

Introduction

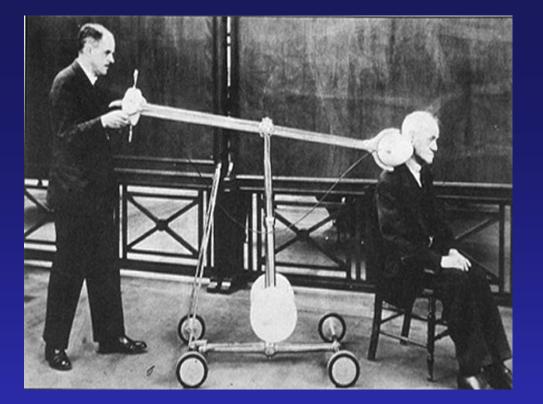




110 years after

From 50 to 65% of cancer patients receive RT





Radium

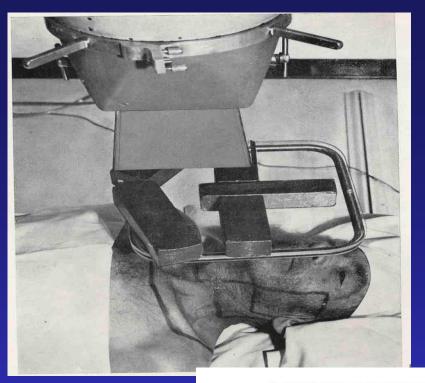


Paris schedule cervix uteri

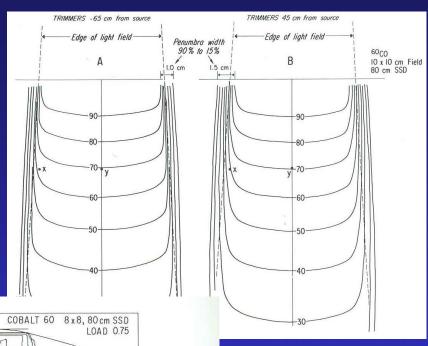
Continous treatment for 120 hours
Uterine tube of 33.3 mg radium
Two vaginal cylindrical corks: 13.3 mg radium
each

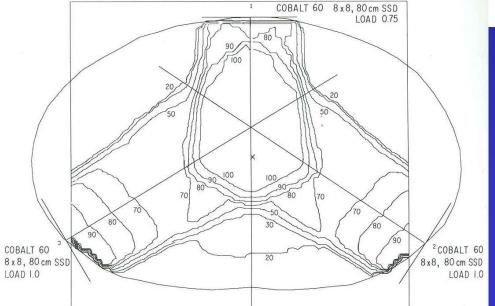


Orthovoltage rendement en profondeur (%) RT 100 localisateur 7 cm x 7 cm D.S.P. 30 cm 70 60 50 40 0 0,5 1,0 1,5 2,0 2,5 3,0 3,5 4,0 4,5 5,0 5,5 6,0 6,5 7,0 7,5 8,0 8,5 profondeur 230 kV CDA 1 mm Cu CDA 2 mm Cu 100 100 BITTHE THE THE PERSON AS 10 15 20 20 Ø 10 cm - D.S.P. 50 cm

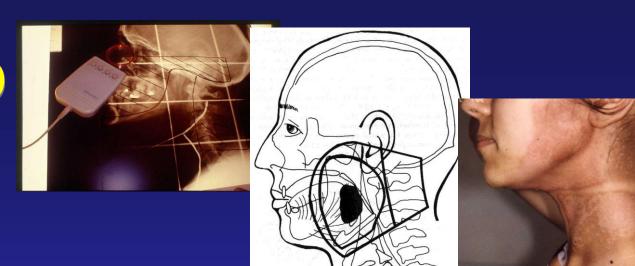


Megavoltage



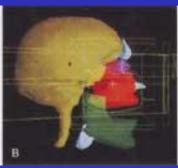


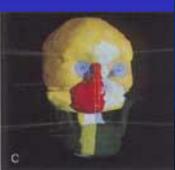
From 2-D

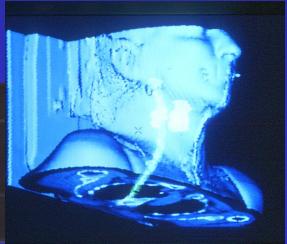


To 3-D









H&N DCR's



H&N Treatment Plans



Image -Guided IMRT



Pencil Beam

Fan Beam

Cone Beam

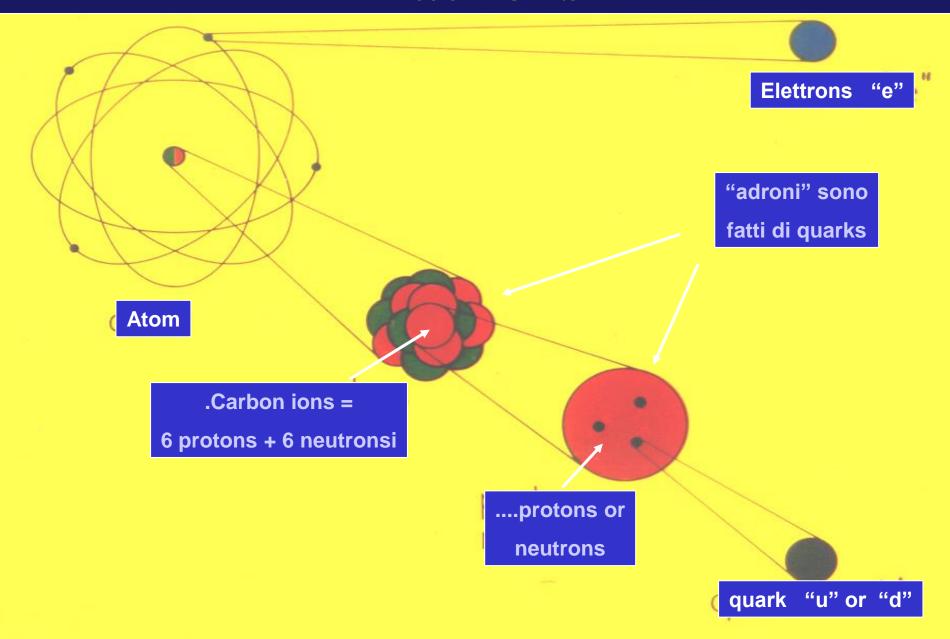








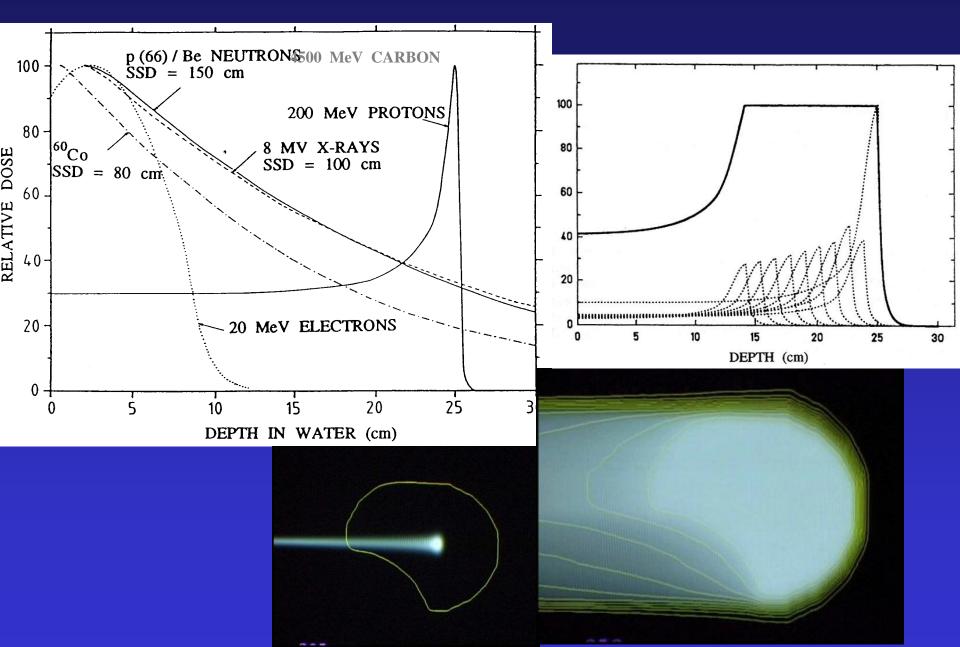
Hadrons



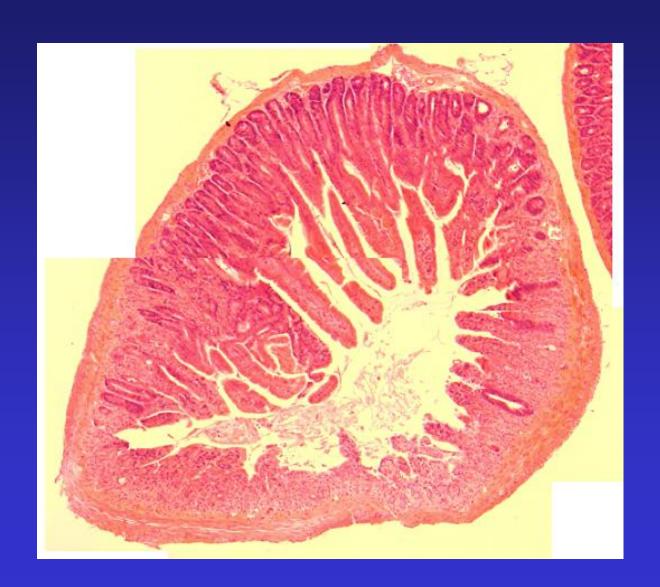
Hadrontherapy:

Why?

Physical selectivity



Bragg Pick in mouse bowel



Advantage of Protons

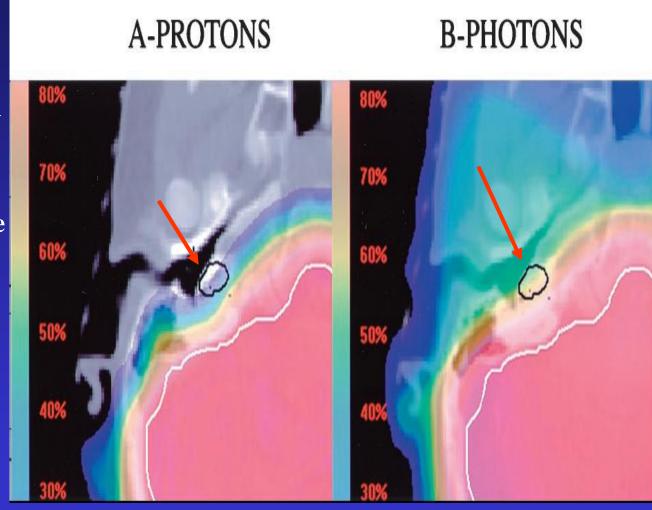
• 9 children primary CNS malignancies

- Choclea:

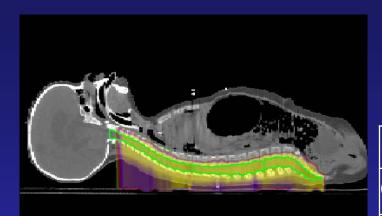
 average mean of 25

 4% of the prescribed dose from PRT; 75

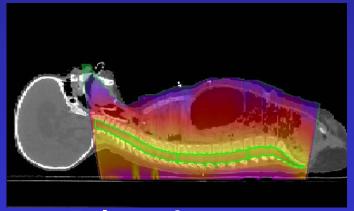
 6% from photons
- 40% of temporal lobe volume was completely excluded using protons; with photons 90% of the temporal lobe received 31% of the dose



Advantage of Protons



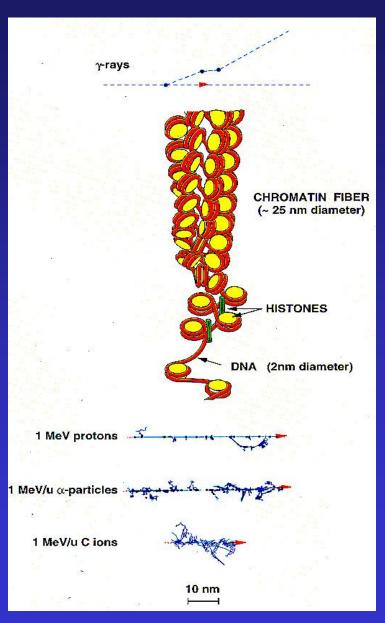
Protons

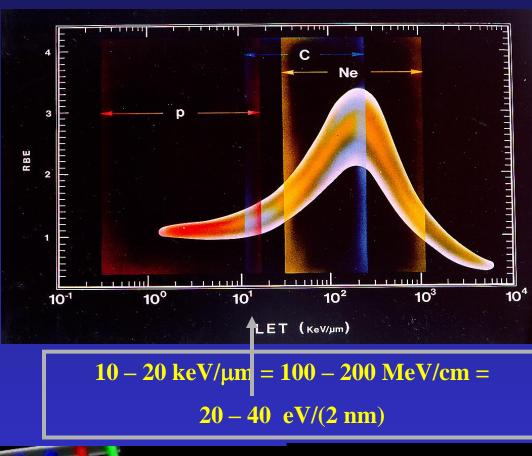


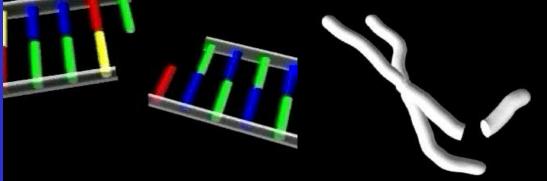
Photons

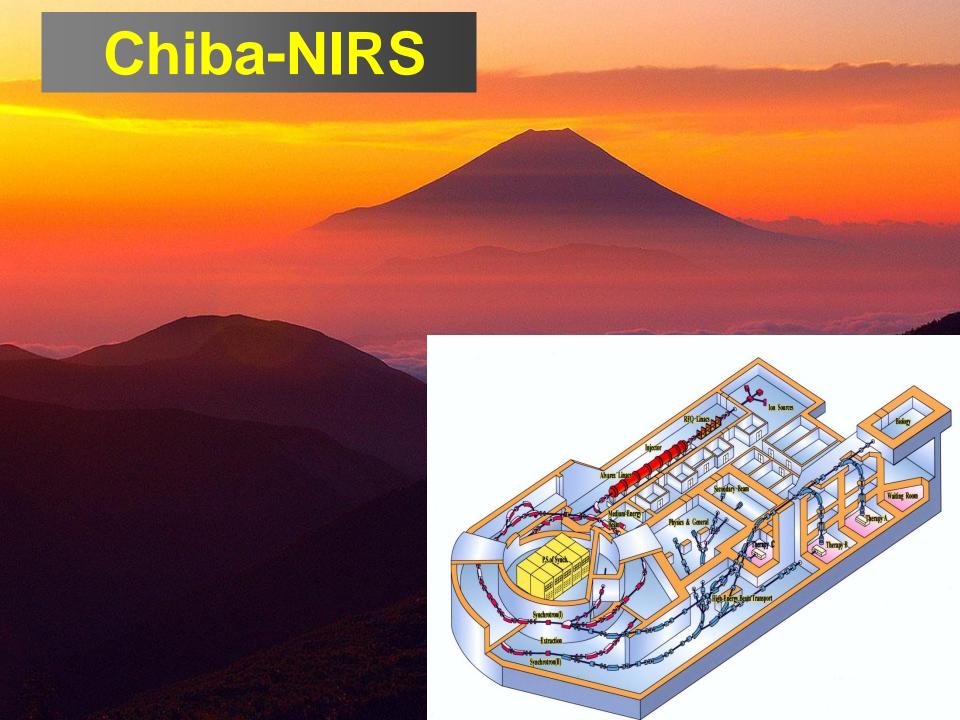
	X-ray	IMRT	Proton
CTV	90%	90%	90%
Heart	18.2	17.4	0.1
Right lung	3.5	21.9	0.1
Esophagous	11.9	32.1	10.2
Stomach	3.7	20.6	0.1
Right kidney	3.3	29.8	0.1
Transvers colon	2.6	18.0	0.1

Biological selectivity. RBE

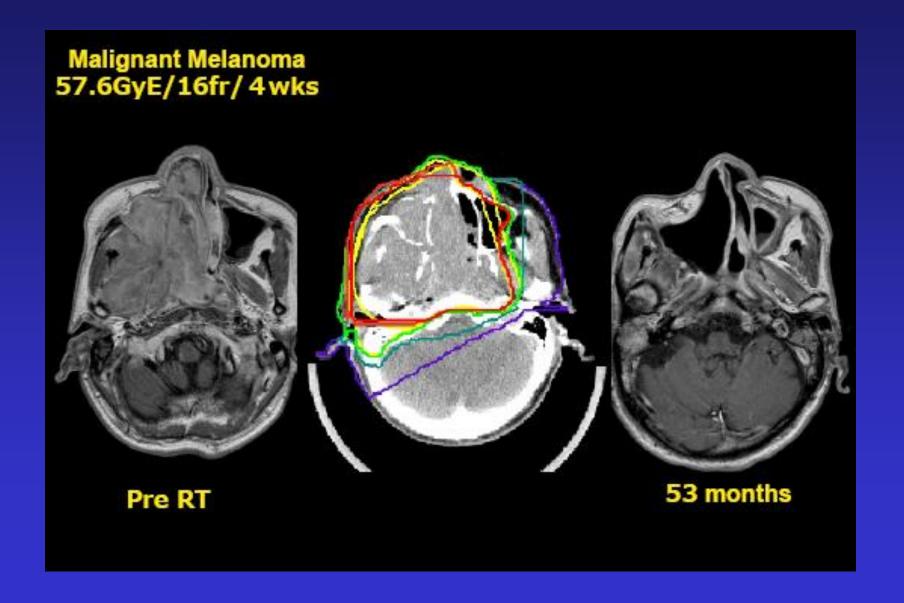








Carbon ion RT at NIRS



Hadrontherapy:

To whom?

WORLD WIDE CHARGED PARTICLE PATIENT TOTALS January 2005

wно	WHERE	WHAT	DATE FIRST RX	DATE LAST RX	RECENT PATIENT TOTAL	DATE OF TOTAL
Berkeley 184	CA. USA	p	1954	— 1957	30	
Berkeley	CA. USA	He	1957	— 1992	2054	
Uppsala (1)	Sweden	p	1957	— 1976	73	
Harvard	MA. USA	p	1961	— 2002	9116	
Dubna (1)	Russia	p	1967	— 1996	124	
ITEP, Moscow	Russia	p	1969		3785	Dec-04
Los Alamos	NM. USA	π -	1974	— 1982	230	
St. Petersburg	Russia	p	1975		1145	April-04
Berkeley	CA. USA	ion	1975	— 1992	433	-
Chiba	Japan	p	1979		145	Apr-02
TRIUMF	Canada	π -	1979	— 1994	367	
PSI (SIN)	Switzerland	π -	1980	— 1993	503	
PMRC (1), Tsukuba	Japan	p	1983	- 2000	700	
PSI (72 MeV)	Switzerland	p	1984		4182	Dec-04
Uppsala (2)	Sweden	p	1989		418	Jan-04
Clatterbridge	England	p	1989		1372	Dec-04
Loma Linda	CA. USA	p	1990		9585	Nov-04
Louvain-la-Neuve	Belgium	p	1991	- 1993	21	
Nice	France	p	1991		2555	April-04
Orsay	France	p	1991		2805	Dec-03
iThemba LABS	South Africa	p	1993		468	Nov-04
MPRI (1)	IN USA	p	1993	- 1999	34	
UCSF - CNL	CA USA	p	1994		632	June-04
HIMAC, Chiba	Japan	C ion	1994		1796	Feb-04
TRIUMF	Canada	p	1995		89	Dec-03
PSI (200 MeV)	Switzerland	p	1996		209	Dec-04
G.S.I Darmstadt	Germany	C ion	1997		198	Dec-03
H. M. I, Berlin	Germany	p	1998		546	Dec-04
NCC, Kashiwa	Japan	p	1998		300	Oct-04
Dubna (2)	Russia	p	1999		296	Dec-04
HIBMC, Hyogo	Japan	p	2001		483	Dec-04
PMRC (2), Tsukuba	Japan	p	2001		492	July 04
NPTC, MGH	MA USA	p	2001		973	Dec-04
HIBMC, Hyogo	Japan	C ion	2002		30	Dec-02
INFN-LNS, Catania	Italy	p	2002		82	Oct-04
WERC	Japan	p	2002		19	Oct-04
Shizuoka	Japan	p	2003		100	Dec-04
MPRI (2)	IN USA	p	2004		21	July -04
Wanjie, Zibo	China	p	2004		1	Dec-04
					1100	pions
					4511	ions
				TOT 17	40801	protons
				TOTAL	46412	all particles

Overall hadrontherapy patients

Protons: > 55 000
lons: > 6000
Neutrons (20 000)
Pions (1 000)

Published Data in the years

STUDIES YEARS	CLINIC	PHYSICS	BIOLOGY	TOTAL
2004- 2007	100	41	21	162
2000- 2003	46	29	18	93
1995- 1999	27	33	8	68

2008-2010:
"Heavy Charged Particles"
577 papers

EBM2

VOLUME 26: NUMBER 2 · JANUARY 10 2008

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

VOLUME 25 · NUMBER 8 · MARCH 10 2007

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

Michael Goitein, Department of Radiation Oncology, Harvard M James D. Cox, Division of Radiation Oncology, The University Radiotherapy and Oncology 86 (2008) 142–147 www.thegreenjournal.com

Special communication

Proton Therapy in Clinical Practice: Current Clinical Evidence

Michael Brada, Madelon Pijls-Johannesma, and Dirk De Ruysscher

Radiotherapy and Oncology 83 (2007) 105–109 www.thegreenjournal.com

Editorial

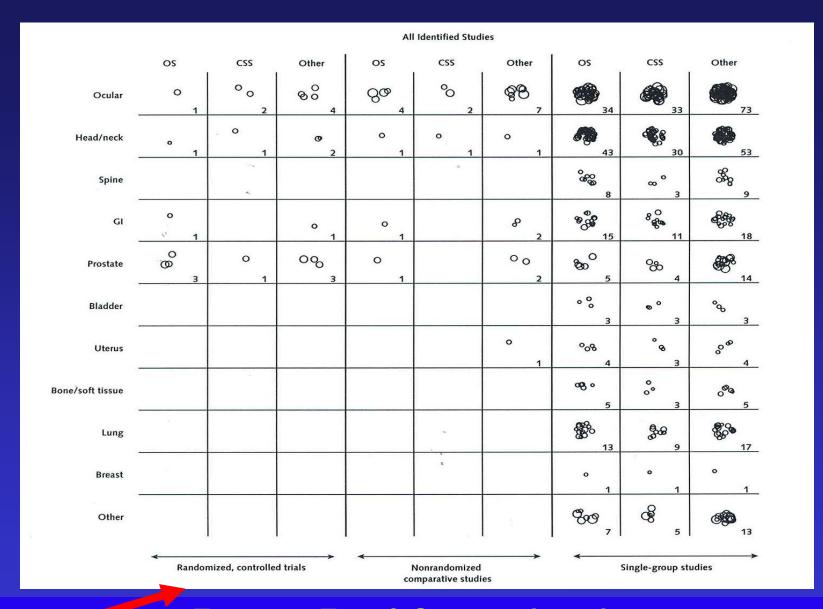
Randomized controlled trials in health technology assessment: Overkill or overdue?

Søren M. Bentzen*

Departments of Human Oncology, Medical Physics, Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA Proton beam therapy — Do we need the randomised trials and can we do them?

Bengt Glimeliusa,b,*, Anders Monteliusa

*Department of Oncology, Radiology and Clinical Immunology, Uppsala University Hospital, Uppsala, Sweden, *Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden



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

Category A

• All the tumors in which the use of hadrontherapy is clearly demonstrated to be advantageous, being the only way to give a curative dose to the target volume minimizing the incidence of severe side effects



Category B

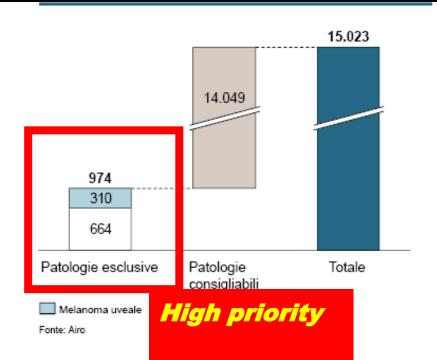
 A great variety of tumors characterized mainly by a local evolution, with a limited probability of distant spread, and therefore potentially cured if the locoregional control can be obtained



Working Group 2003, 2008, 2009

Estimated 15.000 new eligible patients in Italy

for protons (2008)



- 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

Category A. First Priority. Protons

Tumours	New pts / year	N. Pts eligible for protons	% eligible for protons
Uveal melanoma	310	310	100%
Chordoma	45	45	100%
Chondrosarcoma	90	90	100%
Meningioma (base of skull)	250	125	50%
Paraspinal tumours	140	140	100%
Schwannoma (cranial nerves)	300	45	15%
Pituitary adenoma	750	75	10%
Paediatric solid tumours	960	144	15%

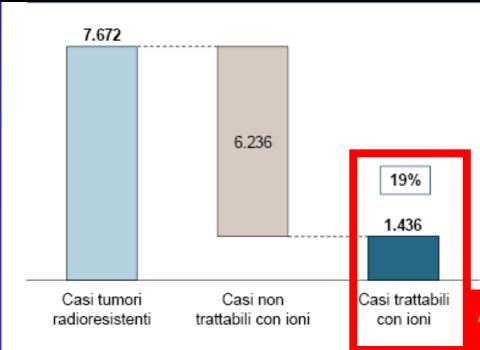
TOTAL 1'885 974



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 zione

High priority

Fonte: Airo MIL-0101-08512-004-065-02

Category A. First Priority. C-ions

Tumours	New pts / year	N. eligible for carbon ions	% eligible for carbon ions
Salivary gland tumours	620	310	50%
ENT mucosal melanoma	30	30	100%
Adenoca sinuses	450	45	10%

1'360

520

4500

7672

136

104

450

225

1436

10%

20%

10%

Soft tissue sarcoma

Recurrent tumours

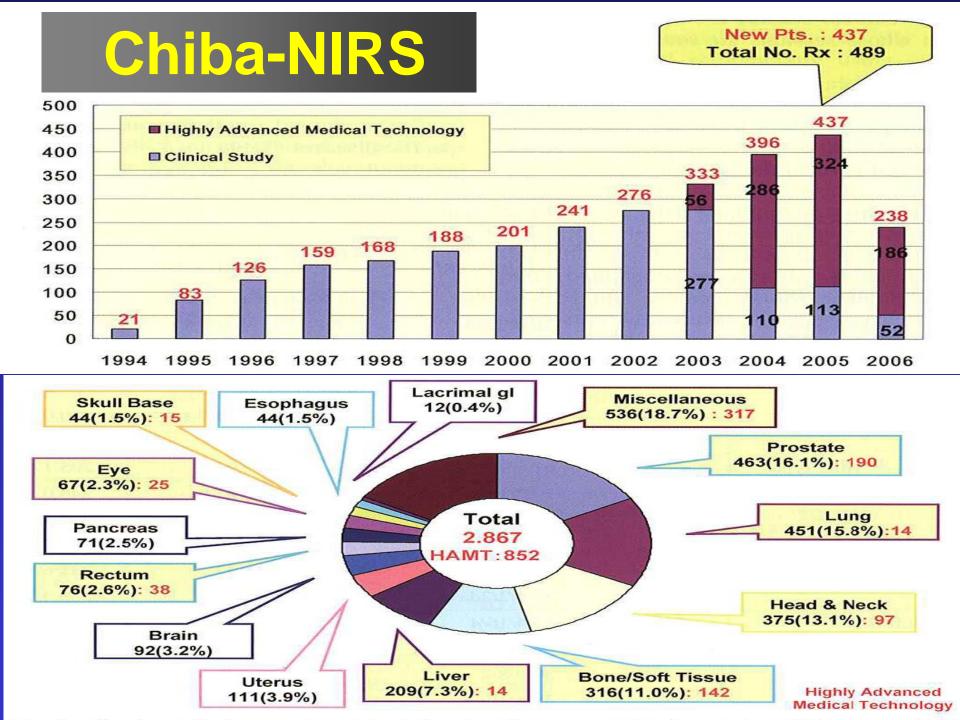
Liver/Pancreas/BT carcinomas

TOTAL

Bone sarcoma

EU Patients for Hadrontherapy

country	year of evaluation	patients	% of irradiated pts / year
Austria	2003	2.044	~ 13%
Czech Republic, Slovakian Republic Slovenia, Hungaria	2003 (by MedAustron)	8.700	~ 12%
Italy	2003	~ 15.000 hadrons	~ 12%
France	2003	77/532 pts (1-d –analysis)	~ 14%
Germany	1998	~ 8.000	~ 7%

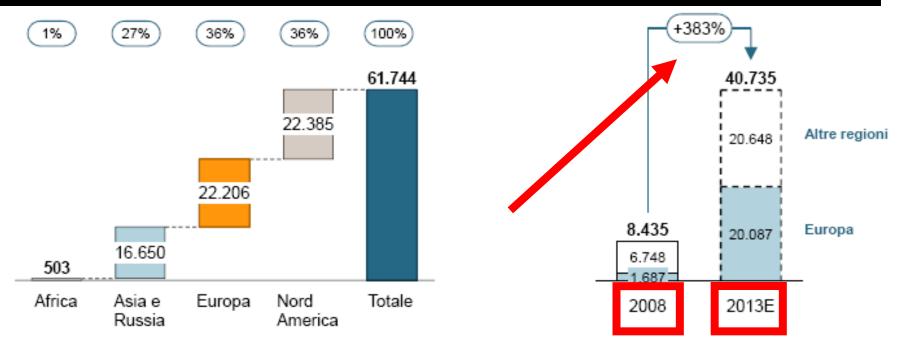


Hadrontherapy:

How much?

Development of Hadrontherapy

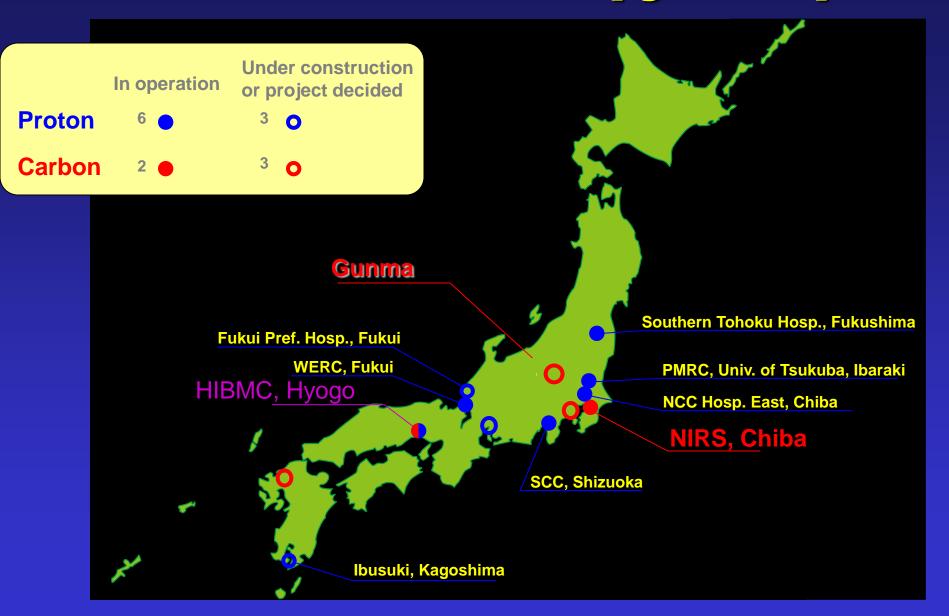
Up to day, more than 60.000 patients have been treated. This number is expected to be strongly increased

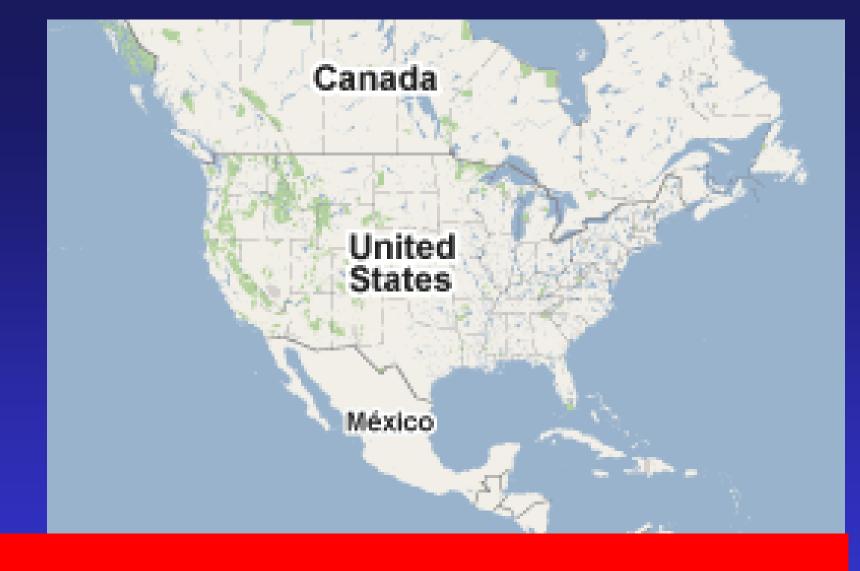


Stima al 2013 effettuata considerando una media di 400 pazienti/anno per sala di trattamento

Fonte: PTCOG (Particle Therapy Co-Operative Group)

Hadrontherapy in Japan

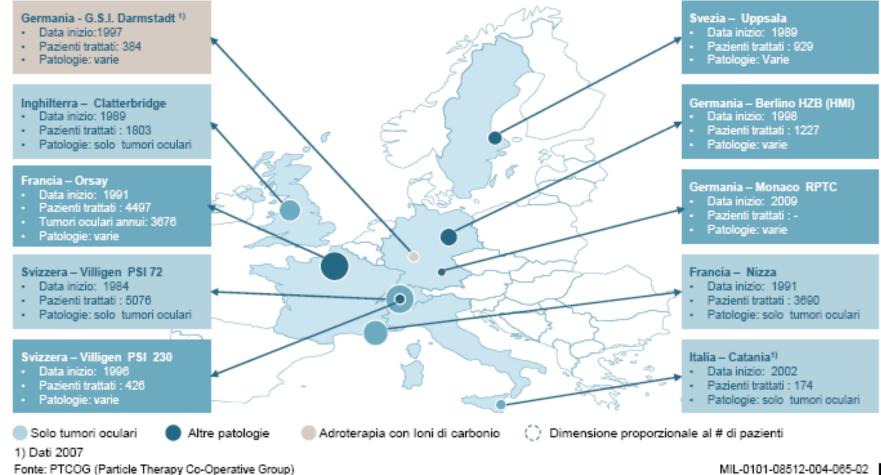




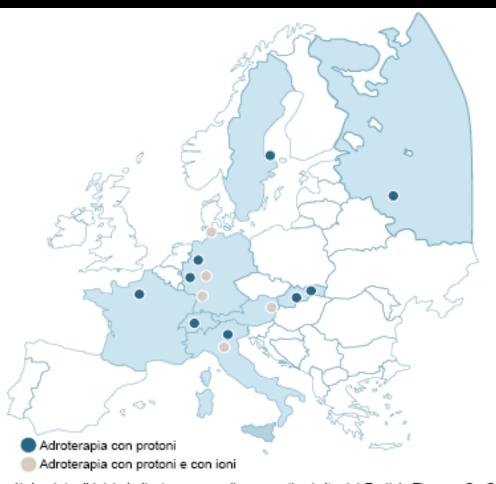
More than 20 centers in the next 5 years

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

Centri di adroterapia attivi in Europa [2008]



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 B Europa dell'Est

- 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
- C Italia

D Francia e Svizzera

Slovacchia, Bratislava:
 Inizio probabile: 2010

Slovacchia, Ruzomberok;

di sale:1

Inizio: 2010

di sale: 1

Inizio: 2010

di sale: 1

di sale: 2

Svezia, Uppsala:

Inizio probabile 2012

Russia. Protvino:

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

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

Hadrontherapy:

Which?

Loma Linda University Medical Center: first patient 1992

 First hospital-based proton-therapy centre

2005:160 sessions/day

7m synchroiron



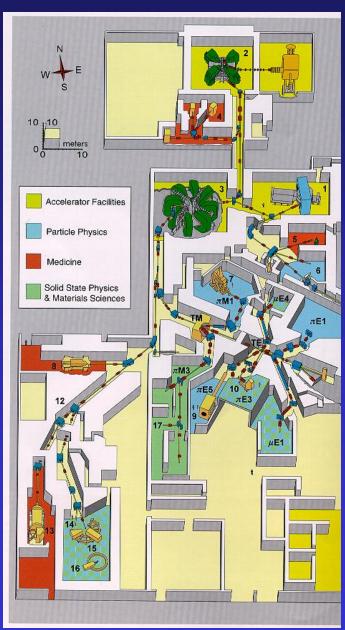
Europe: first active system at PSI → PROSCAN

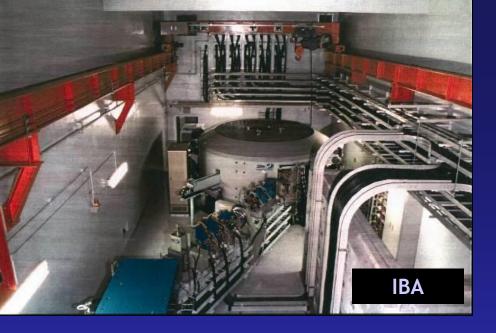
PSI Villigen

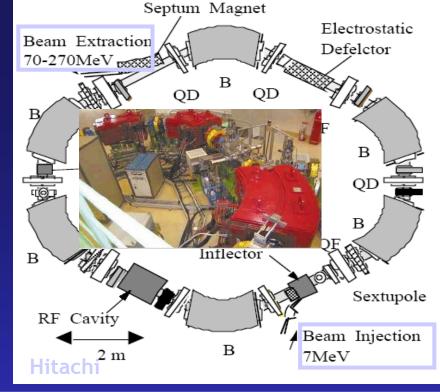
Optis – eye: 4000 patients

PSI Gantry: 250 patients













98.60 В Α 52.60 † B PIANTA PIANO TERRA QUOTA +0.00 PIANTA COPERTURA QUOTA +11.90 HORESSO PRINCIPALE В В Α

PIANTA PIANO PRIMO INTERRATO QUOTA -6.40

ACCESSO DAL PARCHEDGIO

PIANTE

DATI DIMENSIONALI:

AREA

SUPERFICIE COPERTA ALTEZZA IN GRONDA SUPERFICIE PROTONTERAPIA SUPERFICIE SERVIZI SANITARI PARCHEGGI 225+225 p.a.

mq 18.000 mq 5.650 m 11.50 mq 9.330 mq 4.270 mq 6.130

PIANO INTERRATO

SUPERFICIE PROTONTERAPIA mq 3.580

SUPERFICIE SERVIZI SANITARI mq 1.600

PIANO TERRA

SUPERFICIE PROTONTERAPIA

mq 2.825 SUPERFICIE SERVIZI SANITARI mq 1.570

PIANO PRIMO

SUPERFICIE PROTONTERAPIA mg 2.925

SUPERFICIE SERVIZI SANITARI

mq 1.100



ISTITUTO EUROPEO DI ONCOLOGIA I.R.C.C.S.

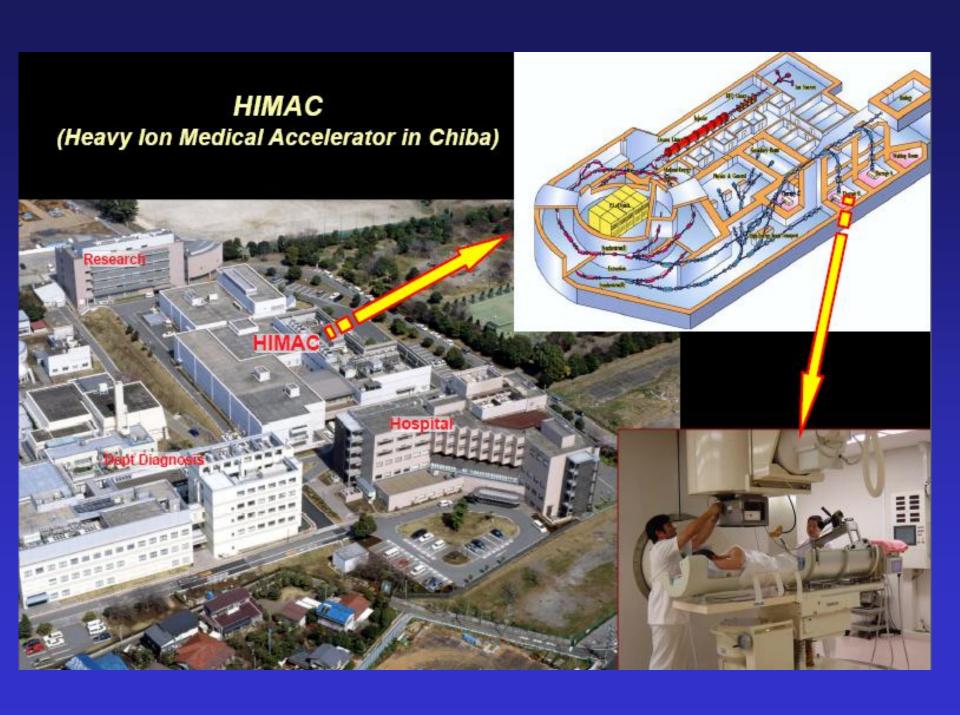
VIA G. RIPAMONTI, 435 -MILANO

PMCK

В

PIANTA PRIMO PIANO QUOTA +5.50

07/11/2005





Treatment halls by **Siemens Medical**

HIT ad Heidelberg

Siemens Medical: Marburg+Kiel

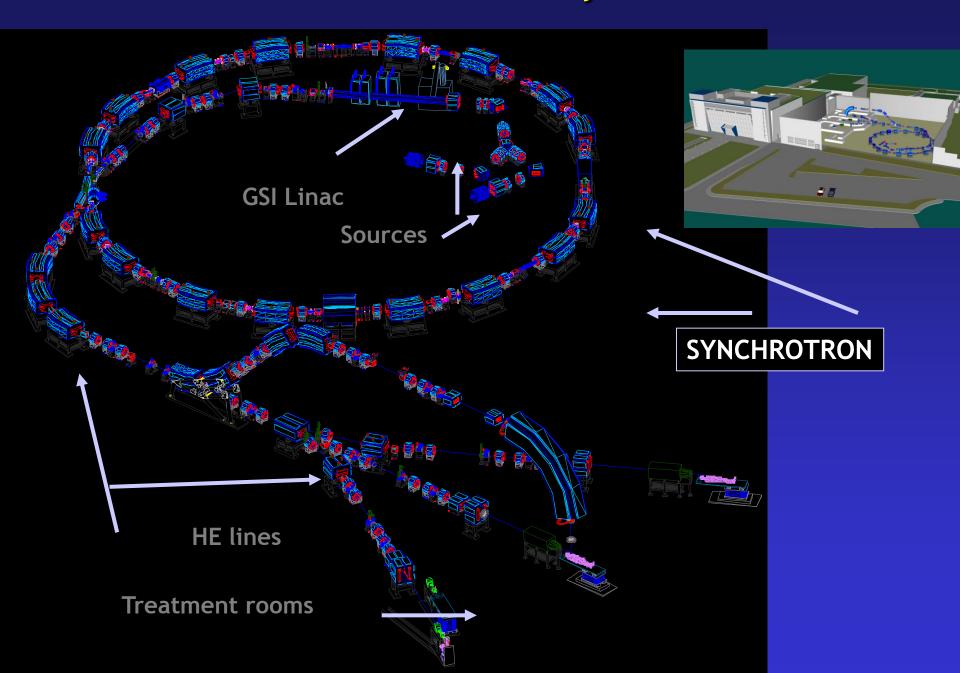
Quality

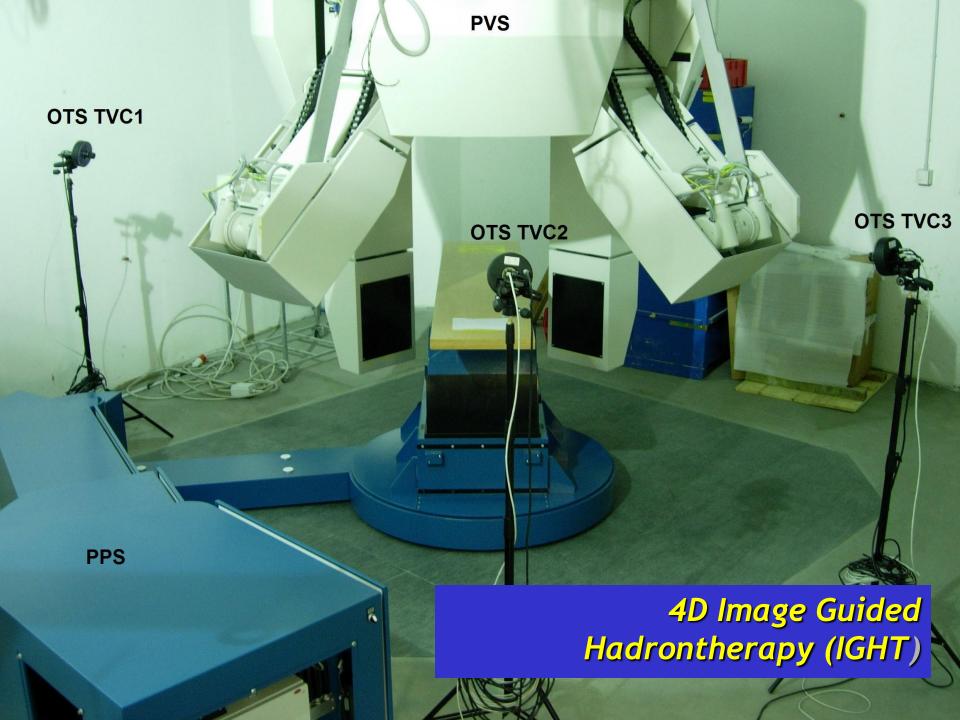
Gantry

Assurance



The "core" of CNAO





Results



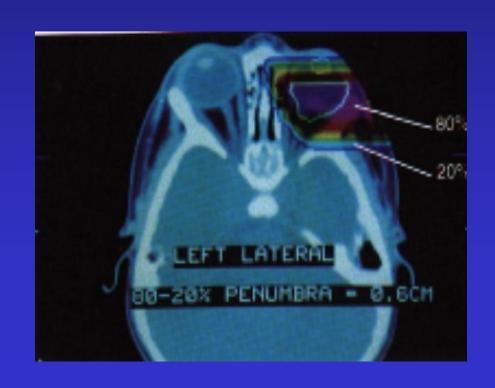
UVEAL MELANOMA

 More than 10,000 patients treated (MGH/HCL Boston, PSI Villingen, Nice & Orsay, Clatterbridge)

• 5y-LC rate >95%

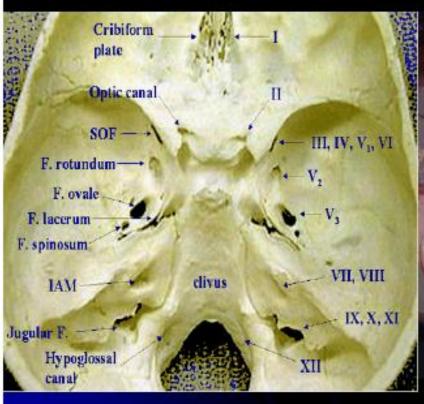
• Eye preservation >90%

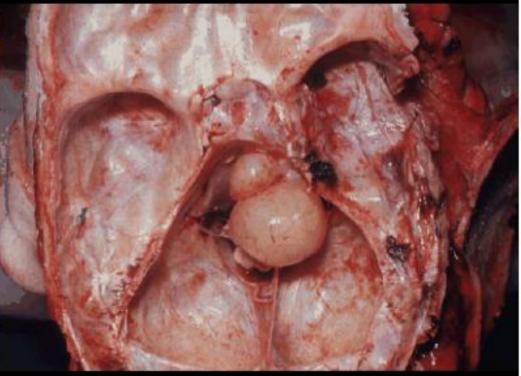
• Visual acuity >45%



Chordoma: Base of Skull

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



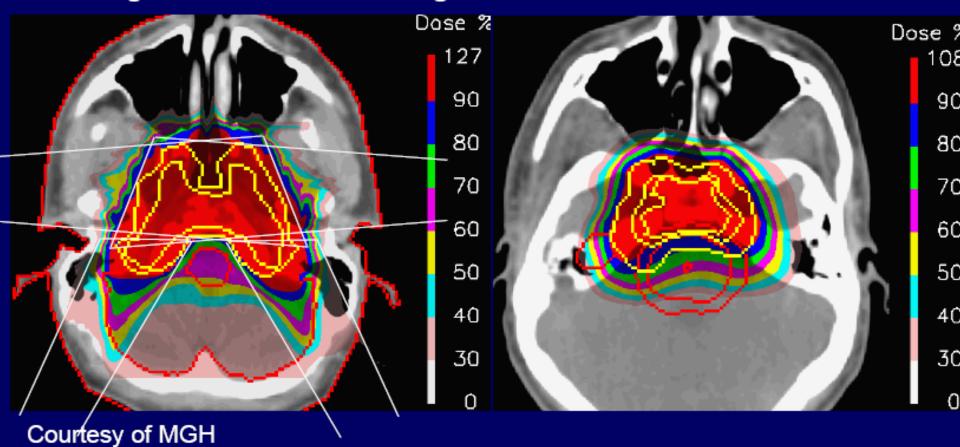


Passive scattering - MGH

Spot-scanning technique - PSI

Field patching

Matching distal and lateral field edges









Skull Base Chordomas: Proton series



	n	Radiation	Mean dose	LC 3 -yr	LC 5 -yr	LC 10 -yr
Munzenrider, 1999	290	PT, RT	76		73 \	54
Terahara, 1999	115	PT, RT	69		59 \	44
Hug, 1999	33	PT, RT	71	67	59	
Noel, 2005	100	PT, RT	67	86 2y	53 4y	
Schulz-Ertner, 2007	96	Carbon, RT	60*	81	70	
lgaki, 2004	13	PT, RT	72	67	46	
Ares 2008	42	PT	74		81	

^{*}at 3.0 CGE per fraction

Chordoma of the sacrum





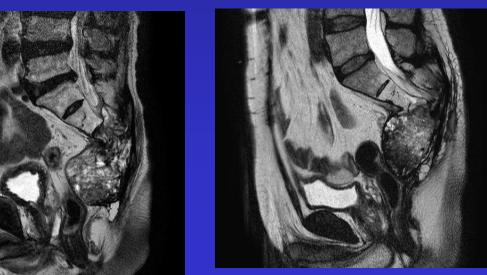


4 years

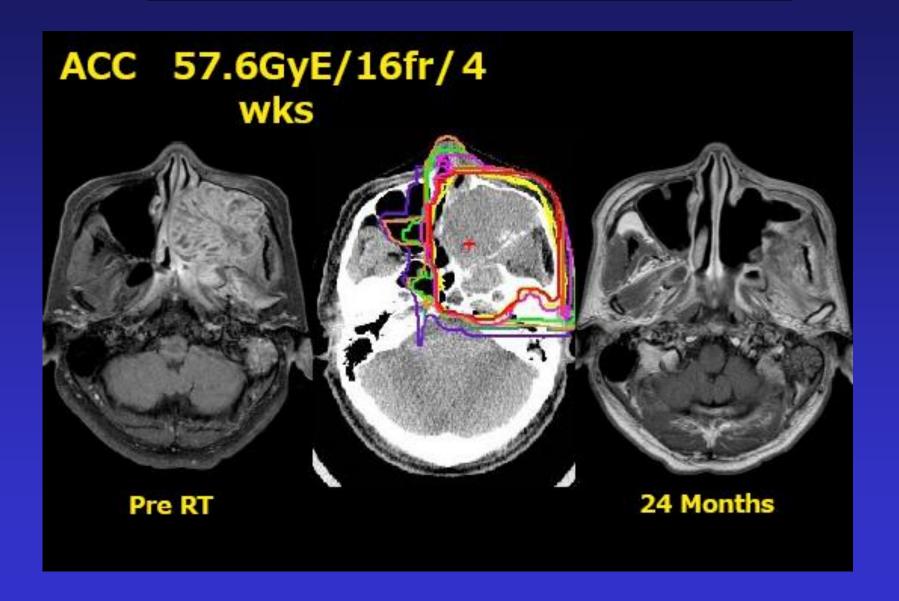




4.5 years



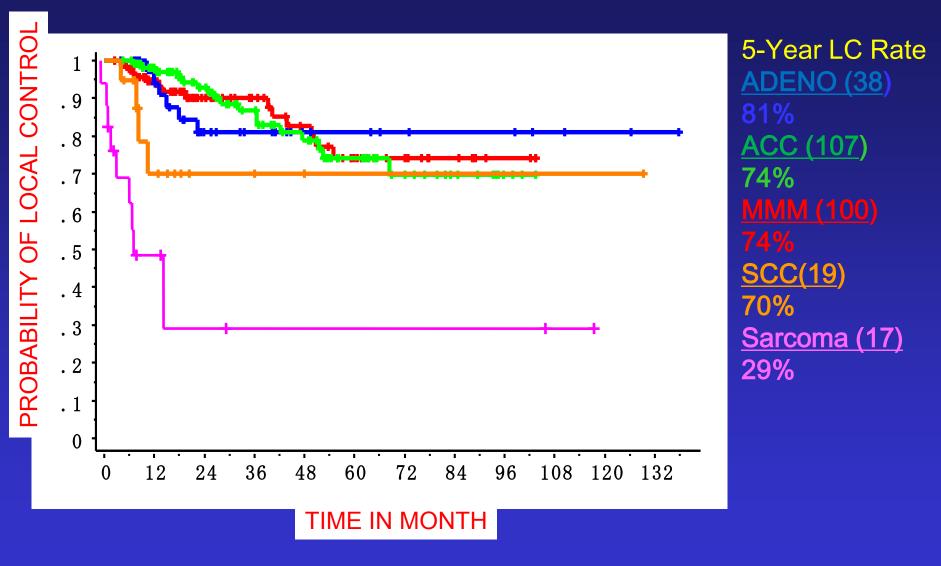
Carbon ion RT at NIRS



Histology/Site	ParaNasal Sinus	Nasal Cavity	Salivary Gland	Oral Cavity	Orbita	Pharynx	Thyroid	Ears	Others	Total
Adenoid Cystic Carcinoma	32	12	19	22	15	17		3		120
Malignant Melanoma	27	51	2	12	7	3		0		102
Adenocarcinoma	13	6	6	2	7	4		2		40
Squamous Cell Carcinoma	6	1		3	1	4		4		19
Papillary Adenocarcinoma	1			1			11			13
Mucoepidermoid Ca.	2	1	5			3				11
Osteosarcoma	3					1			2	6
Acinic Cell Carcinoma			6							6
Undifferentiated Carcinoma	1				4					5
Others	6		4	3	4	4			6	27
Total	91	71	43	43	38	36	11	9	7	349

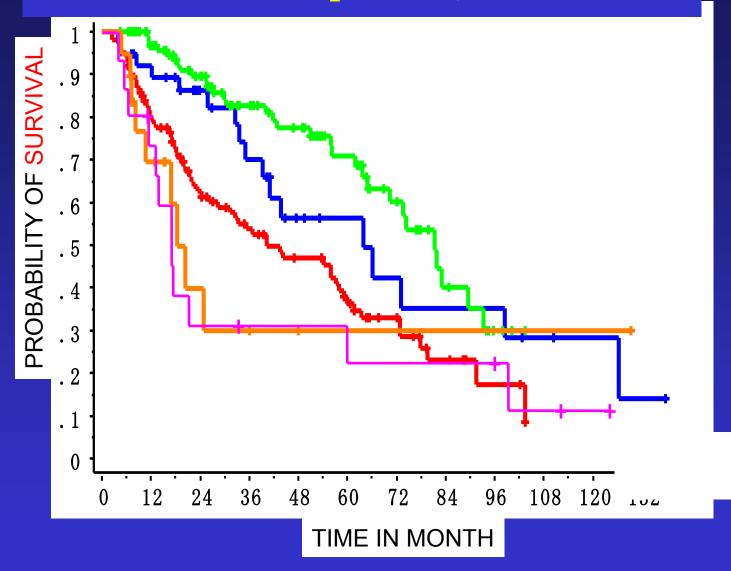
T3: 53 (14.3%); T4: 151 (43.0%)

9602 All cases (325patients, 328 sites)



9602: Local Control by Histology

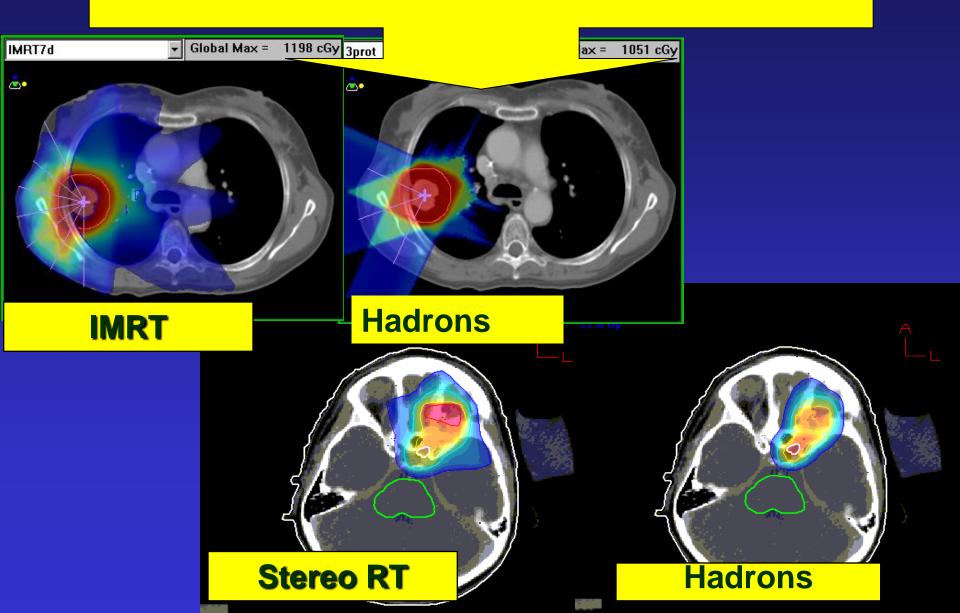
9602 All cases (325patients, 328 sites)



5-Year OS
ADENO (38)
56%
ACC (106)
68%
MMM (100)
36%
SCC(19)
30%
Sarcoma (17)
30%

Hemangiopericytoma 70.4 GyE/16f./4 wks Pre RT 5 years

Other endpoints in Results

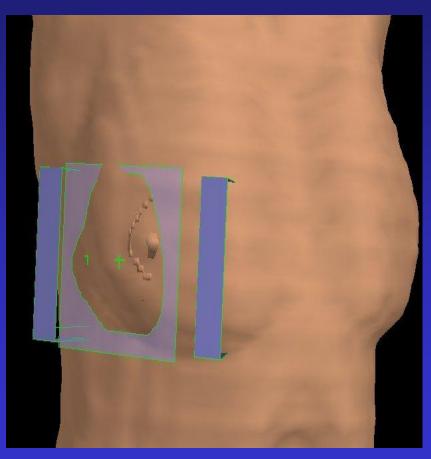


COMPARISON

APBI: Protons

APBI: Photons / Electrons
MGH technique

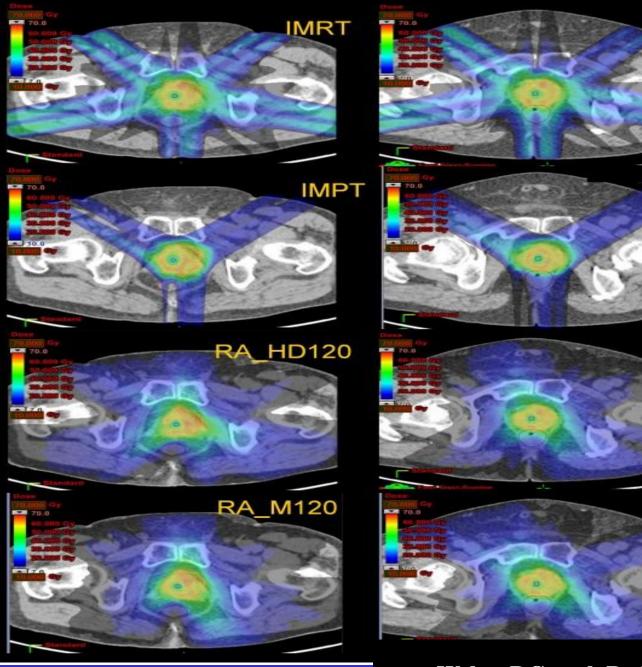




Comparison between APBI using Protons vs Photons/electrons technique Doses to **HEART**

	3 D photons/e	3D protons	P-value
Max dose (Gy)	5.3	2.9	0.0001
Mean dose (Gy)	0.3	0.04	0.0001
D20 (Gy)	0.4	0.0	0.0001
D10 (Gy)	0.7	0.0	0.0001
D5 (Gy)	1.1	0.1	0.0001

D20 → Dose received by 20% of the tissue



Integral Dose
3 times higher
for all
photon's
techniques

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

Chung CS et al (Harvard & MGH, Boston).

Comparative analysis of second malignancy in patients treated with proton therapy versus conventional photon therapy.

50 th ASTRO Meeting, Boston, 2008

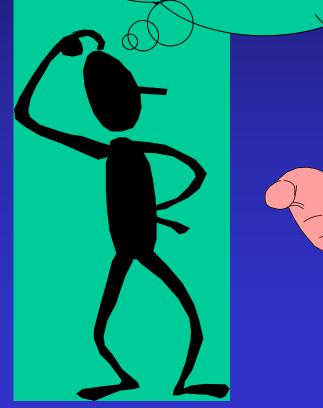
"treatment with photon therapy was significantly associated with an increased risk of a second malignancy (1.87 to 3.98, p<0.0001)"

Hadrontherapy:

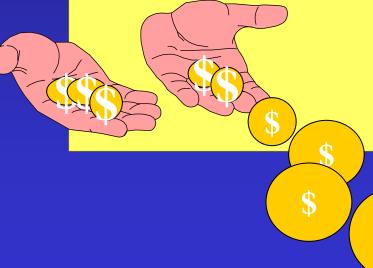
Cost?

Yes, it's fine!

But too expensive



Hadrons



Radiother Oncol. 2010 Jan 25. [Epub ahead of print]

How costly is particle therapy? Cost analysis of external beam radiotherapy with carbonions, protons and photons.

<u>Peeters A, Grutters JP, Pijls-Johannesma M, Reimoser S, De Ruysscher D, Severens JL, Joore MA, Lambin P.</u> Maastricht Radiation Oncology (MAASTRO Clinic), The Netherlands; Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital Maastricht, The Netherlands.

PURPOSE: Particle therapy has potentially a better therapeutic ratio than photon therapy. However, investment costs are much higher. This study provides an estimation and comparison of the costs of these therapies.

METHODS: Within an extensive analytical framework capital and operational costs, cost per fraction, and four tumor specific treatment costs are calculated for three facilities: combined carbon-ion/proton, proton-only, and photon.

RESULTS: Capital costs for the combined, proton-only and photon facilities are: euro 138.6 million, euro 94.9 million, euro 23.4 million. Total costs per year are: euro 36.7 million, euro 24.9 million, euro 9.6 million. Cost per fraction is: euro 1128 (euro 877-1974), euro 743 (euro 578-1300), euro 233 (euro 190-407). Cost ratio particle/photon therapy is 4.8 for the combined and 3.2 for the proton-only facility. Particle treatment costs vary from euro 10,030 (c-ion: lung cancer) to euro 39,610 (proton: head & neck tumors). Cost difference between particle and photon therapies is relatively small for lung and prostate cancer, larger for skull-base chordoma and head & neck tumors

CNAO. Estimated Cost per Cycle

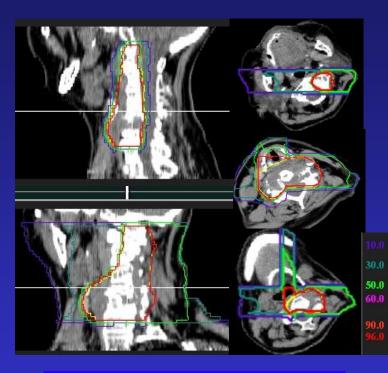
			Euro
Proton/C12 therapy			
Stereotactic	Reimbursement rate per patient (EUR)		16.500
Boost	Reimbursement rate per patient (EUR)		11.500
Entire cycle	Reimbursement rate per patient (EUR)		26.000

Only cost or cost-effectiveness?

Treatment	beatign because i	Treatment costs in ϵ
Conventional photon RT	Treatment planning	1200
	Treatment delivery	2300
Carbon ion RT	Planning + delivery	20000
Neurosurgical resection	Surgery	11 000
	Hospitalization	12600
Total costs for conv. RT	test stimulate delegantes	27100
Total costs for ion RT		43 600

5-Year local control rate	Cost of primary therapy in ϵ	Cost of recurrencies in ϵ	Total costs in €		
ing land was thin stead on	PER PREVIOUS ON THE LO		Scenario A	Scenario B	
35% (conv. RT)	27100	52 956	80056	ay r Tur 126.85	
50% (conv. RT)	27100	40735	67835	ill Alexandria je	
60% (Carbon RT)	43 600	32 588	76188	72 188	
70% (Carbon RT)	43 600	24441	68041	64041	

Sarcoma of the cervical spine



64 GyE/16 fx/4weeks Patch technique

Before





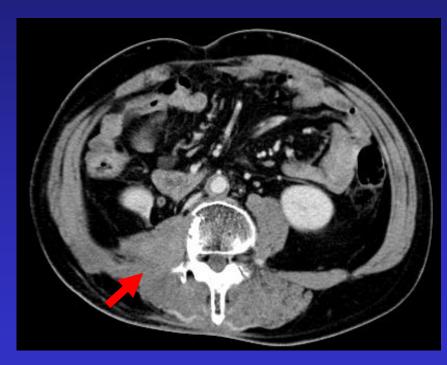
7 years after

(Lancet Oncology 2006)

Retro-peritoneal rhabdomyosarcoma



Before

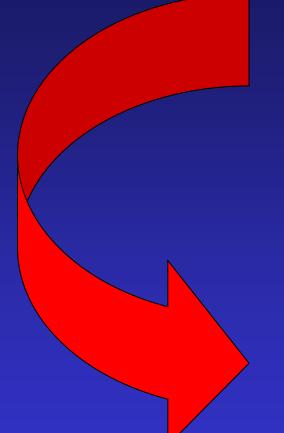


After 5 years

Conclusions







- Ideal dose distribution
- Excellent results in specific tumour sites
- Al least equivalent results in almost all cancer, including radioresistant tumours
- Less morbibdity, in principle

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Territoria, Et al III

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HCPBM

10" Workshop on **HEAVY CHARGED PARTICLES** IN BIOLOGY AND MEDICINE

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4th Meeting of the

EUROPEAN NETWORK FOR LIGHT ION HADRON THERAP

OROPA (Biella) 15 - 19 June 2005

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PARTNER

Particle Training Network for European Radiotherapy



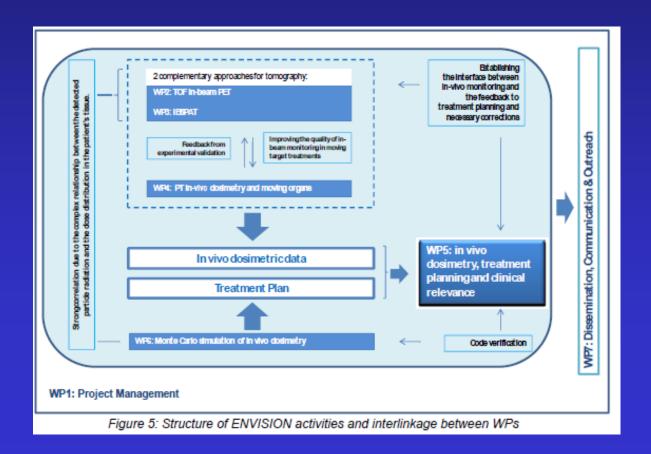
ULICE

Union of Light Ion Centers in Europe



Envision

European NoVel Imaging Systems for ION therapy



Therapy on individuals

