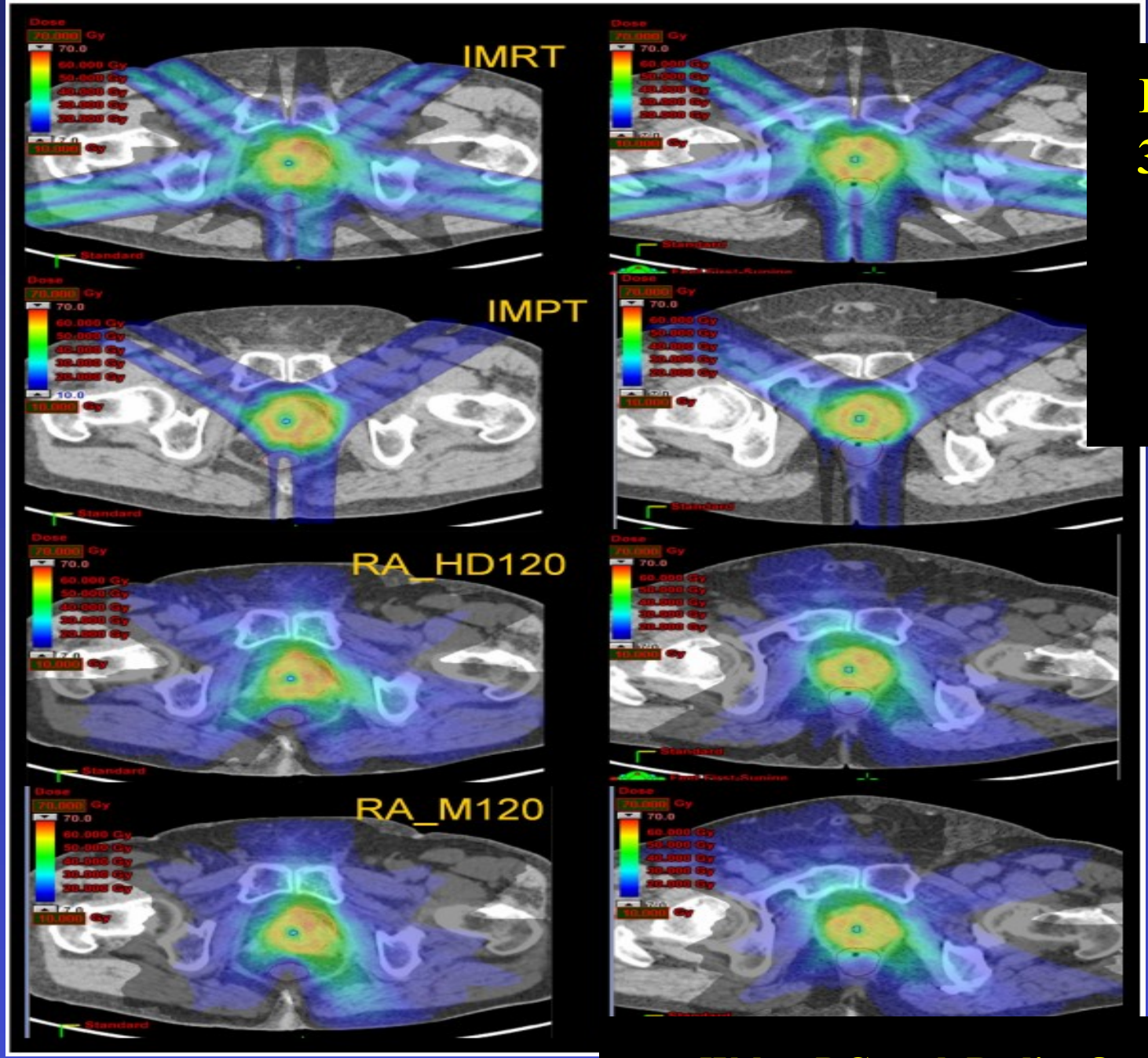
Pollack A et al, IJROBP, 2002



Zietman AL et al, JAMA, 2005

Update at 10 years
b-NED

High Dose	**83.7%**
Conventional Dose	**64.7%**
(P=0.0001)	



Integral Dose 3 times higher for all photon's techniques

Weber DC et al, Radiat Oncol, 2009; 4:34

Original Article

Early Findings on Toxicity of Proton Beam Therapy With Concurrent Chemotherapy for Nonsmall Cell Lung Cancer

Samir Sejpal, MD[1]; Ritsuko Komaki, MD[1]; Anne Tsao, MD[2]; Joe Y. Chang, MD, PhD[1]; Zhongxing Liao, MD[1]; Xiong Wei, MD[1]; Pamela K. Allen, PhD[1]; Charles Lu, MD[2]; Michael Gillin, PhD[3]; and James D Cox, MD[1]

Corresponding author: James D Cox, MD, Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030; jcox@mdanderson.org

Cancer July 1, 2011

Median total radiation dose was 74 Gy(RBE) for the proton group versus 63 Gy for the other groups. Rates of severe (grade ≥3) pneumonitis and esophagitis in the proton group (2% and 5%) were lower despite the higher radiation dose (3D-CRT, 30% and 18%; IMRT, 9% and 44%; $P<.001$ for all).

Table 2. Acute Nonhematologic Toxicity After Photon Versus Proton Therapy for Nonsmall Cell Lung Cancer

Toxicity and Treatment	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Unknown	*P*
Esophagitis								<.001
Chemotherapy+3D-CRT	3 (4)	25 (34)	33 (45)	13 (18)	0	0	0	
Chemotherapy+IMRT	4 (6)	9 (14)	24 (36)	26 (39)	3 (4.5)	0	0	
Chemotherapy+PBT	13 (21)	22 (35.5)	24 (39)	3 (5)	0	0	0	
Pneumonitis								<.001
Chemotherapy+3D-CRT	23 (31)	9 (12)	20 (27)	22 (30)	0	0	0	
Chemotherapy+IMRT	19 (29)	24 (36)	17 (26)	4 (6)	0	2 (3)	0	
Chemotherapy+PBT	13 (21)	30 (48)	18 (29)	1 (2)	0	0	0	
Dermatitis								<.001
Chemotherapy+3D-CRT	6 (8)	54 (73)	9 (12)	5 (7)	0	0	0	
Chemotherapy+IMRT	5 (8)	33 (50)	17 (26)	11 (17)	0	0	0	
Chemotherapy+PBT	2 (3)	22 (35.5)	23 (37)	15 (24)	0	0	0	
Fatigue								.002
Chemotherapy+3D-CRT	0	20 (24)	28 (34)	24 (29)	2 (2)	0	0	
Chemotherapy+IMRT	12 (18)	16 (24)	27 (41)	10 (15)	1 (1.5)	0	0	
Chemotherapy+PBT	3 (5)	12 (19)	32 (52)	12 (19)	3 (5)	0	0	

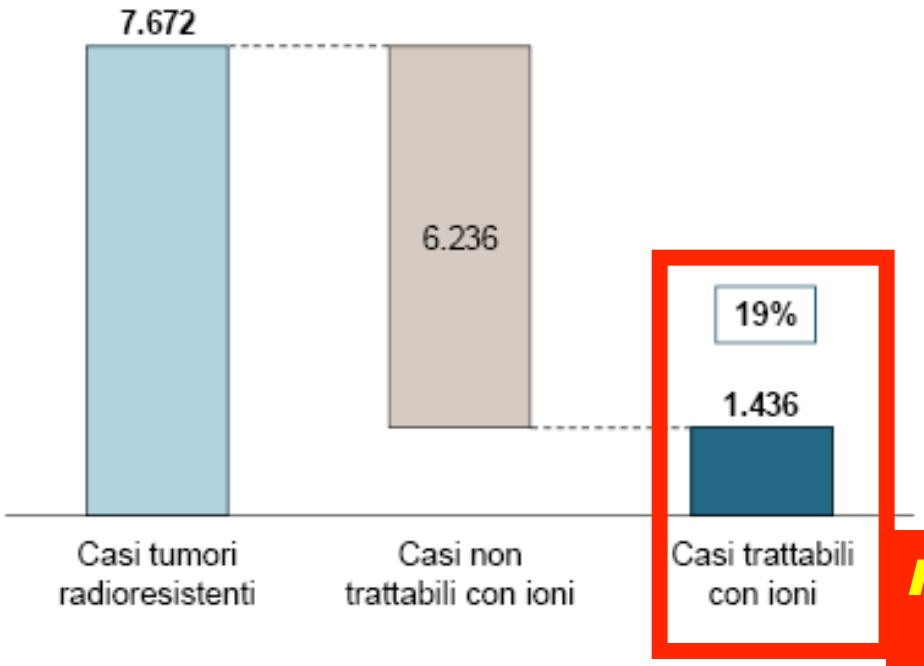
All data are expressed as No. of patients (%).
3D-CRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy.

Statisticamente significativo e quantitativamente molto rilevante diminuzione della tossicità dose limitante anche con un incremento della dose di prescrizione

Working Group 2003, 2008, 2009

Estimated 7.000 patients with "radioresistant tumors" in Italy (2008)

About 20% of these tumors should be treated by ions



- Le terapie con ioni di carbonio potrebbero 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

High priority

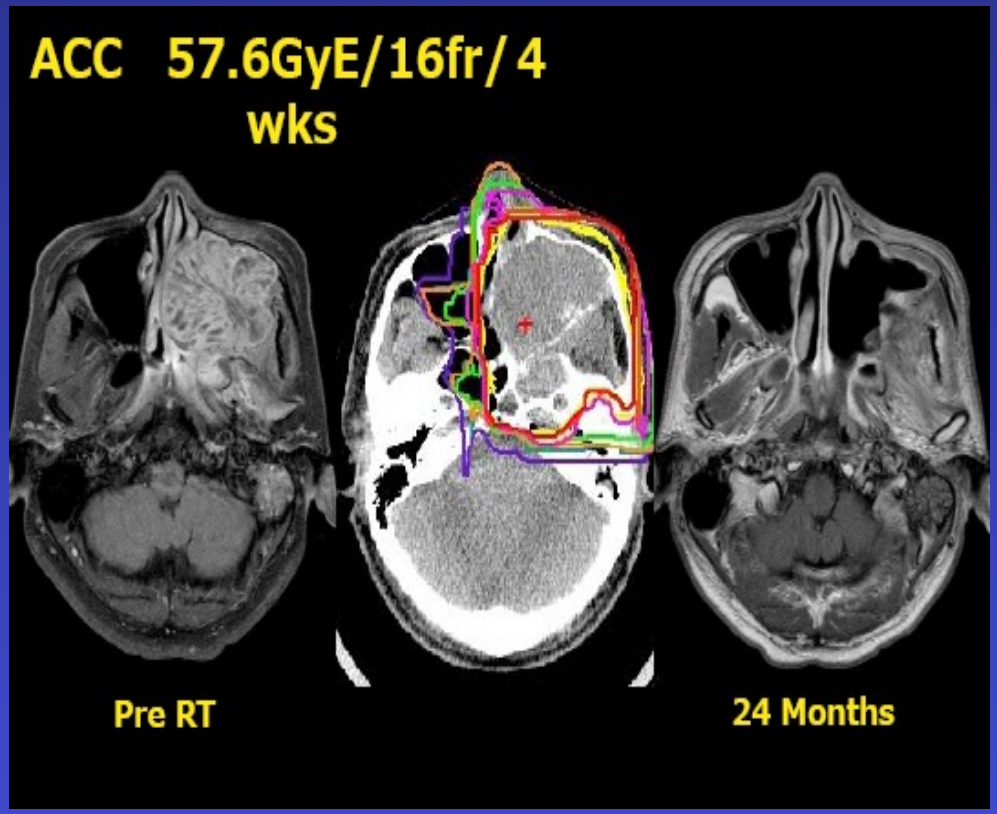
Fonte: Airo

Malignant Head and Neck Tumors

NIRS experience – Phase II Clinical Trial (Protocol 9602):

375 patients (378 lesion treated) . From April 1997 to February 2010

Dose 64.0 GyE in 16 fractions over weeks (57.4 GyE when wide area of skin within target volumes)



5 yrs LC : 75 %
5 yrs OS: 54 %

Adenocarcinoma (N=46)
5 yrs LC: 79 % 5 yrs OS: 66 %

Adenoid Cyctic Carcinoma (N=134)
5 yrs LC : 81 % 5 yrs OS 72 %

Malignant Melanoma (n= 102)
5 yrs LC: 78 % 5 yrs OS 36 %

Okada T et al, J Radiat Res 2010
Hasegawa A et al, 2010 (personal communication)

Head and Neck Sarcomas

Institution (year)	Histology	Treatment	*n*	MOP (mo)	5-year LC (%)	5-year OS (%)
MSCMCC (12) (1970–2001)	Soft-tissue sarcoma	Surgery ± X-ray ± chemo	112	139	45	35
RMH (21) (1944–1988)	Soft-tissue sarcoma	Surgery ± X-ray ± chemo	103	50	47	50
MGH (22) (1972–1993)	Soft-tissue sarcoma	Surgery ± X-ray ± chemo	46	50	69	74
UCSF (23) (1961–1993)	Soft-tissue sarcoma	Surgery ± X-ray ± Chemo	65	64	66	56
NCI (24) (1985–1996)	Osteosarcoma	Surgery ± X-ray ± chemo	496	—	—	59.7
NIRS (current study) (2001–2008)	Bone and soft-tissue sarcoma	Carbon ion RT	27	37.0	80.4	57.6

Abbreviations: LC = 5-year local control rate; MOP = median observation period; MSCMCC = M. Sklodowska-Curie Memorial Cancer Center; NCI = national cancer institute; NIRS = National Institute of Radiological Sciences; OS = 5-year overall survival; RMH = Royal Marsden Hospital; UCSF = university of california san francisco.

Jingu K et al, IJROBP, July 2011 – In press

Comparison in Local Failure

Radiotherapy	Dose	No.pts.	No.failure	Local failure (%)
RTOG 9413*				
Whole P + Boost	70.2Gy/39f	641	49	7.6%
Prostate only	70.2Gy/39f	638	46	7.2%
MDA Trial#				
Conventional	70.0Gy/35f	150	12	8.0%
3DCRT	78.0Gy/39f	151	7	4.6%
Carbon	63.0~66.0/20f, 57.6/16f	545	4	0.7%

Comparison in Survival Rate with Results of 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+ Hormone		114	76%	138	79%	103	63%
Carbon							
RT+ Hormone	66.0/20	187	99%	186	94%	77	84%

*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

ARTICLE IN PRESS

2011

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journal homepage: www.thegreenjournal.com

Original article

Re-irradiation with scanned charged particle beams in recurrent tumours of the head and neck: Acute toxicity and feasibility

Alexandra D. Jensen [a,*], Anna Nikoghosyan [a], Malte Ellerbrock [b], Swantje Ecker [b], Jürgen Debus [a], Marc W. Münter [a]

[a] Department of Radiation Oncology, Heidelberg, Germany; [b] Department of Medical Physics, Heidelberg Ion Therapy Centre (HIT), Germany

Conclusion

Charged particle radiotherapy for re-irradiation so far seems feasible has demonstrated a very favourable acute toxicity profile in all observed locations and promising response rates in non-chordoma/chondrosarcoma histologies. SD could be achieved in 4/5 patients with chordoma/chondrosarcoma. While acute reactions and response rates are promising, further follow-up is needed to prove that this also holds true for late radiation-induced side effects. Meanwhile a phase II study protocol for re-irradiation of recurrent or secondary primary tumours with carbon ion therapy is in preparation.

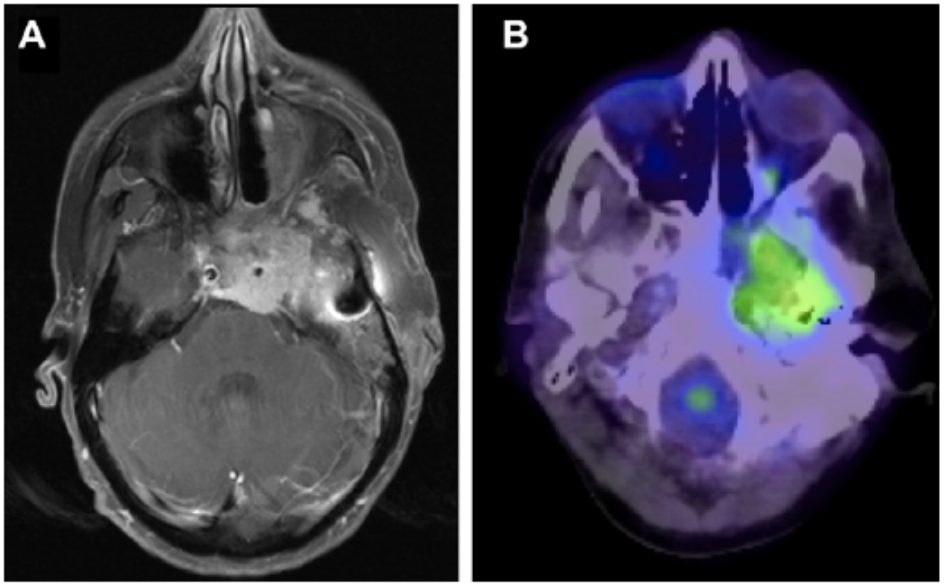


Fig. 1. Planning scans; (A) contrast-enhanced MRI and (B) PET-CT.

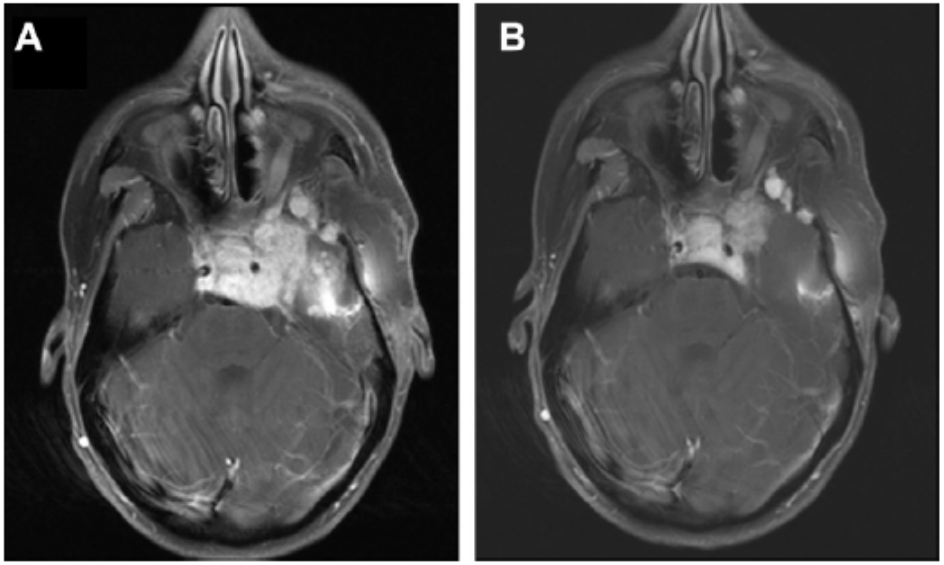
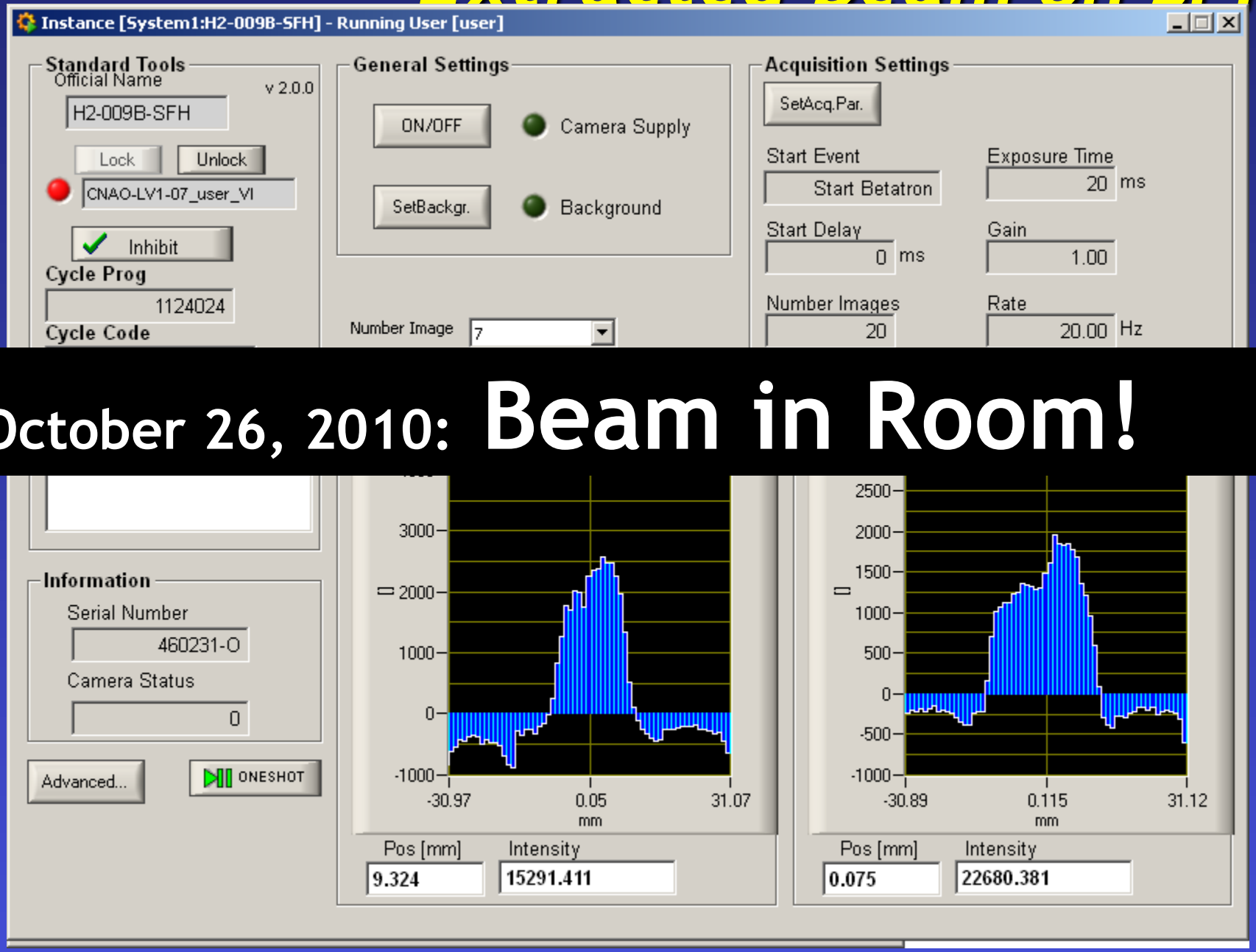


Fig. 2. Follow-up: (A) SD 8 weeks post RT and (B) PR 6 months post RT.

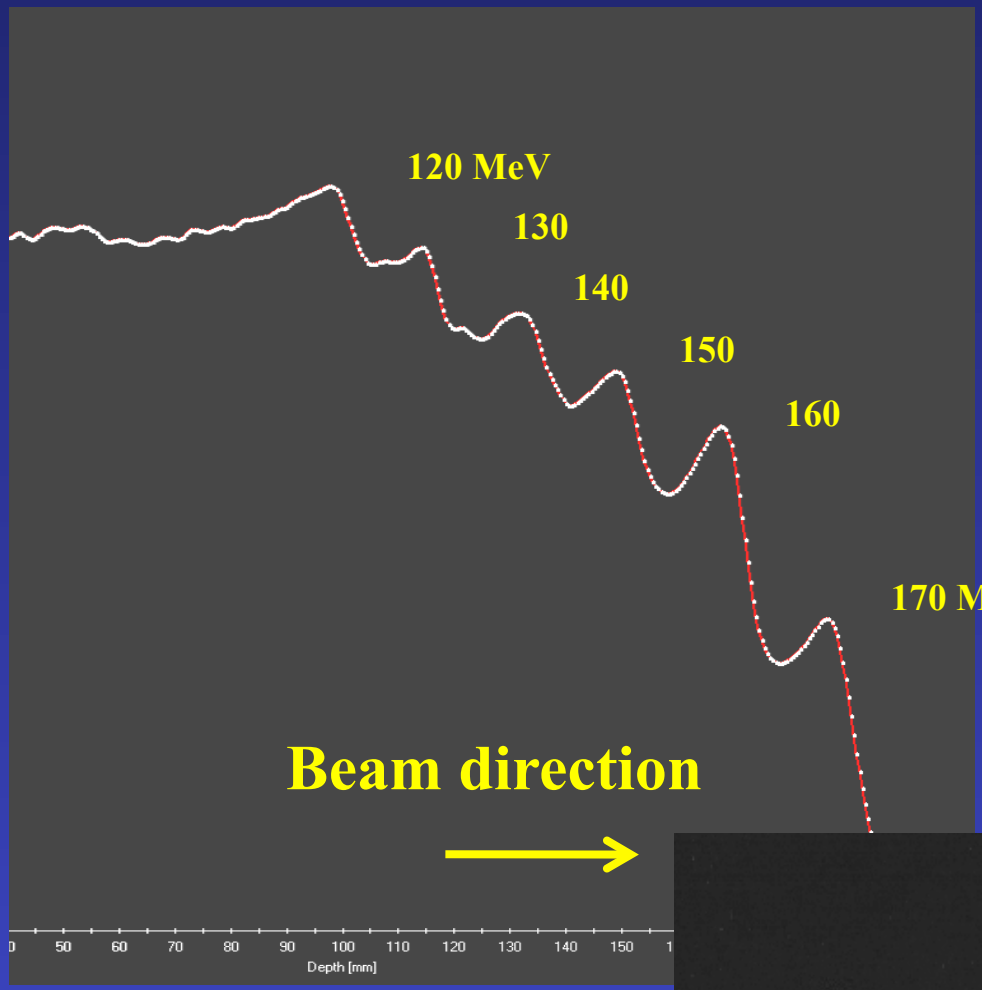
Adroterapia:

Un po’ di Italia …

Extracted beam on SFH

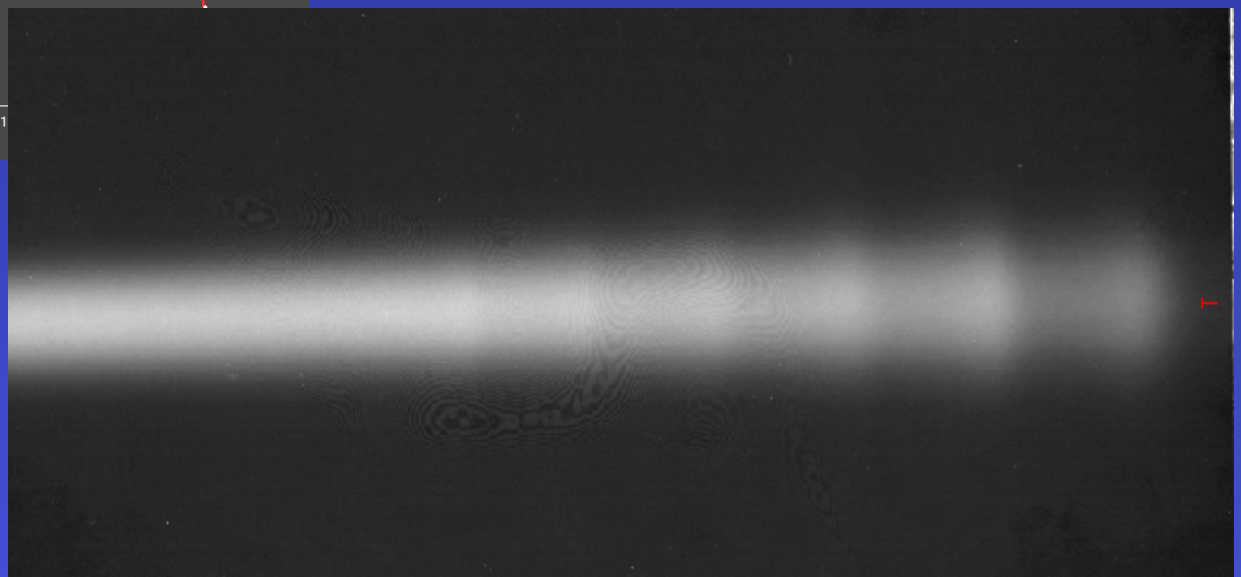


October 26, 2010: Beam in Room!

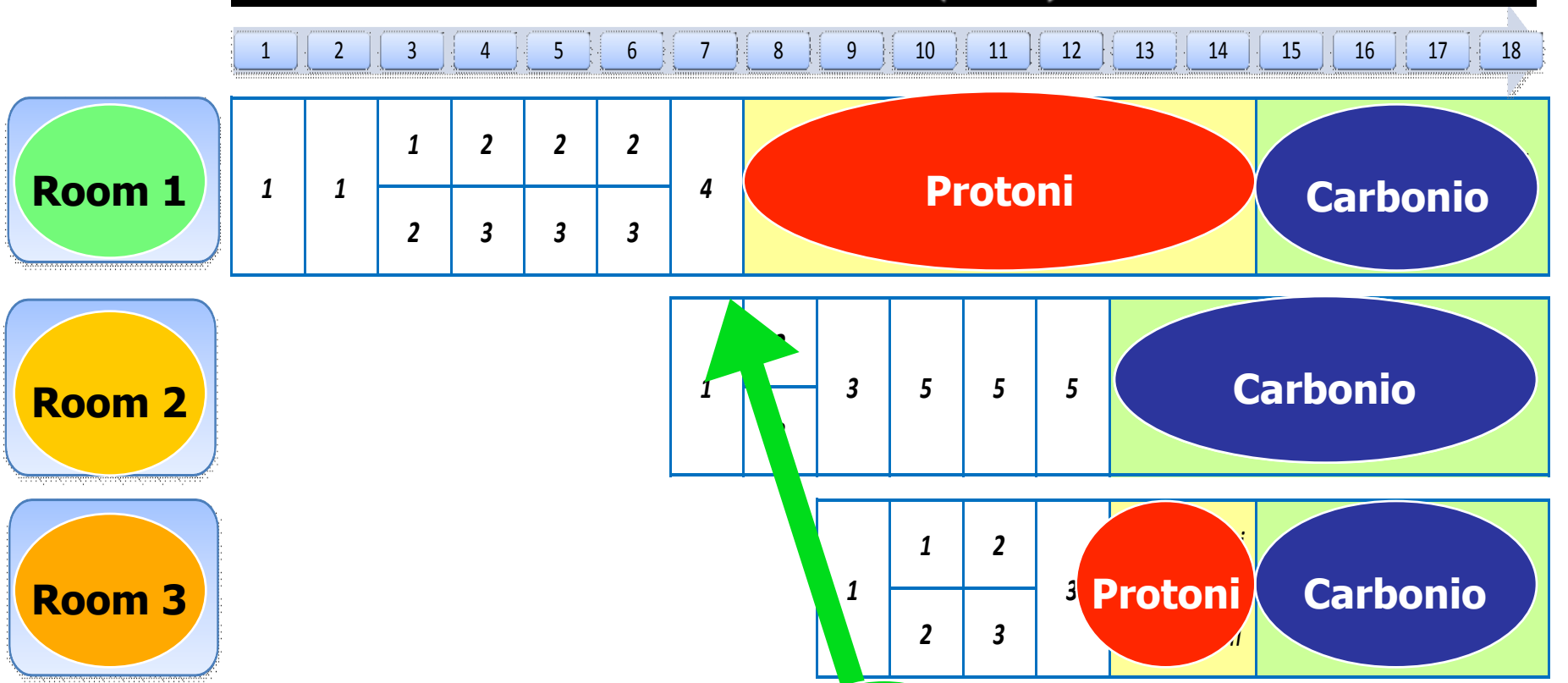


Spead Out Bragg Pick

SOBP



Time Plan (mesi)



Ministero della Salute

Oggetto: autorizzazione alla messa in servizio per uso compassionevole dell'apparato per adroterapia ad alta tecnologia (ATA) già installato presso il Centro Nazionale di Adroterapia Oncologica di Pavia.

IL MINISTRO

VISTA la richiesta presentata dal Centro Nazionale di Adroterapia Oncologica (Pavia) alla Direzione Generale della Ricerca Scientifica e Tecnologica, in merito al progetto di sperimentazione clinica relativo a "Attività propedeutica alla sperimentazione sui pazienti relativa alle attività di caratterizzazione fisica e radiobiologica dei fasci di adroni" ed in merito all'uso dell'apparato per adroterapia, già installato presso il CNAO, ai sensi dell'art. 11, comma 14 del decreto legislativo 46/97;

VISTO che le procedure di marcatura CE previste dal decreto legislativo 46/97 per i dispositivi medici non sono state espletate o completate per l'apparato in oggetto;

VISTO che il richiamato art. 11, comma 14 prevede che il Ministero della Salute, su richiesta motivata, autorizza la messa in servizio di singoli dispositivi medici, per i quali non sono state espletate o completate le procedure di marcatura CE, il cui impiego è nell'interesse della salute;

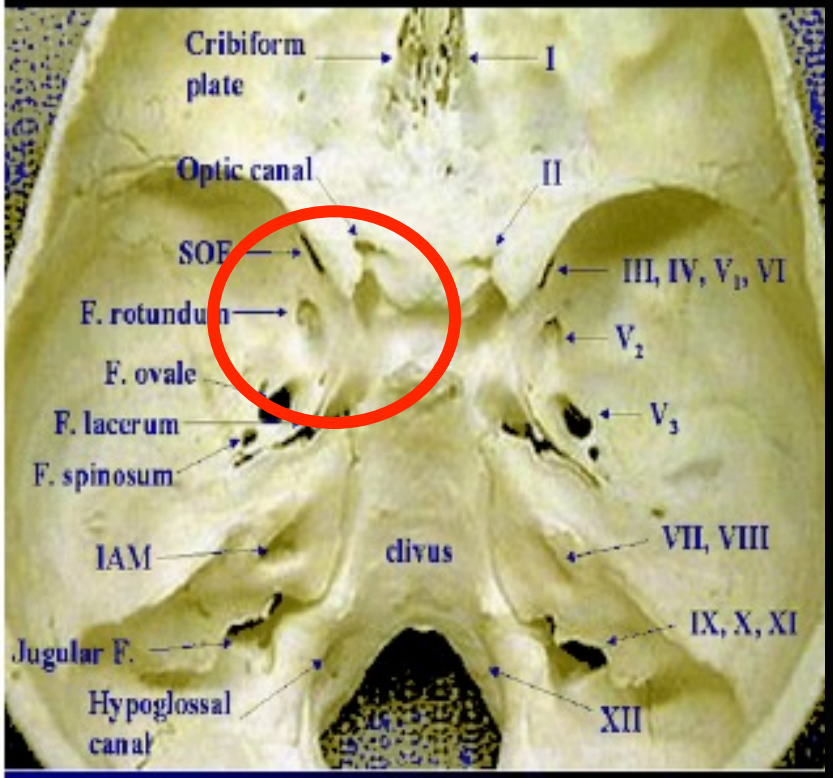
TENUTO CONTO che il Consiglio Superiore di Sanità (CSS), presso il quale è stato istituito un gruppo di lavoro ad hoc, nelle sedute del 13 luglio 2010, 17 maggio e 14 giugno 2011, ha, tra l'altro, rilevato che:

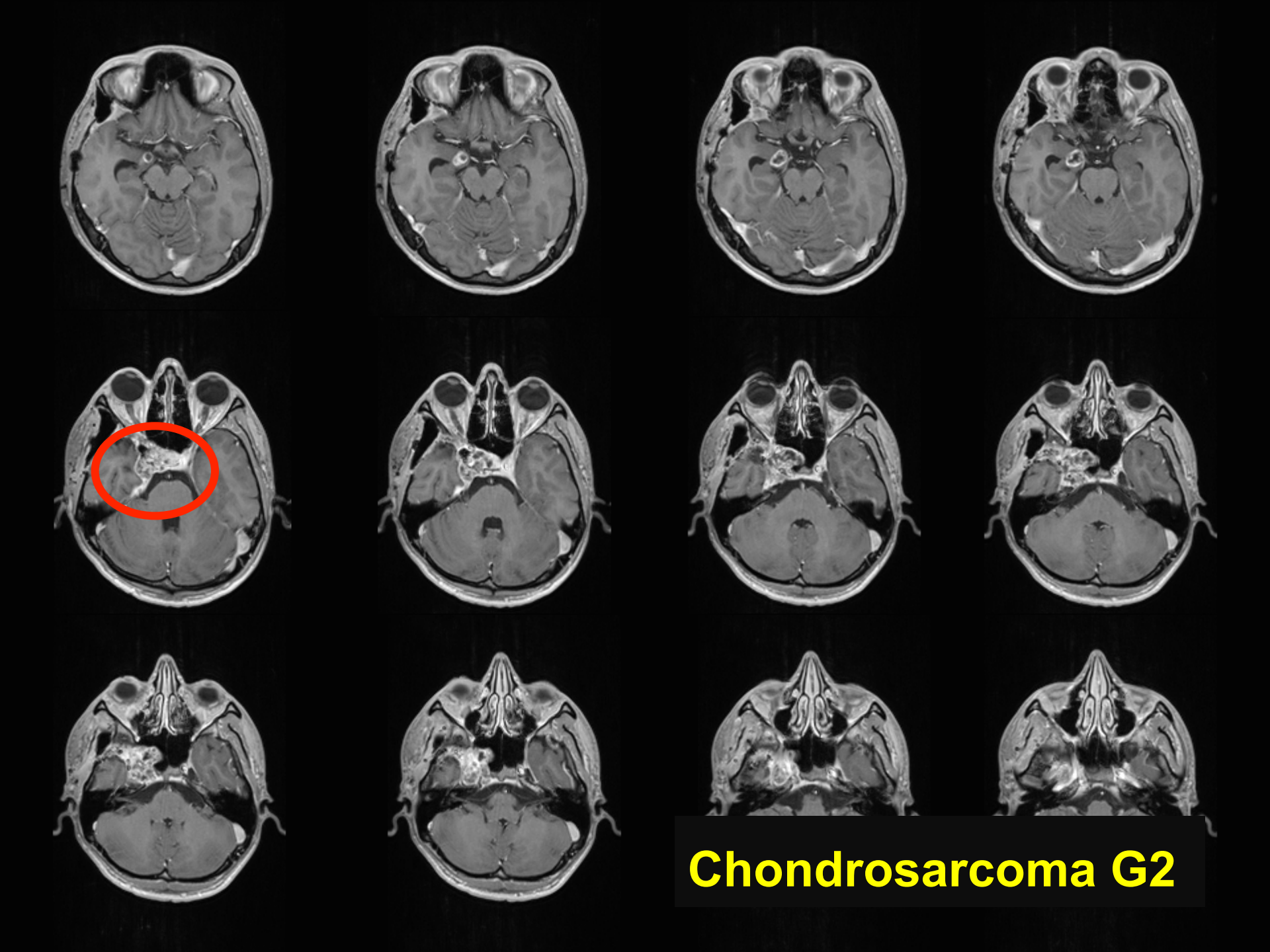
- il CNAO rappresenta una struttura all'avanguardia per il trattamento di pazienti oncologici con fasci di protoni e ioni carbonio;

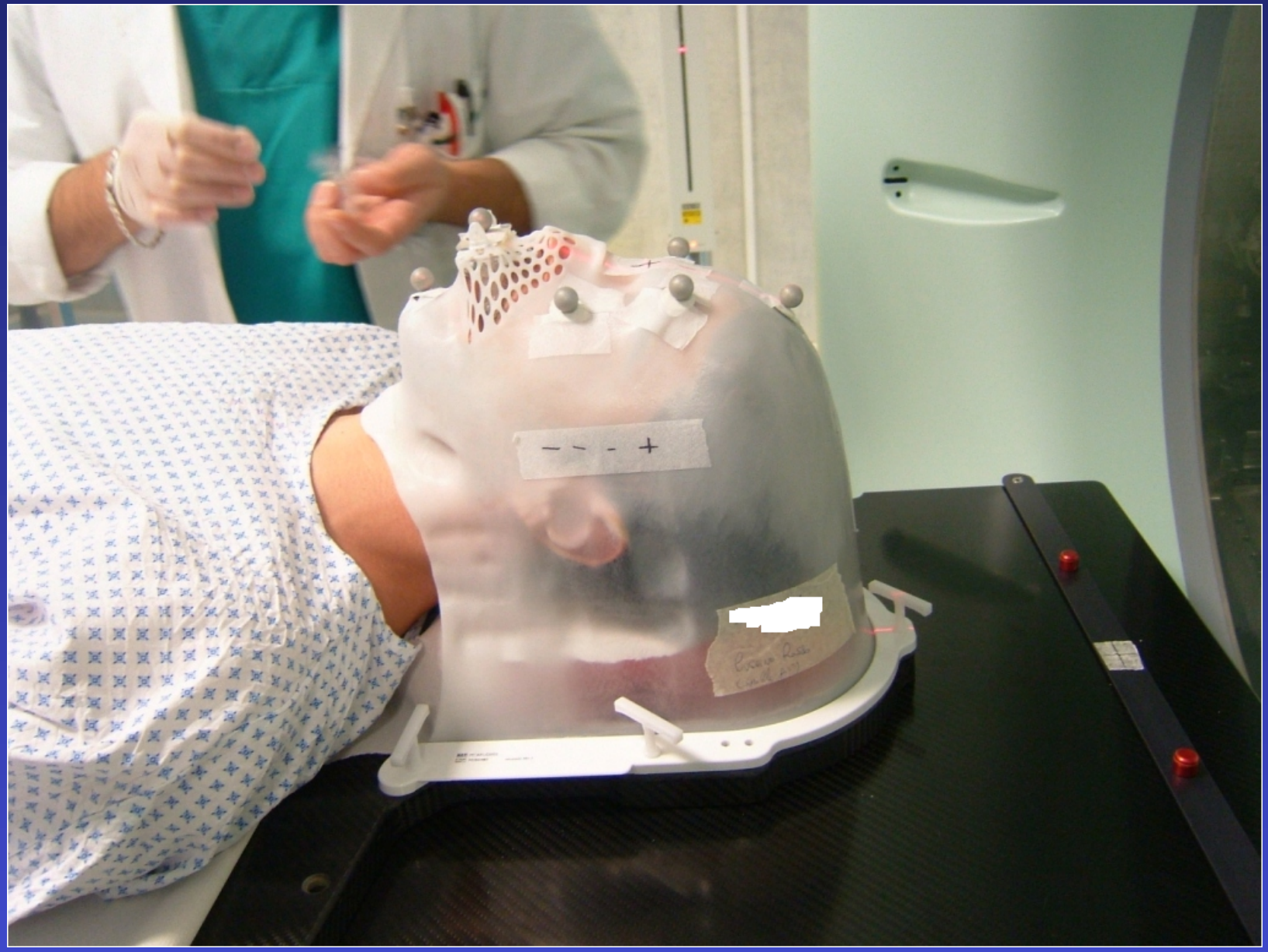
patologie per le quali tale trattamento ha già dimostrato di essere vantaggioso, ossia le patologie (cordomi e condrosarcomi della base del cranio, cordomi e condrosarcomi del rachide, meningiomi intracranici) oggetto dei protocolli sperimentali già inviati dal CNAO al CSS;

Chondrosarcoma G2

- **Base of Skull**



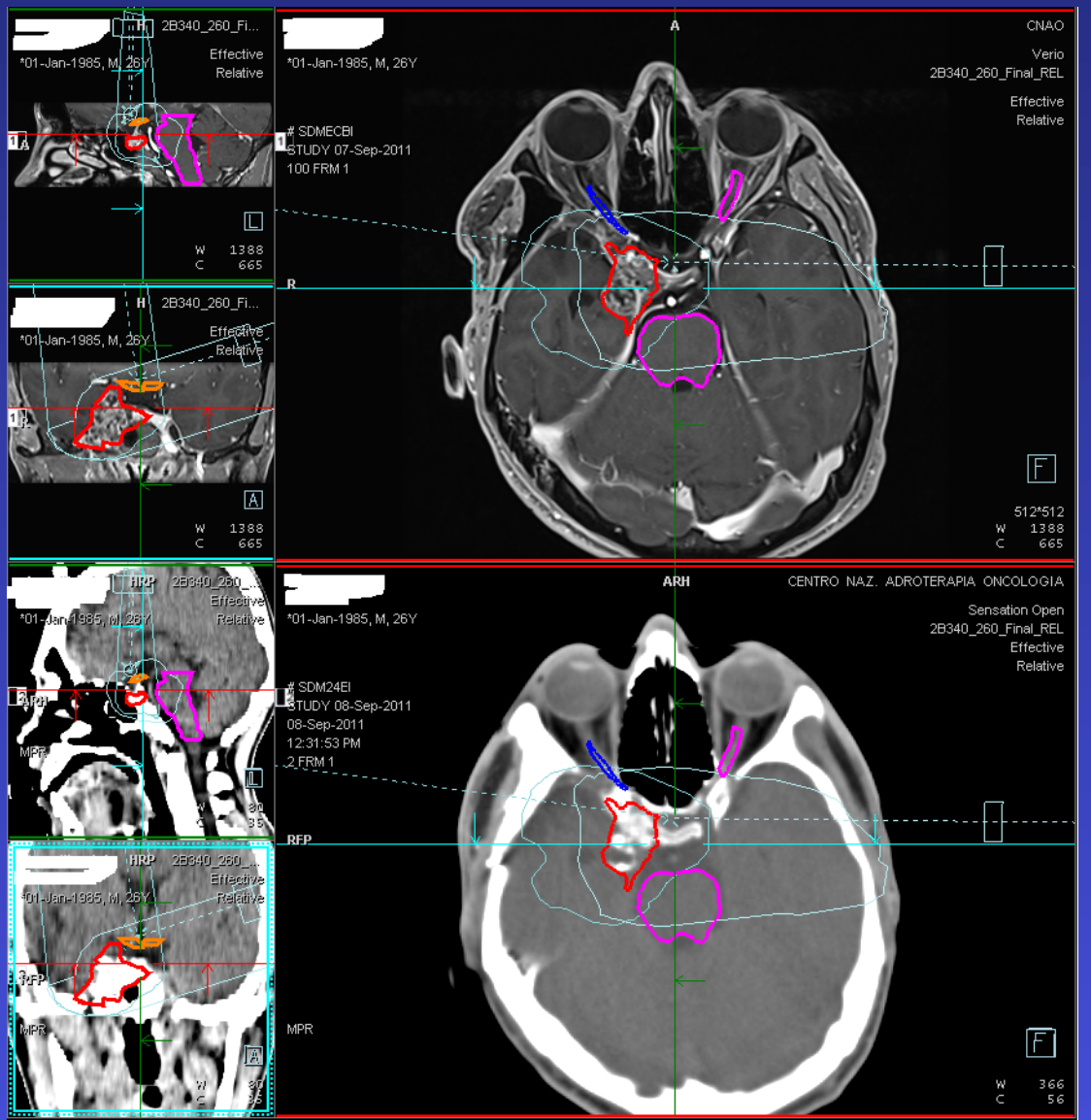

Chondrosarcoma G2

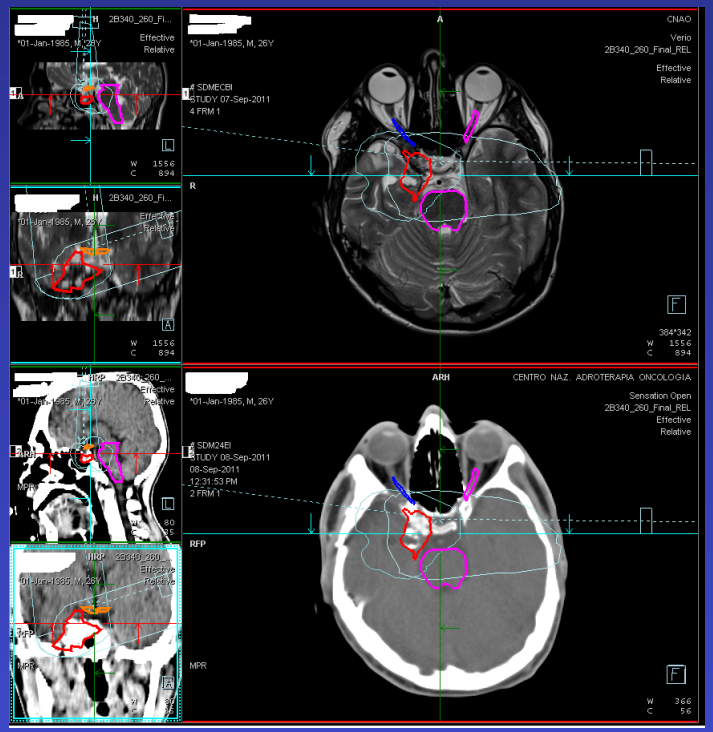


Maschera termoplastica con bite e marker riflettenti agli IF
Maschera non traforata in corrispondenza dell'ingresso del fascio

Contornamento con image fusion TC/RM

T1 post gadolinio





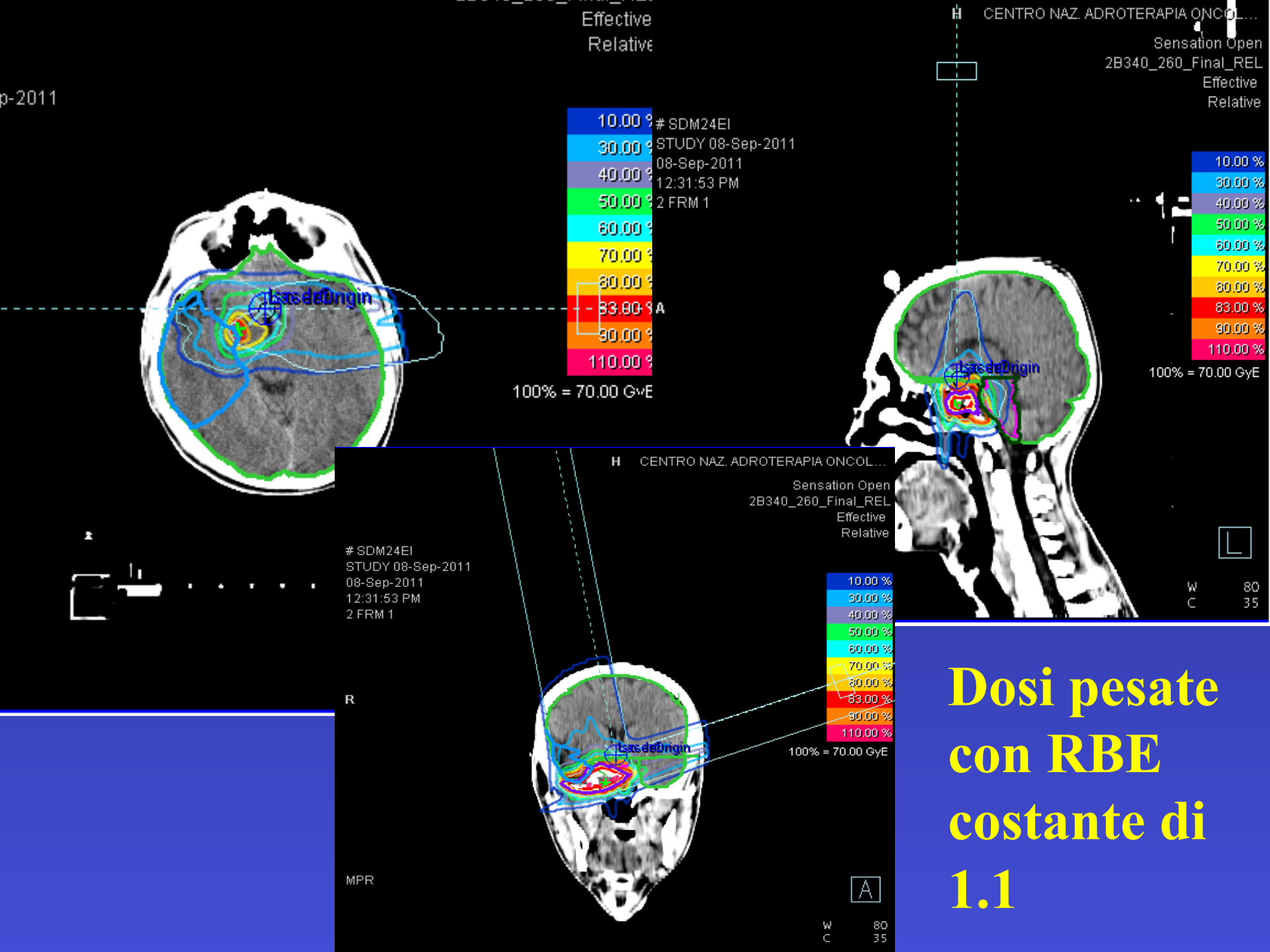
sequenze in T2

Dose di prescrizione:

70 Gy (RBE) in 35 sedute da 2 Gy (RBE)

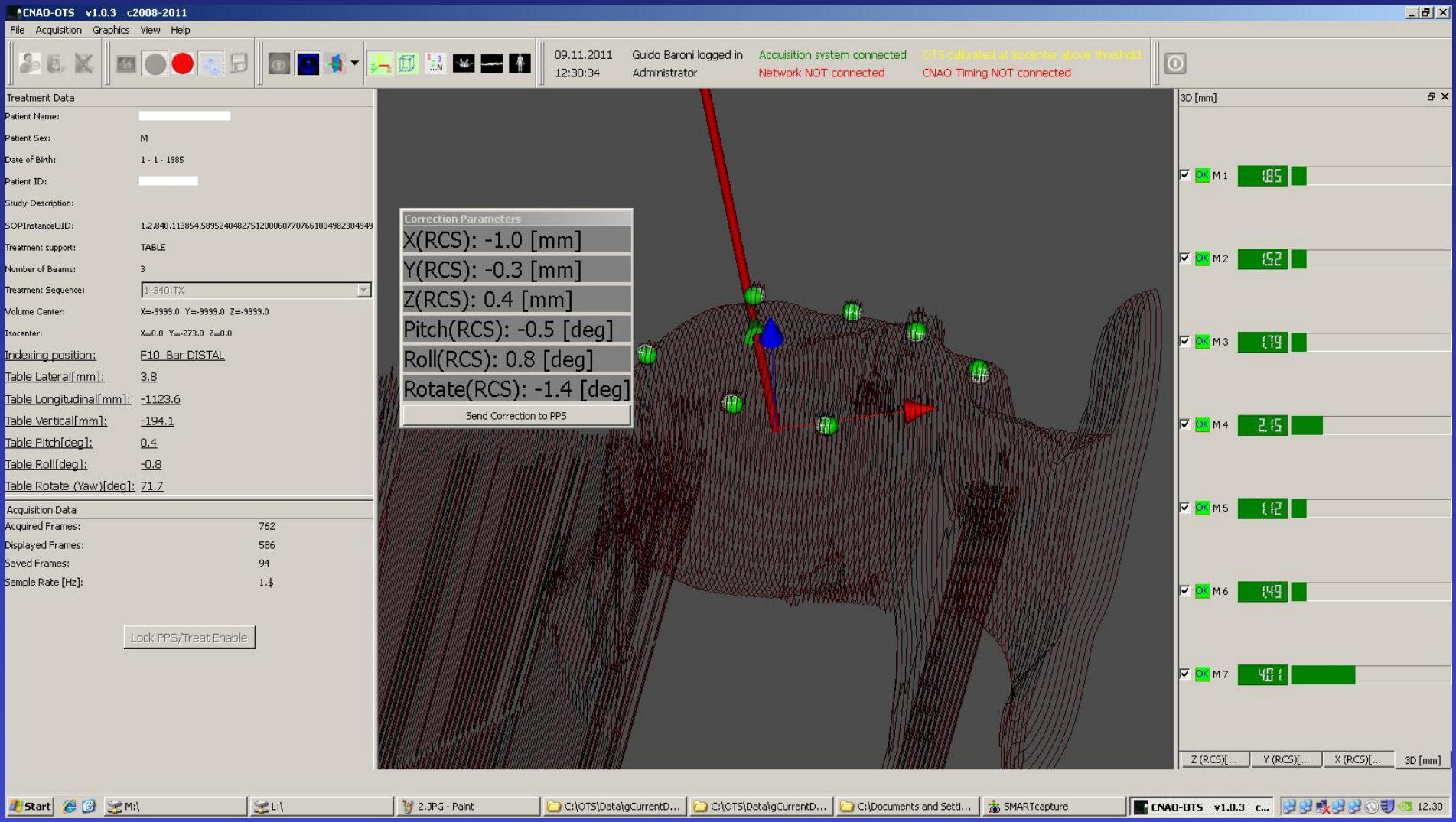
Constraints:

Tronco encefalico : superficie 64 Gy (RBE) – centro 53 Gy (RBE)
Chiasma ottico: dose massima 56 (RBE) dose media 50 (RBE)
Nervo ottico: dose massima 54 (RBE) dose media 50 (RBE)



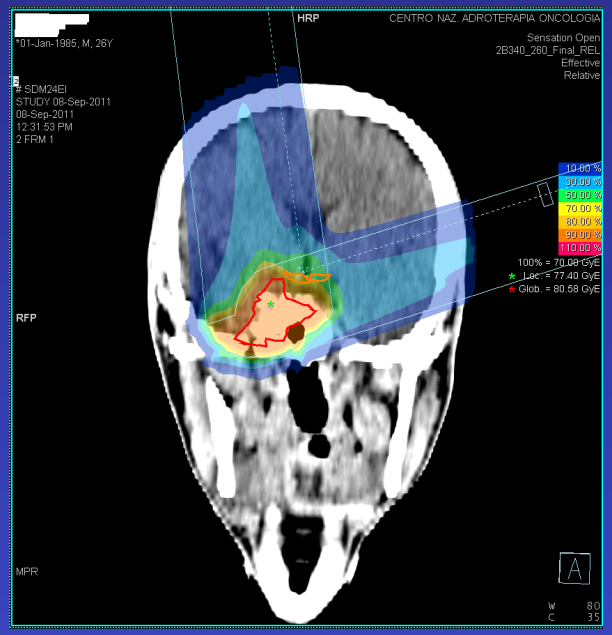
Dosi pesate con RBE costante di 1.1

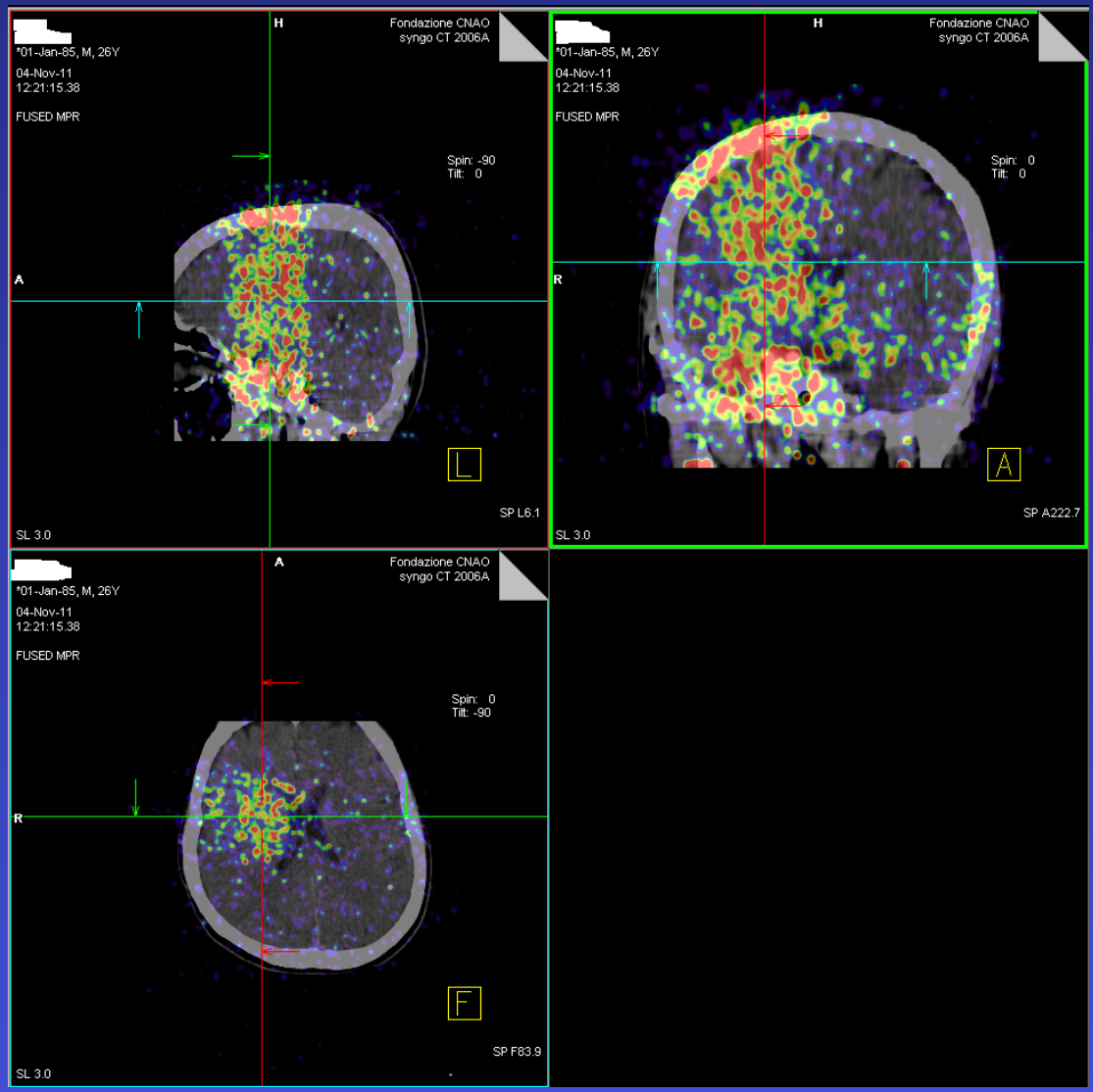
22 Settembre 2011

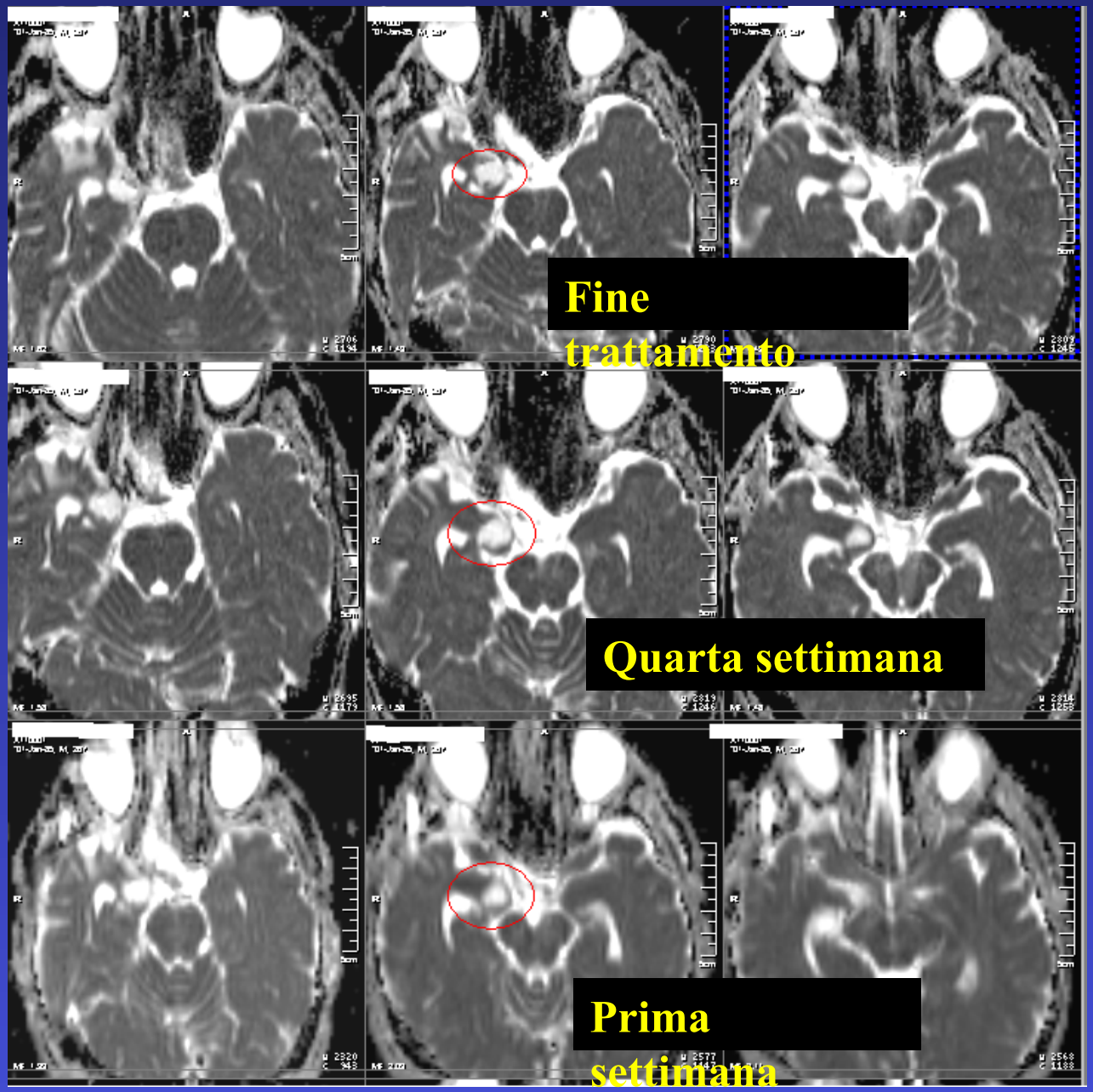


Verifica st-up mediante sistema optoelettronico

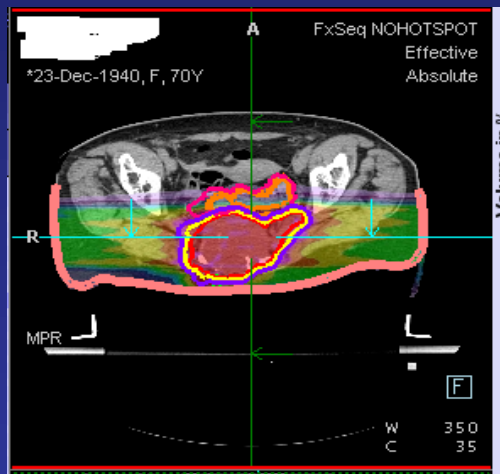
Verifica (qualitativa) mediante PET di auto attivazione off-line

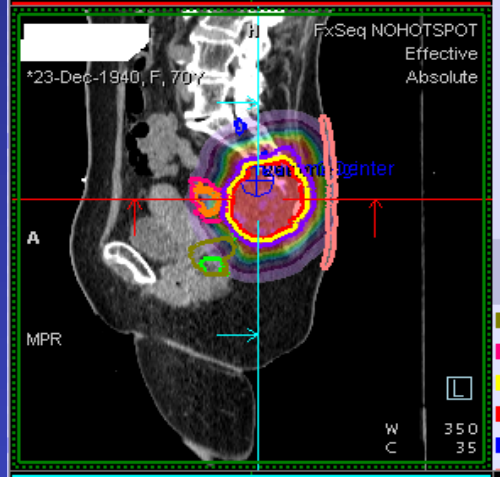


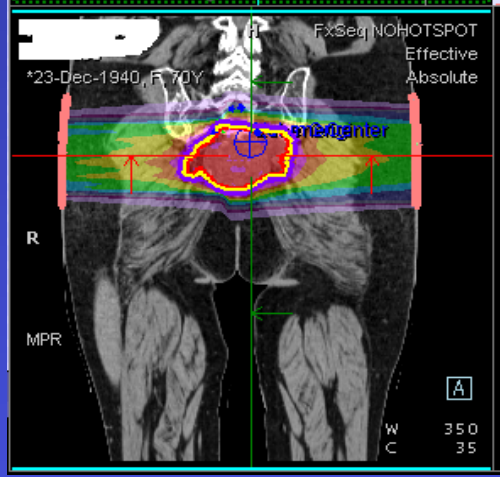


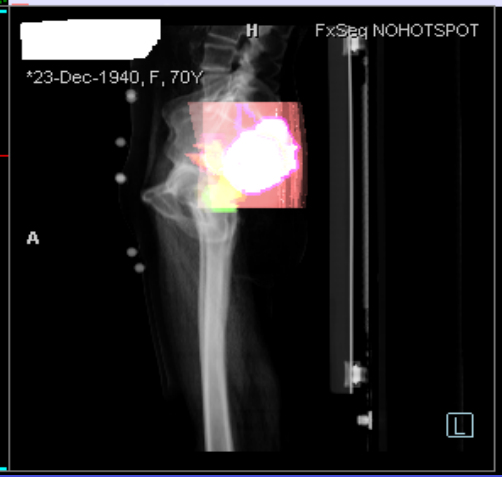


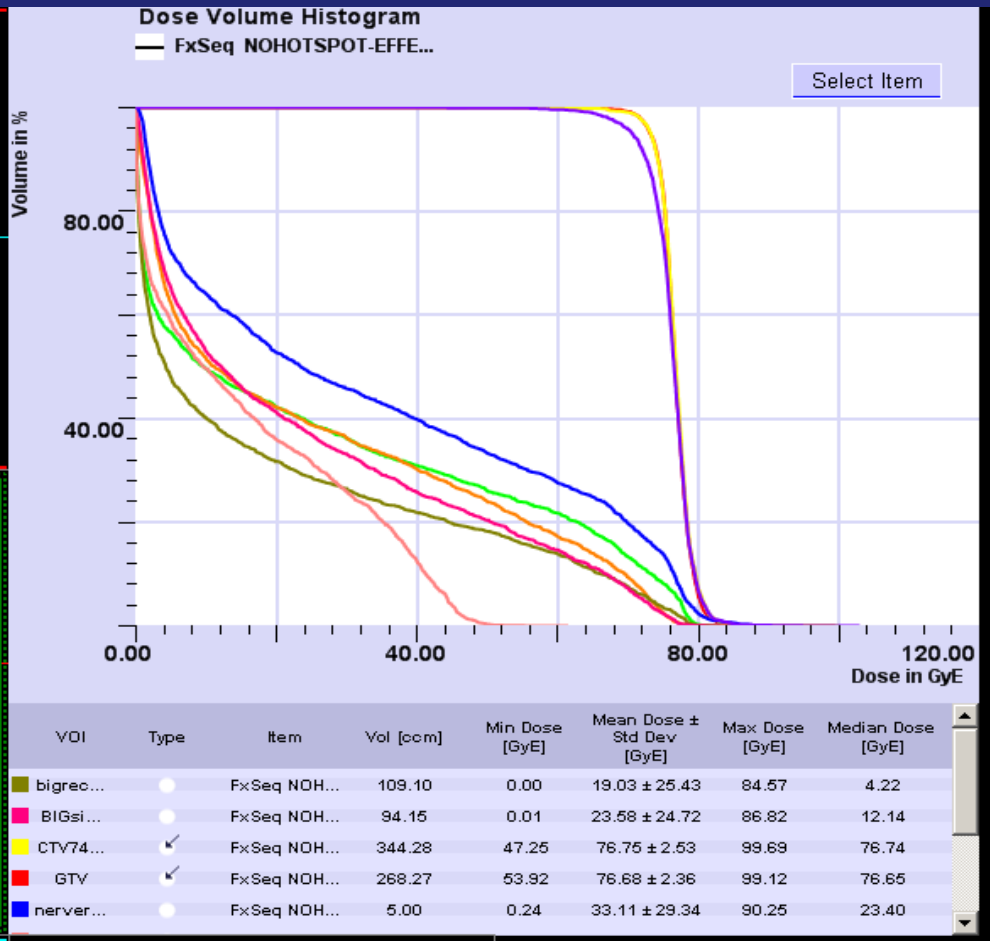
Non sono apprezzabili variazioni significative di ADC in corso di terapia







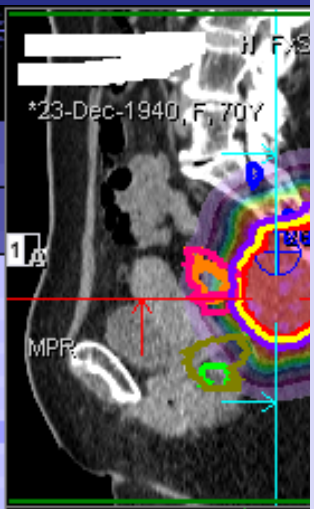


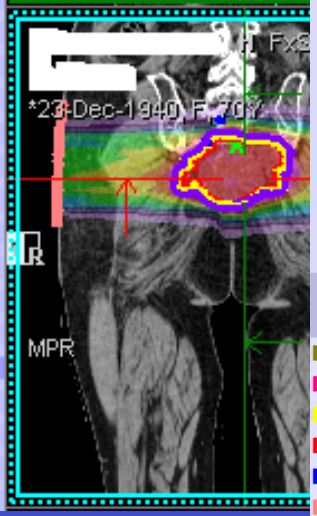


VOI	Type	Item	Vol [ccm]	Min Dose [GyE]	Mean Dose ± Std Dev [GyE]	Max Dose [GyE]	Median Dose [GyE]
bigrec...		FxSeq NOH...	109.10	0.00	19.03 ± 25.43	84.57	4.22
BIGsi...		FxSeq NOH...	94.15	0.01	23.58 ± 24.72	86.82	12.14
CTV74...	✓	FxSeq NOH...	344.28	47.25	76.75 ± 2.53	99.69	76.74
GTV	✓	FxSeq NOH...	268.27	53.92	76.68 ± 2.36	99.12	76.65
nerver...		FxSeq NOH...	5.00	0.24	33.11 ± 29.34	90.25	23.40

Dose 74 Gy (RBE)

Chordoma

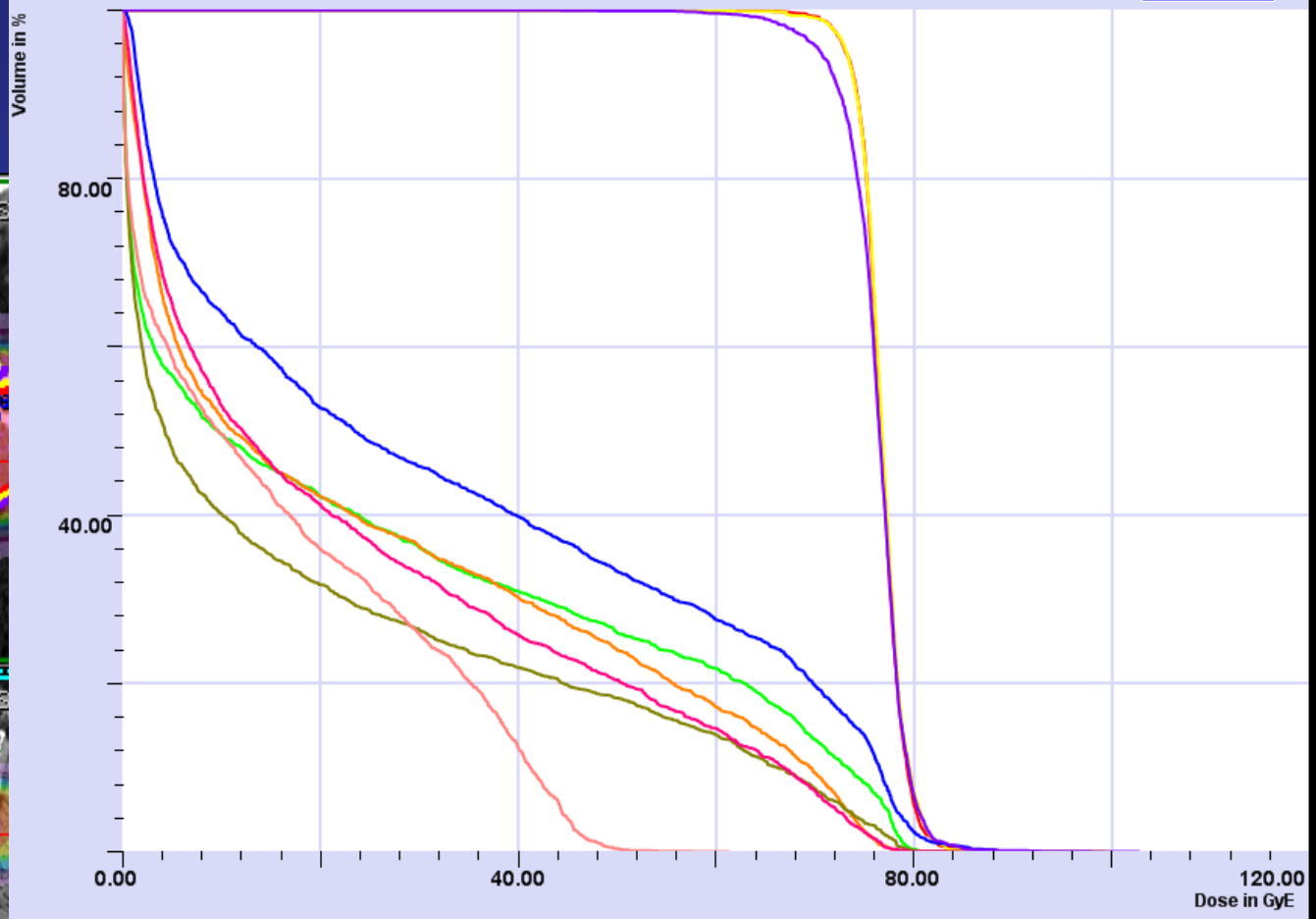




Dose Volume Histogram

FxSeq NOHOTSPOT-EFFECTIVE

Select Item

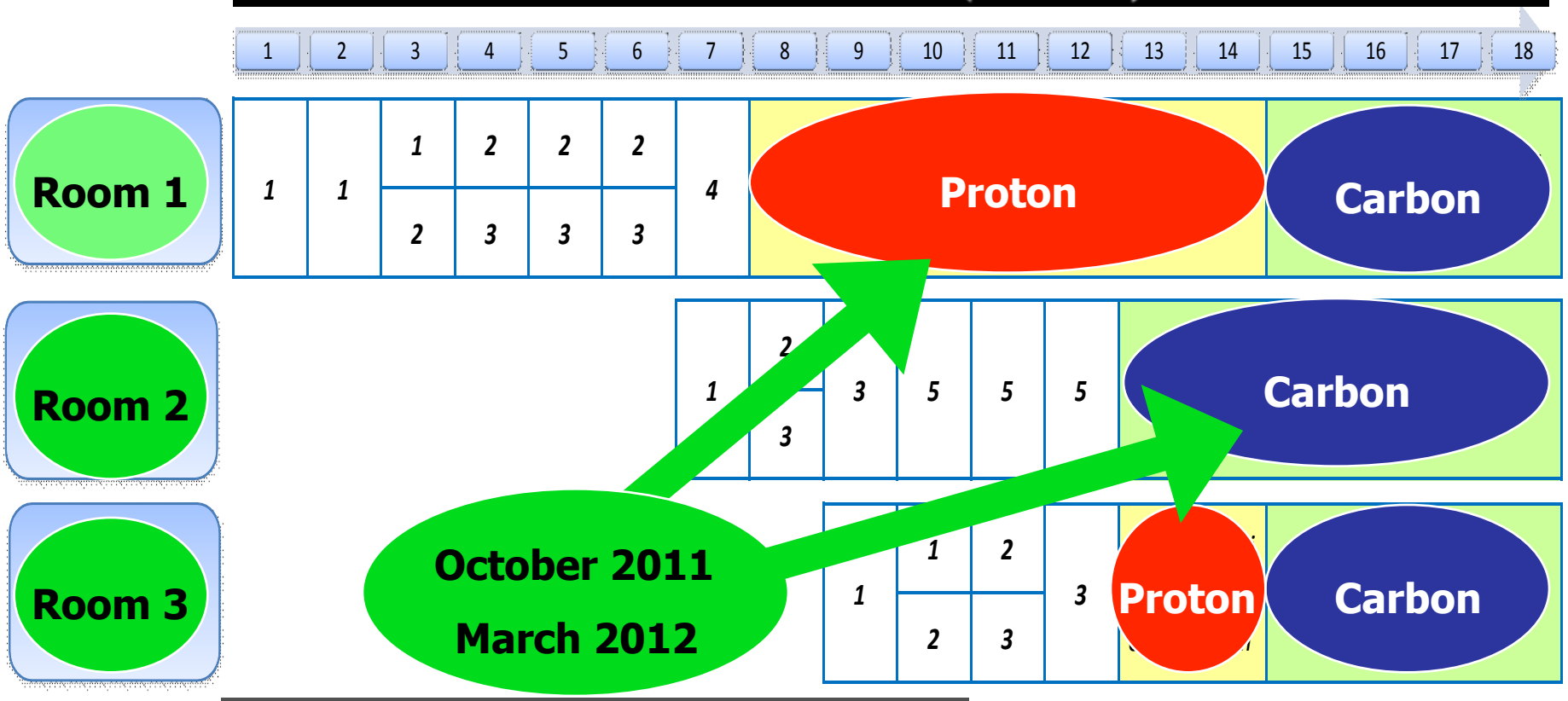


VOI	Type	Item	Vol [ccm]	Min Dose [GyE]	Mean Dose ± Std Dev [GyE]	Max Dose [GyE]	Median Dose [GyE]
bigrectum		FxSeq NOHOTSPO...	109.10	0.00	19.03 ± 25.43	84.57	4.22
BIGsigmoid		FxSeq NOHOTSPO...	94.15	0.01	23.58 ± 24.72	86.82	12.14
CTV74GyE	↙	FxSeq NOHOTSPO...	344.28	47.25	76.75 ± 2.53	99.69	76.74
GTV	↙	FxSeq NOHOTSPO...	268.27	53.92	76.68 ± 2.36	99.12	76.65
nerveroots		FxSeq NOHOTSPO...	5.00	0.24	33.11 ± 29.34	90.25	23.40
pelle		FxSeq NOHOTSPO...	370.22	0.00	15.93 ± 16.16	61.17	9.64
PTV74GyE	↙	FxSeq NOHOTSPO...	466.21	44.38	76.14 ± 3.44	102.65	76.49
rectalWALL		FxSeq NOHOTSPO...	23.70	0.00	25.51 ± 28.81	87.14	9.64
sigmoidWALL		FxSeq NOHOTSPO...	26.03	0.01	25.03 ± 26.34	83.89	11.19

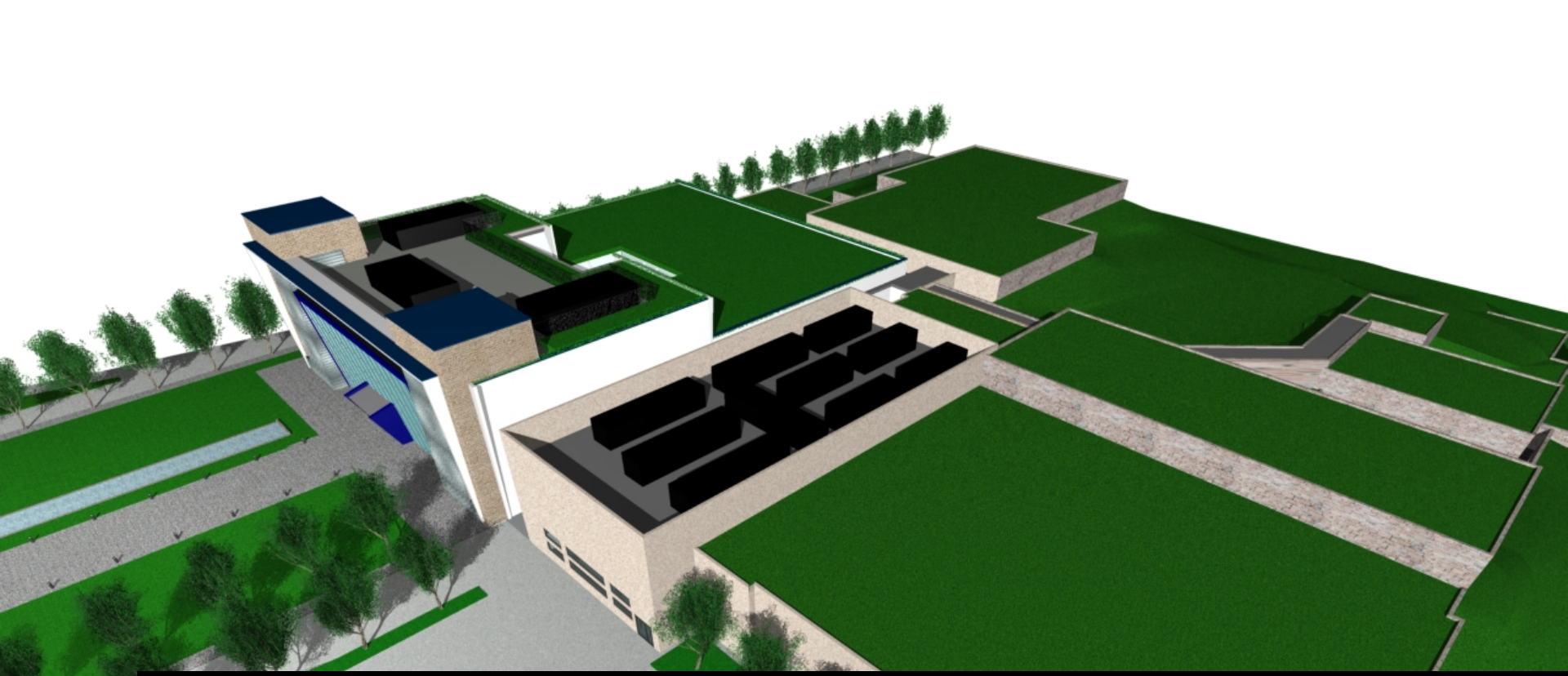
Adroterapia:

Un po’ di cose da fare …

Time schedule (months)



Task 1	Syncrotron Check and Dose delivery
Task 2	Experimental Dosimetry
Task 3	TPS Check and Input
Task 4	Proton Radiobiology
Task 5	Carbon Radiobiology
Task 6	Proton Treatment
Task 7	Carbon Treatment



ITALIAN NETWORK

INTERNATIONAL NETWORK

National CNAO clinical links

University of Milan, Milan

University of Pavia, Pavia

European Institute of Oncology, IEO, Milan

San Matteo Foundation & Policlinic Hospital, Pavia

Istituto Nazionale Tumori, INT, Milan

Neurological Institute Besta, Milan

Policlinicic Foundation & Hospital, Milan

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National CNAO clinical links

Creazione

Centri Regionali di Riferimento

Grazie !