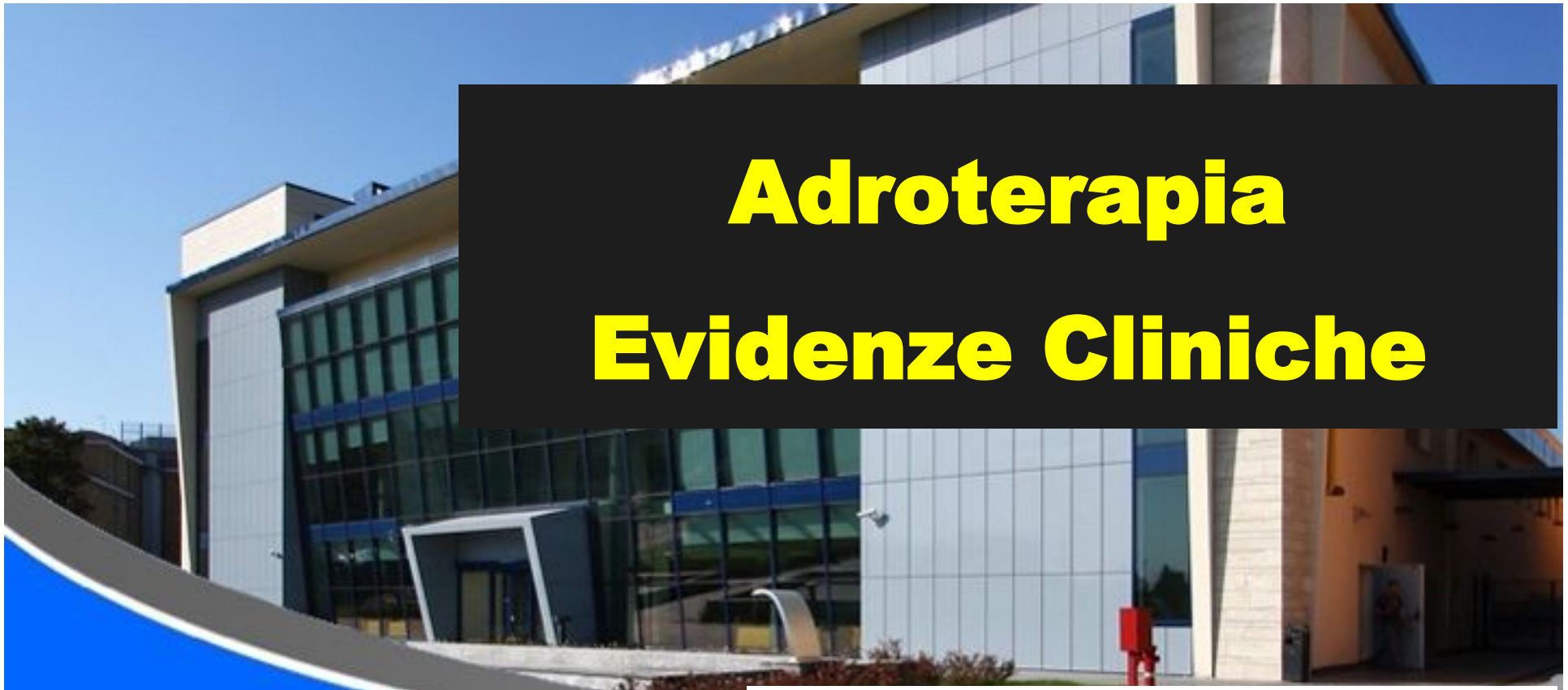


Adroterapia
Evidenze Cliniche

Roberto Orecchia
Cattedra di Radioterapia, Università di Milano
Direttore Scientifico, Istituto Europeo di Oncologia, Milano
e Centro Naztonale di Adroterapia Oncologica, Pavia

XXIV CONGRESSO NAZIONALE
AIRO 2014
Padova,18-11 Novembre 2014

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

Improvment in Technology

Improvment in Dose Distribution

Improved Dose Distribution

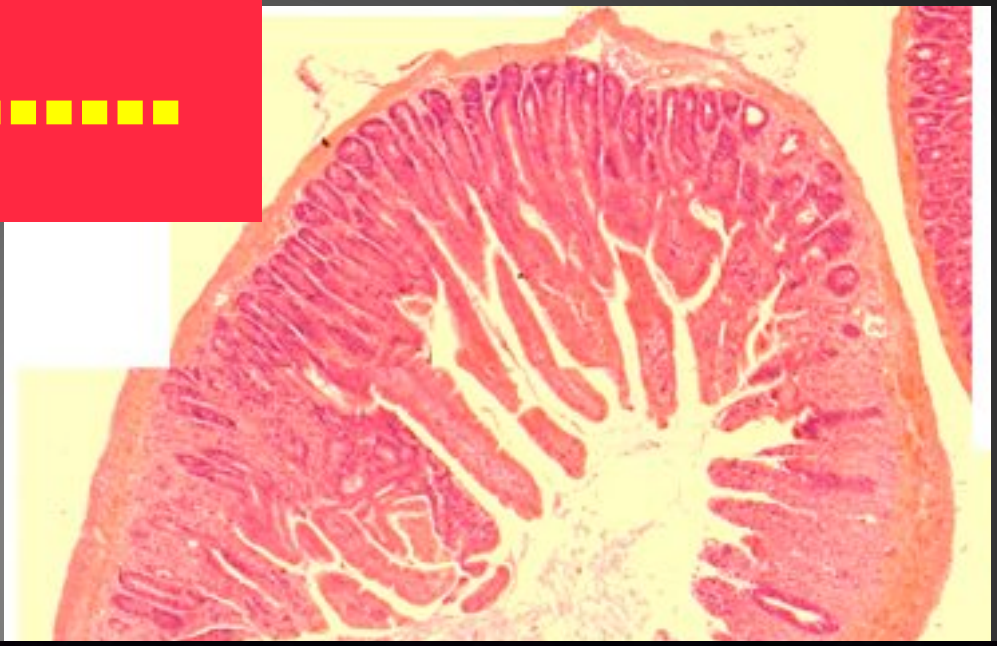
Technology

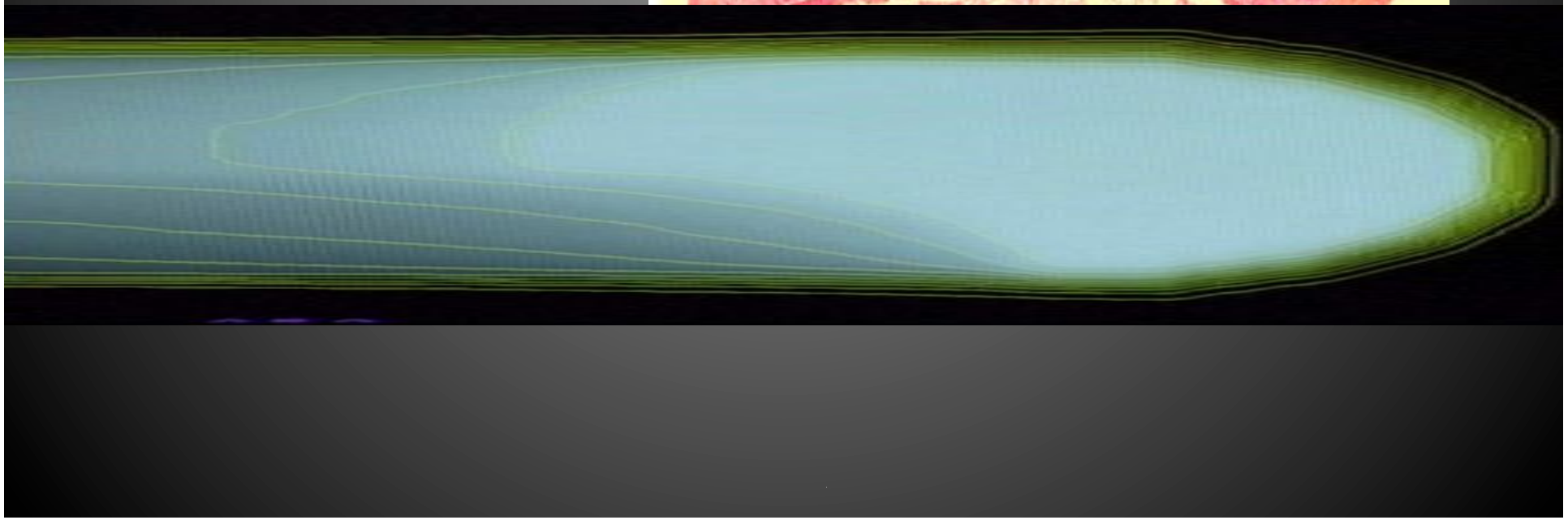
Smaller volume + Higher dose =

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

Inverse Square Law

Hadrons. A new dimension .....

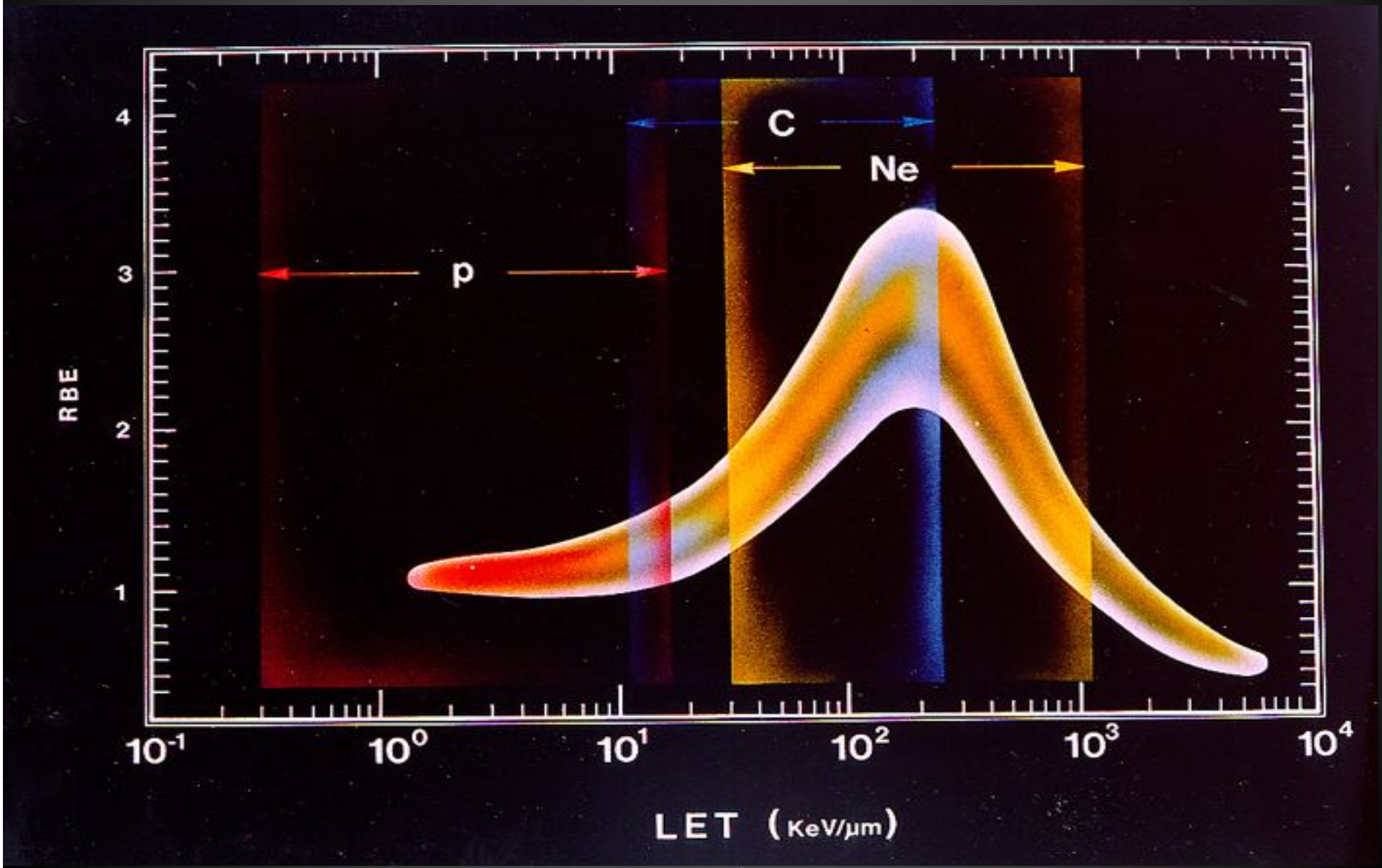




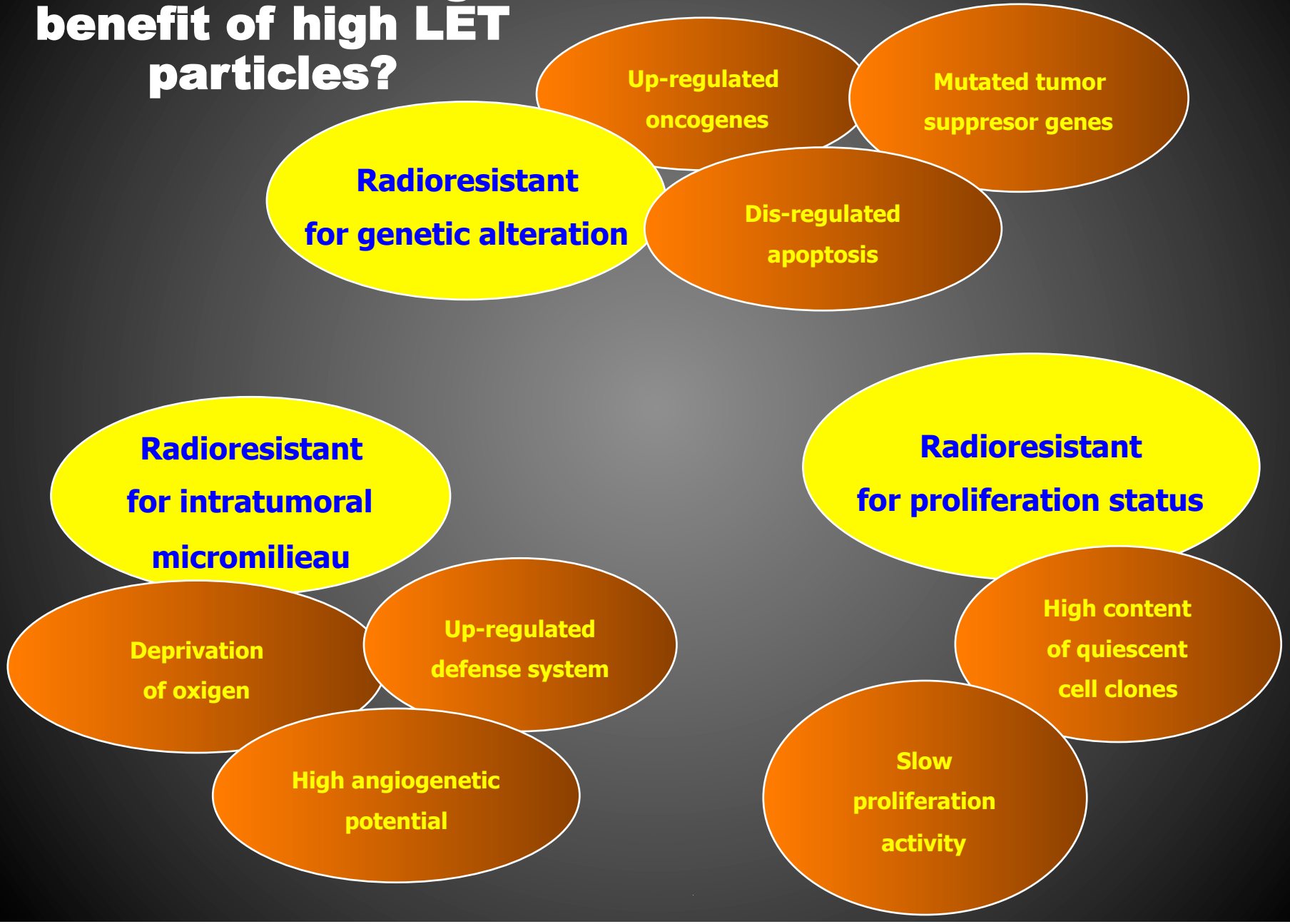
Physical Selectivity

- Inverted depth dose profile (Bragg peak)
- Defined penetration depth
- Less lateral scattering ($_{1}H \neq C_{12}$)
- Reduction of integral dose

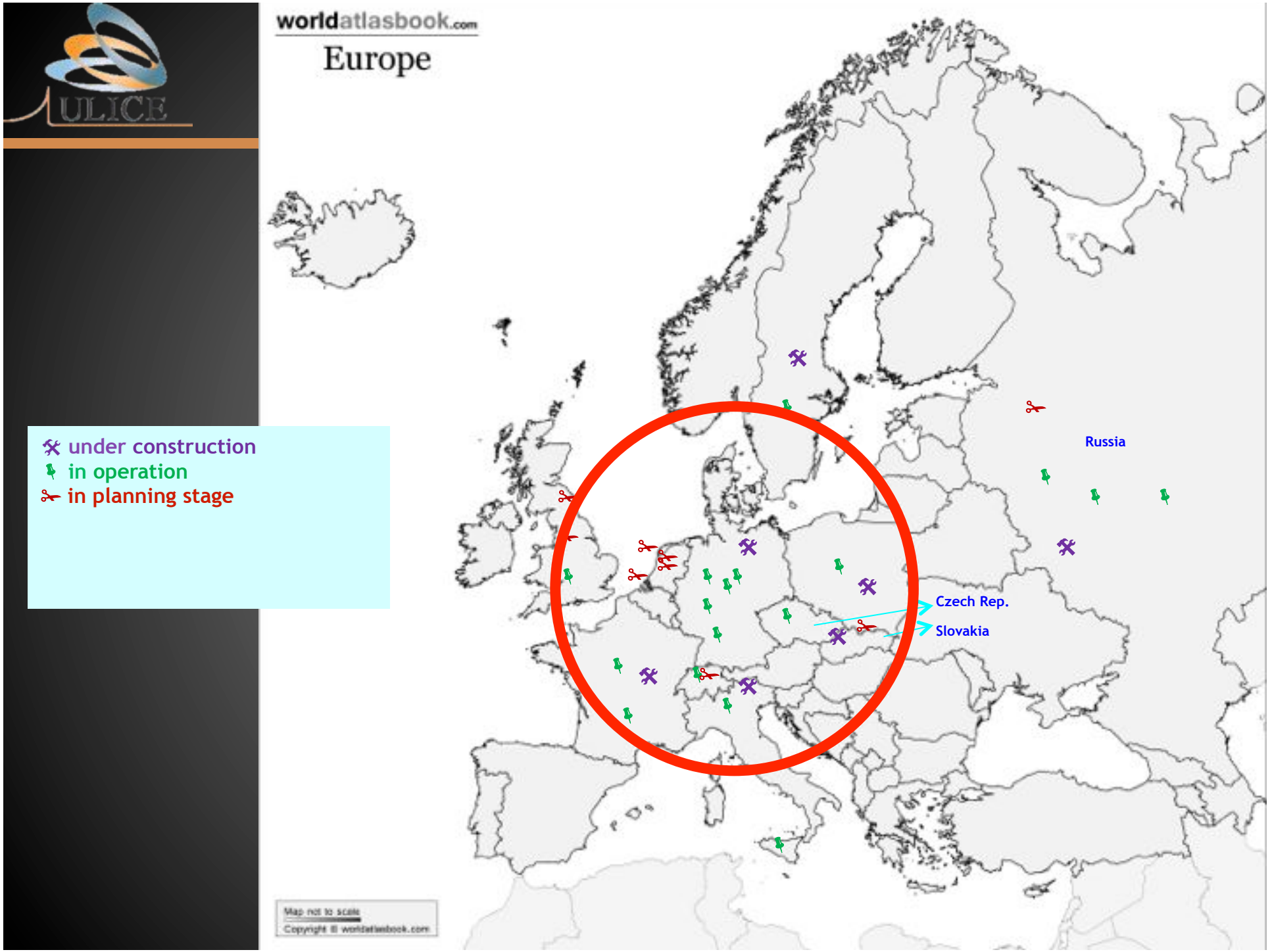
Radiobiology of particles



Which tumors might benefit of high LET particles?




Worldwide Access to Hadrons


worldatlasbook.com
Europe
under construction
in operation
in planning stage
Russia
Czech Rep.
Slovakia
Map not to scale
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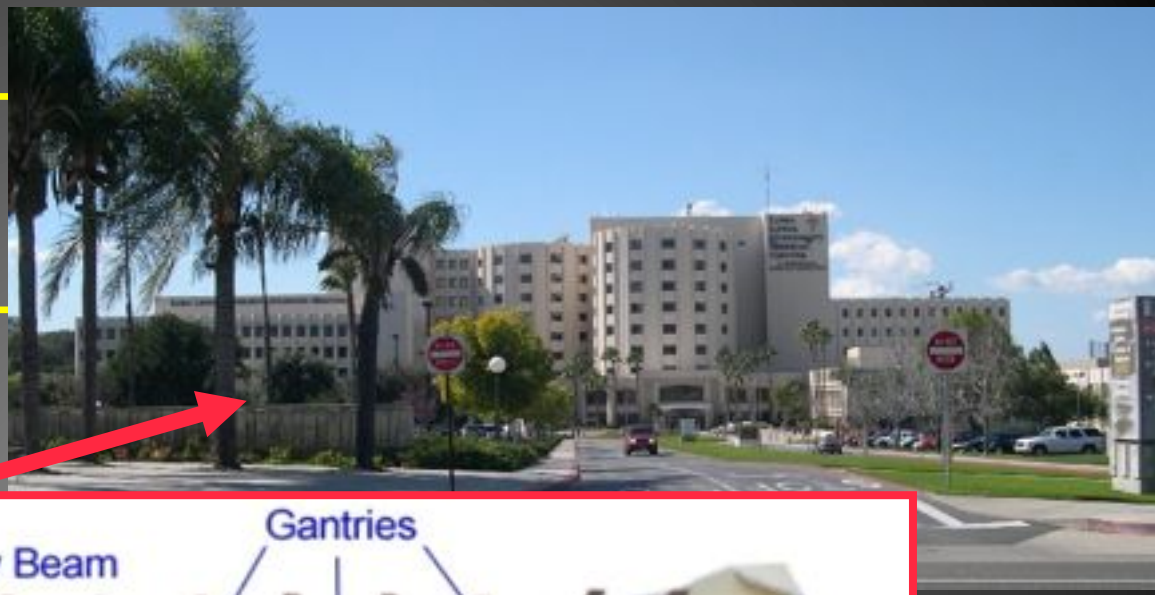
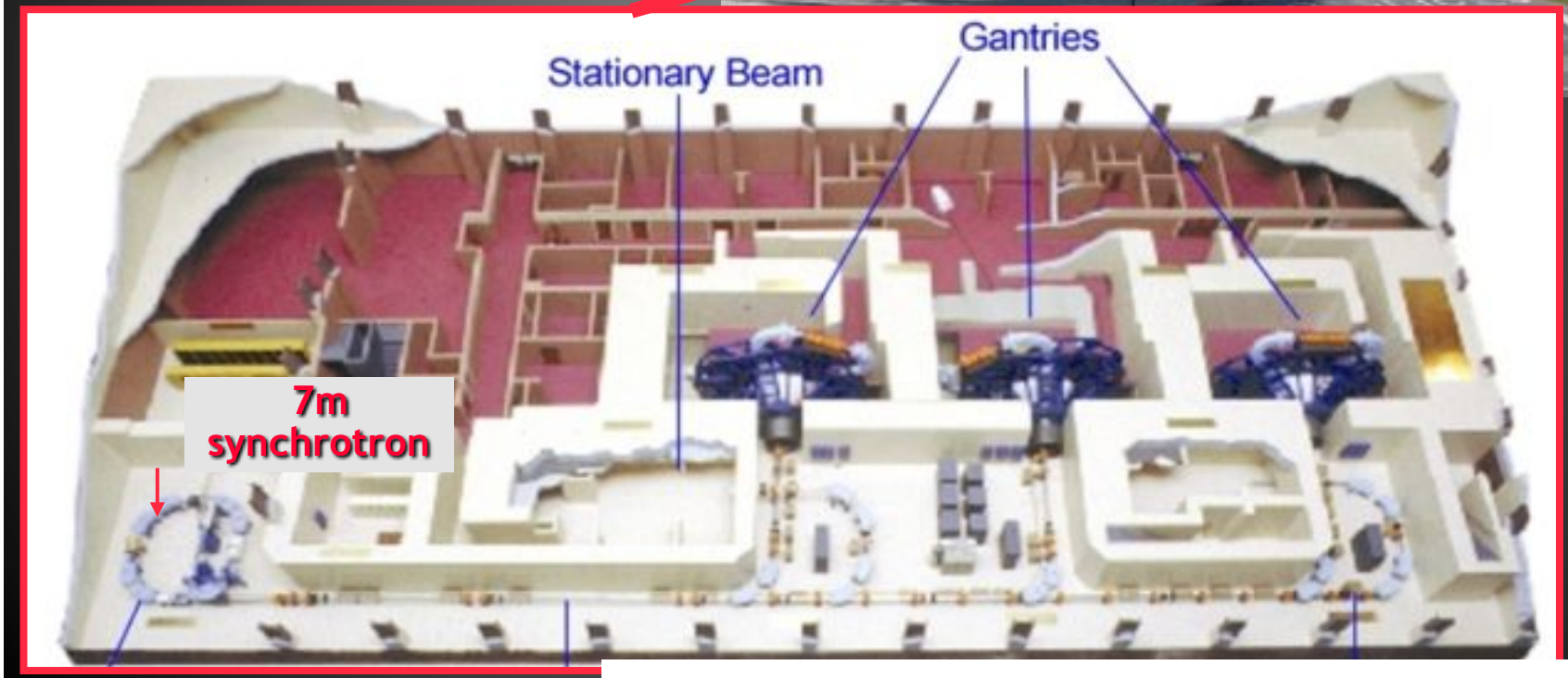
Loma Linda University Medical Center

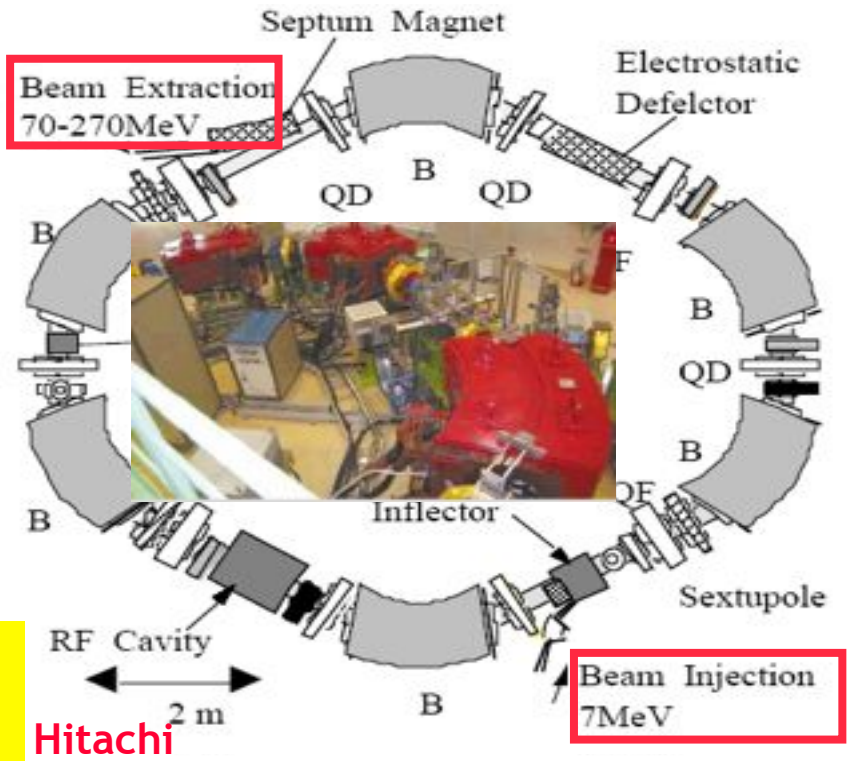
First hospital based protontherapy centre (1992)





Optivus Ltd. commercialises this centre

IBA



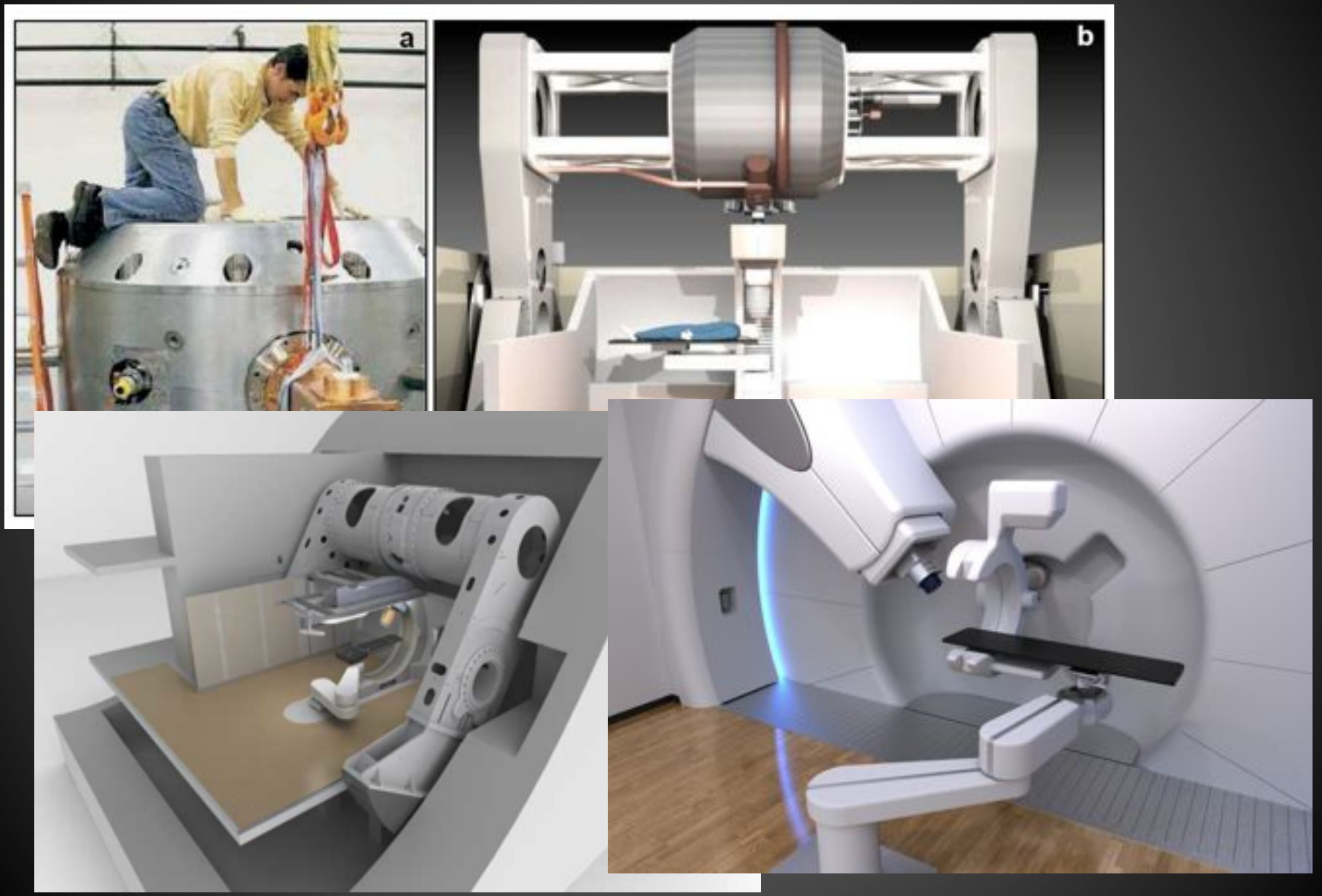
Hitachi

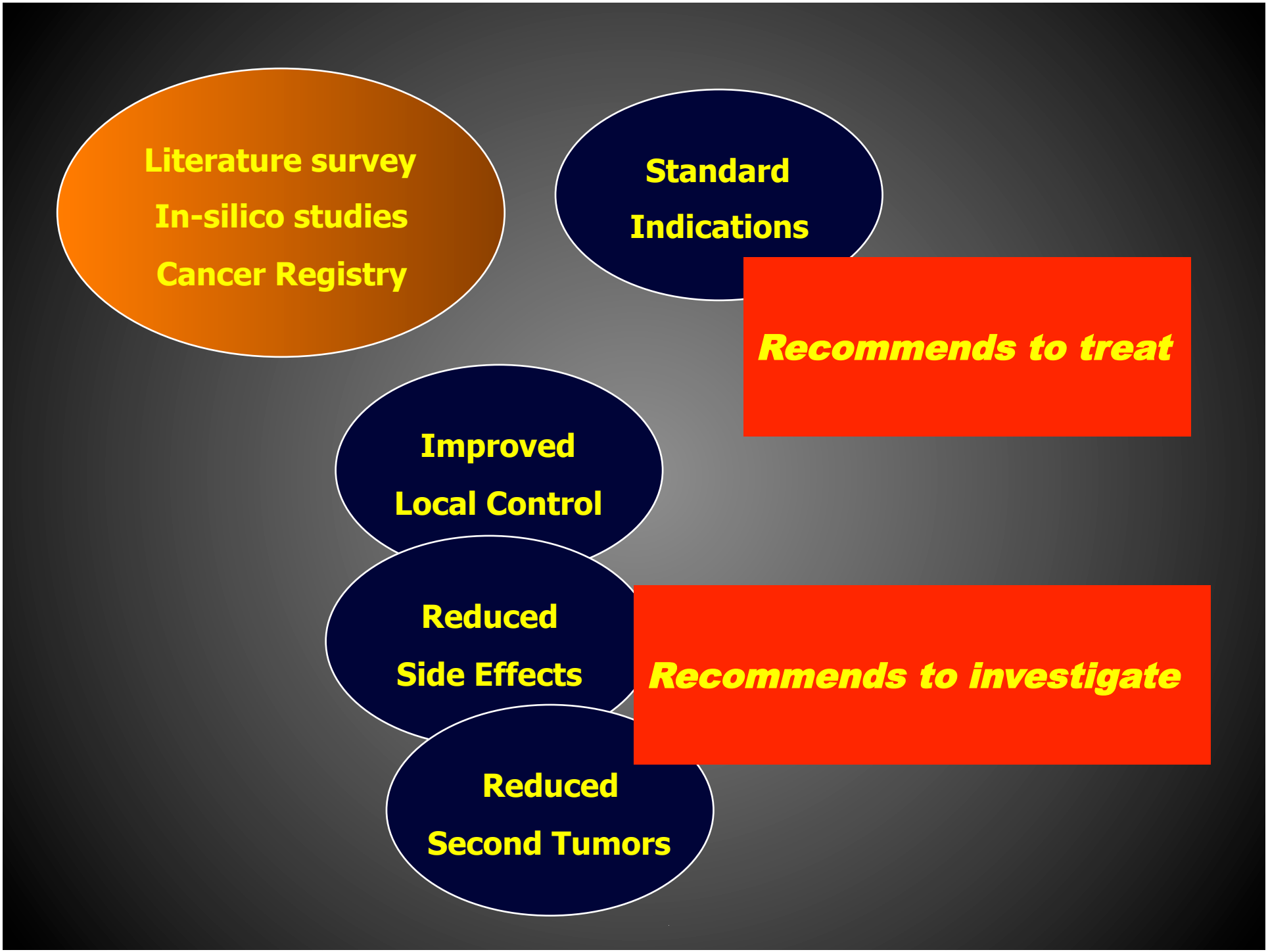
Protontherapy: a market exists …

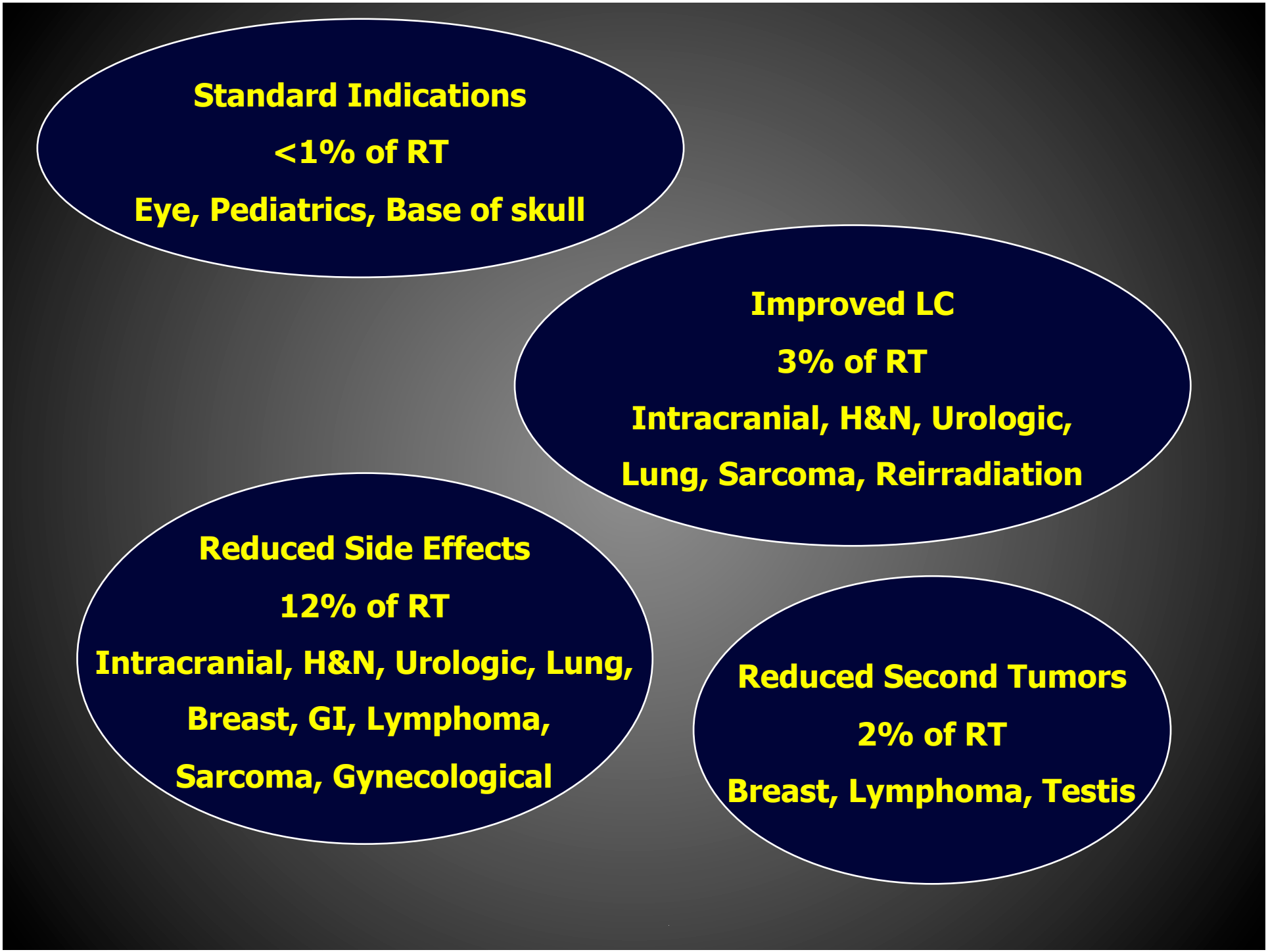
Mitsubishi

Varian

Coming up: single room facility

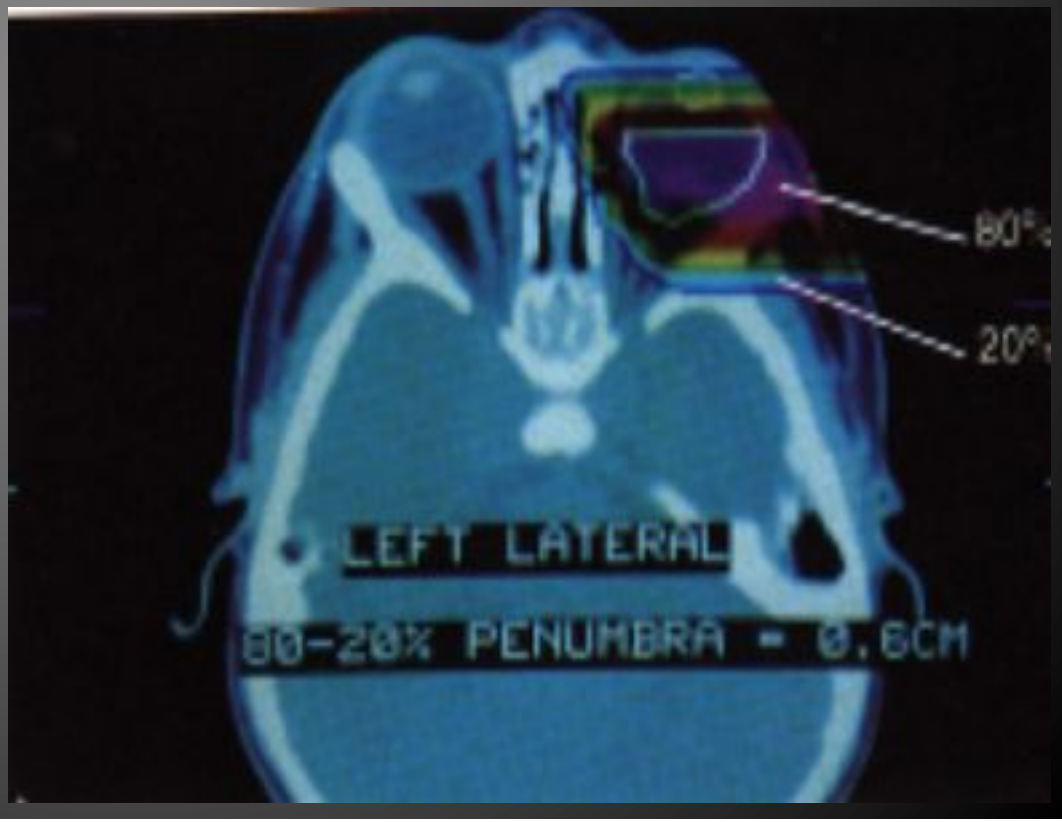



Literature survey
In-silico studies
Cancer Registry
Standard
Indications
Recommends to treat
Improved
Local Control
Reduced
Side Effects
Recommends to investigate
Reduced
Second Tumors


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

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%

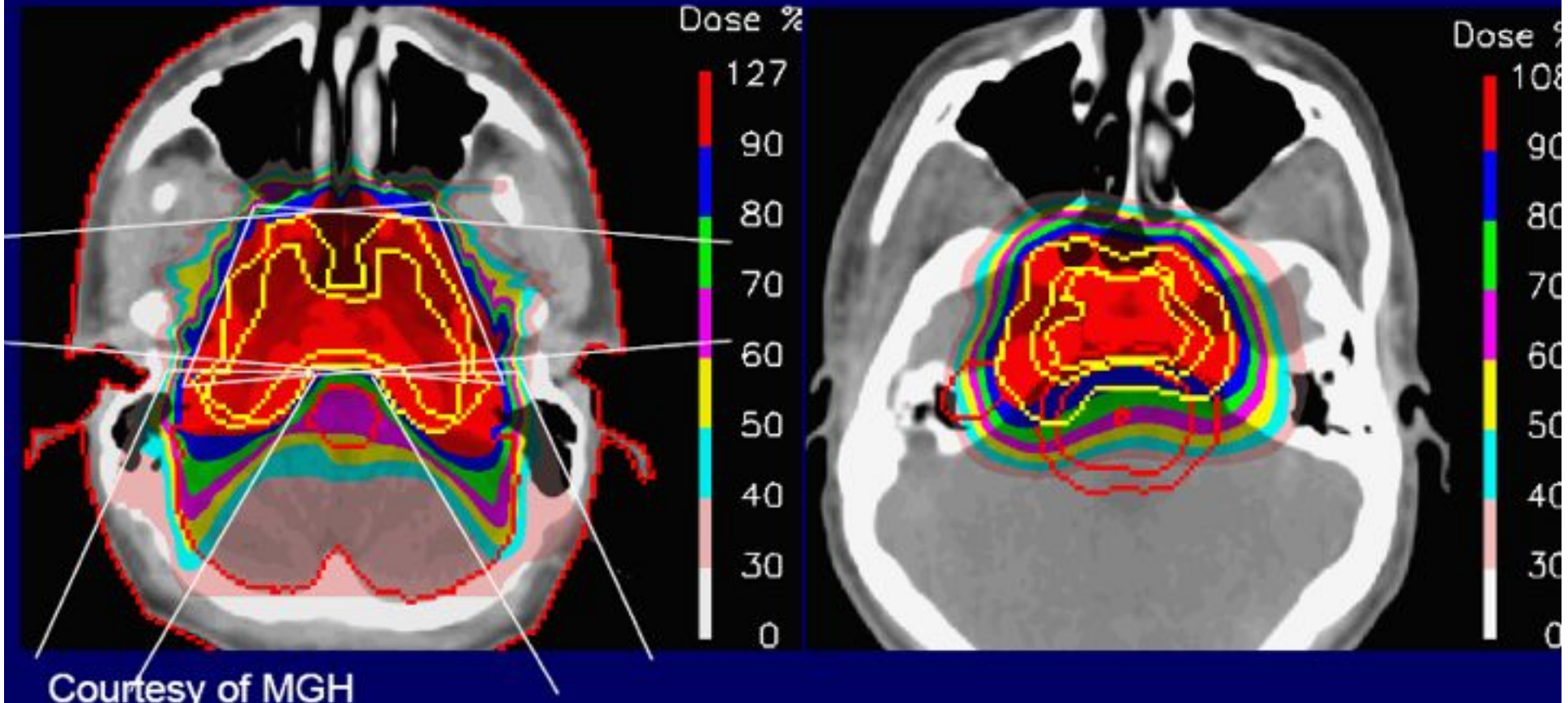


Passive scattering - MGH

Field patching

Matching distal and lateral field edges

Spot-scanning technique - PSI



Courtesy of MGH

PT in Skull Base Chordomas and Chondrosarcomas

Proton Therapy Program

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%

Carbon ion therapy in Skull Base Chordomas and Chondrosarcomas

Ref	Institution	Pts	Histo	RT	GTV Mean	Dose , mean (CGE)	% LC	Fu (Months)
Schulz-Ertner D et al, 2007	**GSI**	96	C	CRT	80.3 ml (13.9-594.2)	Median 60 (60-70) 3.0-3.5 GyE x 7 weekly	80 % at 3 yrs 70 % at 5 yrs	Mean 31 mo (3-91)
Schulz-Ertner D et al , 2007	**GSI**	54	CS	CRT	57.2 mL (range, 13.1–255.7 mL)	Median 60 (57-70) 3.0 GyE x 7 weekly	96.2 % at 3 yrs 89.8 % at 4 yrs	Median 33 months (3-84 mo.)
Mizoe et al, 2009 **Hasegawa *, 2010**	**NIRS**	39	C	CRT	51 cm3 (2-328)	48-57.6 (10) 60.8 (29) 16 fractions for 4 weeks 3.0-3.6 / Fr 3.8/Fr	60 % at 5 for 48-57.6 Gy E 95 % at 5 for 60.8 GyE p =0.03	Mean 53 mo. (8-129)
		12	CS		NA	48-57.6 (2) 60.8 (10) 16 fractions for 4 weeks 3.0-3.6 / Fr 3.8/Fr	100 % at 5y	NA

•Up-dated analysis at international meeting

Proton therapy for Atypical and Malignant Meningiomas

Hug E, Journal of Neuro-Oncol 2000

Parameters/Results	Atypical Meningioma (AM)	Malignant Meningioma (MM)	p-Value
Photon RT only	4/15 (27%)	11/16 (73%)	—
Combined Proton/Photon RT	11/15 (73%)	5/16 (31%)	—
Mean RT Target Doses (Gy/CGE)	62	58	—
Range	50–68	40–72	—
Local Control	7/15 (47%)	6/13 (46%)*	—
At 5 years (actuarial)	38%	52%	—
At 8 years (actuarial)	19%	17%	—
Failure site			
In-field	6/8 (75%)	7/7 (100%)	—
Marginal	1/8	—	—
Not evaluable	1/8	—	—
RT Target Dose ≥60 versus <60 Gy/CGE	90% vs. 0%	100% vs. 0% (at 5 years)	0.025 (AM) 0.002 (MM)
Distant Metastasis	0/15	3/16 (19%)	—
Survival			
Alive	14/15 (93%)	6/16 (38%)	—
no evidence of disease	10/15 (67%)	6/16 (38%)	—
with disease	4/15 (37%)	0	—
Dead of disease	1/15 (07%)	10/16 (63%)	—
of intercurrent disease	0	0	—
At 5 years (actuarial)	89%	51%	0.02
At 8 years (actuarial)	89%	51%	0.02
RT dose ≥60 vs. <60 Gy/CGE	—	87% vs. 15% (at 5 years)	0.025

*excludes 3 pts. who died at or shortly after XRT; Gy = Gray; CGE = Cobalt Gray Equivalent.

PROTON BEAM THERAPY FOR UNRESECTABLE MALIGNANCIES OF THE NASAL CAVITY AND PARANASAL SINUSES

SADAMOTO ZENDA, M.D.,* RYOSUKE KOBAYASHI, PH.D.,* MITSUHIKO KAWASHIMA, M.D.,* SATOKO ARAHIRA, M.D.,* TEIJI NISHIO, PH.D.,* MAKOTO TAHARA, M.D., PHD.,† RYUICHI HAYASHI, M.D.,‡ SEIJI KISHIMOTO, M.D., PH.D.,§ AND TAKASHI OGINO, M.D.*

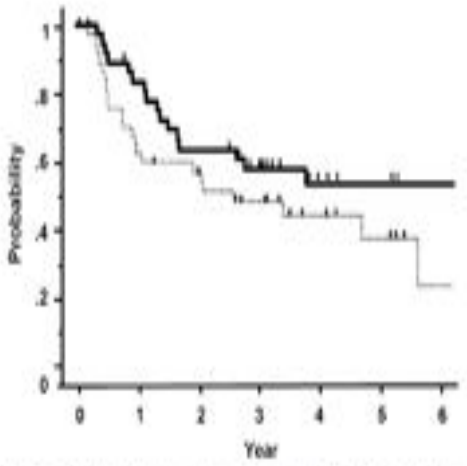


Fig. 2. Overall and progression-free survival. Solid line indicates overall survival curve. 3-year overall 59.3% and 49.1

Table 3. Toxicity in study patients ($N = 39$)

	Grade (CTCAE v.3.0)					
	1	2	3	4	5	% 3–5
Dermatitis	17	13	0	0	0	0
Conjunctivitis	1	1	0	0	0	0
Mucositis	4	4	0	0	0	0
Hearing loss	0	1	0	0	0	0
Cataract	0	0	1	0	0	2.6
CSF leakage	0	0	0	0	1	2.6
Neuropathy						
CN-II	0	1	0	1	0	2.6
CN-VI	0	0	1	0	0	2.6
Brain necrosis	2	1	0	0	0	0
Soft tissue necrosis	0	0	0	0	0	0
Bone necrosis	0	2	1	0	0	2.6
Treatment-related death: 2.6%						

Abbreviations: CN = central nerve; CSF = cerebrospinal fluid; CTCAE v3.0 = common terminology criteria for adverse events v3.0.

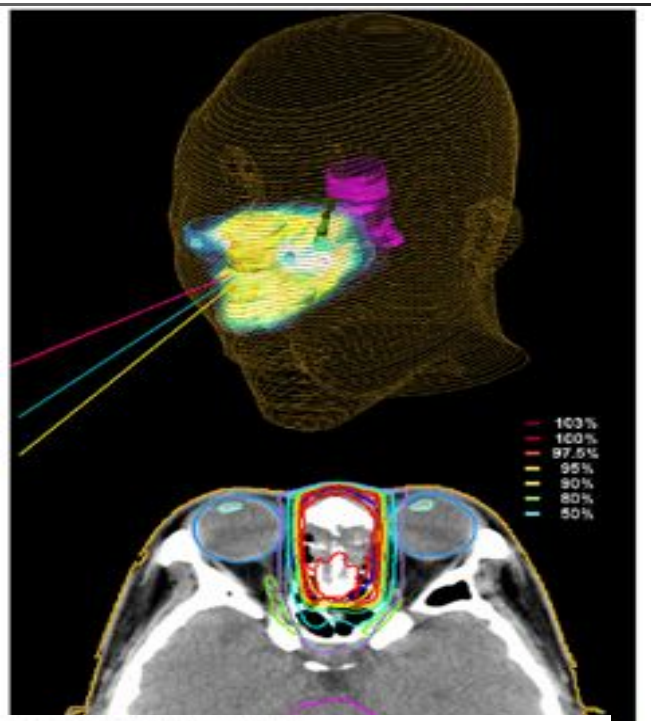


Table 2. Results of univariate analysis ($N = 39$)

Covariate	3-Year OS and PFS rates	Hazard ratio (95% CI)
Age		
OS		1.01 (0.99–1.04)
PFS		1.01 (0.98–1.04)
Sex (female vs. male)		
OS	62.5% vs. 56.9%	0.87 (0.34–2.21)
PFS	48.6% vs. 49.6%	1.17 (0.51–2.65)
Tumor type (SCC vs. other)		
OS	48.0% vs. 63.7%	2.17 (0.81–8.55)
PFS	40.0% vs. 52.1%	1.12 (0.45–2.85)
Primary site (nasal cavity vs. other)		
OS	69.2% vs. 37.0%	0.37 (0.15–0.95)
PFS	60.6% vs. 25.0%	0.55 (0.23–1.30)
Induction chemotherapy (yes vs. no)		
OS	70.0% vs. 56.7%	0.67 (0.22–2.05)
PFS	66.7% vs. 38.5%	0.50 (0.17–1.50)
Radiation dose		
OS		1.04 (0.88–1.22)
PFS		0.94 (0.81–1.08)

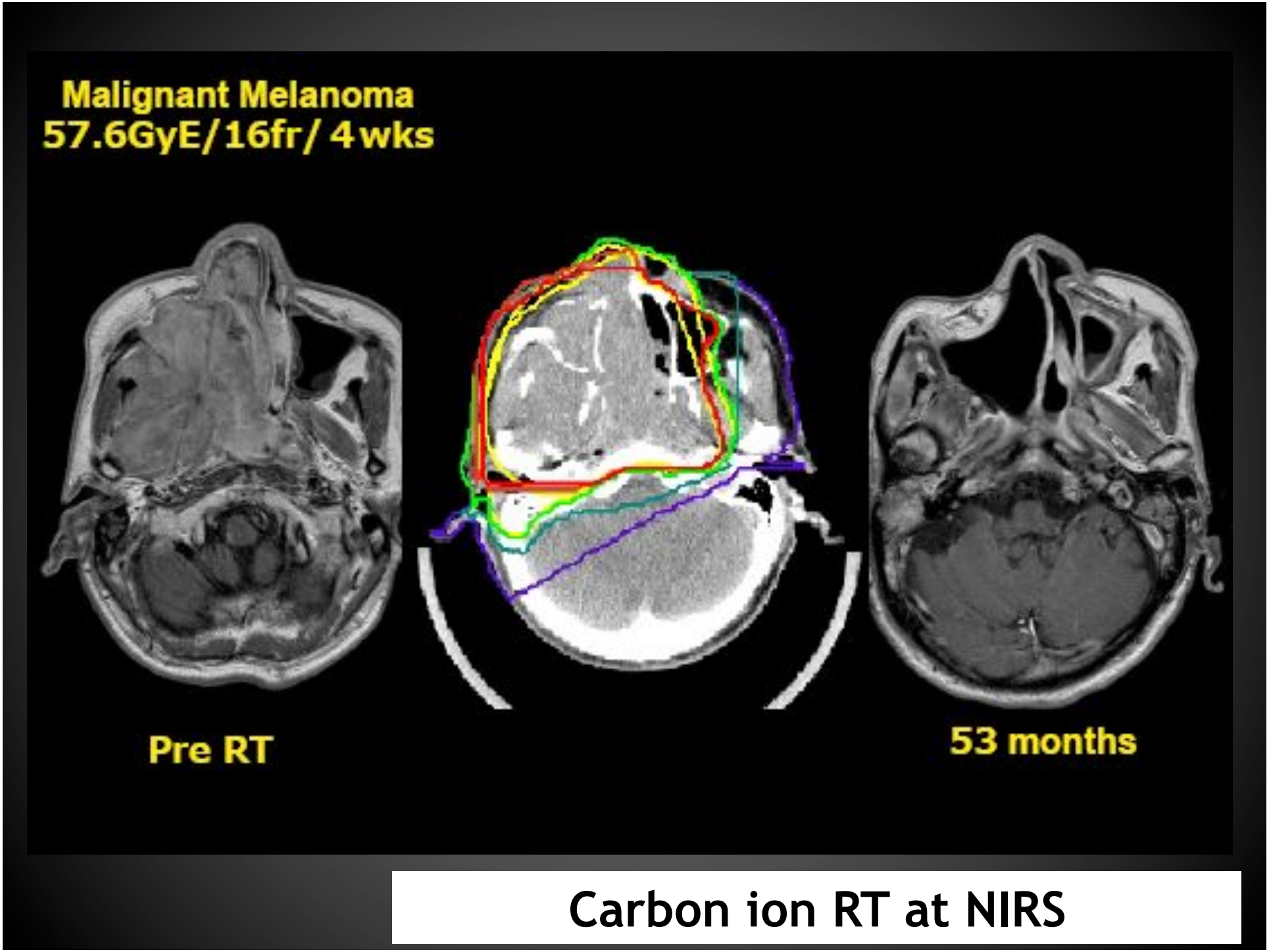
Abbreviations: BED = biologically equivalent dose; CI = confidence interval; OS = overall survival; PFS = progression-free survival; SCC = squamous cell carcinoma.

Table 4. Late toxicity in study: Grade 3–4 (severe toxicity)

Case no.	Age (y)	Sex	Treatment	Tumor site	Toxicity	Time to onset	Recurrence	Status
11	58	Male	IC → PBT (70 GyE/28 fr)	Sphenoid sinus	Brain necrosis Grade 2 CN-VI disorder Grade 3	35.2 mo	None	Alive 65.6 mo
12	61	Female	IC → PBT (65 GyE/26 fr)	Nasal cavity	CSF leakage Grade 5	13.6 mo	None	Treatment-related death
25	63	Male	IC → PBT (65 GyE/26 fr)	Nasal cavity	Bone necrosis Grade 3	38.7 mo	None	Alive 45.4 mo
27	79	Male	PBT (60 GyE/15 fr)	Nasal cavity	Visual Loss Grade 4	16.6 mo	None	Alive 38.1 mo
30	73	Female	PBT (65 GyE/26 fr)	Nasal cavity	Cataract Grade 3	4.0 mo	Distant	Died 23.8 mo

Abbreviations: CSF = cerebrospinal fluid; CN = central nerve; fr = fractions; IC = induction chemotherapy; PBT = proton beam therapy.

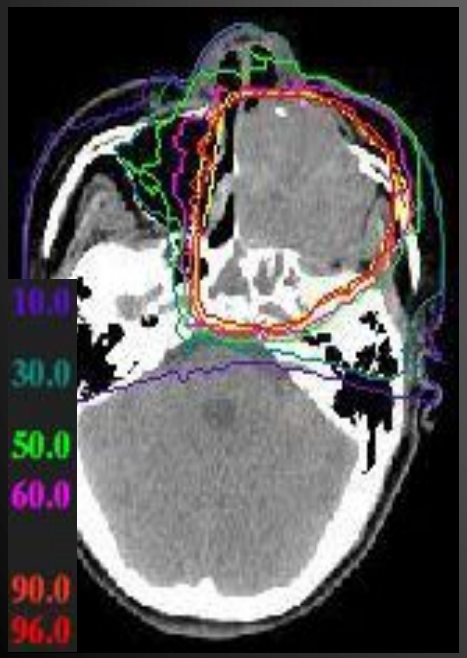
Zenda S et al, IJROBP, 2011



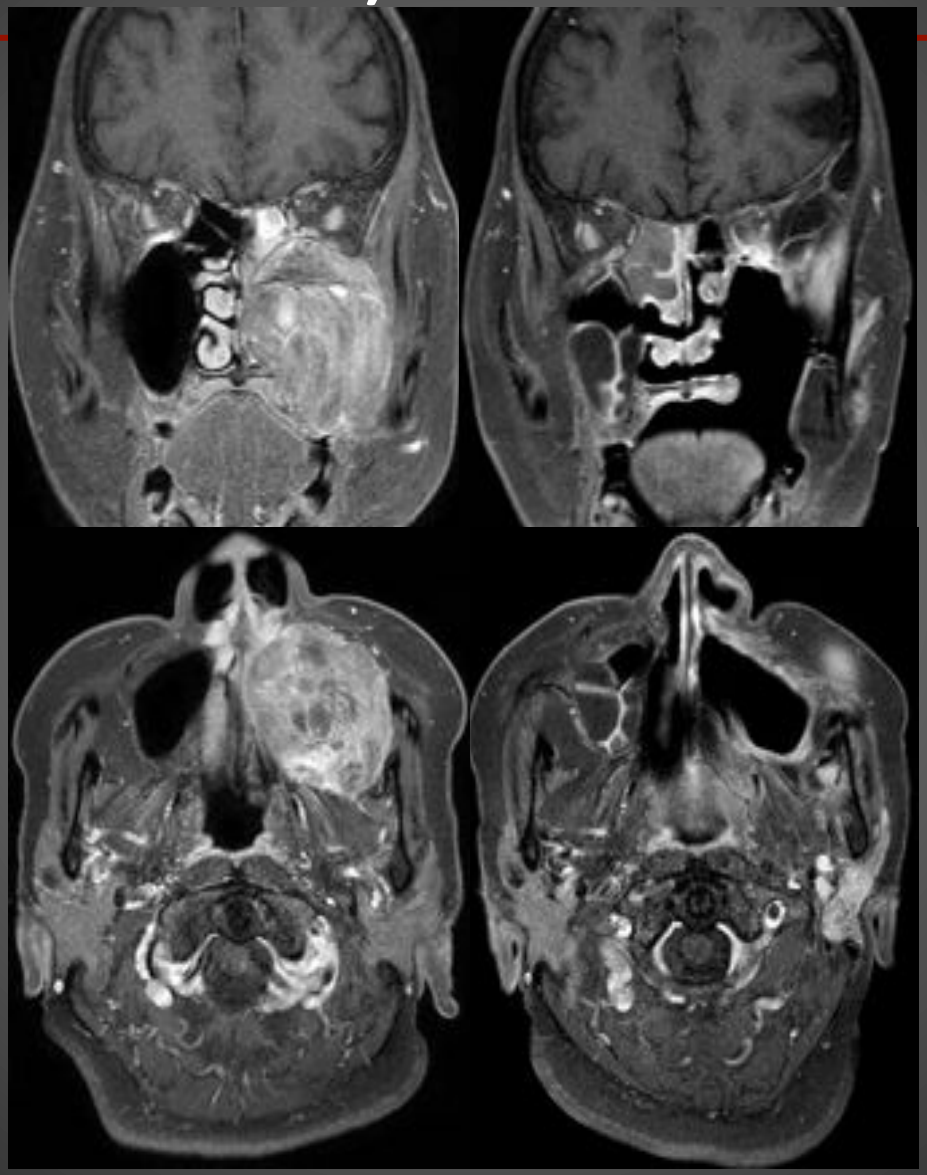
Carbon ion RT at NIRS

Malignant Melanoma in the Left Maxillary Sinus
(Target volume = 151.9 ml)

64 GyE/16 frs.

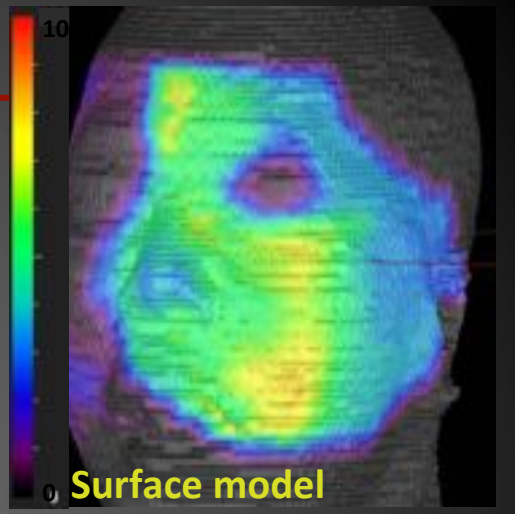


Dose distribution



Pre c-ion RT

Post 25 months



Surface model

Post 6 months

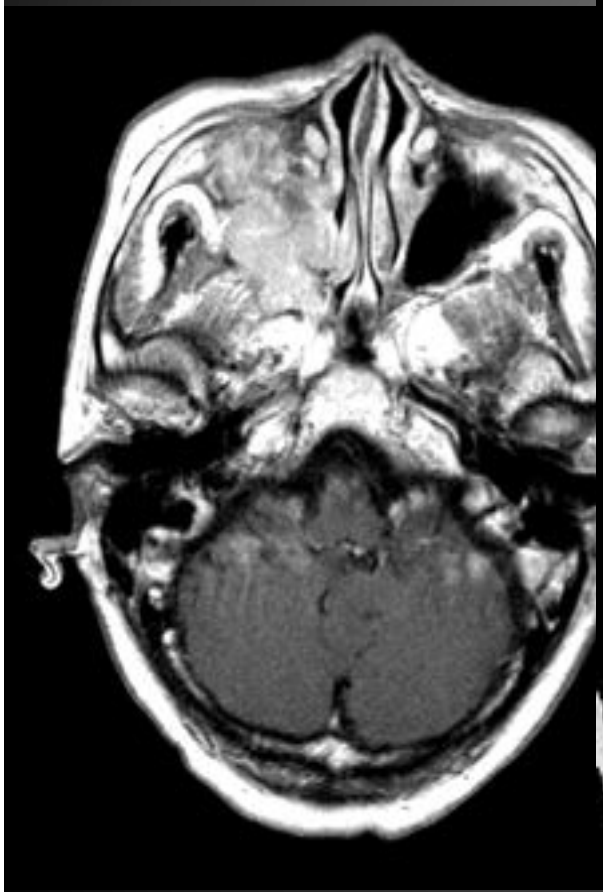
Post 25 months

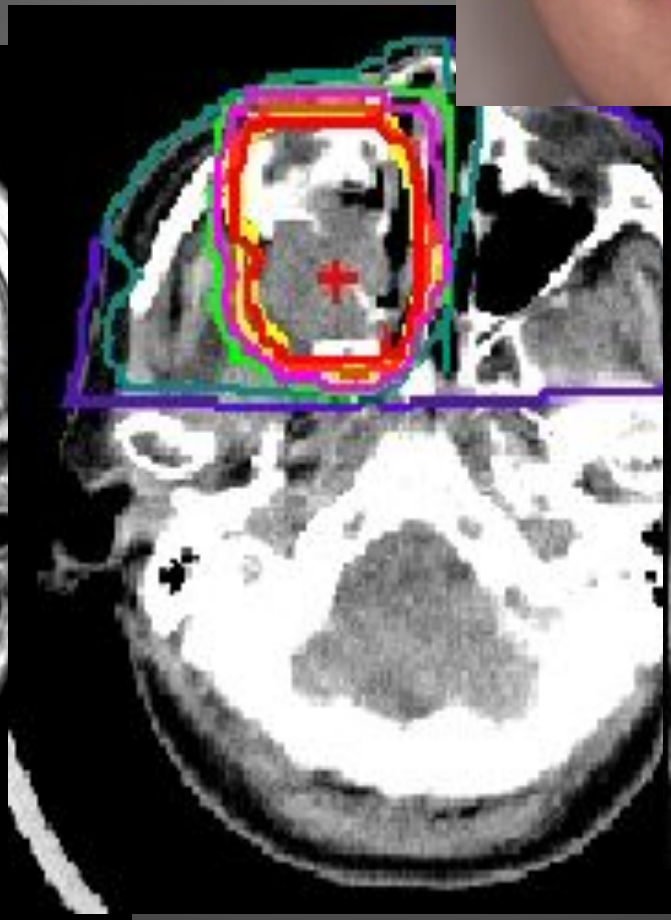
Malignant mucosal melanoma in head and neck

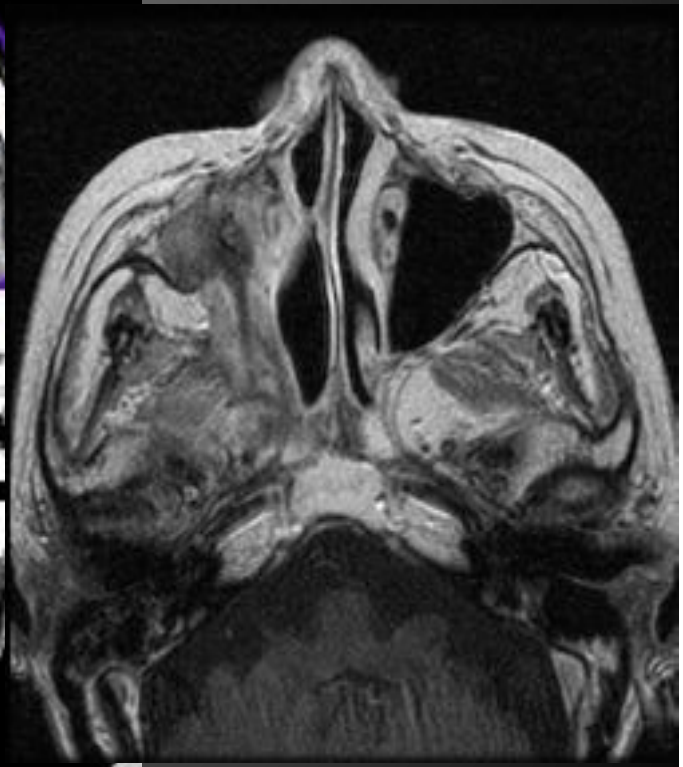
Author	*No.*	*Tumor location*	*Treatment modalities*	*5-year OS (%)*
Gilligan	28	Sinonasal	Radiotherapy	18
Shibuya	28	Upper jaw	Radiotherapy +/- surgery	25
Shah	74	Head and neck	Surgery +/- radiotherapy	22
Chaudhry	41	Head and neck	Surgery+/- radiotherapy+/- chemotherapy	17
Lund	58	Sinonasal	Surgery+/- postoperative radiotherapy+/-chemotherapy (BCG, melphalan)	28
Pandey	60	Head and neck	Surgery+/- radiotherapy+/- chemotherapy	28*
Chang	163	Head and neck	Surgery+/- radiotherapy+/- chemotherapy	32
Patel	59	Sinonasal and oral	Surgery +/- postoperative radiotherapy+/-chemotherapy	35
Stern	42	Sinonasal and oral	Surgery+/- radiotherapy+/- chemotherapy+/-immunotherapy	40
Guzzo	48	Head and neck	Surgery+/- radiotherapy+/- chemotherapy+/-immunotherapy	21
Wada	31	Head and neck	Surgery+/- radiotherapy+/- chemotherapy	33*
NIRS-1(9602)	100	Head and neck	Carbon ion radiotherapy	36
NIRS-2(0007)	82	Head and neck	Carbon ion radiotherapy+ chemotherapy	62

Carbon ion RT at NIRS

Bone and soft-tissue sarcoma







Pre CIRT **70.4 GyE/16fs/4 wks** **5 years**

Table 4. Comparisons of overall survival and local control of sarcomas of the adult head and neck

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 francis

Jingu K et al IJROBP, 2012

CLINICAL INVESTIGATION

CARBON ION RADIATION THERAPY IMPROVES THE PROGNOSIS OF UNRESECTABLE ADULT BONE AND SOFT-TISSUE SARCOMA OF THE HEAD AND NECK

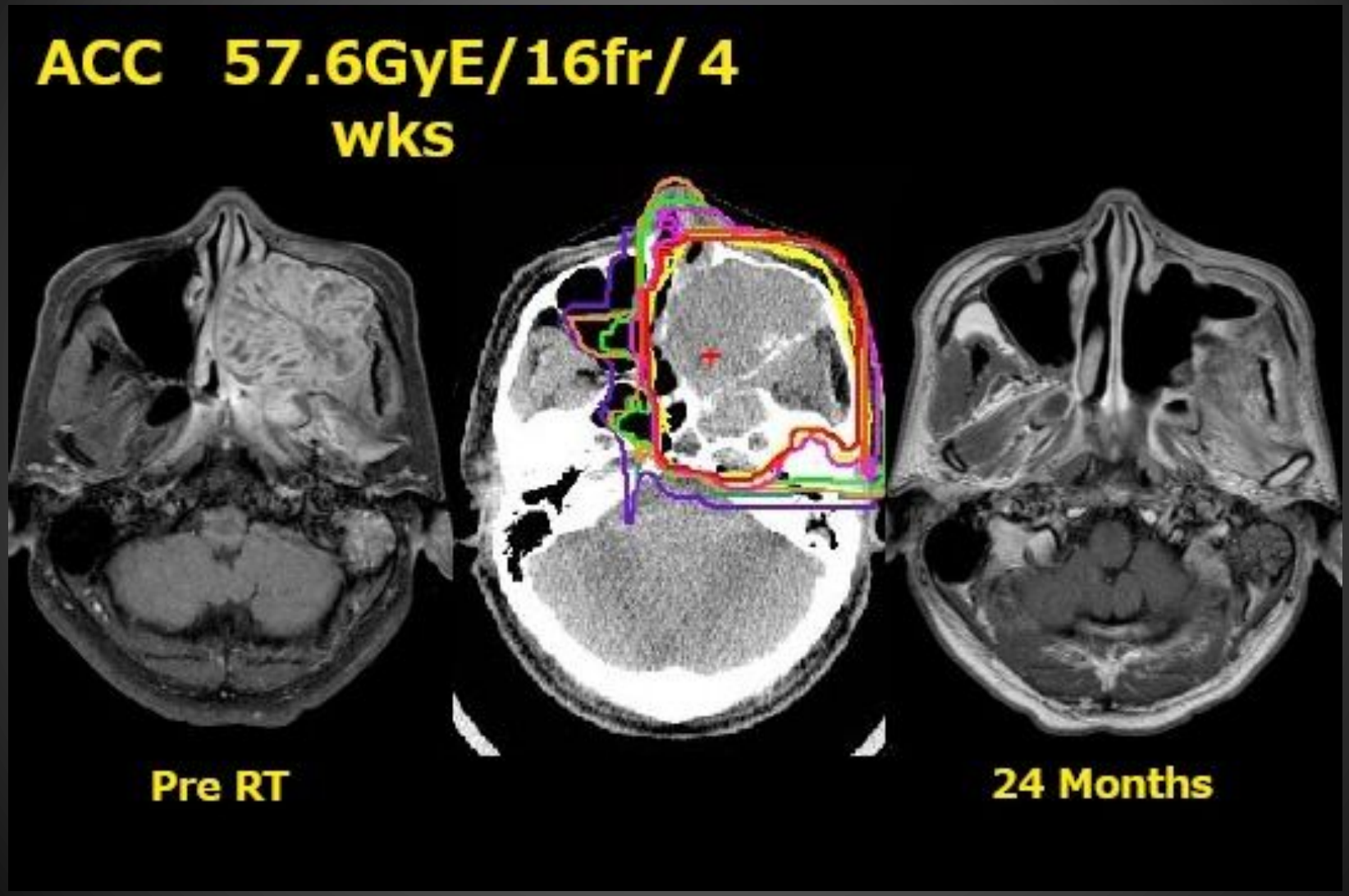
Keiichi Jingu, M.D., Ph.D.,*† Hirohiko Tsujii, M.D., Ph.D.,* Jun-Etsu Mizoe, M.D., Ph.D.,* Azusa Hasegawa, D.D.S., Ph.D.,* Hiroki Bessho, D.D.S., Ph.D.,* Ryo Takagi, D.D.S., Ph.D.,* Takamichi Morikawa, D.D.S.,* Morio Tonogi, D.D.S., Ph.D.,‡ Hiroshi Tsuji, M.D., Ph.D.,* Tadashi Kamada, M.D., Ph.D.,* and Shogo Yamada, M.D., Ph.D. † and Organizing Committee for the Working Group for Head-and-Neck Cancer

From the *Research Center for Charged Particle Therapy, National Institute of Radiological Sciences (NIRS), Chiba, Japan; †Department of Radiation Oncology, Tohoku University School of Medicine, Sendai, Japan; ‡Department of Oral Medicine, Tokyo Dental College, Ichihara, Japan

Purpose: To evaluate the safety and efficacy of carbon ion radiotherapy (C-ion RT) with 70.4 GyE for unresectable bone and soft-tissue sarcoma of the adult head and neck.

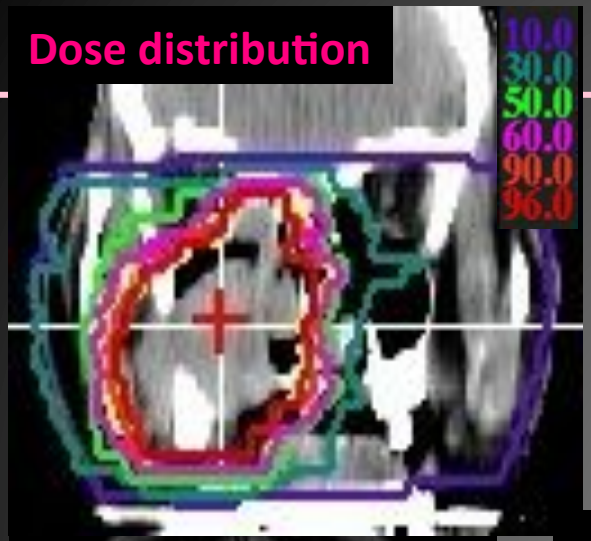
Methods and Materials: Twenty-seven patients (mean age, 46.2 years) were enrolled in this prospective study on C-ion RT with 70.4 GyE/16 fractions (fr) between April 2001 and February 2008. The primary end points were acute and late reactions of normal tissues, local control rate, and overall survival rate. The secondary end point was efficacy of the treatment in comparison to historical results with 57.6 or 64.0 GyE/16 fr.

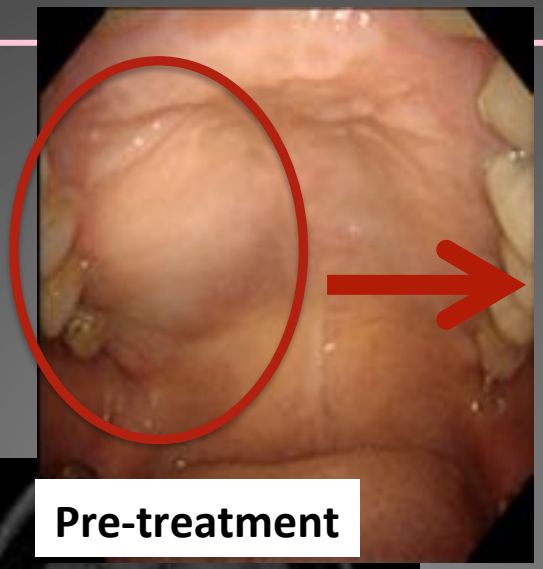
Carbon ion RT at NIRS

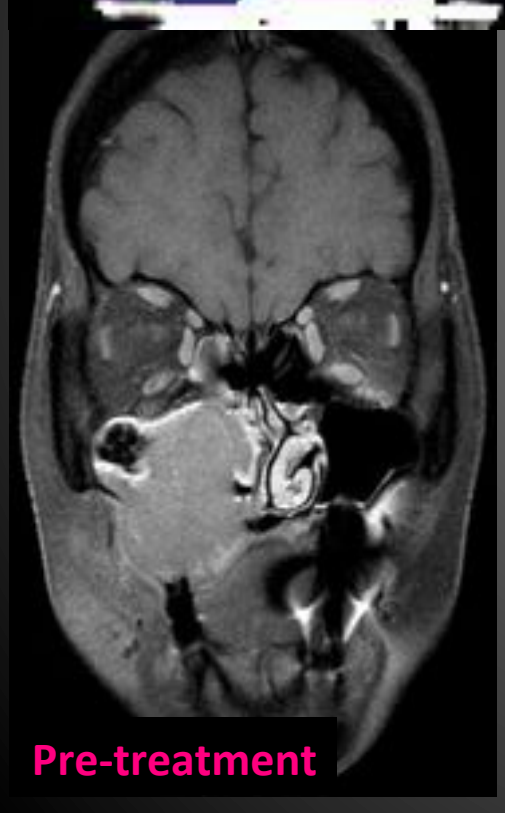


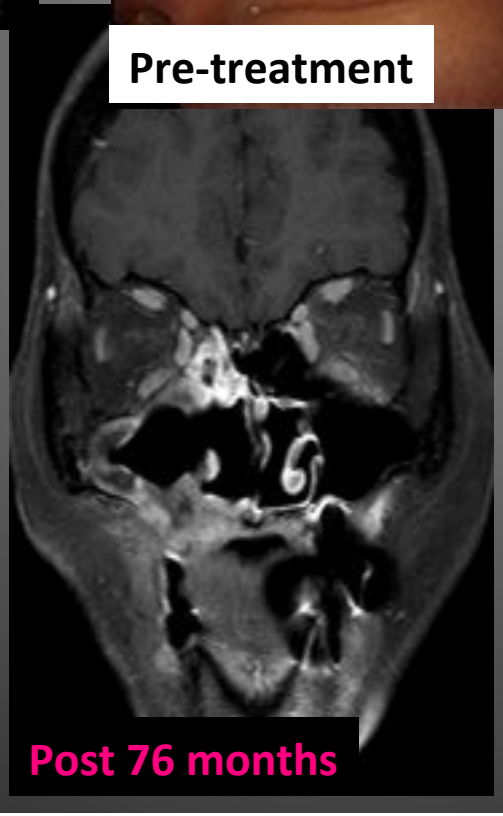
ACC in the Maxillary Sinus (Target volume = 189 ml)

57.6 GyE/16 frs.









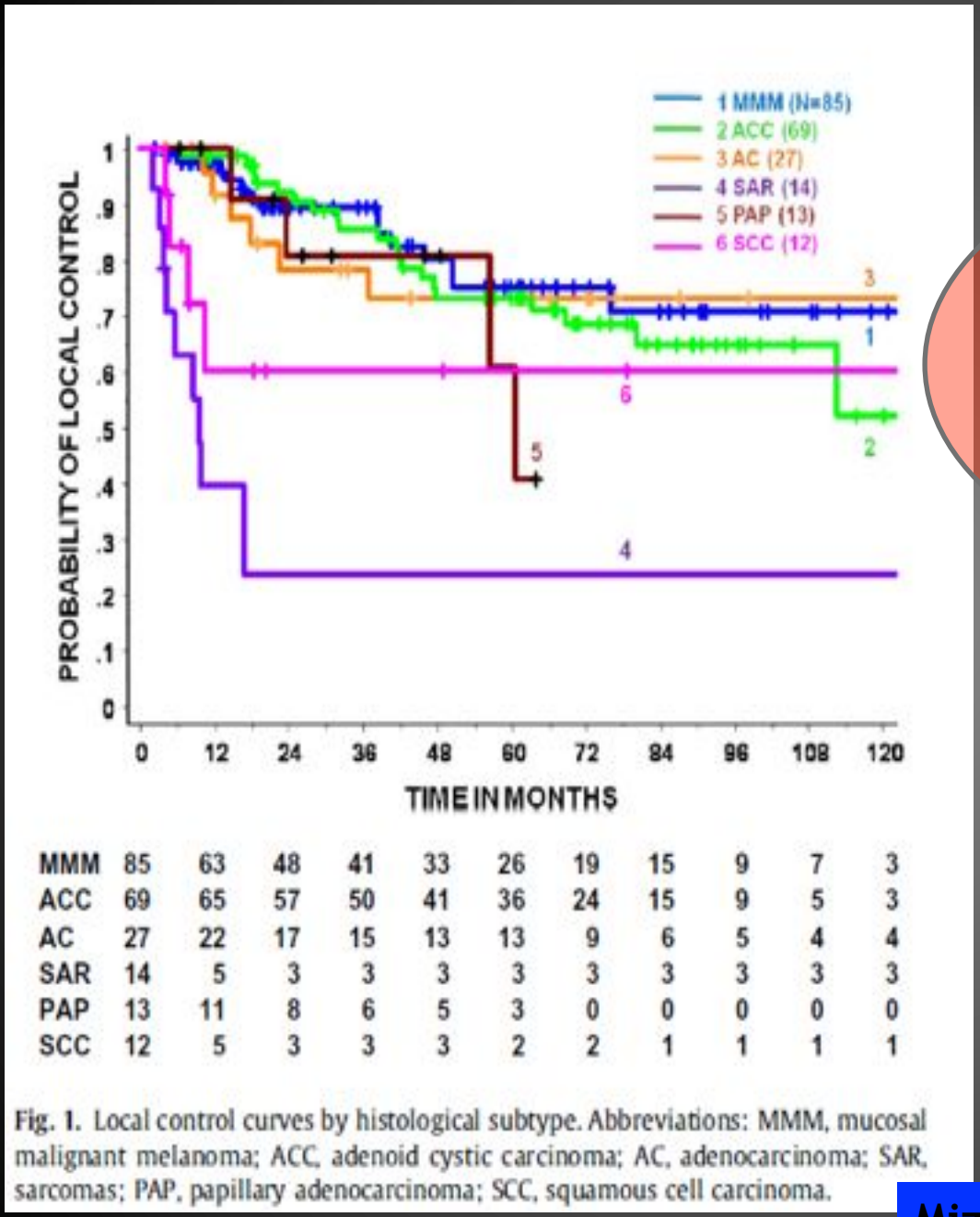


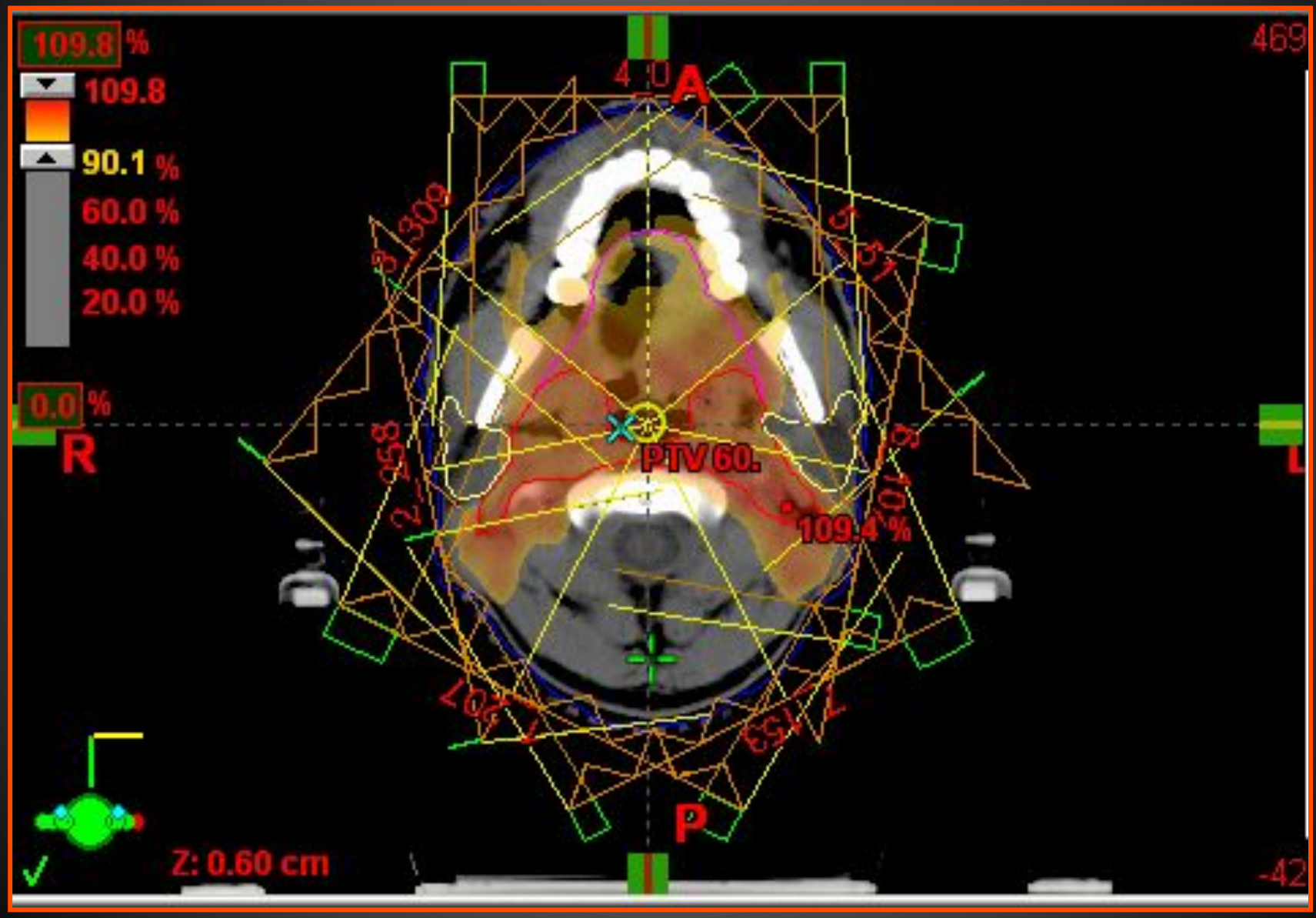
Fig. 1. Local control curves by histological subtype. Abbreviations: MMM, mucosal malignant melanoma; ACC, adenoid cystic carcinoma; AC, adenocarcinoma; SAR, sarcomas; PAP, papillary adenocarcinoma; SCC, squamous cell carcinoma.

5 -year LC rate

Overall	68 %
MMM	75 %
ACC	73 %
Adenoca.	73 %
Papillary Adenoca.	61 %
SCC	61 %
Sarcomas	24 % (with Max 64 GyE)

Mizoe J et al, Radiother Oncol, 2012

IMRT & Parotid Sparing



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

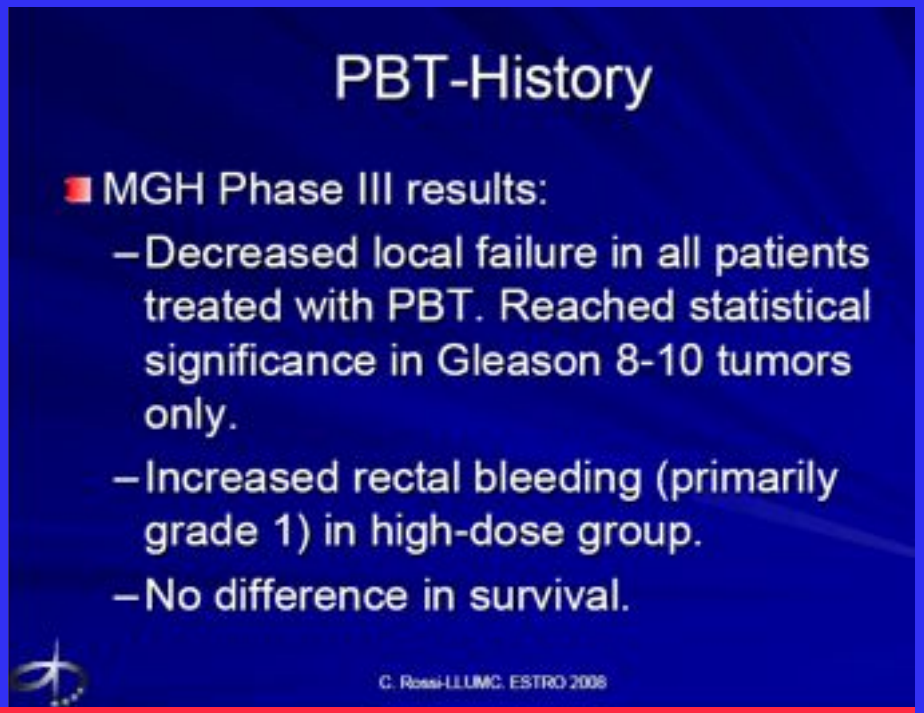
The results of these ISPC studies should be confirmed in properly designed clinical trials

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

Shipley, IJROBP, 1995

MGH

Boston



Prostate Cancer
First Phase III randomized trial

MGH & LLUMC

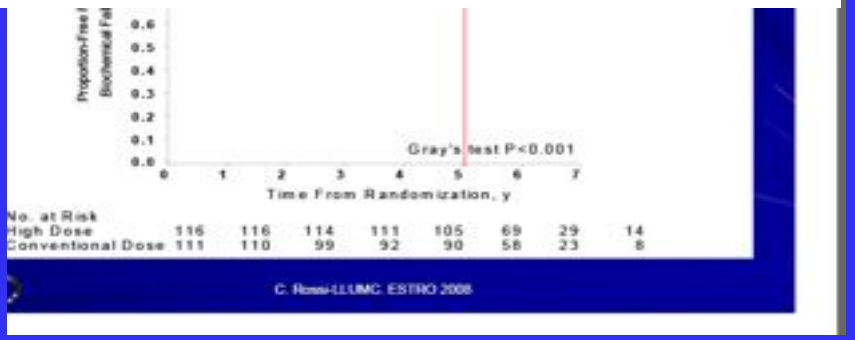
392 patients with early

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)	

Efstathiou J, Bekelman J (MGH, Uni Penn).

Phase III Randomized Trial of Protons vs IMRT (79.2 Gy) for low or low-intermediate risk Prostate Cancer

Primary endopoint *EPIC bowel scores at 6 months

350 patients randomized

EPIC: Expanded Prostate Cancer Index Composite

Treatment Method by Risk

Low Risk;
T-stage≤T2a and
PSA<20.0 and GS≤6

→ C-ion RTx w/o ADT

Intermediate Risk;
PSA<20.0 and
T-stage=T2b or GS=7

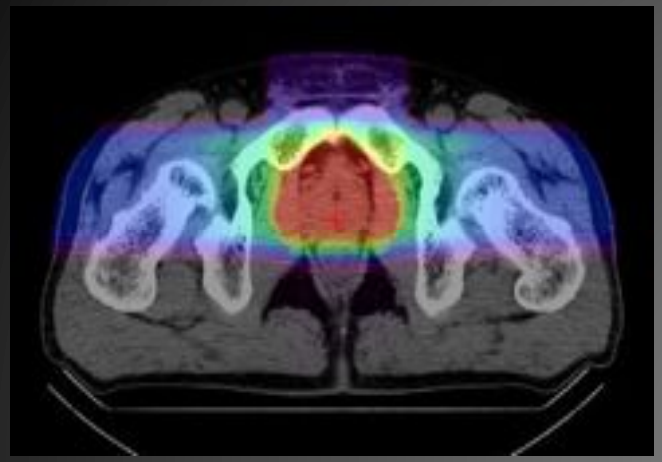
→ C-ion RTx with Short term ADT (6m)

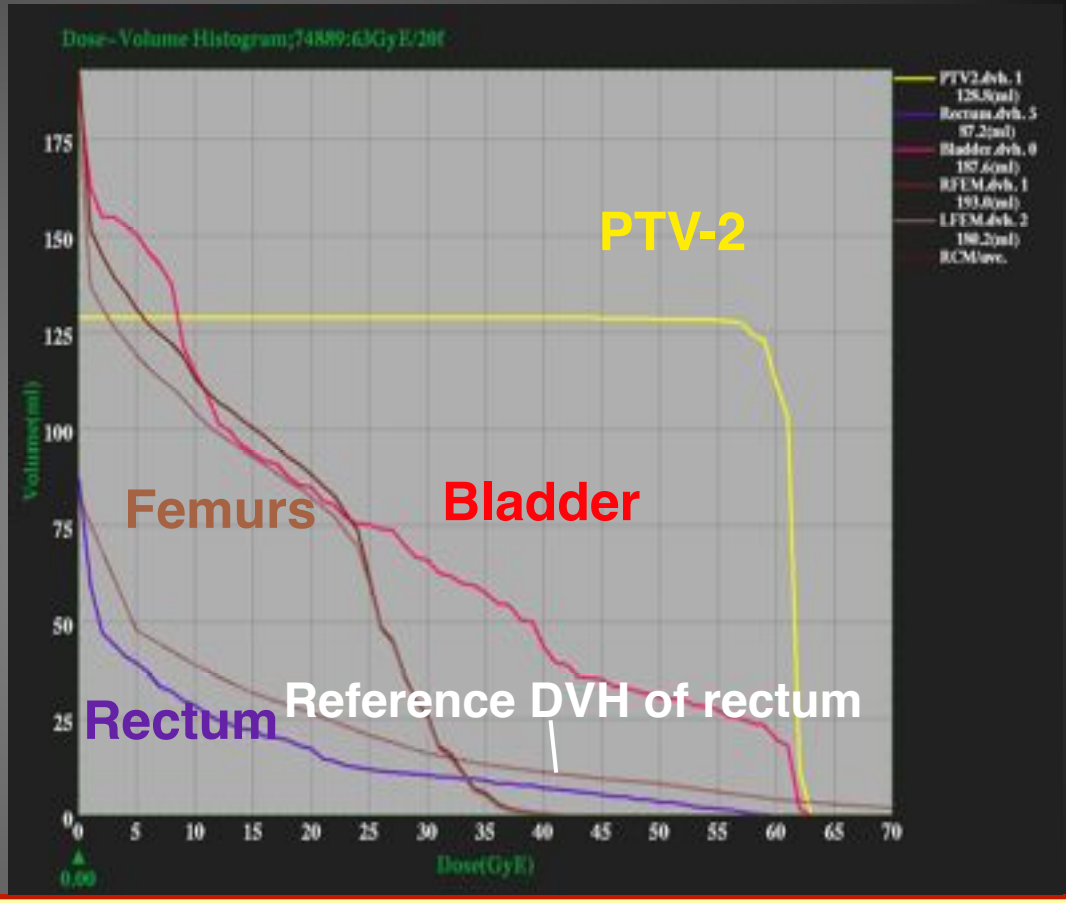
High Risk;
T-stage=T3 or
PSA≥20.0 or GS≥8

→ C-ion RTx with Long term ADT (>24m)

ADT; Androgen Deprivation Therapy

Dose Constraint with Rectum DVH





Dose-Constraints

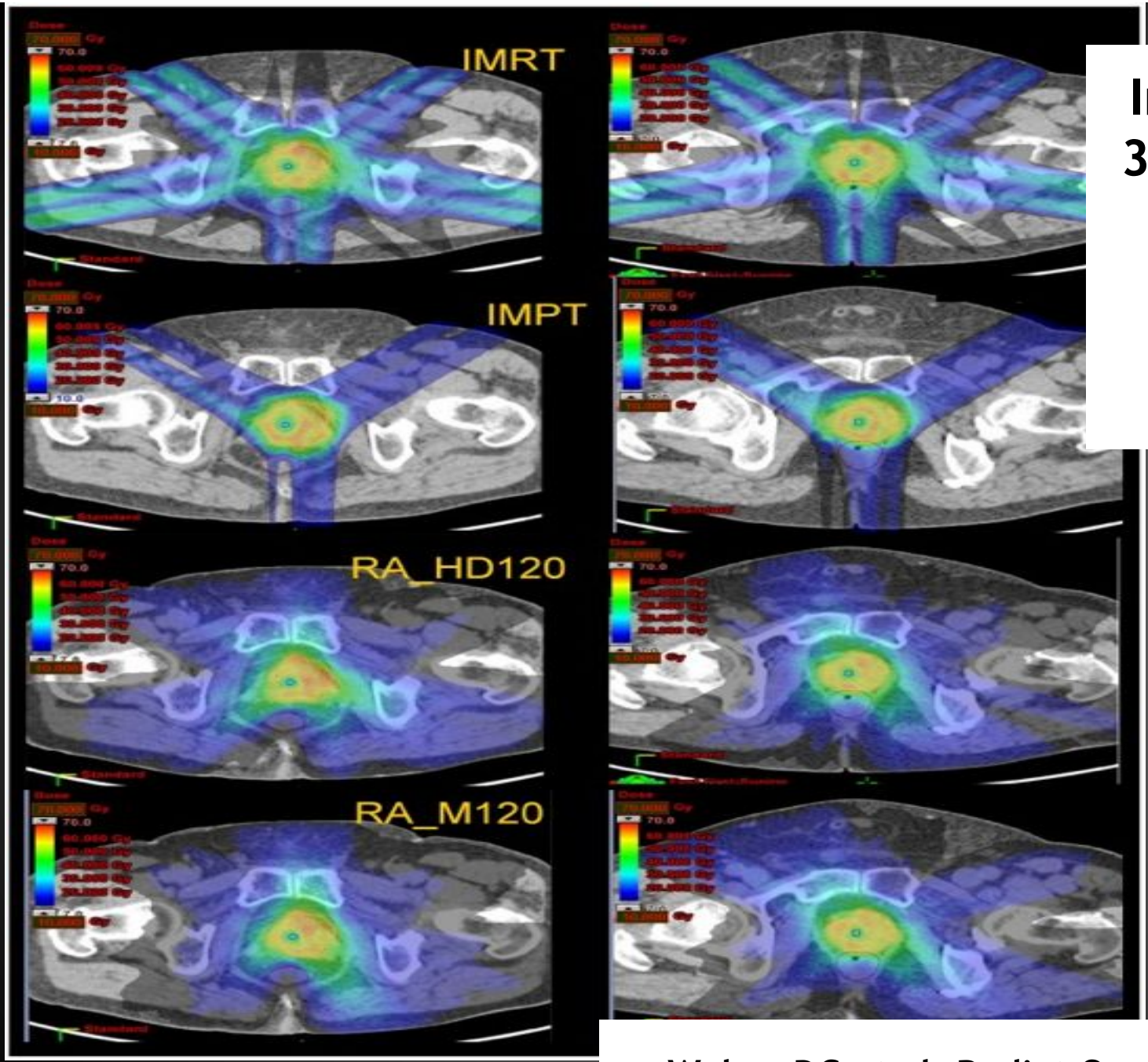
OARs	
Constraints	
Rectum	
D_{max}	≤ 66GyE/20f
V_{50}	< 8cc
Bladder	
D_{max}	≤ 66GyE/20f
V_{50}	< 50cc

Reference DVH: Average DVH of the patients with grade 0~1 rectal toxicity

To make a new plan in order that rectal DVH is below the reference DVH at high dose level.

Biochemical relapse free and Cause-specific survival according to risk factors

			5-year rates (%)				
		No.pts.	*bNED	p-value	#CSS	p-value	All
		861	91.0				94.7
Stage	T1/2	614	94.0	0.0000			100
	0.0001						
	T3	247	84.1				95.8
PSA	< 20	595	92.1	0.0678			99.5
	0.0301						
	20 ≤	266	88.7				97.2
Gleason score	≤ 6	206	92.3	0.0072			100
	0.0110						
	7	412	94.3	0.0004			99.2
	8 ≤	243	83.8				96.6



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)"

New Indications

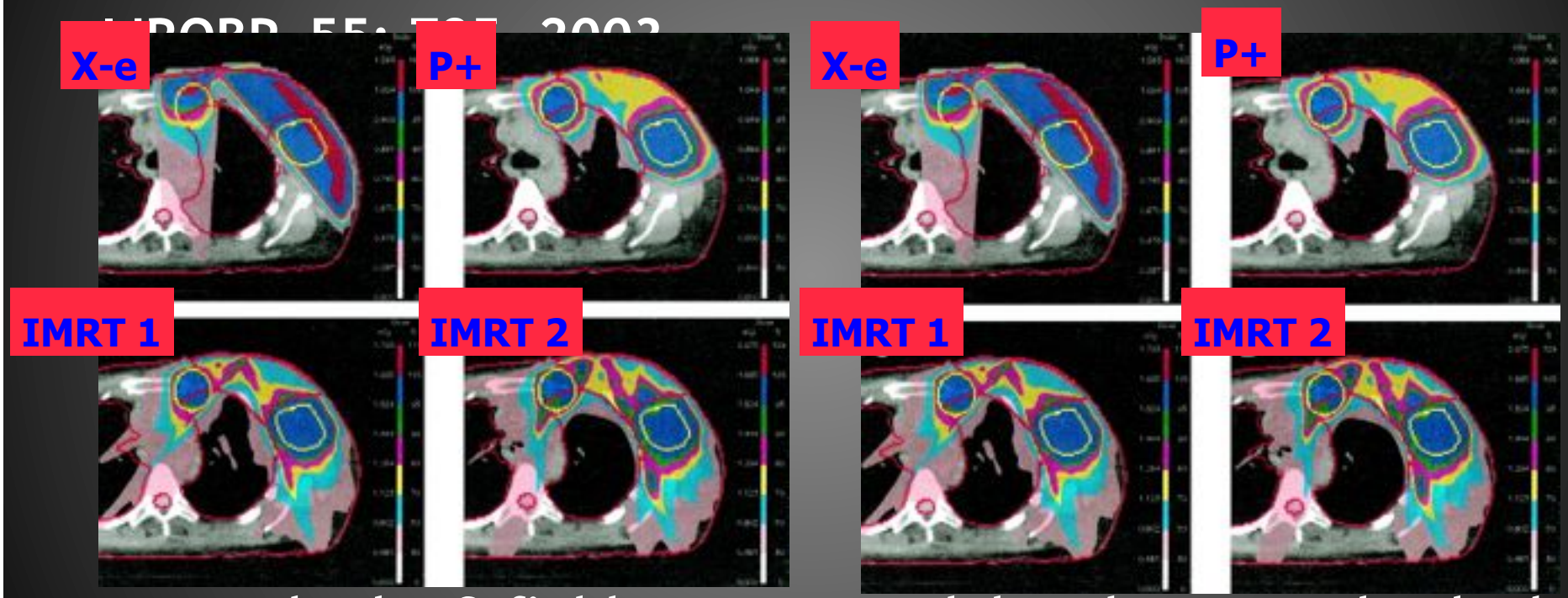
- NSLCC (Early & Advanced)
- Breast (PBI & Locoregional treatment)
- GI (liver, pancreas, rectum)
- GU (prostate, kidney)

Lomax AJ et al (Villigen & Geneva, Switzerland).

Potential role of intensity-modulated photons and protons in

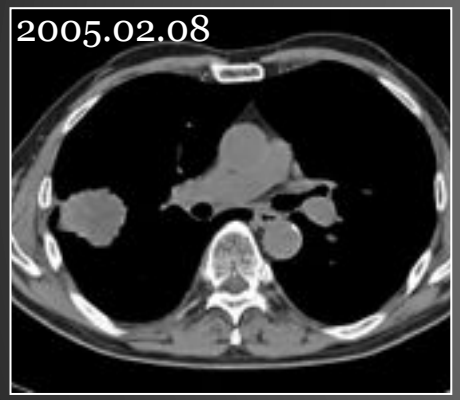
the treatment of the breast and regional nodes.

IJROBP, 55: 785, 2003

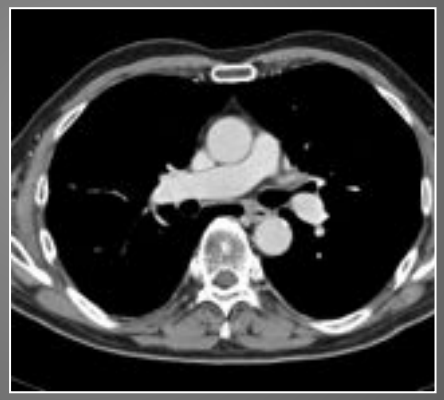


- … only the 2-field, energy-modulated proton plan had the potential to preserve target dose homogeneity while simultaneously minimizing the dose delivered to both lungs, heart, and the contralateral breast

Case: 72yrs male, rt. S^2 adenoca. cT2N0M0 c-stage IB



34.0GyE/1fr.



Lung function

15 mo. after CIRT

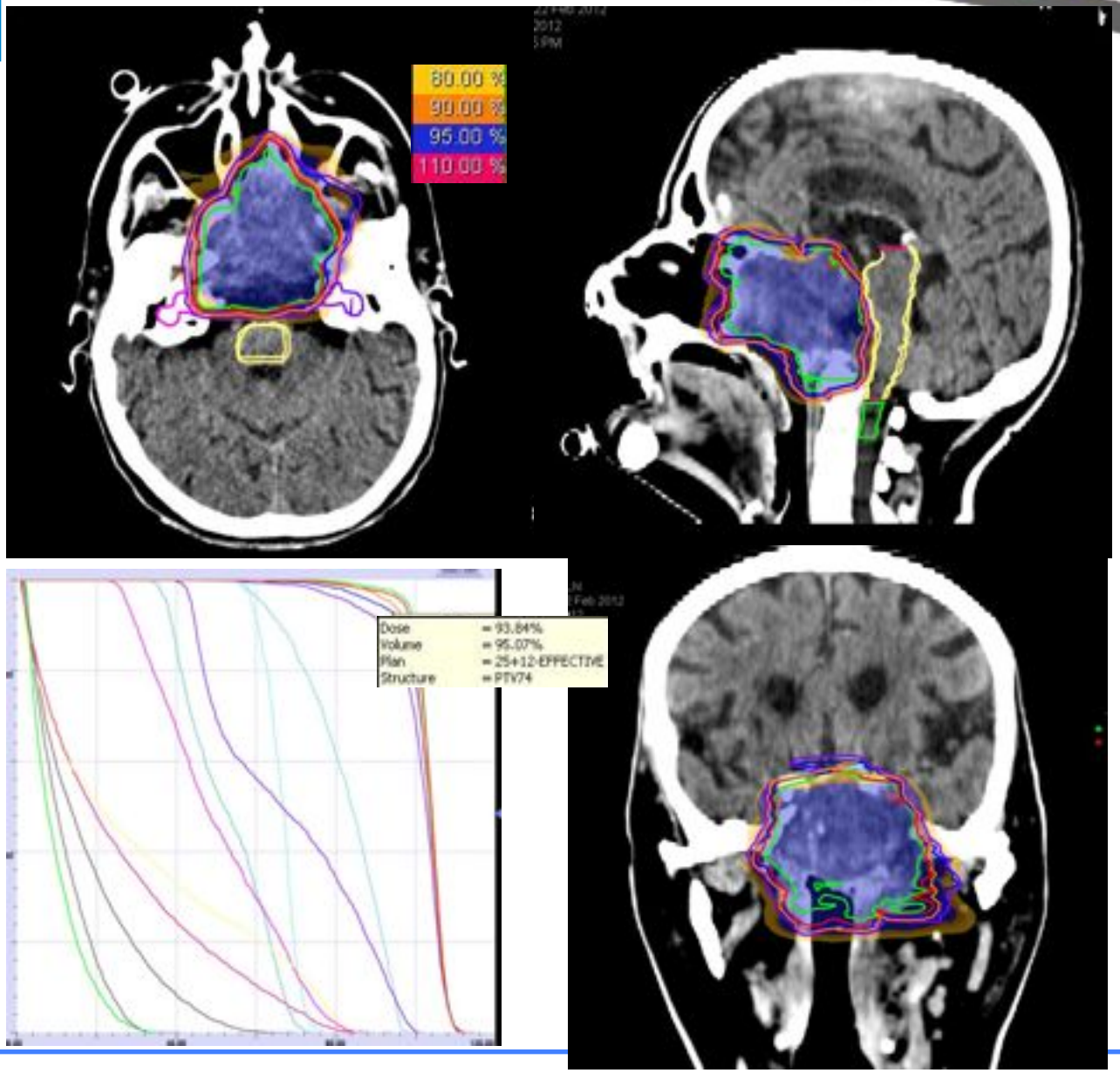
30 mo. after CIRT

%VC	95.4	104.9	92.1
$FEV_{1.0}$%	49.3	57.3	58.8
%DLCO	47.7	43.4	46.0
PaO_2(room air)	64.2	62.4	68.9

fondazione CNAO

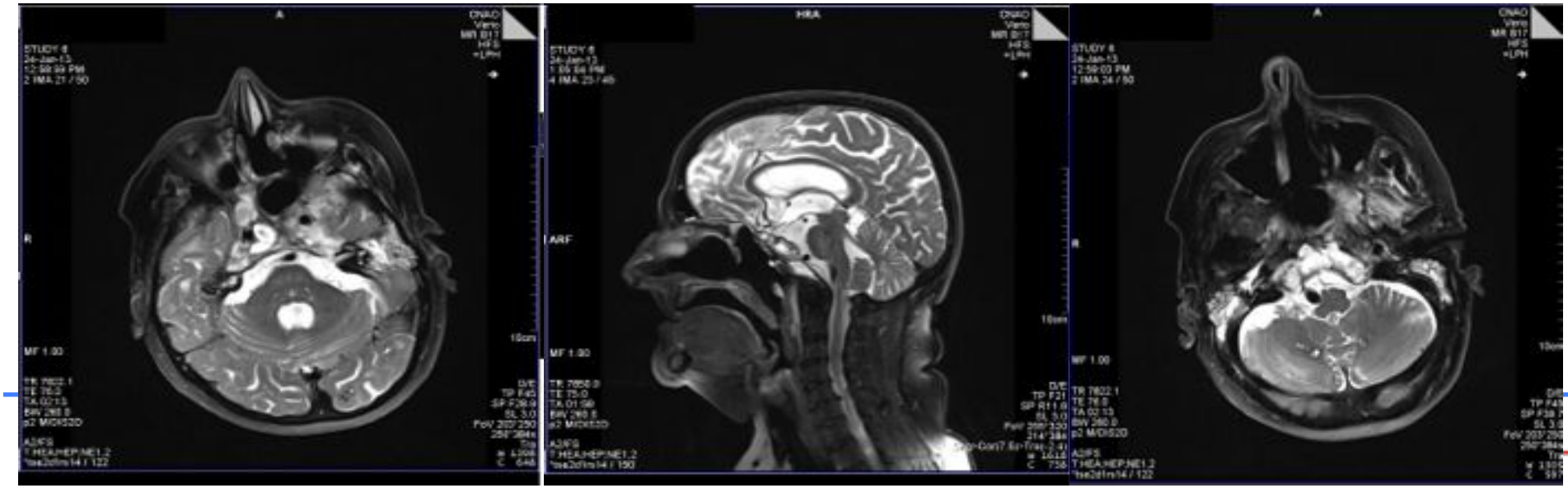
Salivary gland tumors	34
Reirradiation of head and neck tumors	25
Mucosal melanoma	7
Chordoma	119
Chondrosarcoma	23
Sarcoma	32
Retreatment local recurrence rectal cancer	1
HCC	1
Local advanced pancreatic cancer	1

CLINICAL CASE

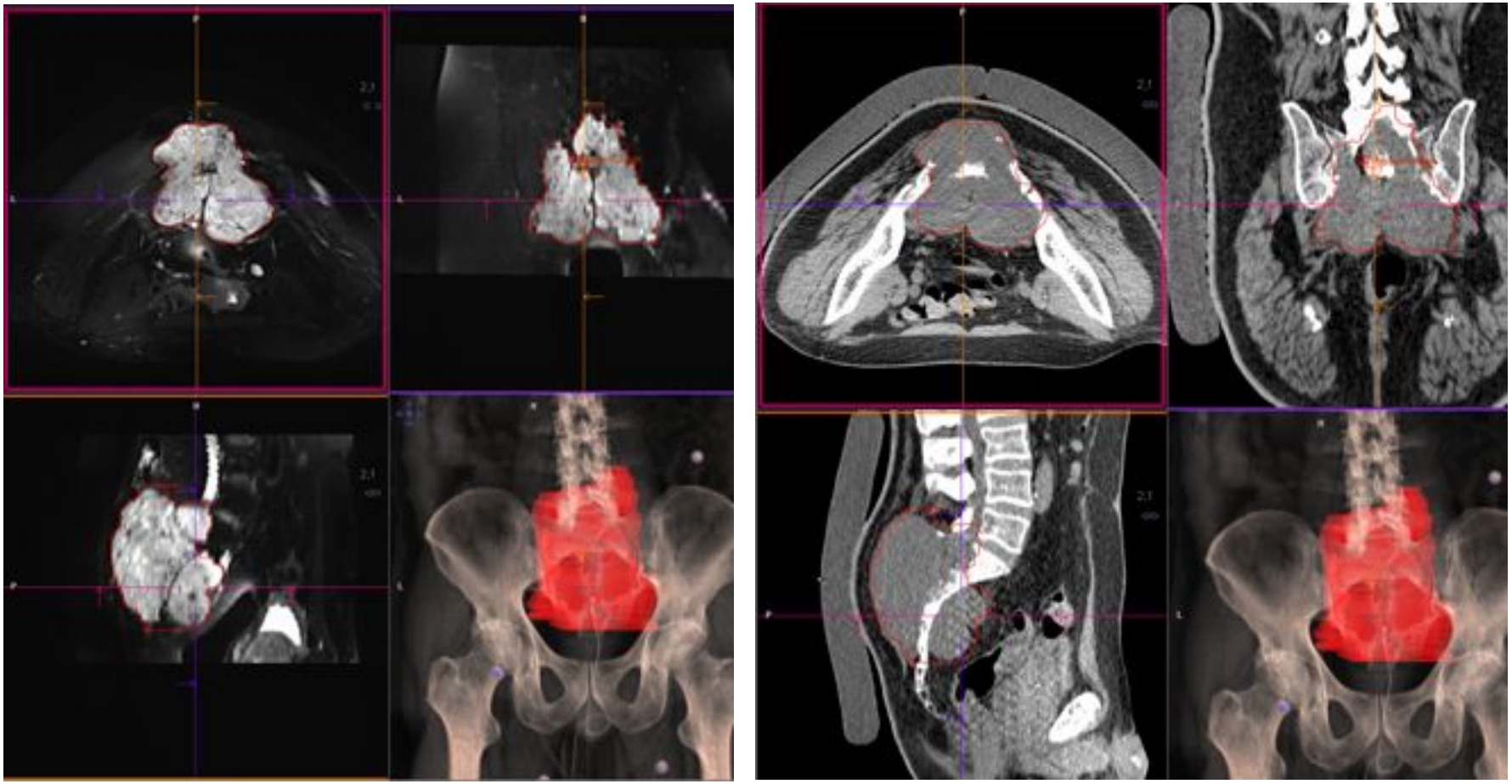


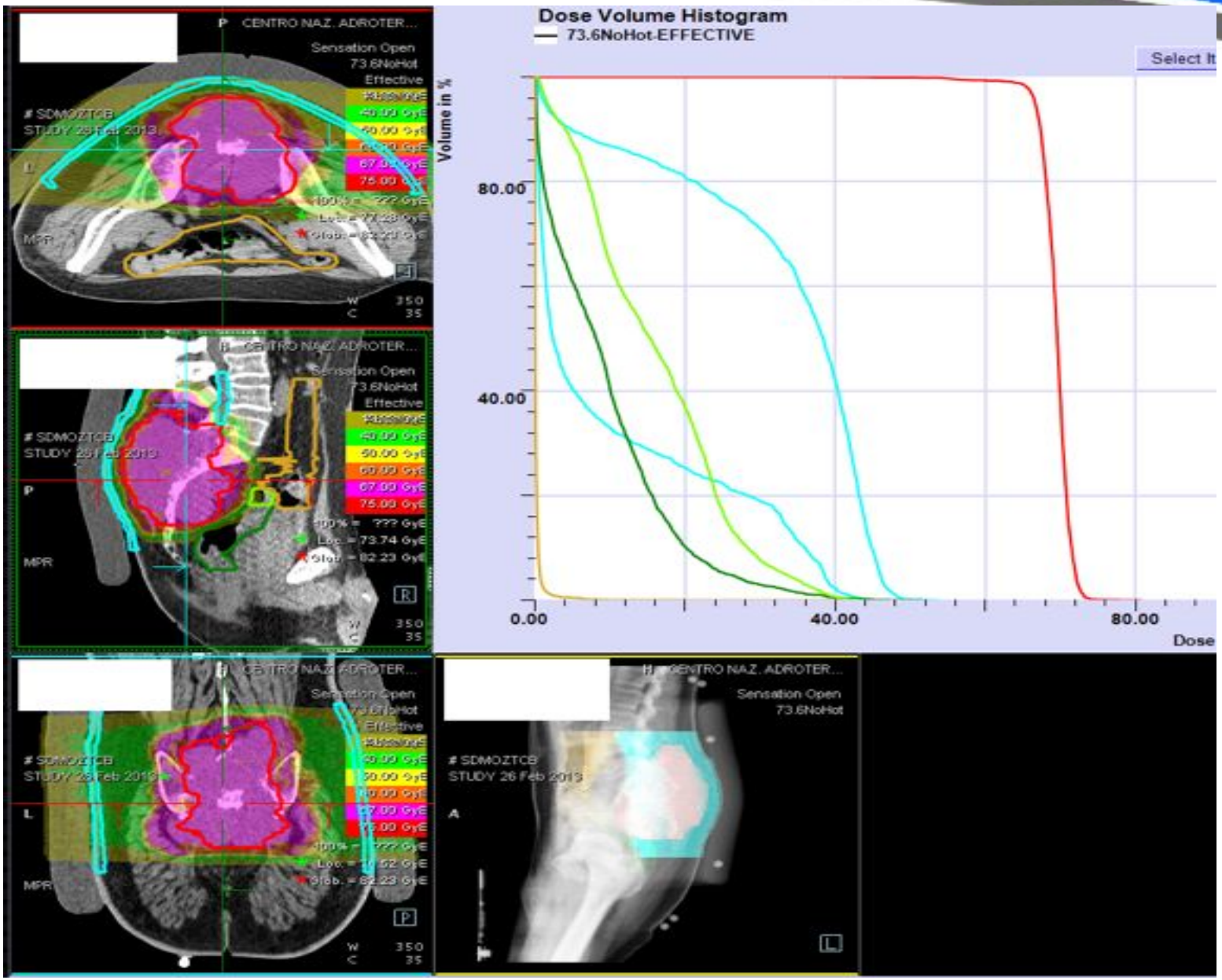
SKULL BASE CHORDOMA: Proton therapy

10 months F-up



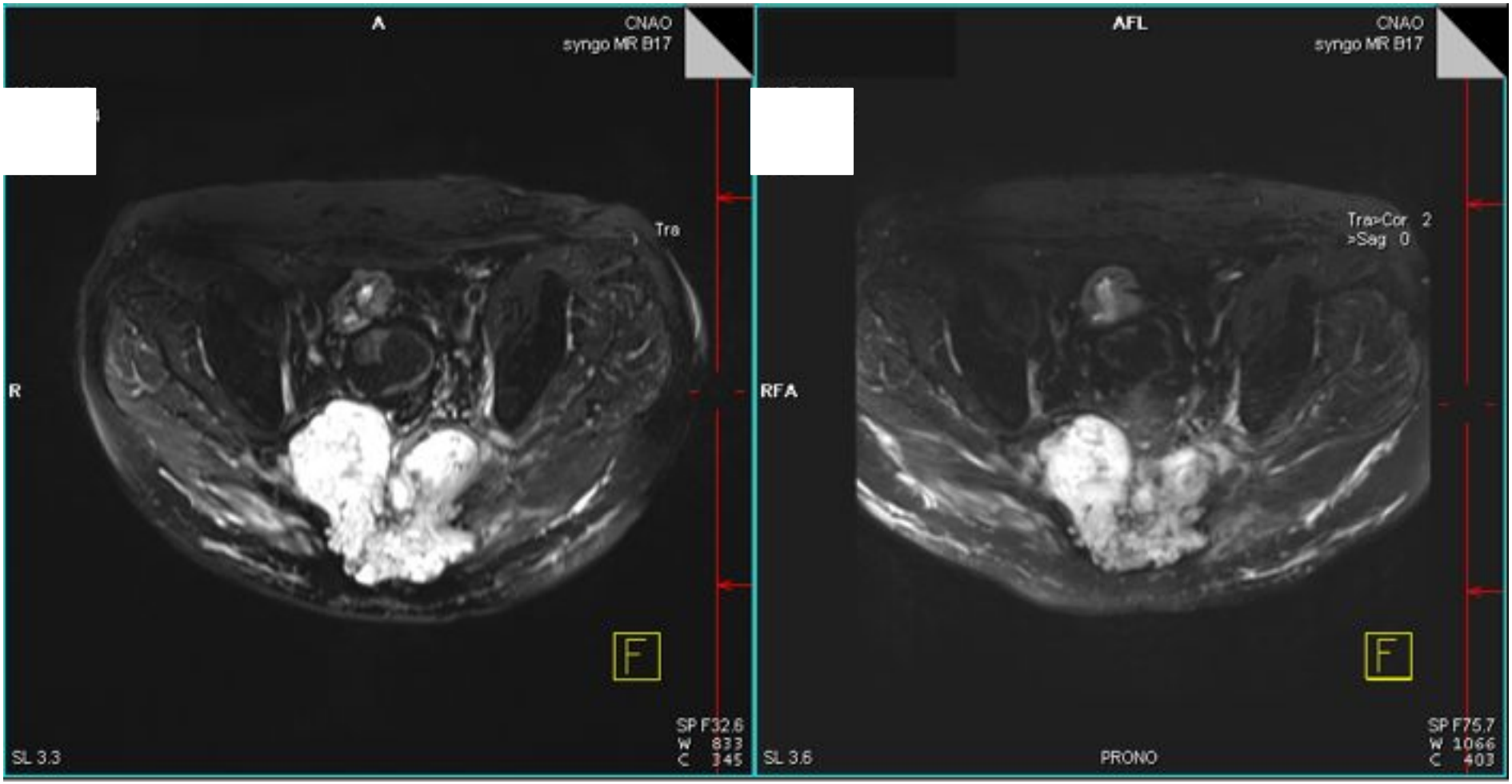
Sacral chordoma, male, 69 years old




Dose Volume Histogram
73.6NoHot-EFFECTIVE
Select It
Volume in %
80.00
40.00
0.00
40.00
80.00
Dose
CENTRO NAZ. ADROTER...
Sensation Open
73.6NoHot
Effective
SDMOZTCB
MPR

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

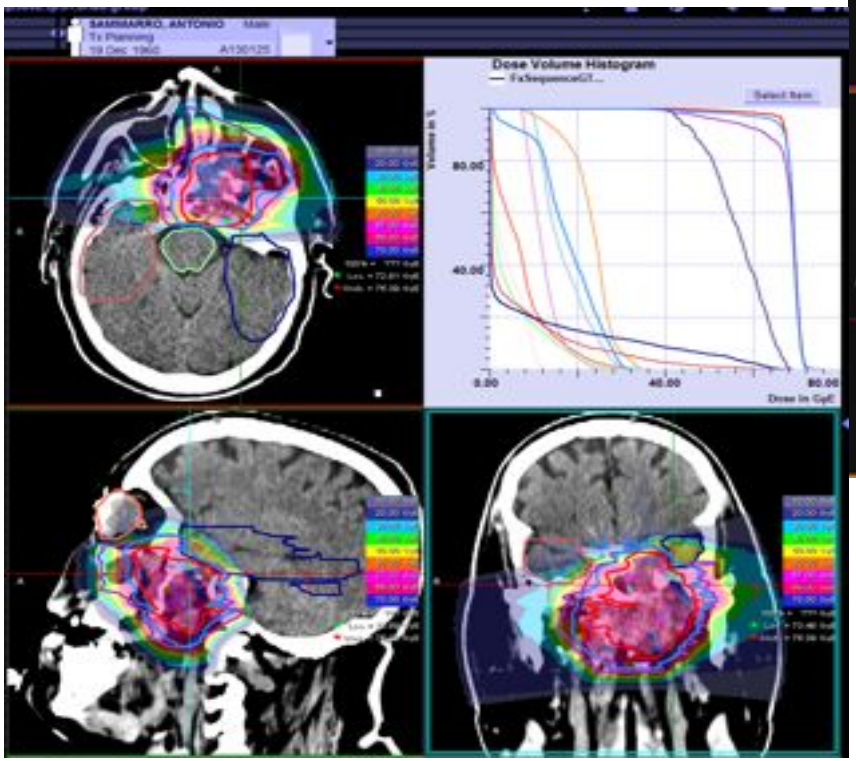
Clinical case

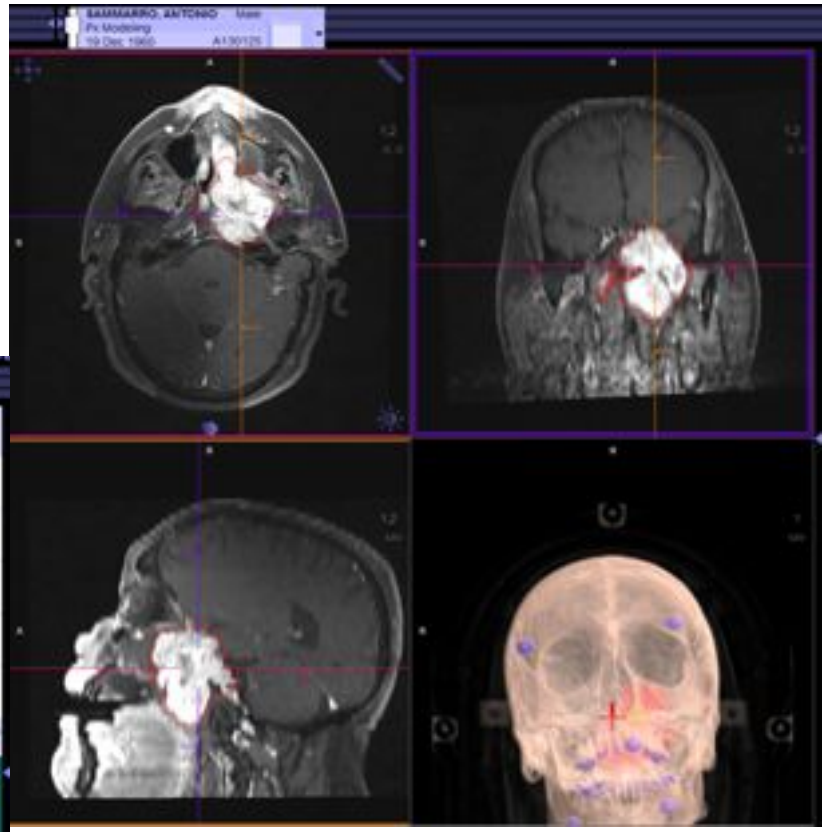
53 year old male

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]



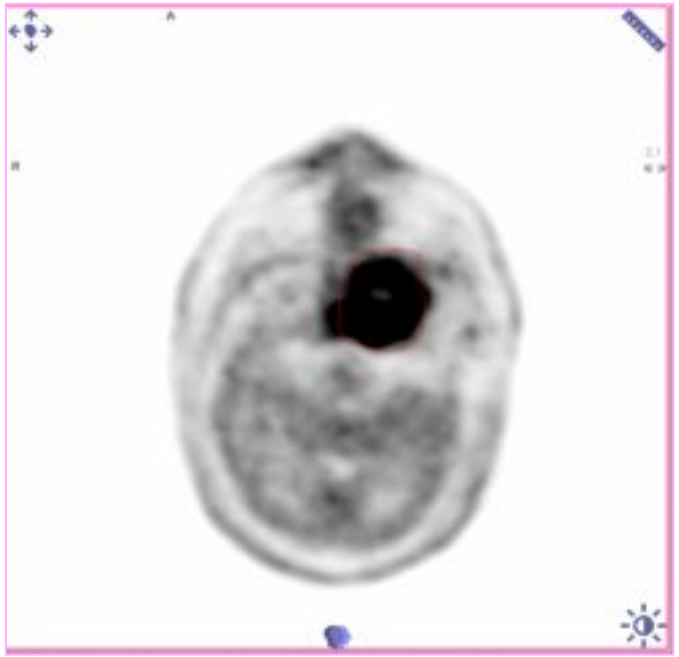


Toxicity at the end of CIRT: erythema G1, mucositis G1

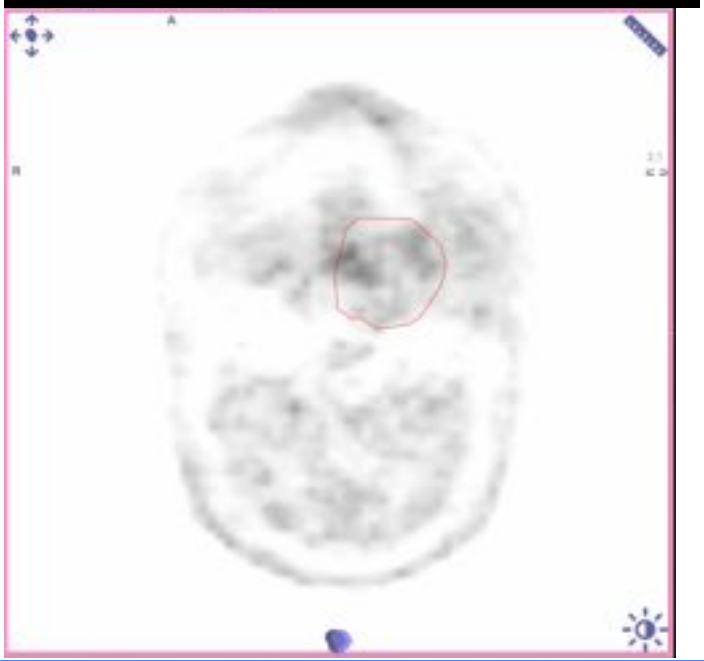
Partial Remission and Acute Toxicity G0 after 3 months

PET metionine: significant decrease in MET uptake after 4 months

PET pre CIRT



PET after 4 months



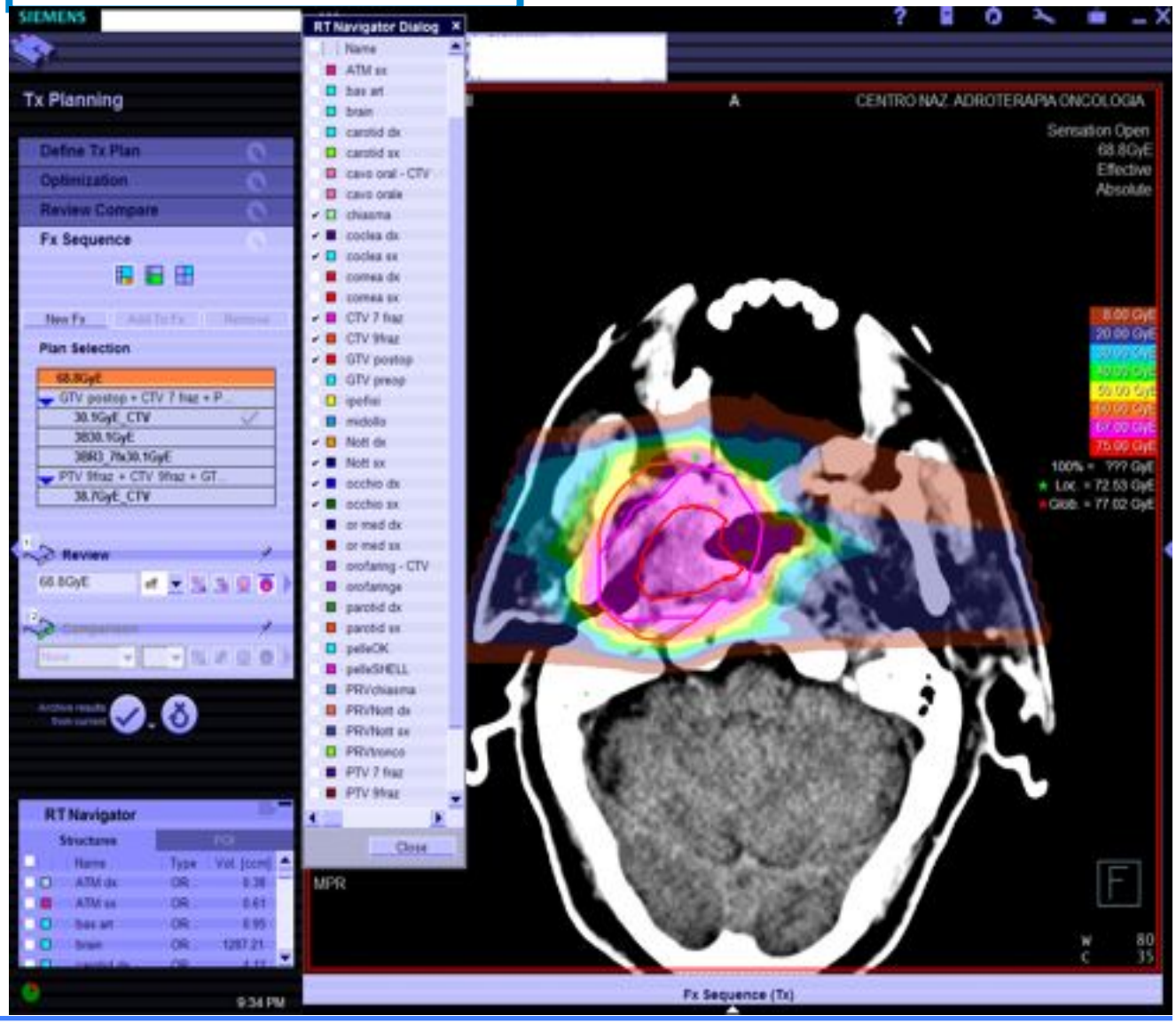
Clinical case

75 year old men

March 2013: endoscopic surgery R2

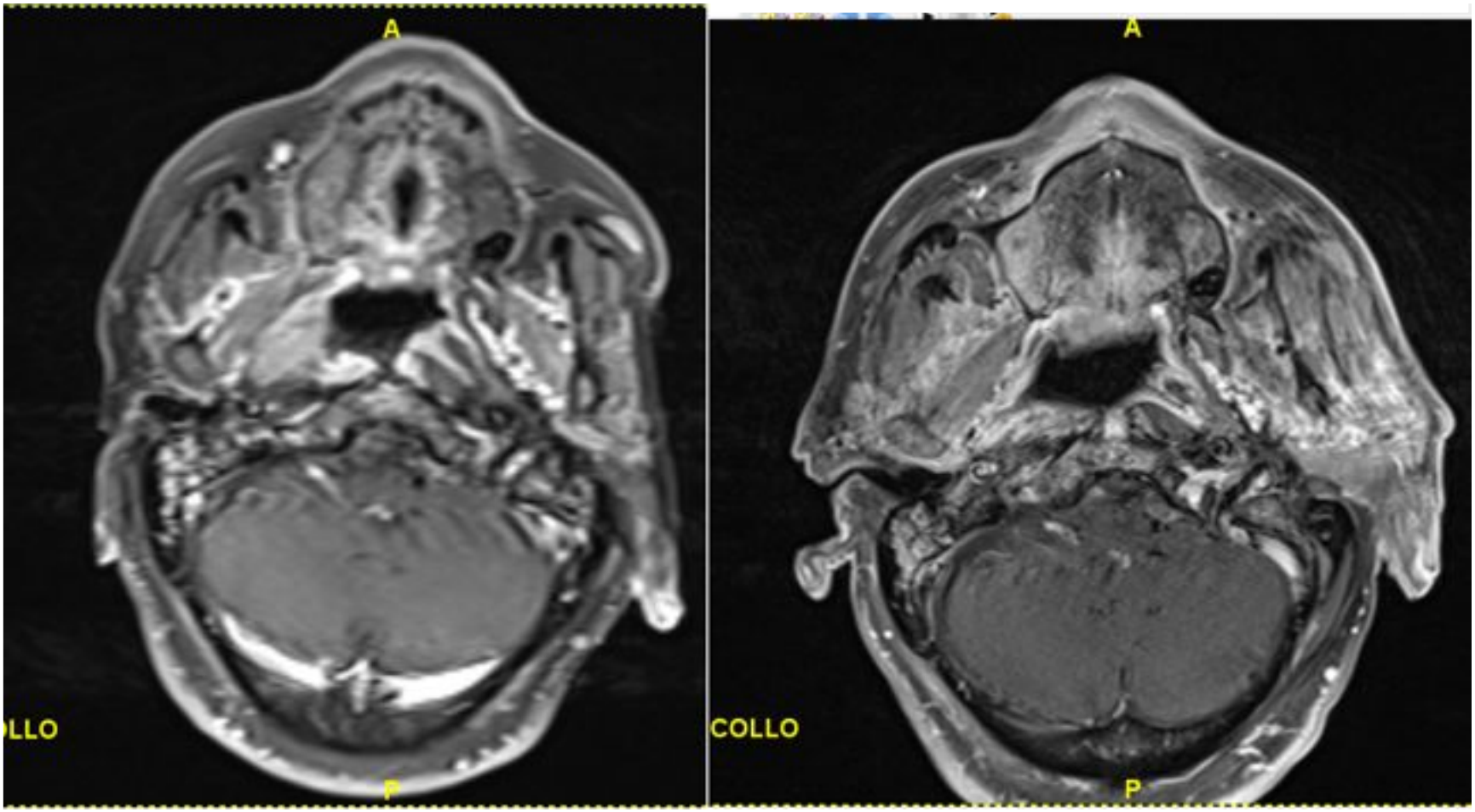
No CT for age and coomorbidity

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

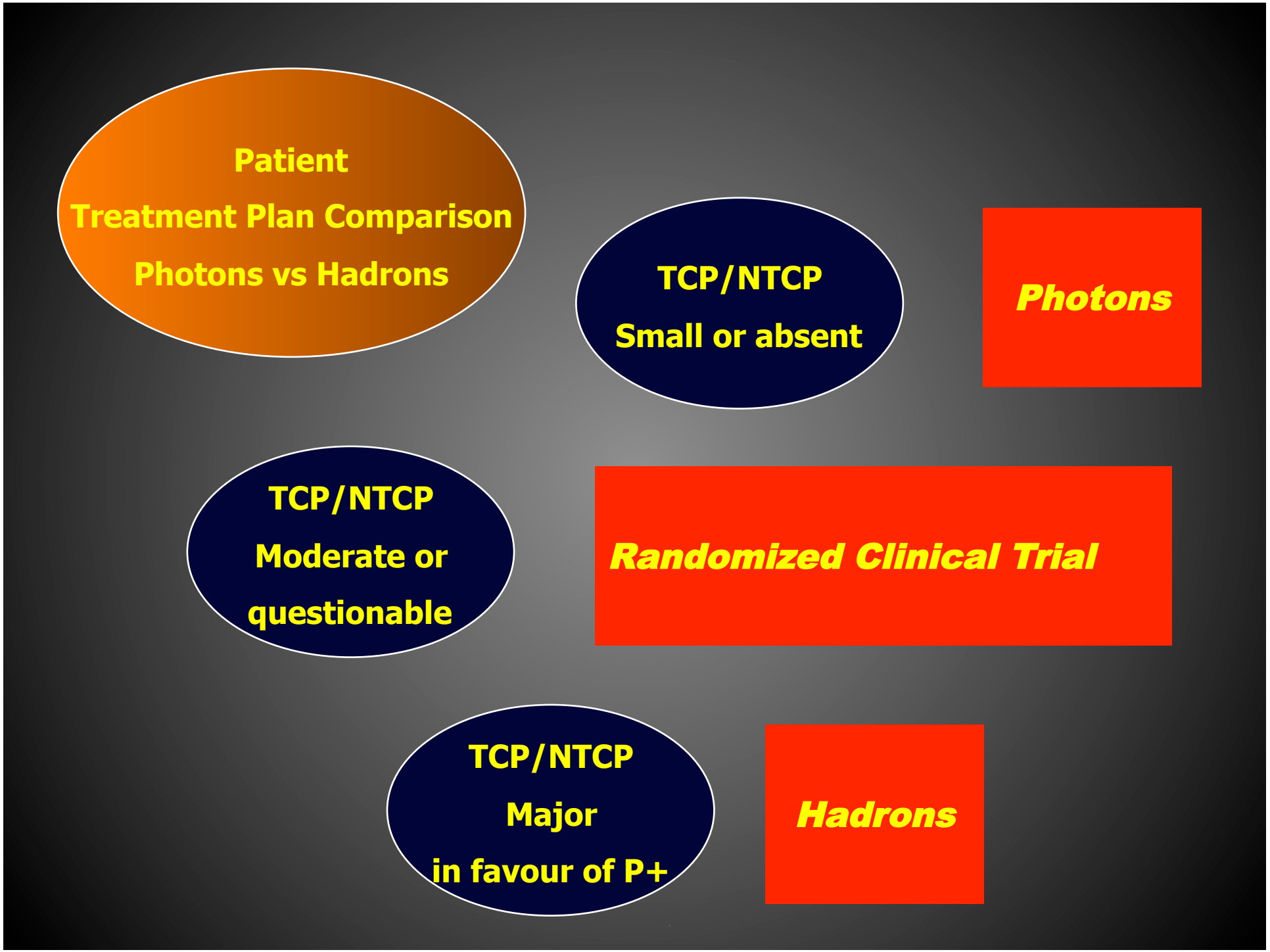
Erytema

6 months

Improvment in Technology

Improvment in Dose Distribution

Technology Transfer in Clinics


Patient
Treatment Plan Comparison
Photons vs Hadrons
TCP/NTCP
Small or absent
Photons
TCP/NTCP
Moderate or
questionable
Randomized Clinical Trial
TCP/NTCP
Major
in favour of P+
Hadrons

Grazie !!!

”Il progresso è reale solo quando i vantaggi di una nuova tecnologia diventano disponibili a tutti”

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica