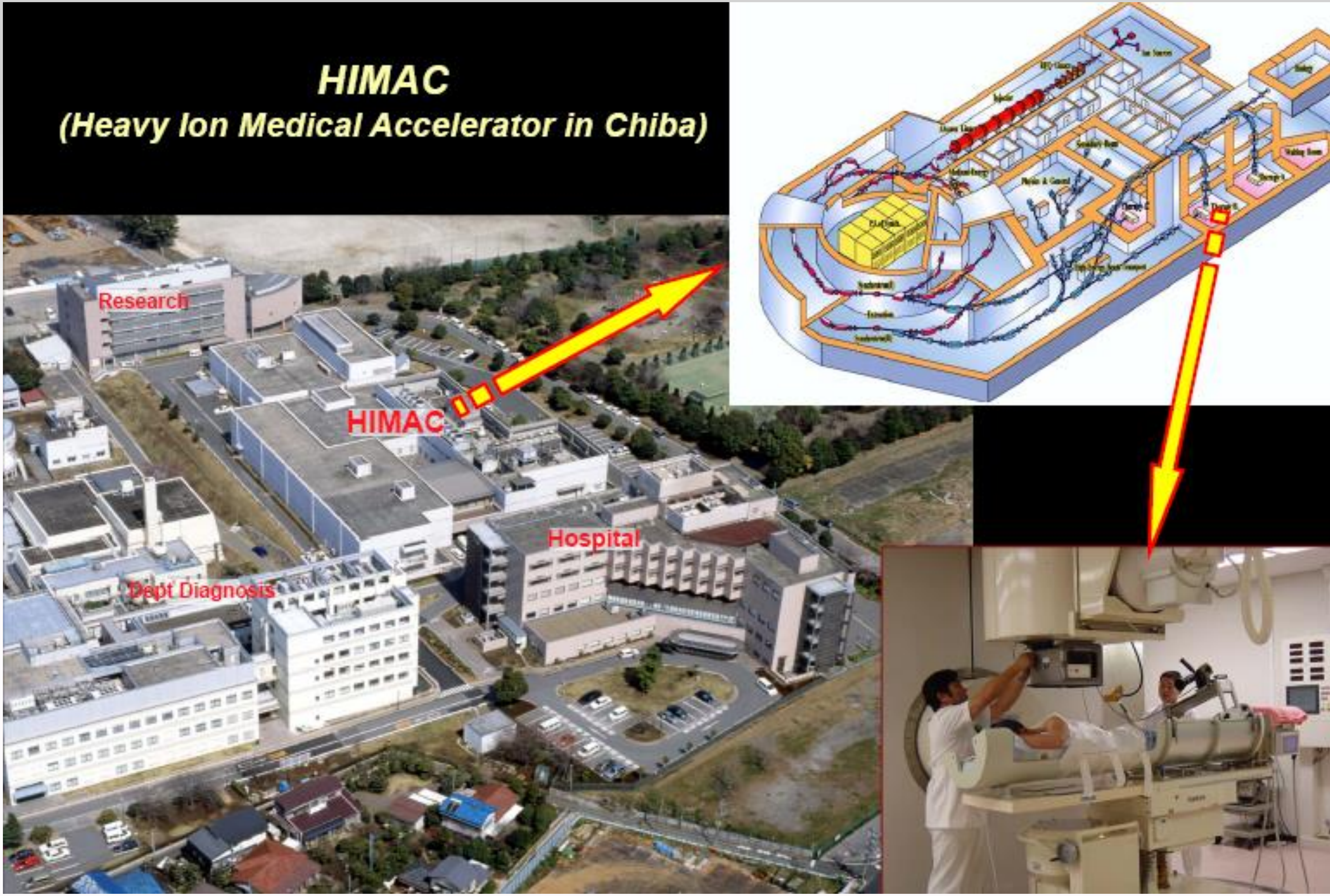
Medical perspectives of Ion Therapy

Ideas and technologies
for a next generation facility
for medical research and therapy with ions

19-21 June 2018
ESI, Archamps, France

Roberto Orecchia

Ions Therapy



Helium Ions Therapy

- Phase III RCT
- Helium ions vs iodine125 plaque brachytherapy
- Significant (P=.0006) improvement in LC
- No difference in OS

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Long-term Results of the UCSF-LBNL Randomized Trial: Charged Particle With Helium Ion Versus Iodine-125 Plaque Therapy for Choroidal and Ciliary Body Melanoma

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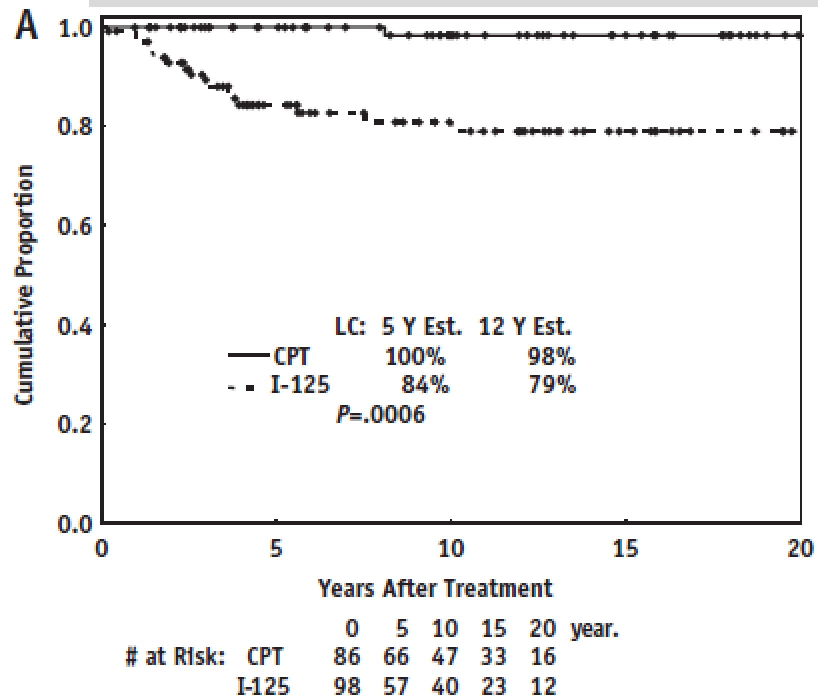
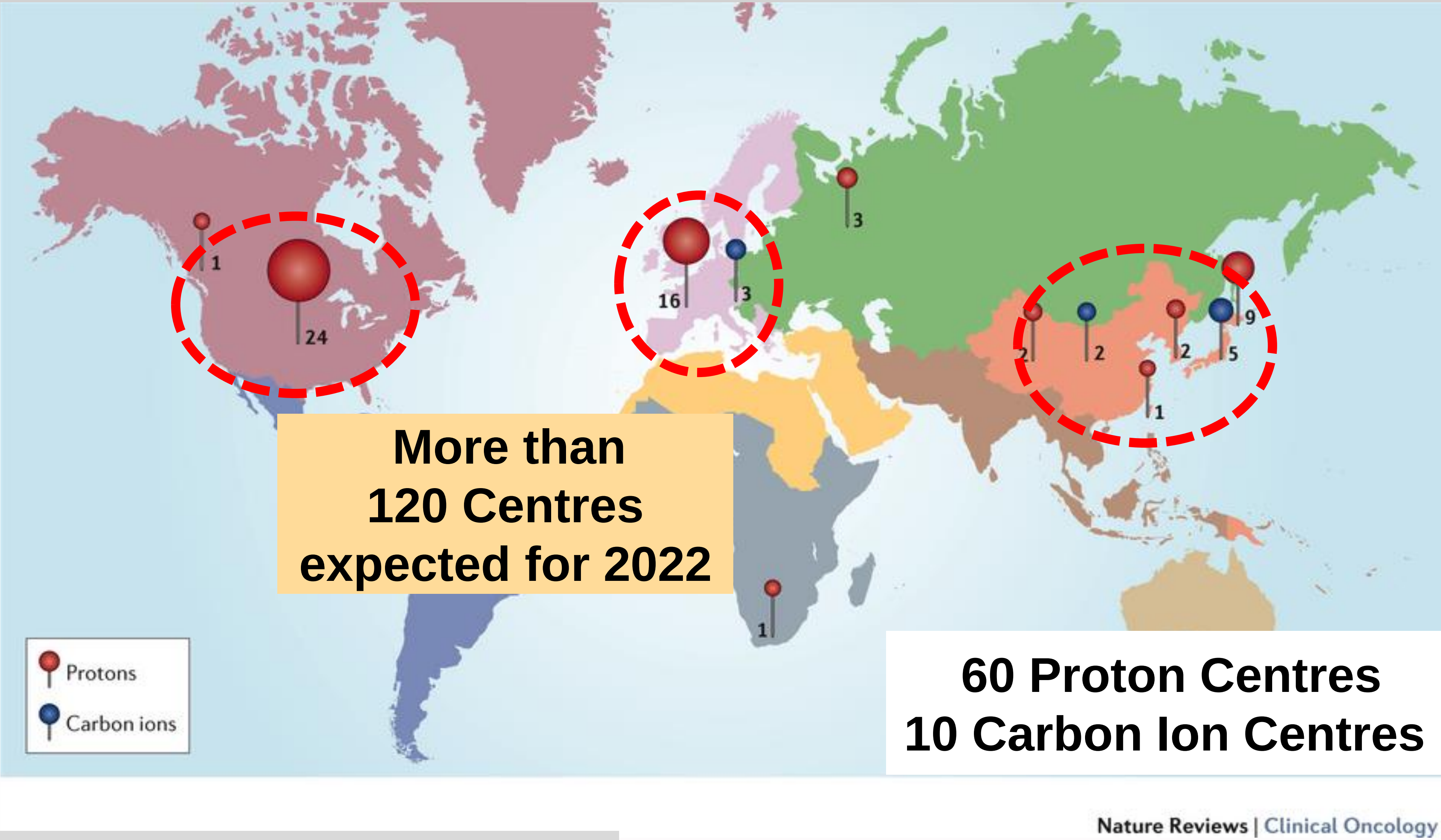
Received Aug 4, 2014, and in revised form Dec 12, 2014. Accepted for publication Jan 20, 2015.



Hadrontherapy Centres

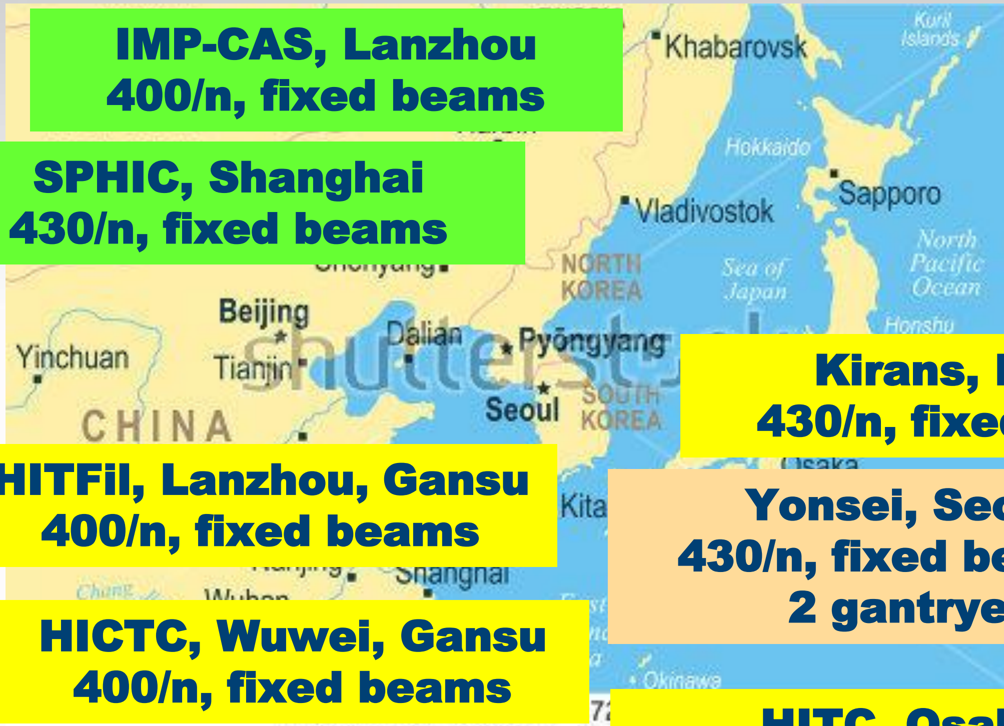


More than
120 Centres
expected for 2022

60 Proton Centres
10 Carbon Ion Centres

Durante M, Orecchia R, Loeffler JS, 2017

Carbon Ions Centres



IMP-CAS, Lanzhou
400/n, fixed beams

SPHIC, Shanghai
430/n, fixed beams

Himac, Chiba
800/n, fixed beams,
1 gantry

Kirans, Busan
430/n, fixed beams

HIBMC, Hyogo
320/n, fixed beams,
1 gantry

HITFil, Lanzhou, Gansu
400/n, fixed beams

Yonsei, Seoul
430/n, fixed beams,
2 gantryes

HICTC, Wuwei, Gansu
400/n, fixed beams

GHMC, Gumna
400/n, fixed beams

HITC, Osaka
400/n, fixed beams

SAGA-Himat, Tosu
400/n, fixed beams

UH, Yamagata
430/n, fixed beams,
1 gantry

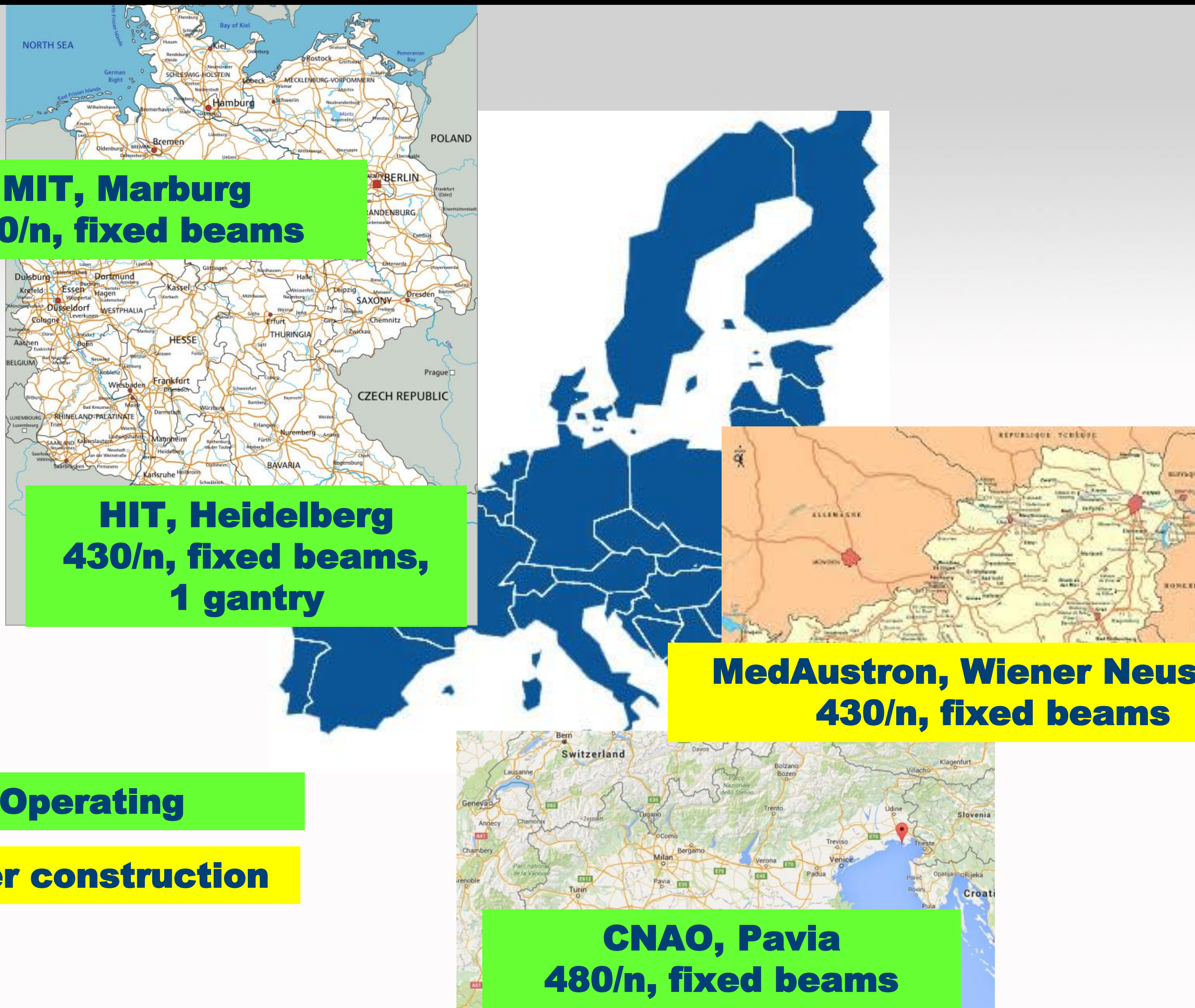
i-Rock Kanagawa
430/n, fixed beams

Operating

Under construction

Planned

Carbon Ions Centres



MIT, Marburg
430/n, fixed beams

HIT, Heidelberg
430/n, fixed beams,
1 gantry

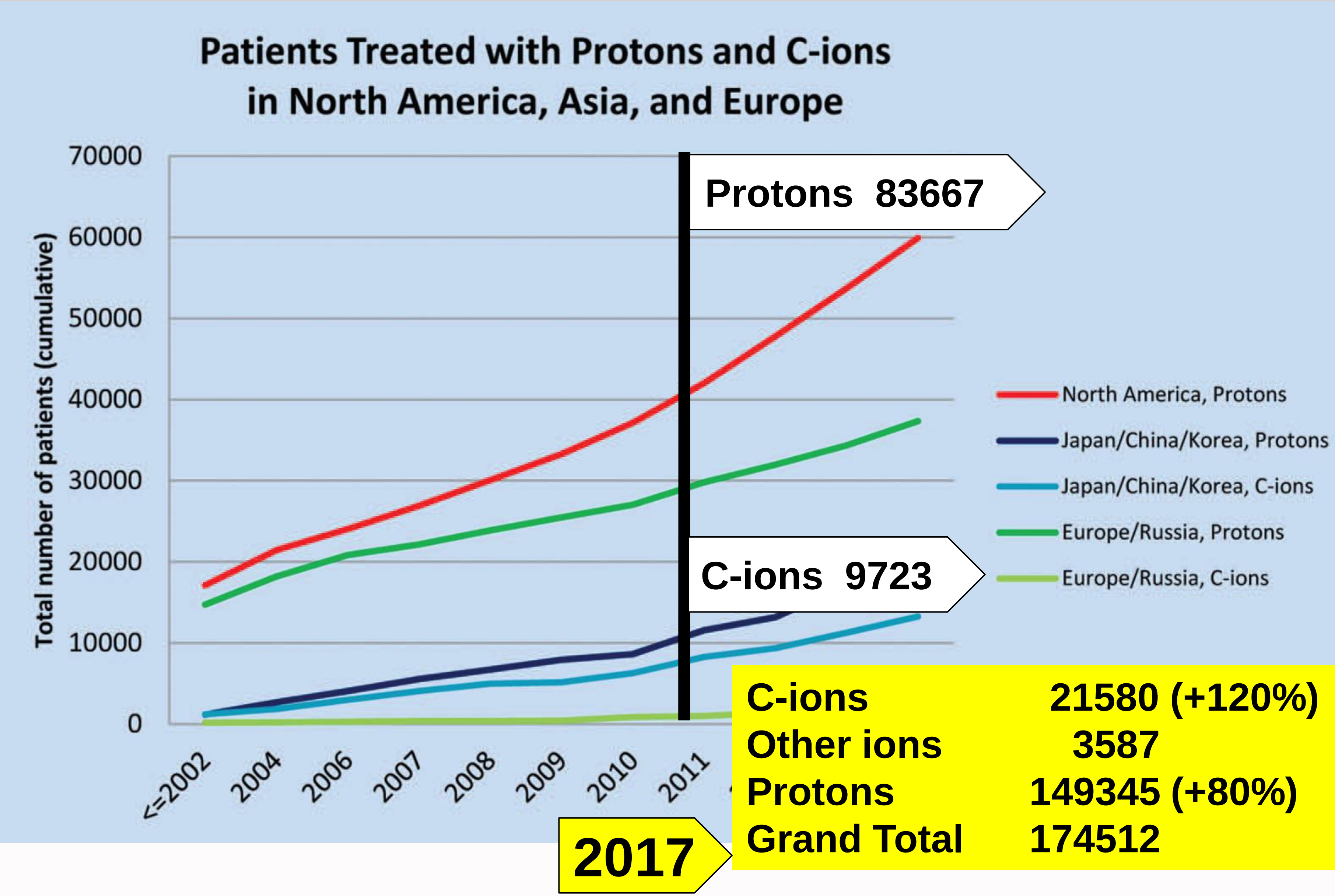
MedAustron, Wiener Neustadt
430/n, fixed beams

CNAO, Pavia
480/n, fixed beams

Operating

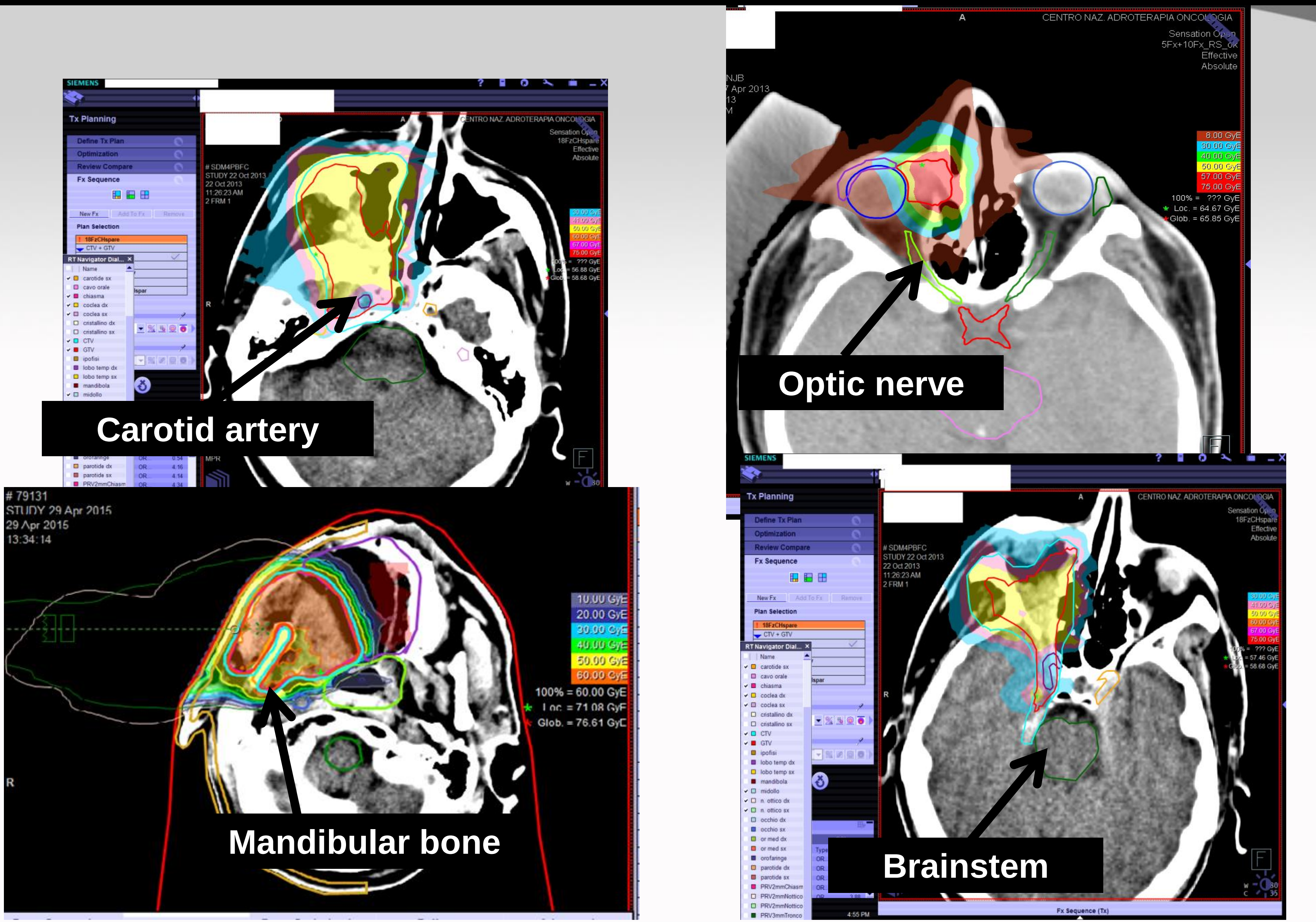
Under construction

Number of treated patients

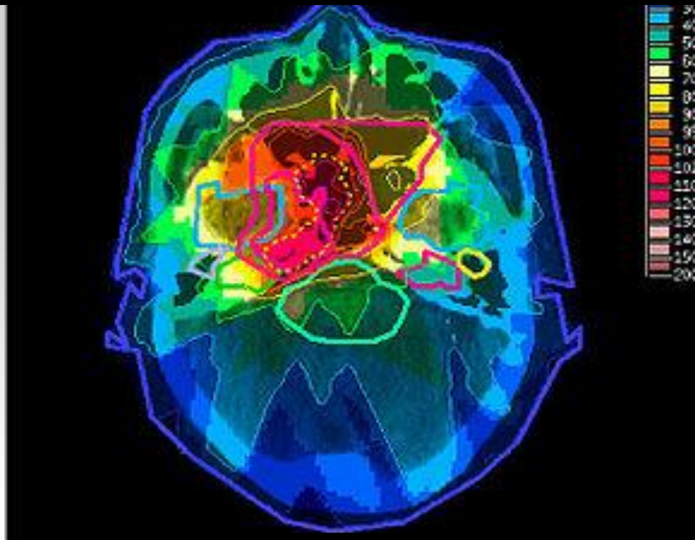


C-ions	21580 (+120%)
Other ions	3587
Protons	149345 (+80%)
Grand Total	174512

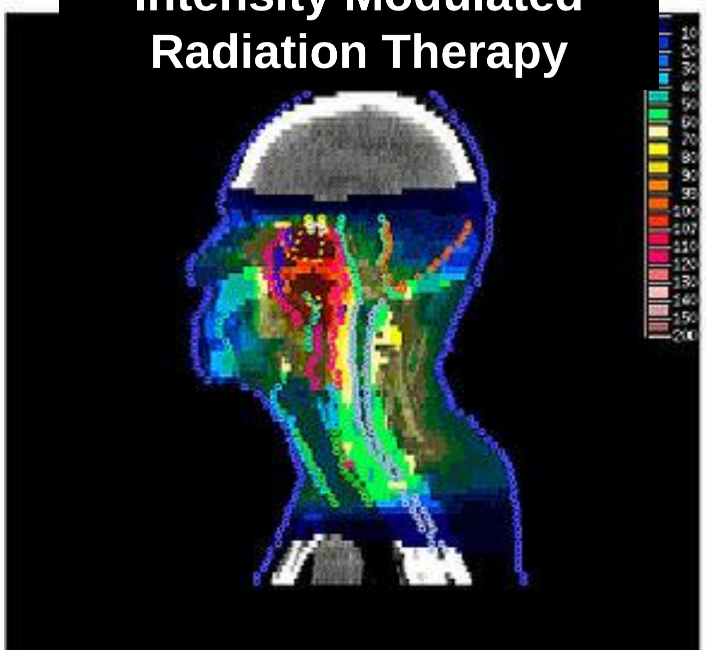
First goal: OaRs sparing

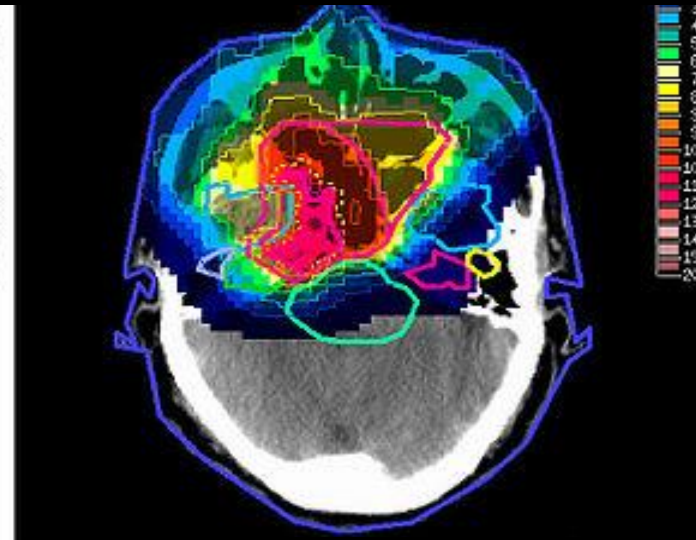


Second goal: less integral dose

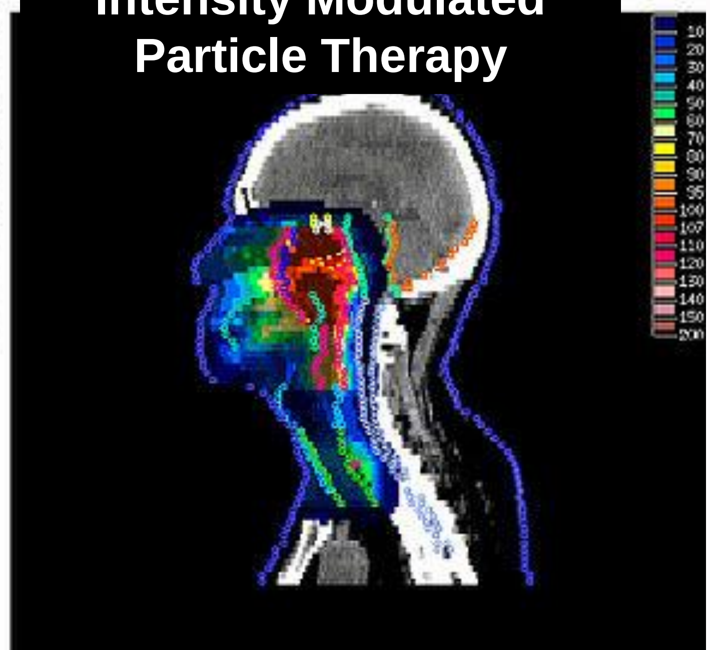


IMRT
Intensity Modulated
Radiation Therapy

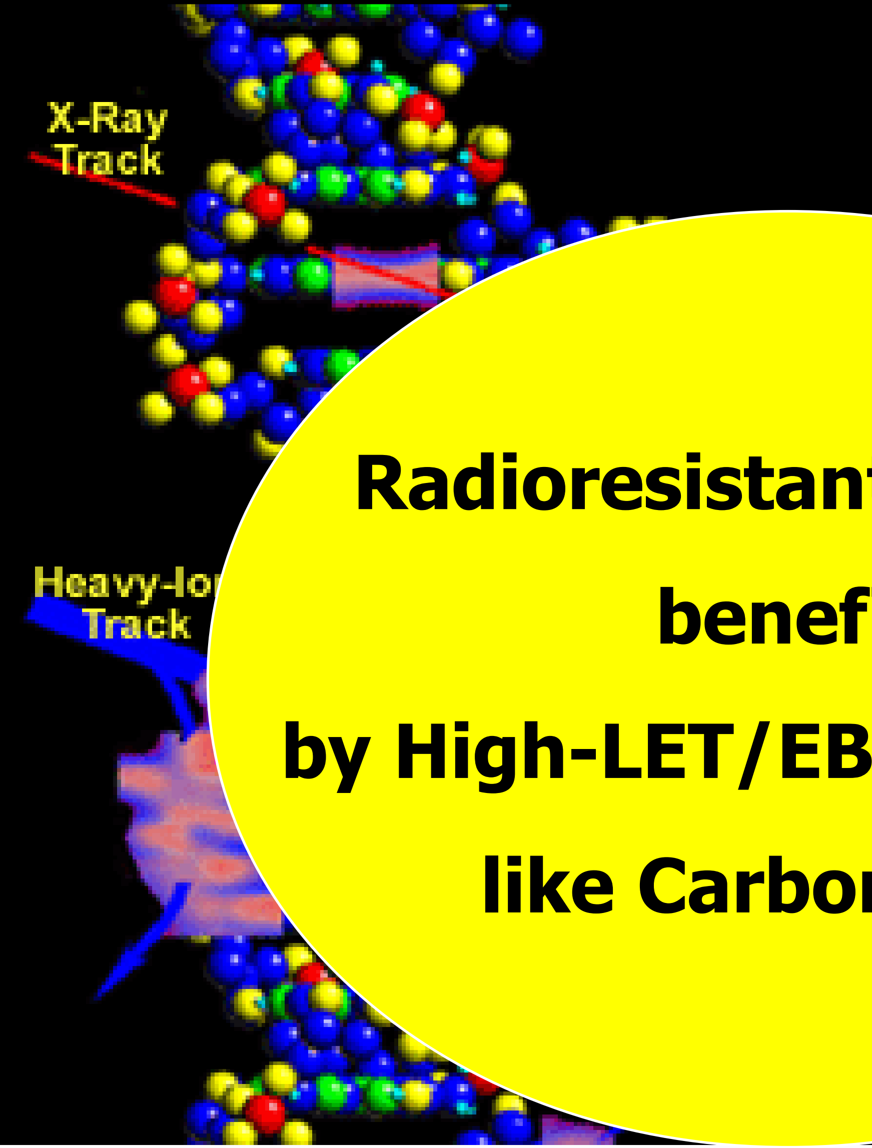


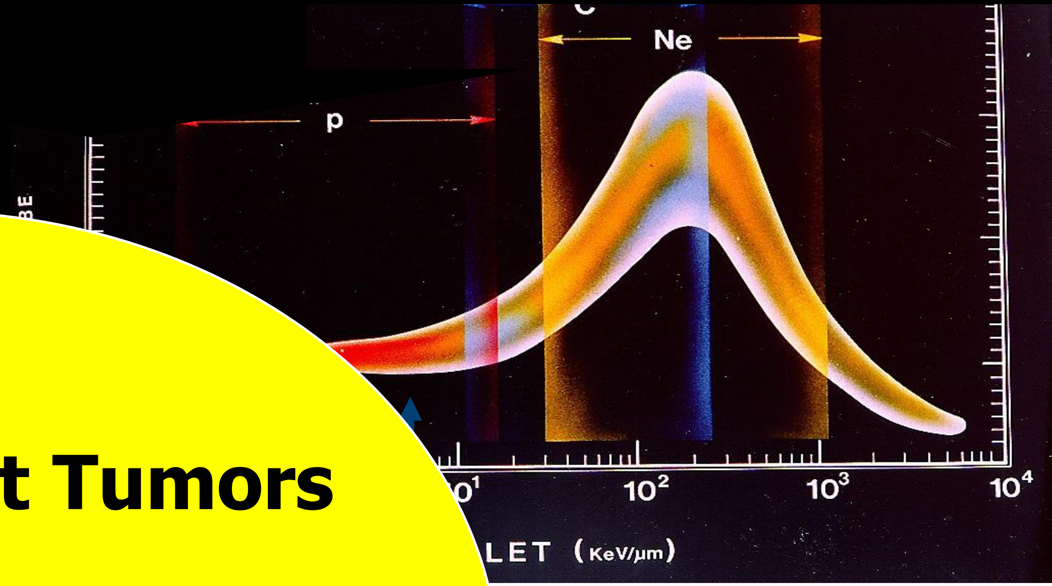


IMPT
Intensity Modulated
Particle Therapy



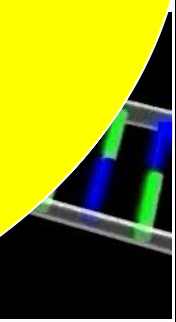
Biological Effectiveness(C12)

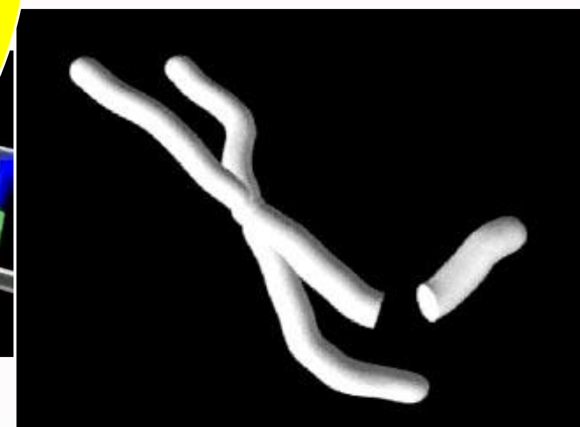




0 – 200 MeV/cm =

/(2 nm)





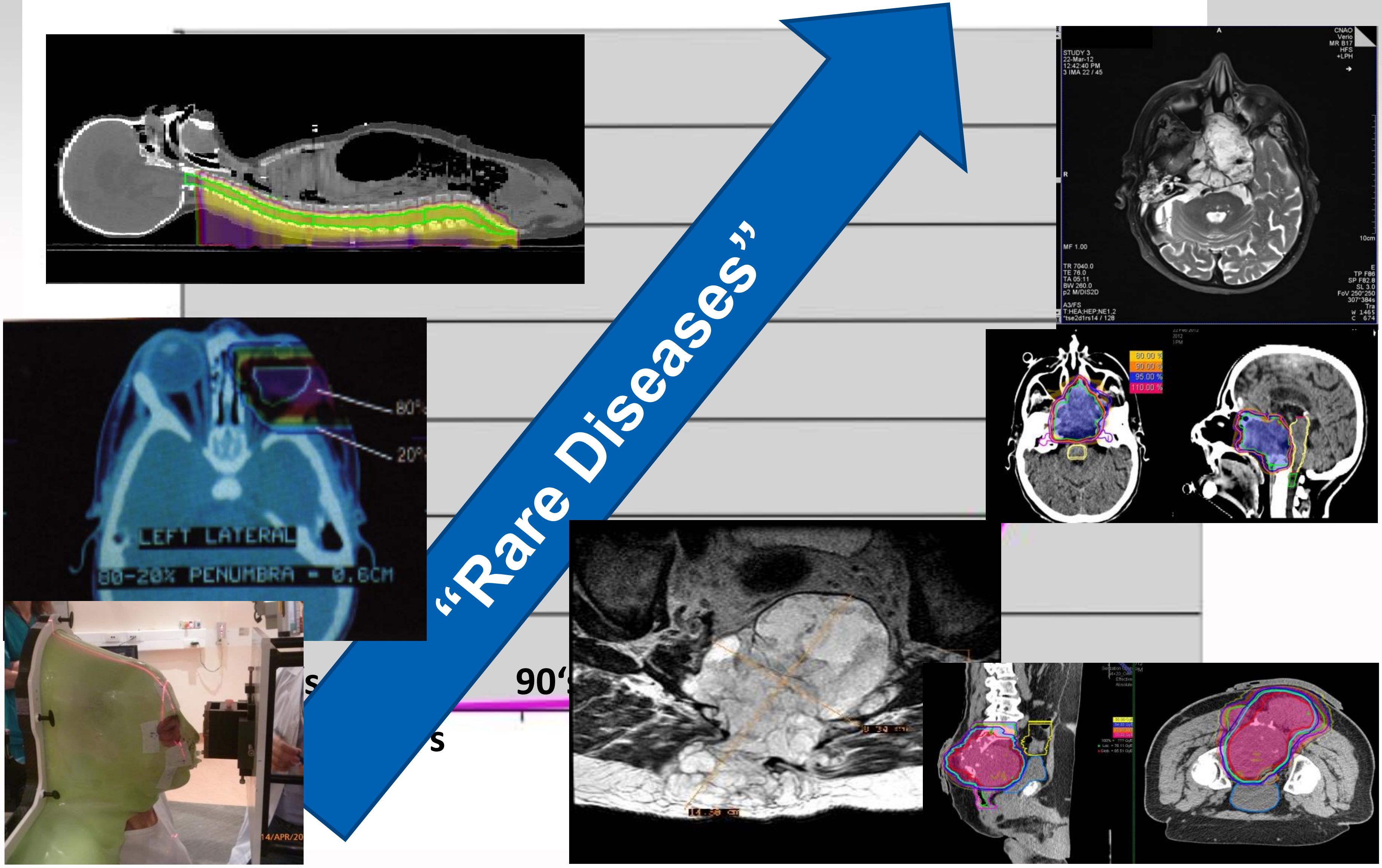
Radioresistant Tumors

benefit

by High-LET/EBR particles

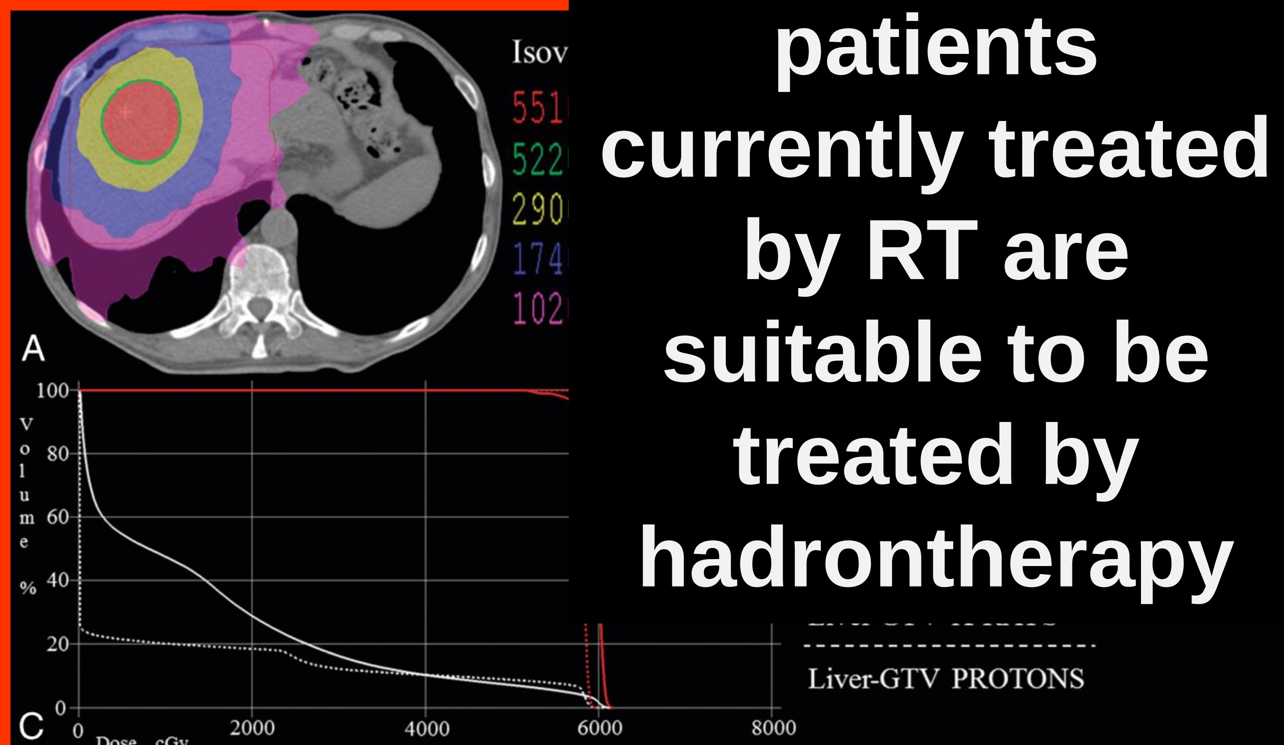
like Carbon Ions

Hadrontherapy: indications



«New» Indications

- Brain
- Head & Neck
- Lung
- Liver
- Pancreas
- Rectum
- Uterus
- Prostate
- Breast



Up to 20% of the total number of patients currently treated by RT are suitable to be treated by hadrontherapy

Number of patients at NIRS

1994-

2017

11,580 patients

Prostate	24.7%
Bone & soft tissue	11.5%
Head & neck	9.6%
Lung	9.2%
Pancreas	5.4%
Liver	5.3%
Rectum	4.9%
Uterus	2.5%
Uveal melanoma	1.8%
Abdominal lymph nodes	1.2%
CNS	0.9%
Skull base	…..
Gastrointestinal tracts	…..
Lacrimal gland	…..
Breast	…..
Kidney	…..
Re-irradiation	9.2%
Others	11.4%

Mohamad O et al, Cancers 2018

Which tumors might benefit of high LET particles?

Radioresistant for genetic alteration

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

Radioresistant for intratumoralmicromilieau

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

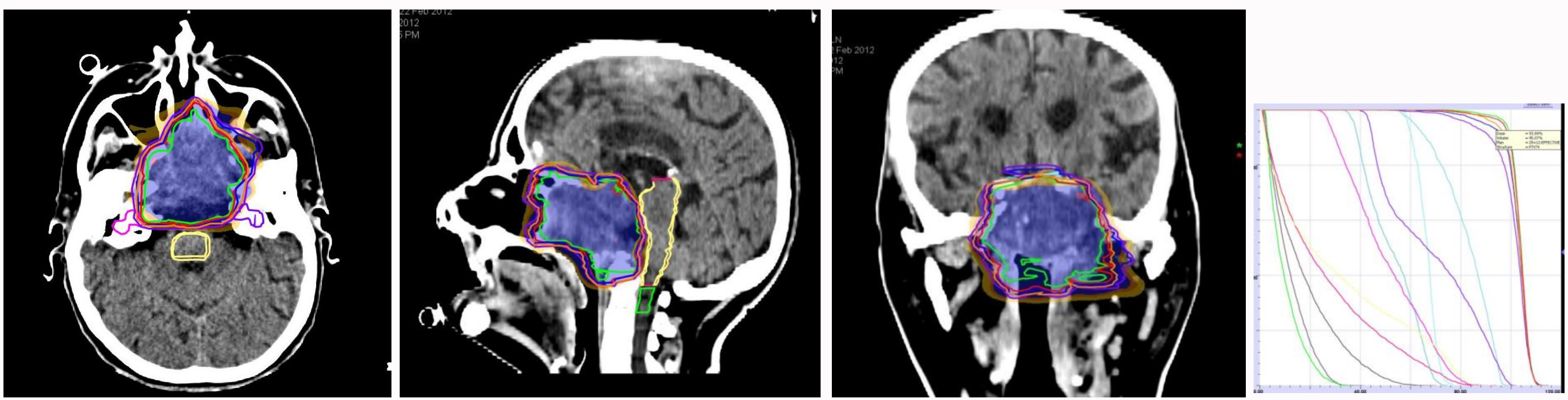
Radioresistant for proliferation status

- High content of quiescent cell clones
- Slow proliferation activity

Comparison of the effectiveness of radiotherapy with photons and particles for chordoma after surgery: a meta-analysis

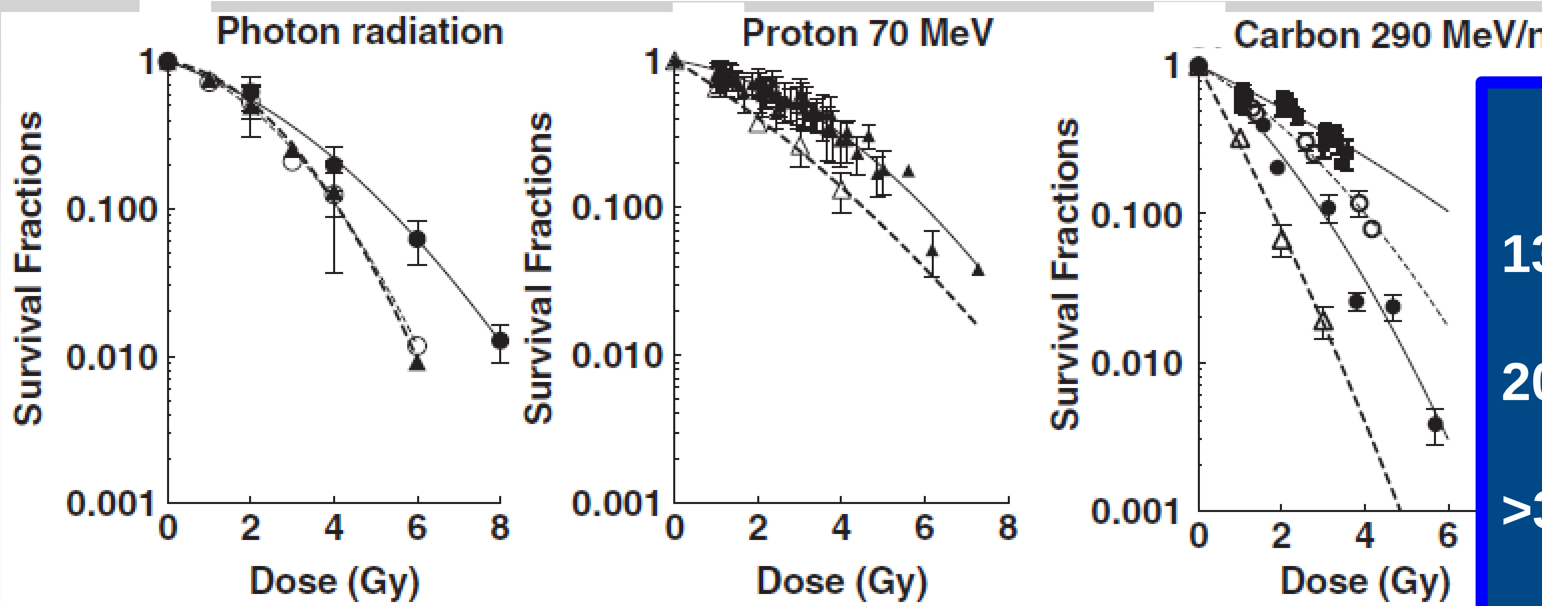
Treatment	3-y OS	5-y OS	10-y OS
CRT	0.70*	0.46*	0.21*
SRT	0.92	0.81	0.40
Proton	0.89	0.78	0.60
Carbon-ions	0.93	0.87	0.45

* P-value < 0.001



Zhou J et al, World Neurosurgery 2018

Comparison of human chordoma cell-kill for 290 MeV/n carbon ions versus 70 MeV protons *in vitro*



LET

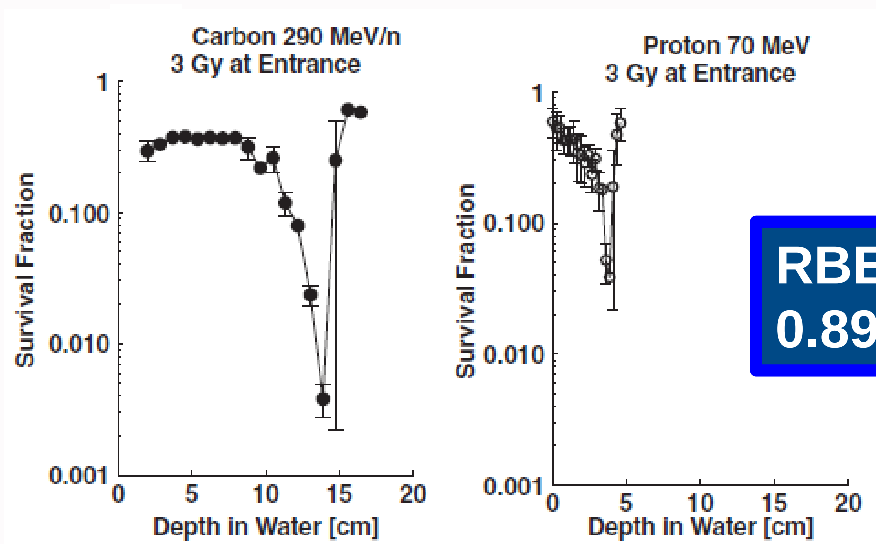
13-20 Kev/μm

20-30 Kev/μm

>30 Kev/μm

70 Kev/μm

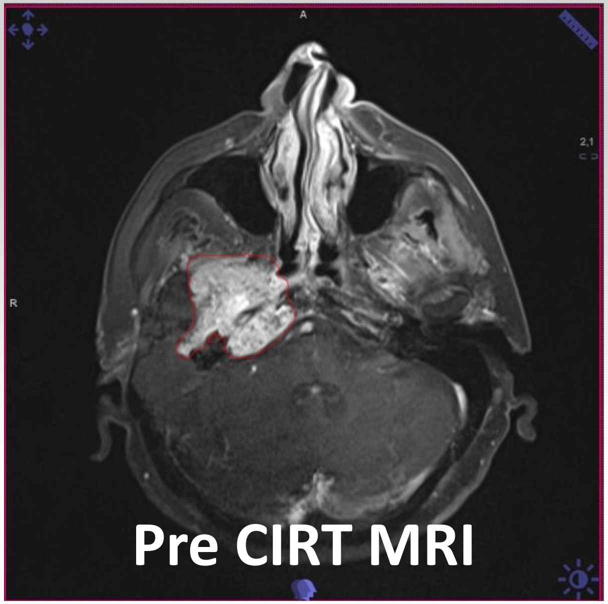
RBE 1.69

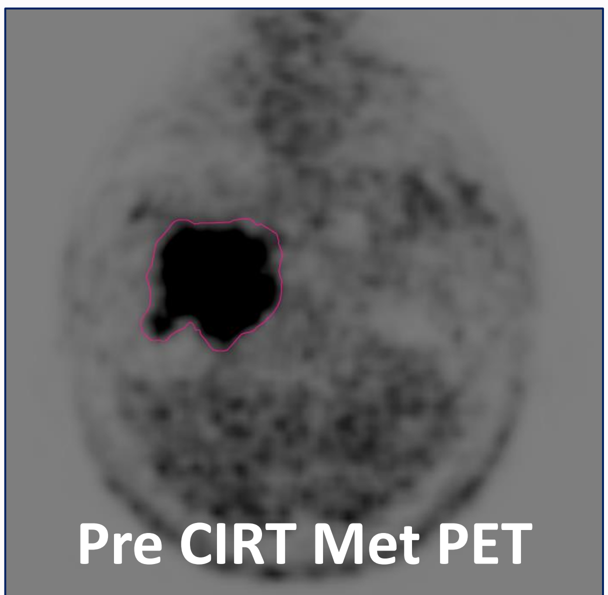


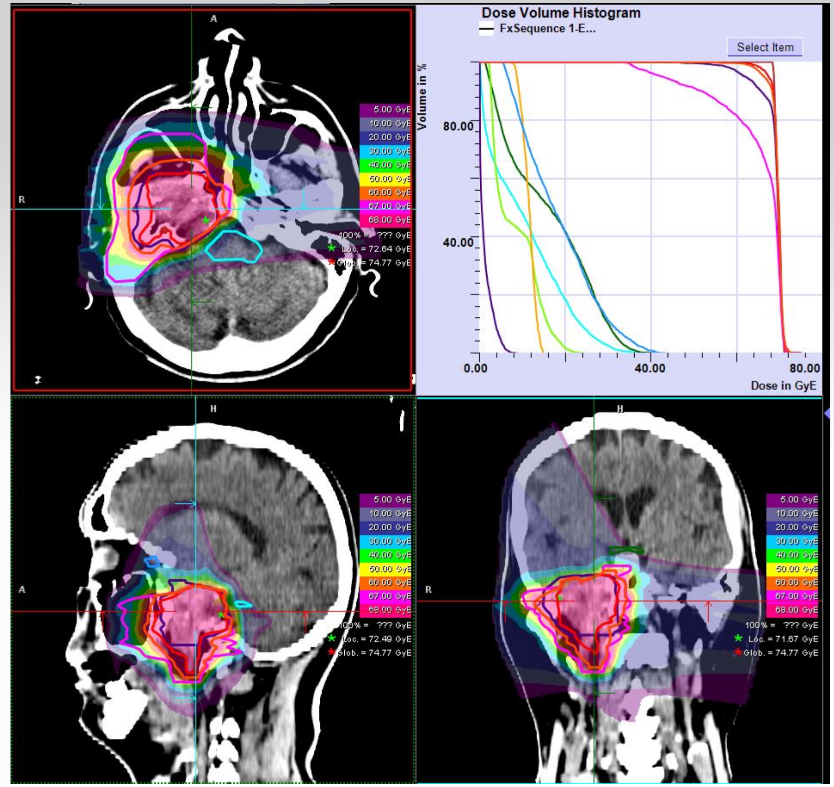
RBE 0.89

Fujisawa H et al, Radiat Oncol 2013

Adenoid Cystic Carcinoma. ACC







IMRT alone *vs* IMRT + Carbon Ion boost

LC at 4 years

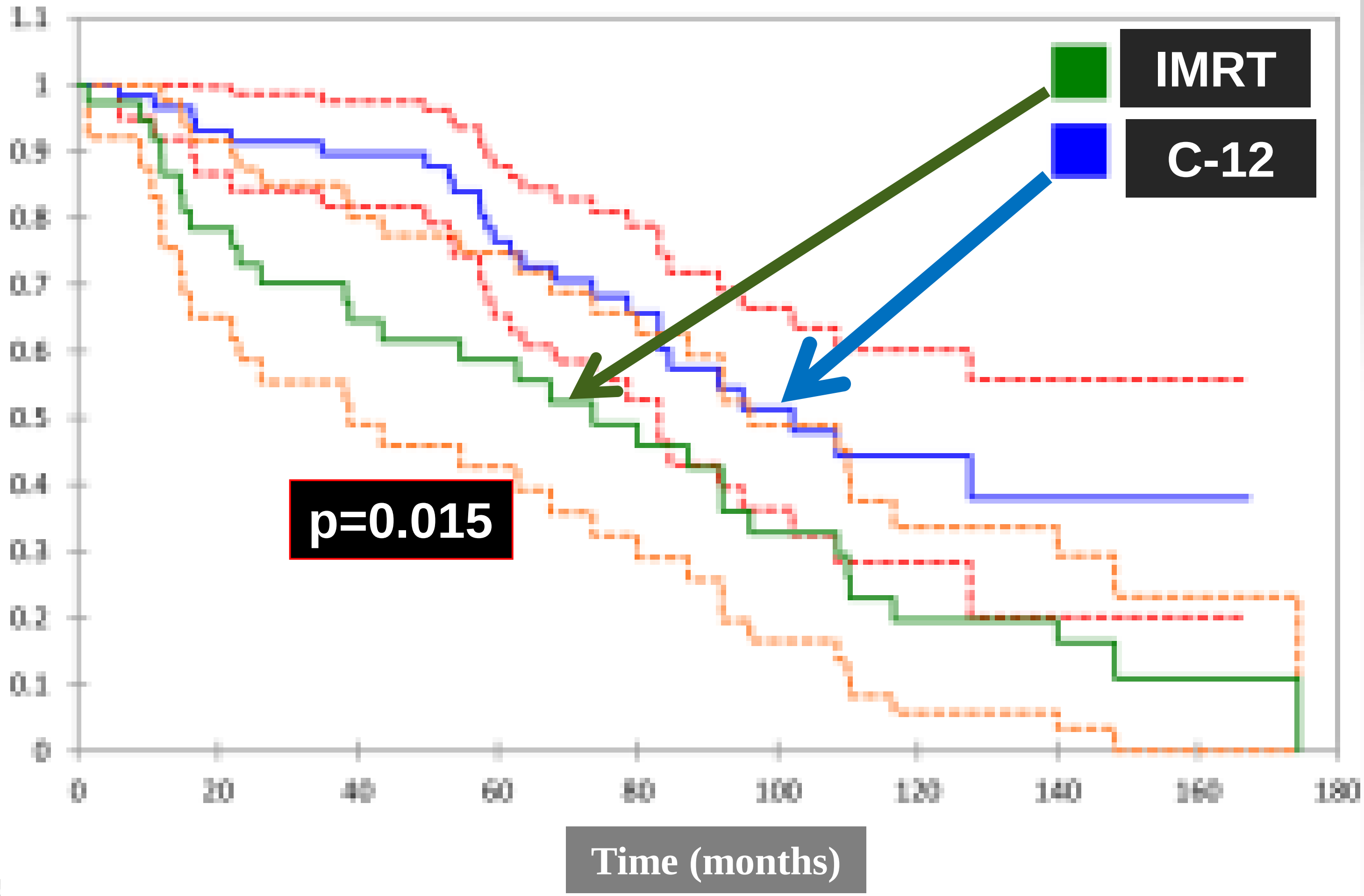
77.5% vs. 24.6%

Schulz-Ertner et al, IJROBP 2003

ACC. Long-term OS

GSI/HIT

10-year Overall Survival



numbers at risk:

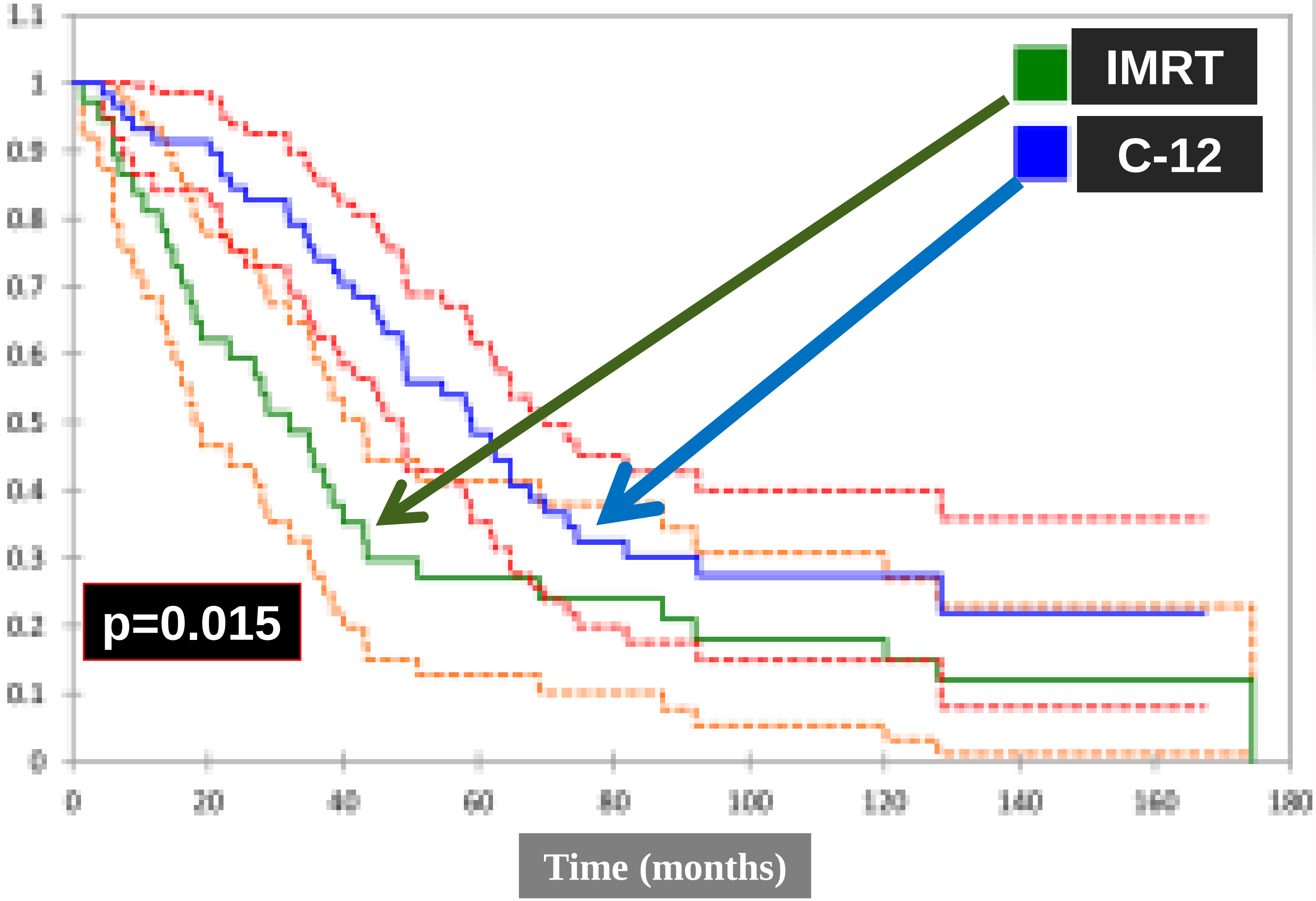
C12:	58	55	50	41	26	16	9	6	2
photons:	37	30	24	20	15	11	7	6	2

Jensen A et al, Cancer 2014; Jensen A et al, Radiother Oncol 2015

ACC. Long-term PFS

GSI/HIT

10-year Progression Free Survival

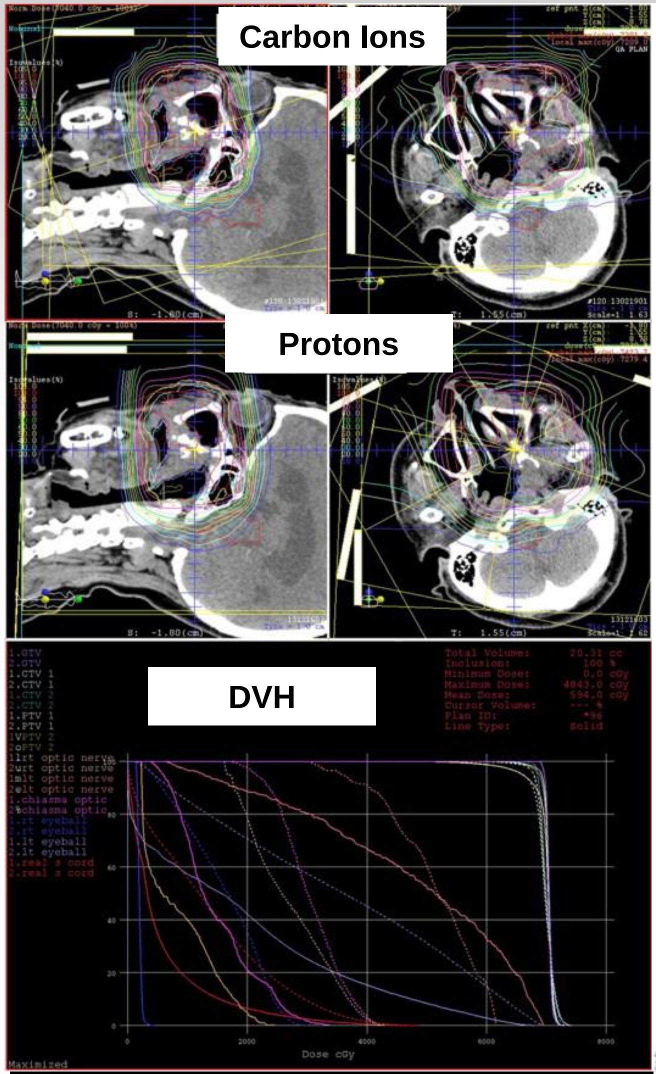


numbers at risk:

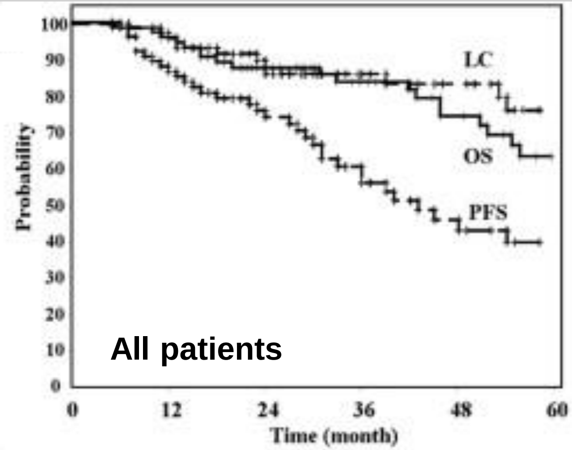
C12:	58	54	40	26	15	10	7	5	2
photons:	37	24	14	10	9	7	7	5	2

Jensen A et al, Cancer 2014; Jensen A et al, Radiother Oncol 2015

ACC at Hyogo. P+ *vs* CIRT

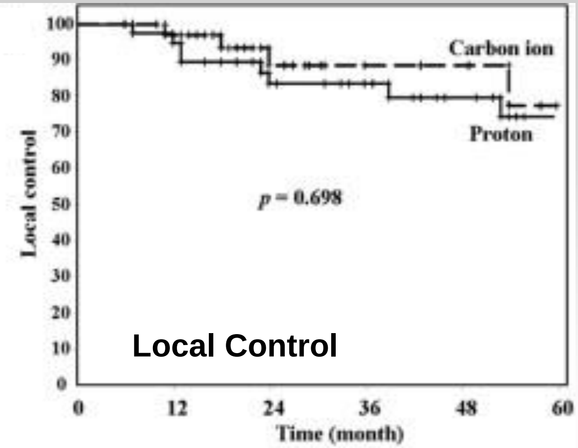


Hyogo Ion Beam Center, Japan



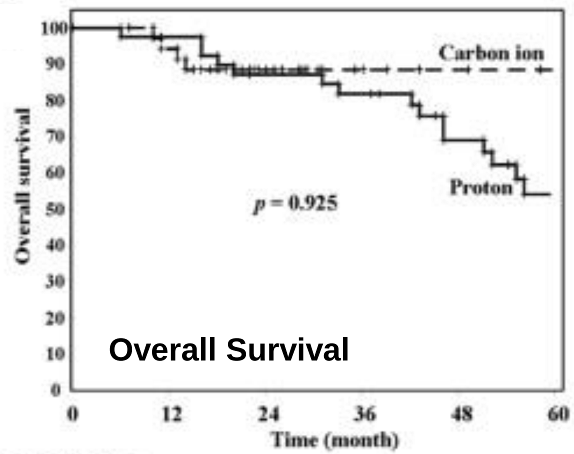
Patient at risk, n

	0	12	24	36	48	60
LC	80	71	49	34	27	17
OS	80	74	55	41	31	20
PFS	80	64	43	26	16	11



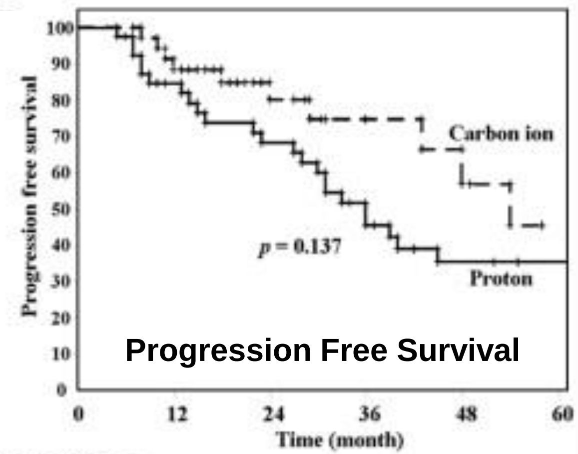
Patient at risk, n

	0	12	24	36	48	60
Carbon	40	34	20	10	6	5
Proton	40	37	29	24	21	12



Patient at risk, n

	0	12	24	36	48	60
Carbon	40	35	21	12	7	5
Proton	40	39	35	29	24	15

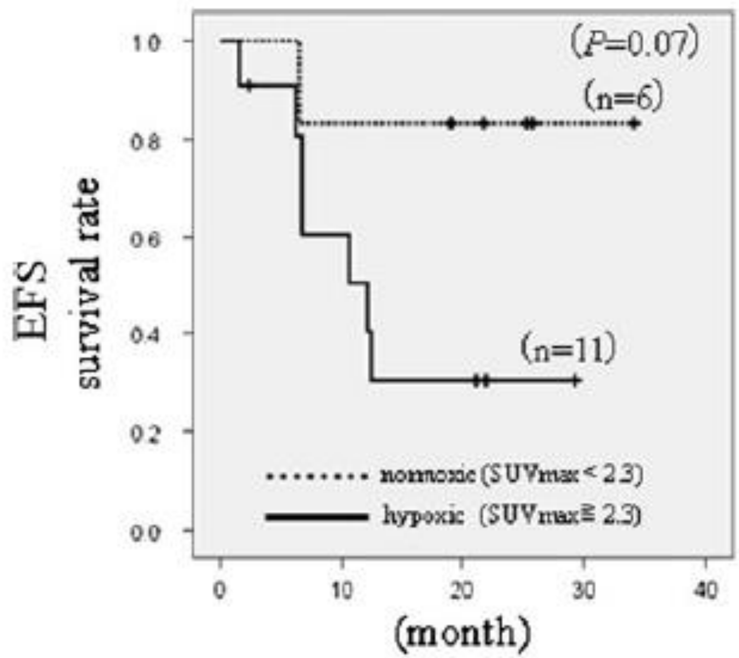


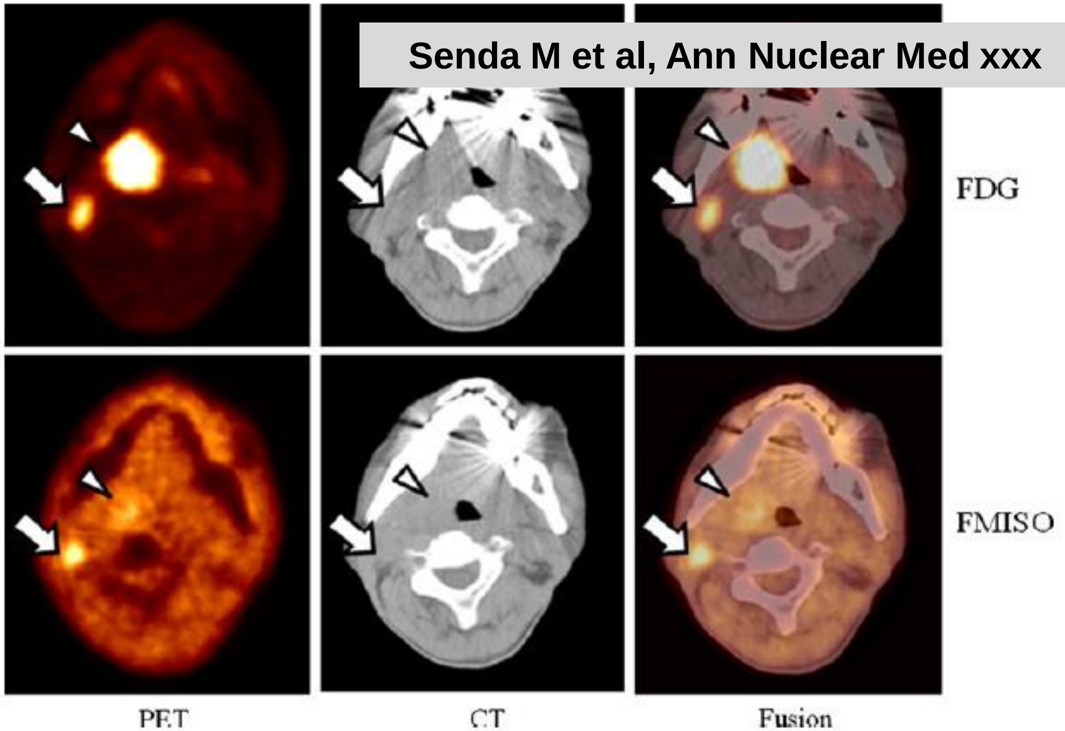
Patient at risk, n

	0	12	24	36	48	60
Carbon	40	31	17	10	6	5
Proton	40	33	26	16	10	6

Takagi M et al, Radiother Oncol 2014

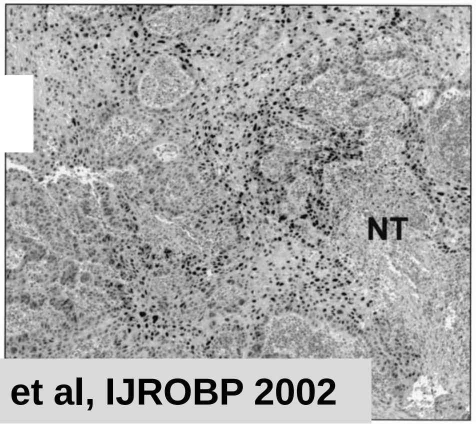
Hypoxia is predictive of outcome in H&N cancer



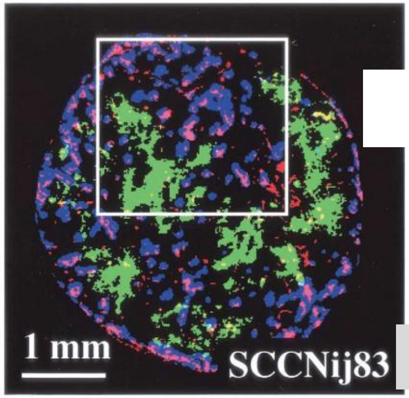


Senda M et al, Ann Nuclear Med xxx

HIF-1α



Janssen HL et al, IJROBP 2002

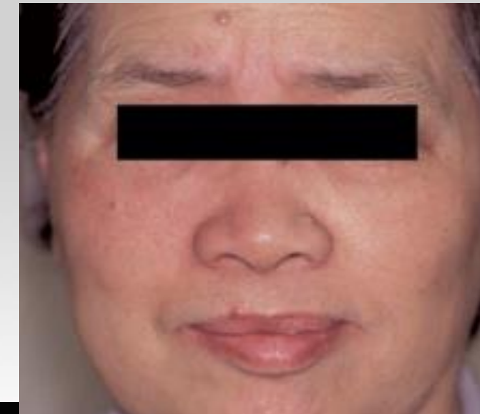


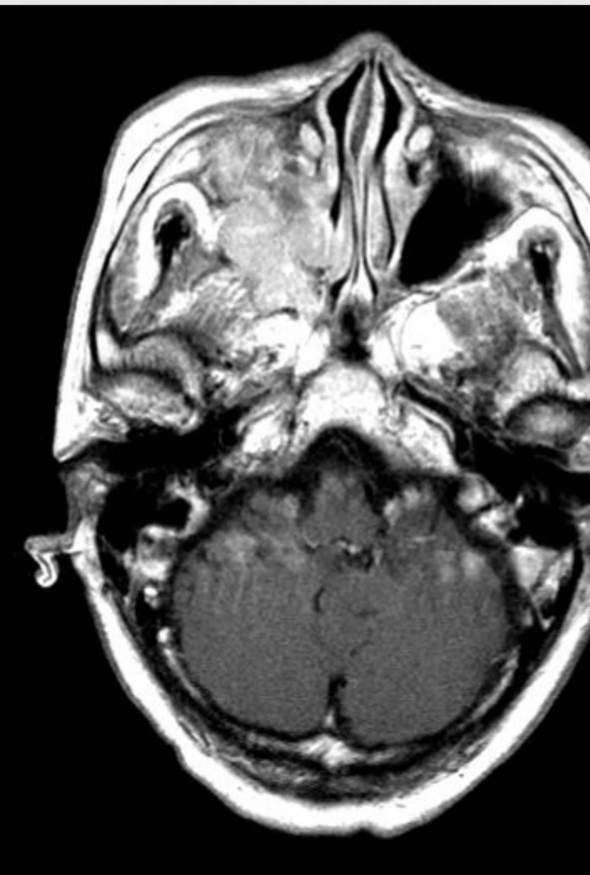
Microenvironment

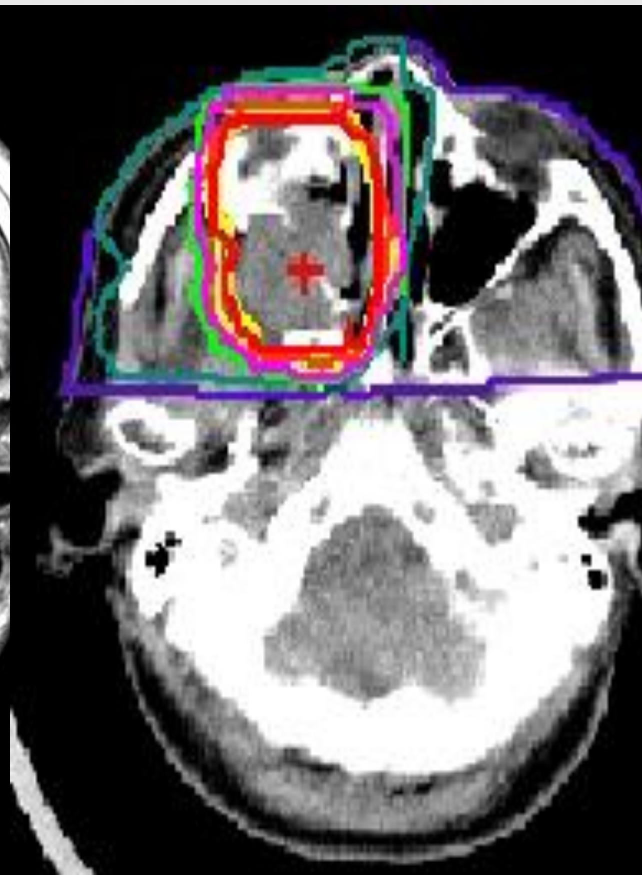
Ljugkvist AS et al, IJROBP 2002

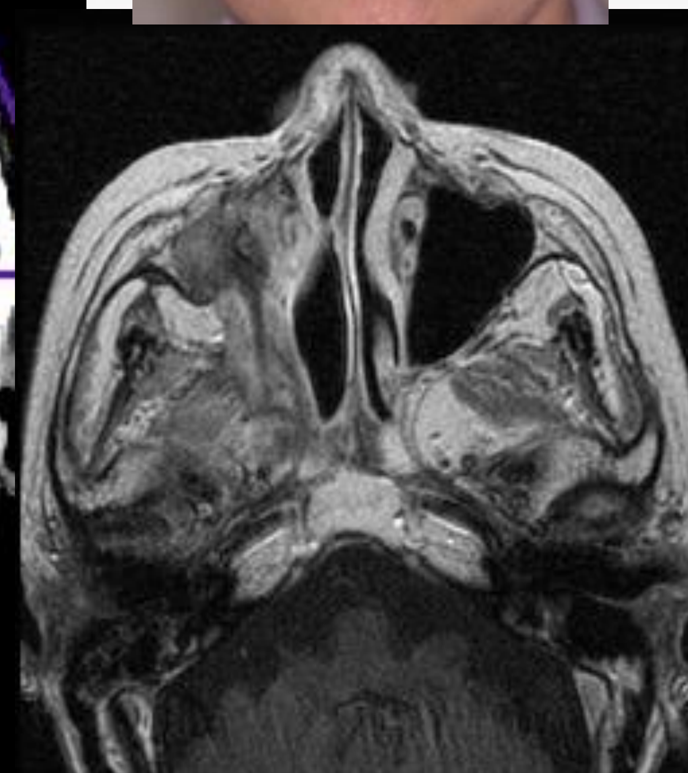
CIRT at NIRS-Chiba

Head & Neck Sarcoma









Pre CIRT | 70.4 GyE/16fx/4 wks | At 5 years

CIRT at NIRS-Chiba

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.

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

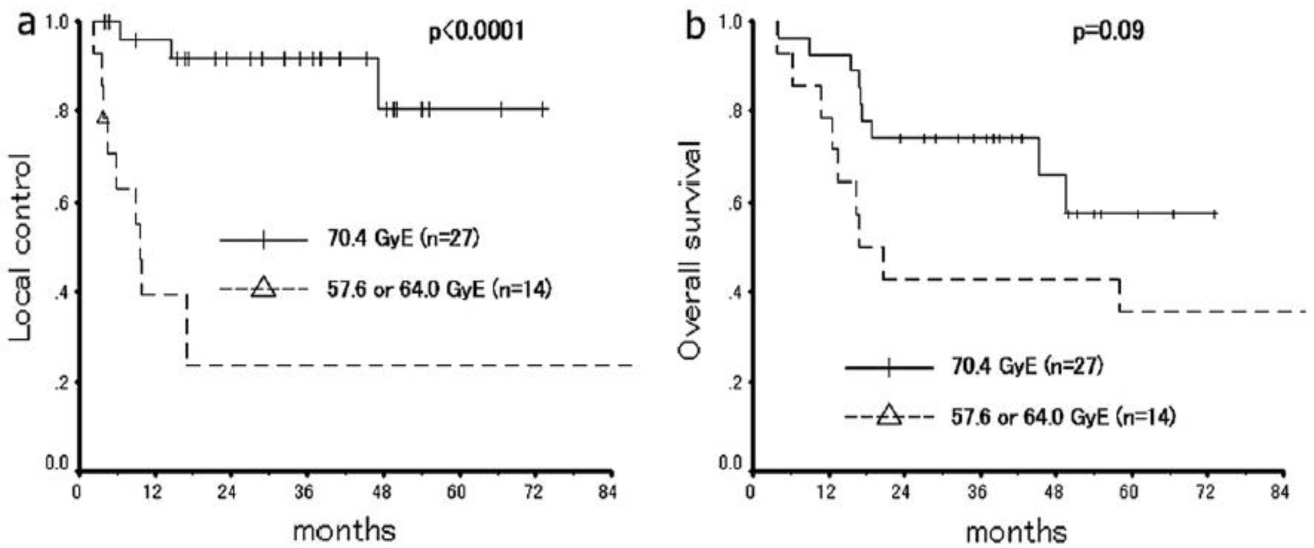
Purpose: To evaluate the safety and efficacy of carbon ion radiotherapy (C-ion RT) with 70.4 GyE for unresectable bone and soft-tissue sarcoma of the adult head and neck.
Methods and Materials: Twenty-seven patients (mean age, 46.2 years) were enrolled in this prospective study on C-ion RT with 70.4 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.

Head & Neck Sarcoma
Comparison of OS and LC

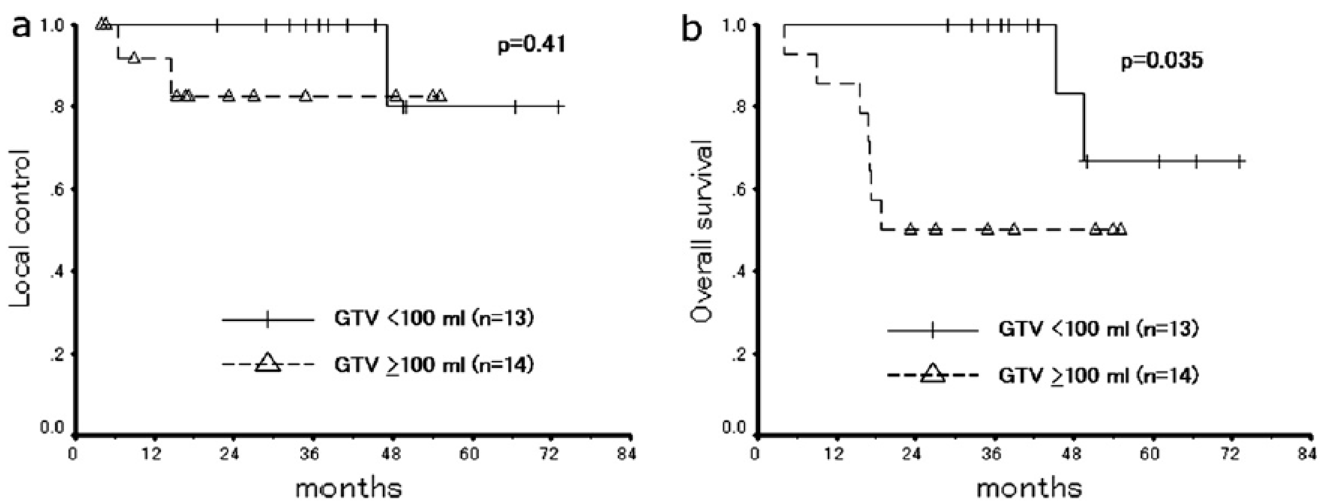
CIRT at NIRS-Chiba

H&N Sarcoma

Jingu K et al IJROBP, 2012



LC (a) and OS (b) according to the dose



LC (a) and OS (b) at dose level of 70.4 GyE according to tumor volume

Etude randomisée comparant l'hadronthérapie par ion carbone à la radiothérapie conventionelle – y compris protonthérapie – pour le traitement de tumeurs radiorésistantes

PHRC ETOILE

Standard Arm

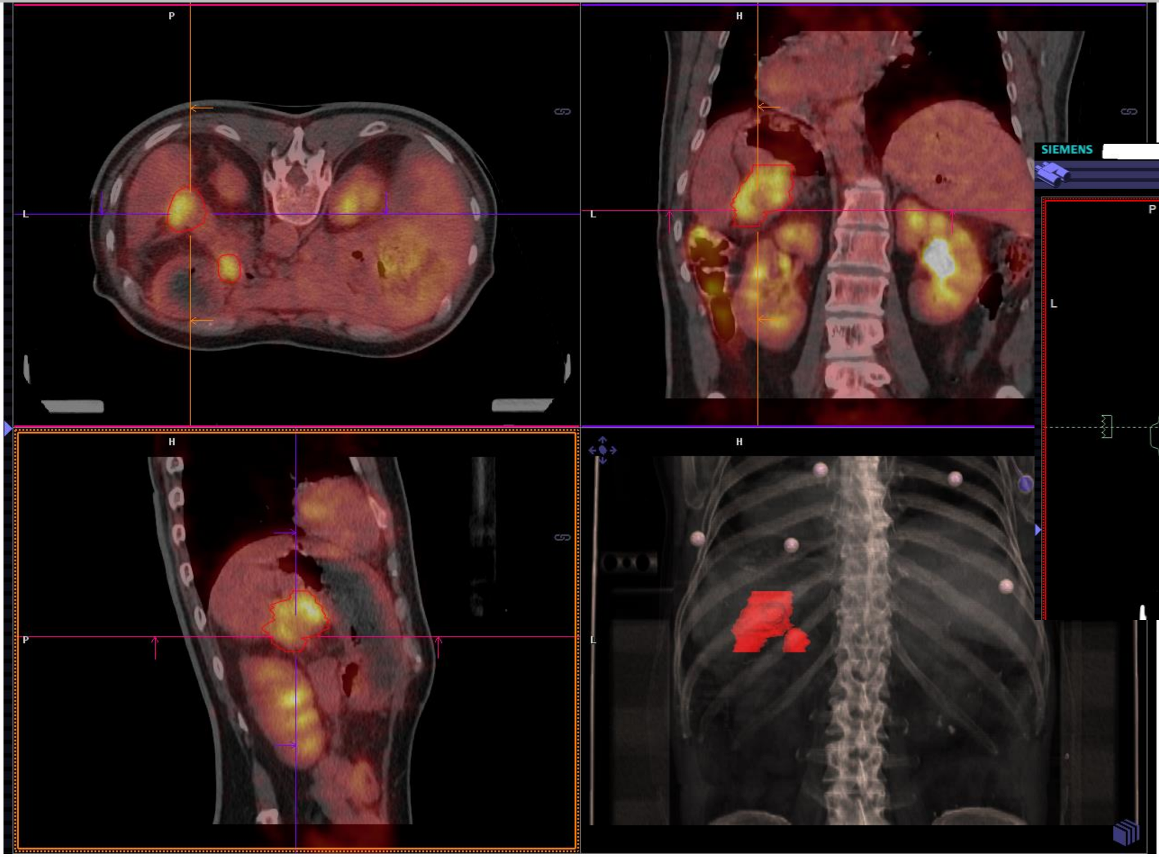
ACC: IMRT integrated boost (2.2Gy/day) up to 66 Gy
High risk CTV: 60 Gy (2.0Gy/day)
Low risk CTV: 54 Gy (1.8Gy/day)
Proton (20 GyE/2.0 GyE/day) + IMRT 50 Gy/2.0Gy/day)
Sarcoma : 64 to 70 Gy, IMRT alone or integrated boost P+
Chordoma: from 66 Gy to 74 Gy (2Gy/day)
if exclusive P+ up to 78 GyE(2GyE/day)

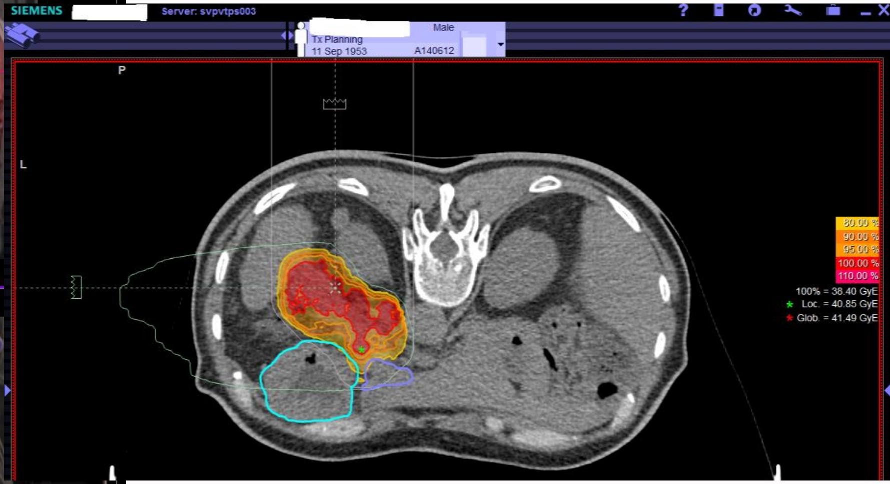
Experimental Arm

ACC: 68.8 GyE in 16 fractions (4.3 GyE each)
Sarcoma & Chordoma: from 70.4 GyE to 76.8 GyE/16 fractions/ from 4.4 GyE to 4.8 GyE each

Pancreatic cancer

Median Survival at 2 years of ≈50%
About the double with respect the best standard RTOG/USA (RT+CT)





Kamada T et al, Lancet Oncol 2015

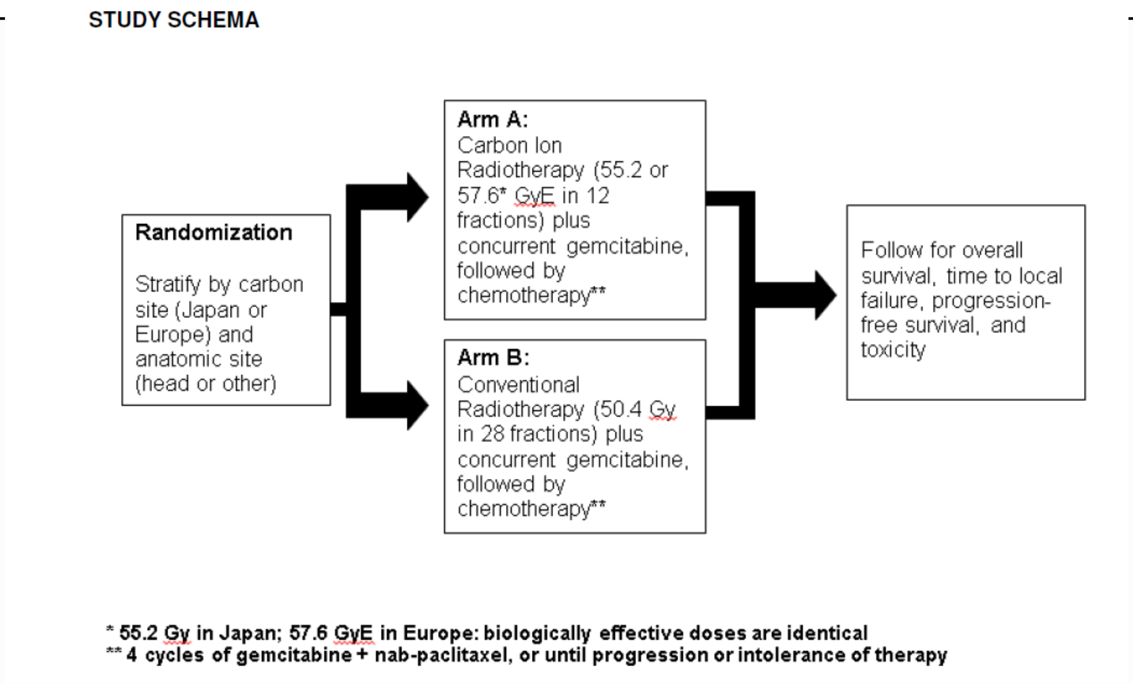
Pancreatic cancer

Treatment	Dose	1-y OS	2-y OS
SRT	25Gy/1 25-30Gy/3-6	21-50% 41-78%	- 18%
Protons	25Gy/5 59.4Gy/33 50-67.5Gy/25	- - 76.8%	42% (with surgery) 31% -
C-12 preop	30.36.8Gy/5	69%	42% (5-y)
C-12 radical	43.2-55.2Gy/12	73%	35%

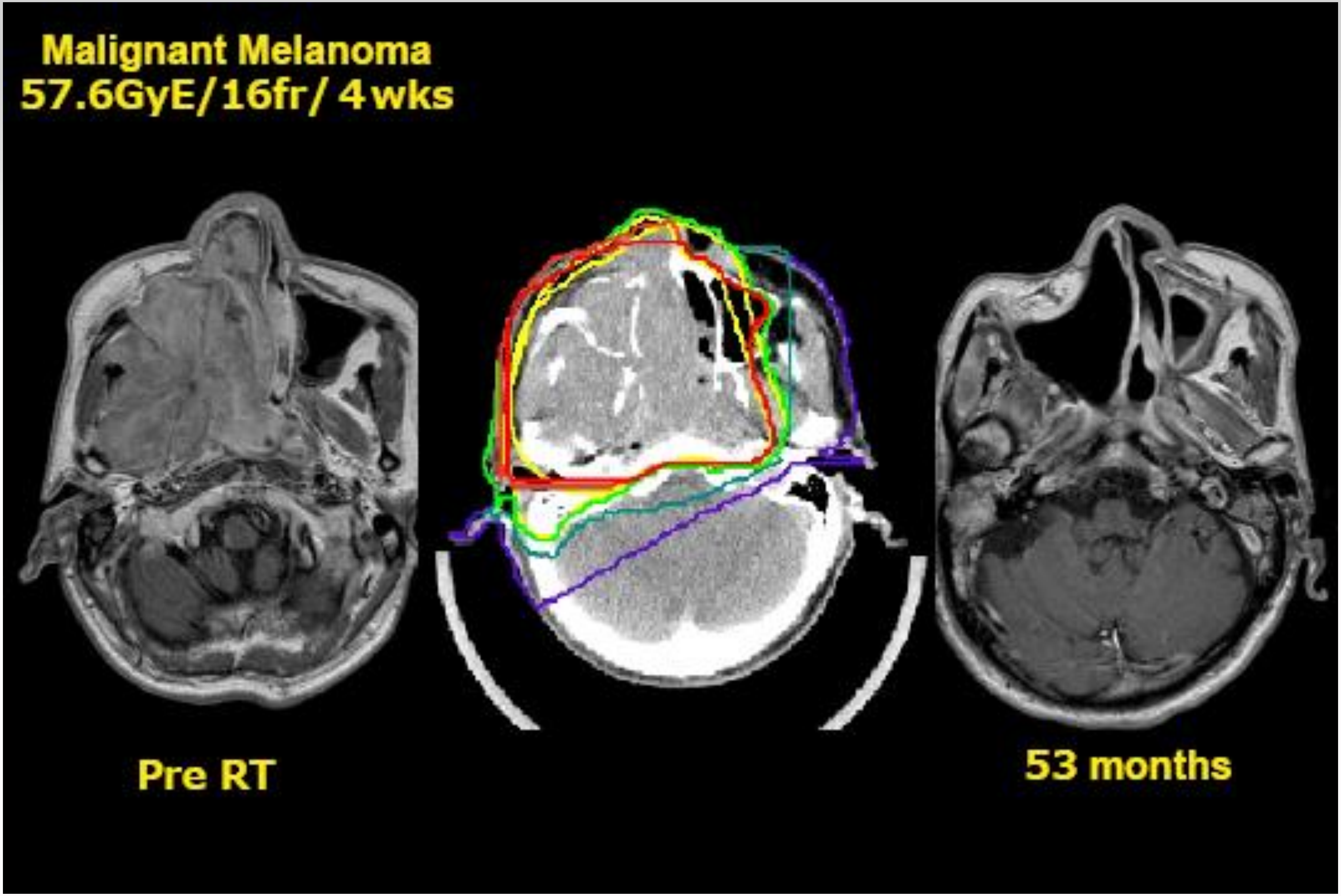
Sweet PN & Herman JM, Cancers 2018, modified

C-12 ongoing randomized trials

Study	Institution	Condition
BAA-N01CM51007-51 C-12 versus IMRT	NCI/Shanghai Phase I/III	Locally advanced pancreatic cancer
CIPHER: C-12 versus IMRT (+ CT)	Dallas/NIRS/ CNAO	Locally advanced pancreatic cancer



CIRT at NIRS-Chiba



CIRT at NIRS-Chiba

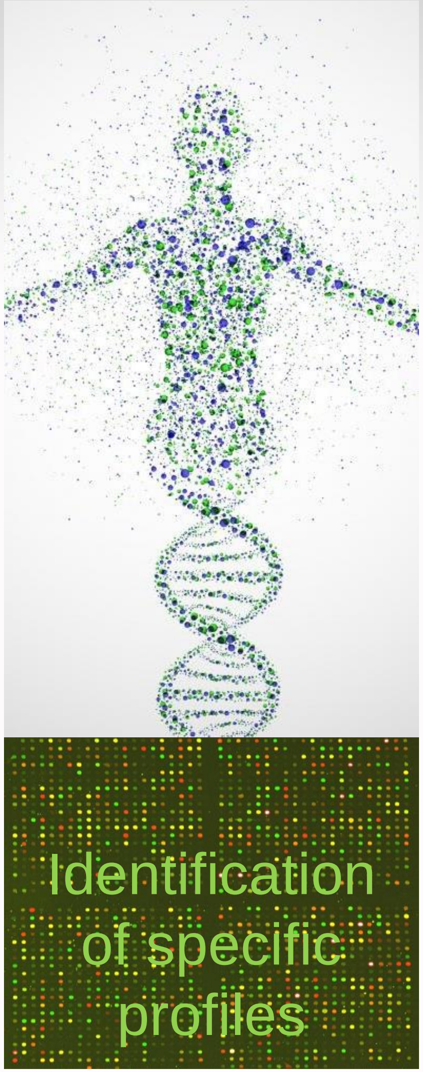
Author	*No.*	*Tumor location*	*Treatment modalities*	*5-year OS (%)*
Gilligan	28	Sinonasal	Radiotherapy	18
Shibuya	28	Upper jaw	Radiotherapy +/– surgery	25
Shah	74	Head and neck	Surgery +/– radiotherapy	22
Chaudhry	41	Head and neck	Surgery+/– radiotherapy+/– chemotherapy	17
Lund	58	Sinonasal	Surgery+/– 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

Modern Oncology

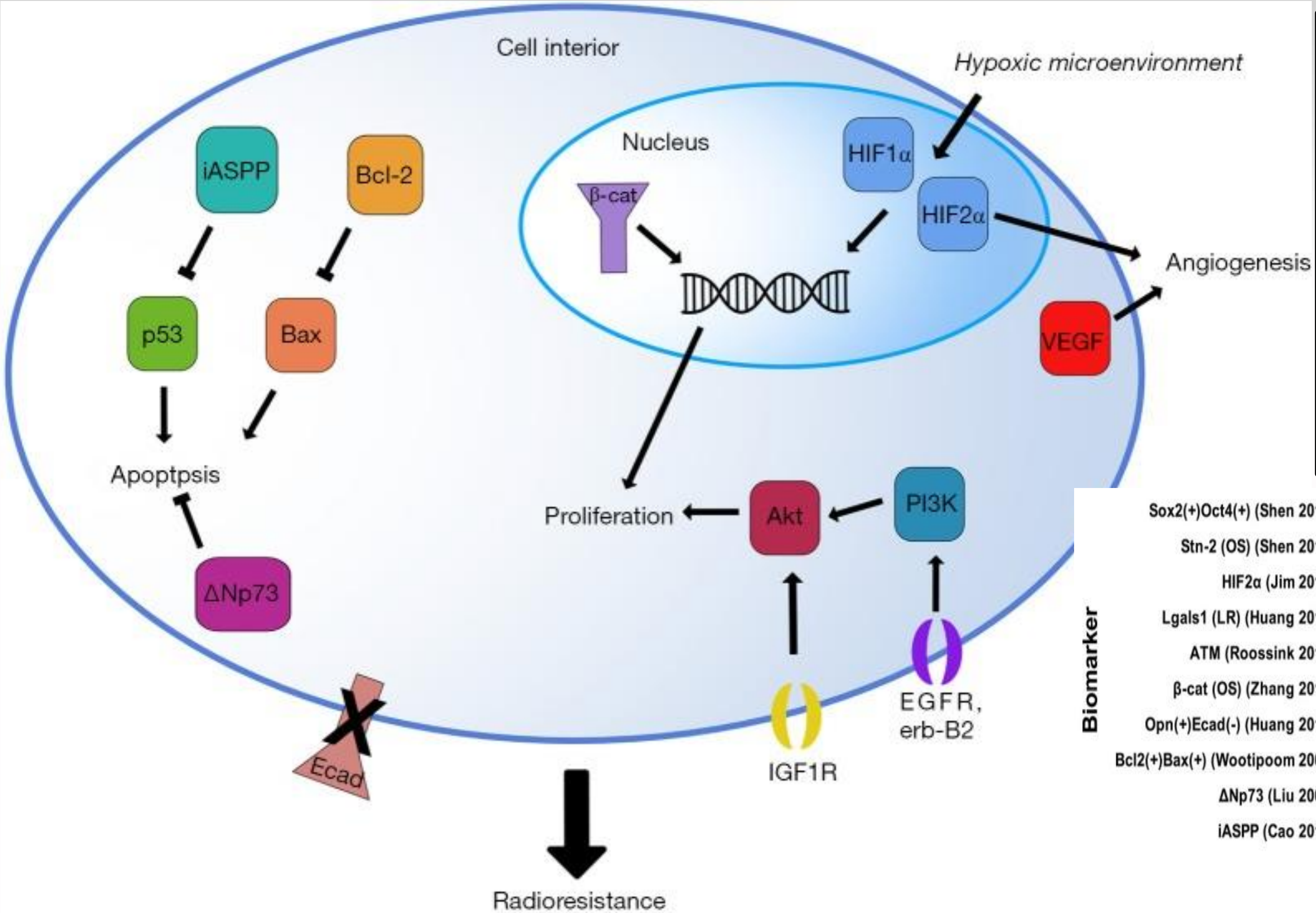
Personalized Medicine

Precision Medicine

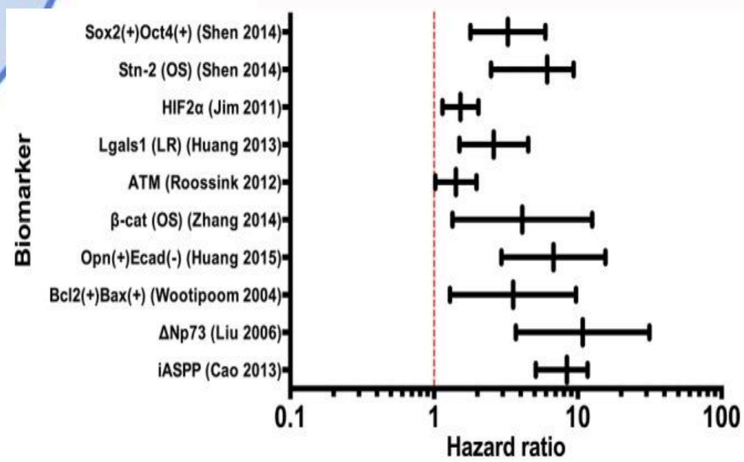
filrouge



Molecular biomarkers for radioresistance



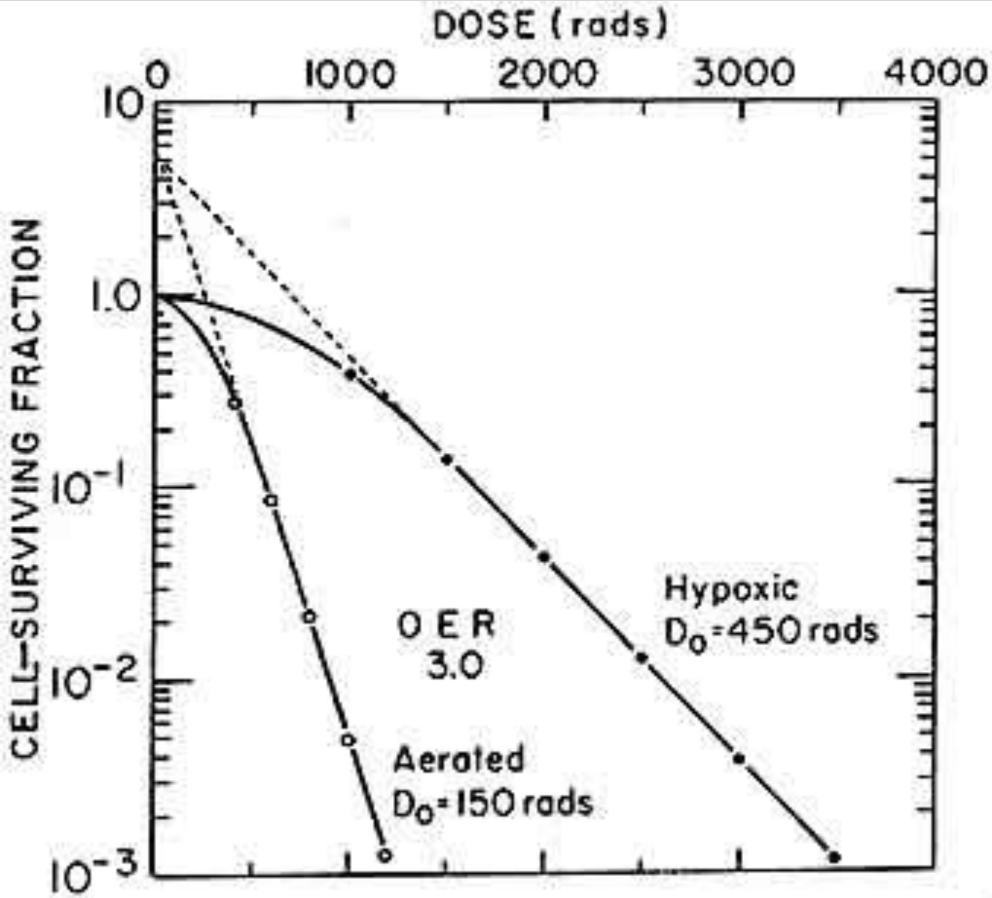
Biomarkers may allow molecular profiling of individual tumors

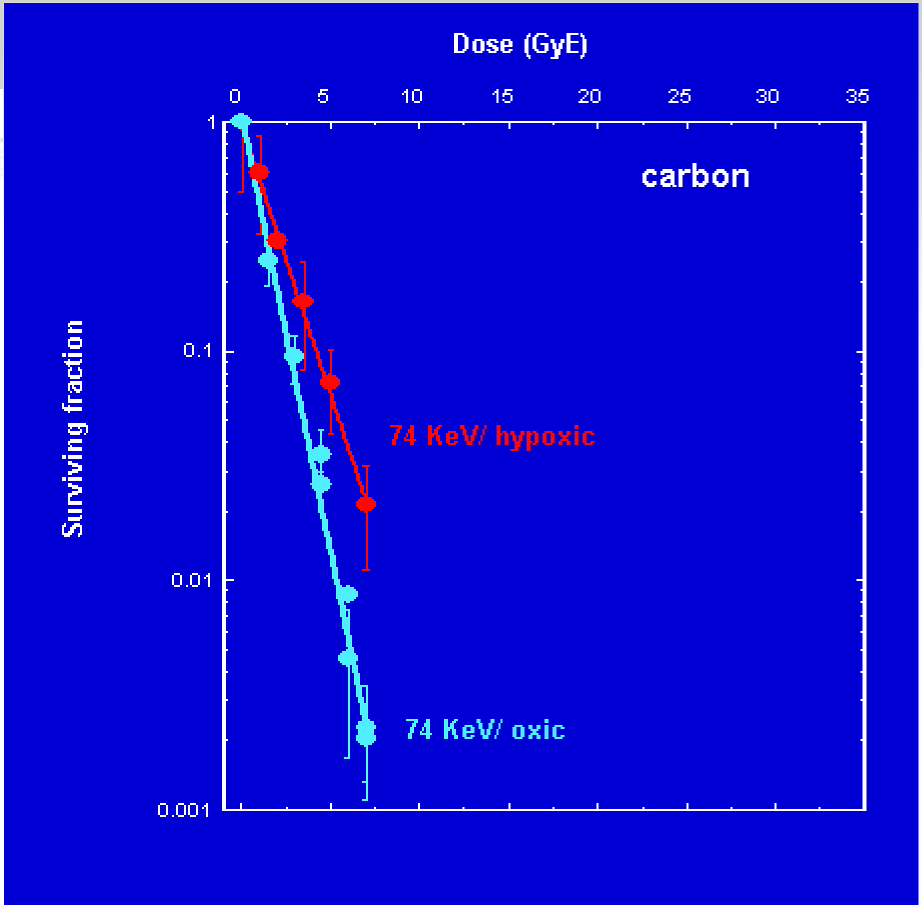


Tailored Hadrontherapy

Kilic S et al, Ann Transl Med 2015

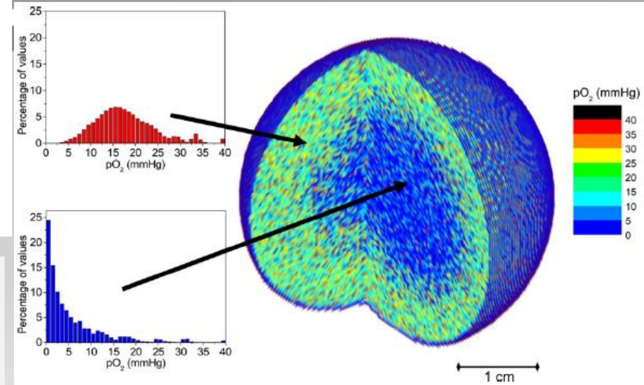
OER (x-rays vs Carbon Ions)



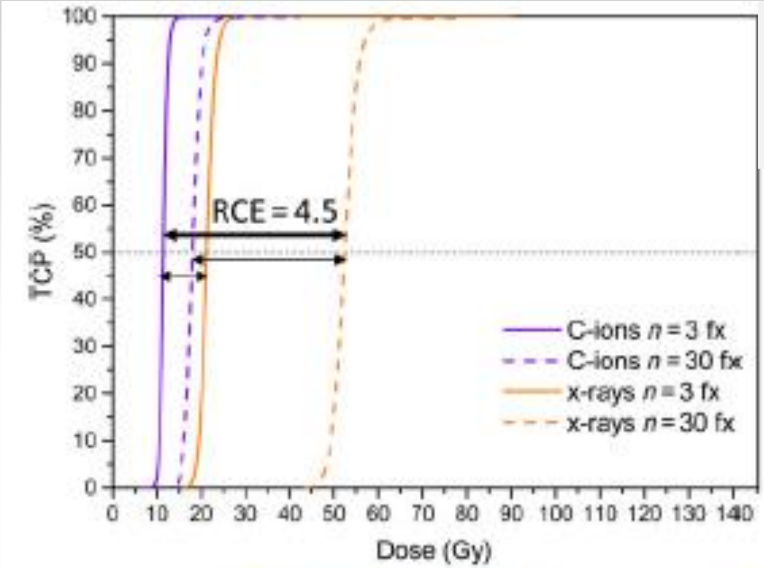


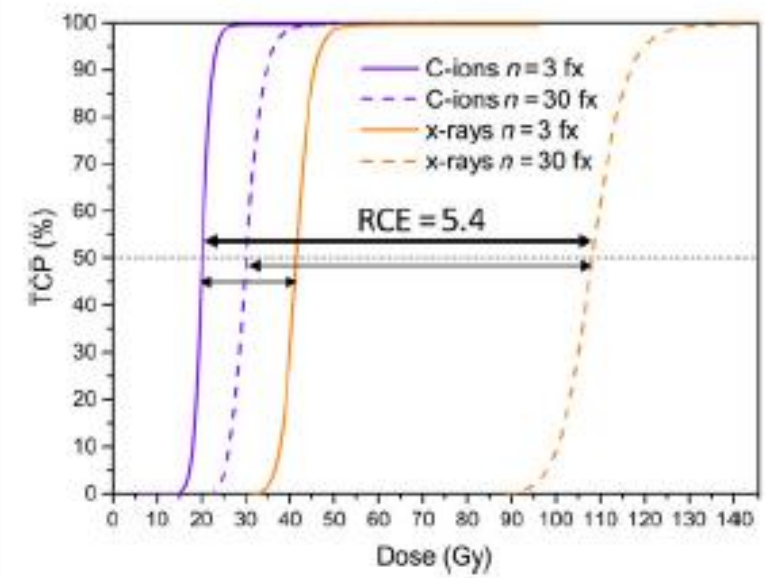
OER is not 1 for 74 KeV/μ carbon

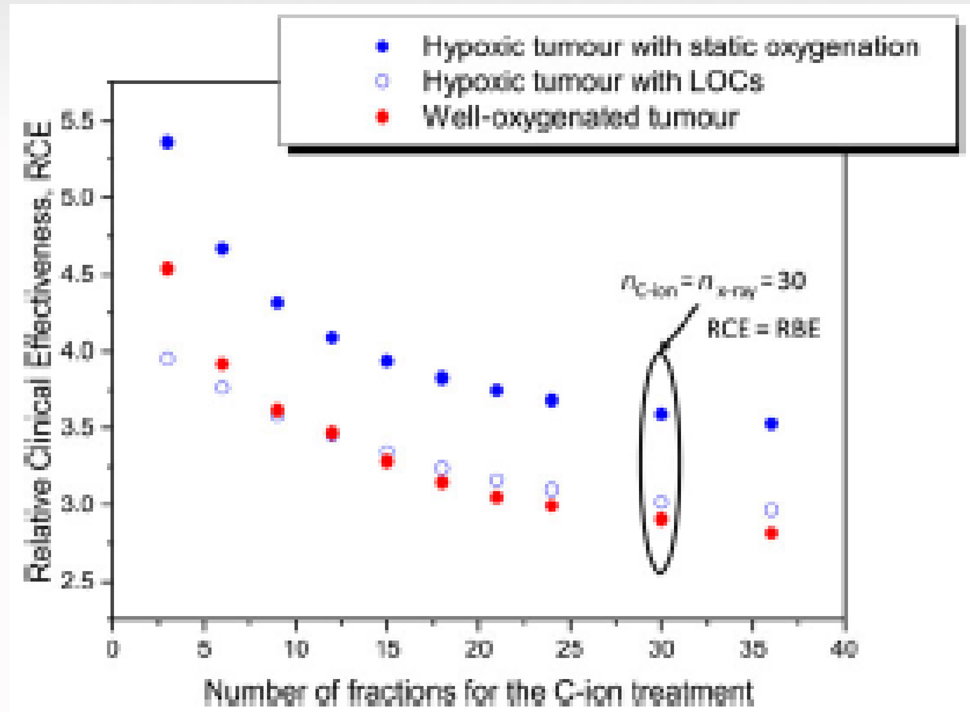
Relative clinical effectiveness of carbon ion radiotherapy: theoretical modelling for H&N tumours



RCE
Relative Clinical Effectiveness



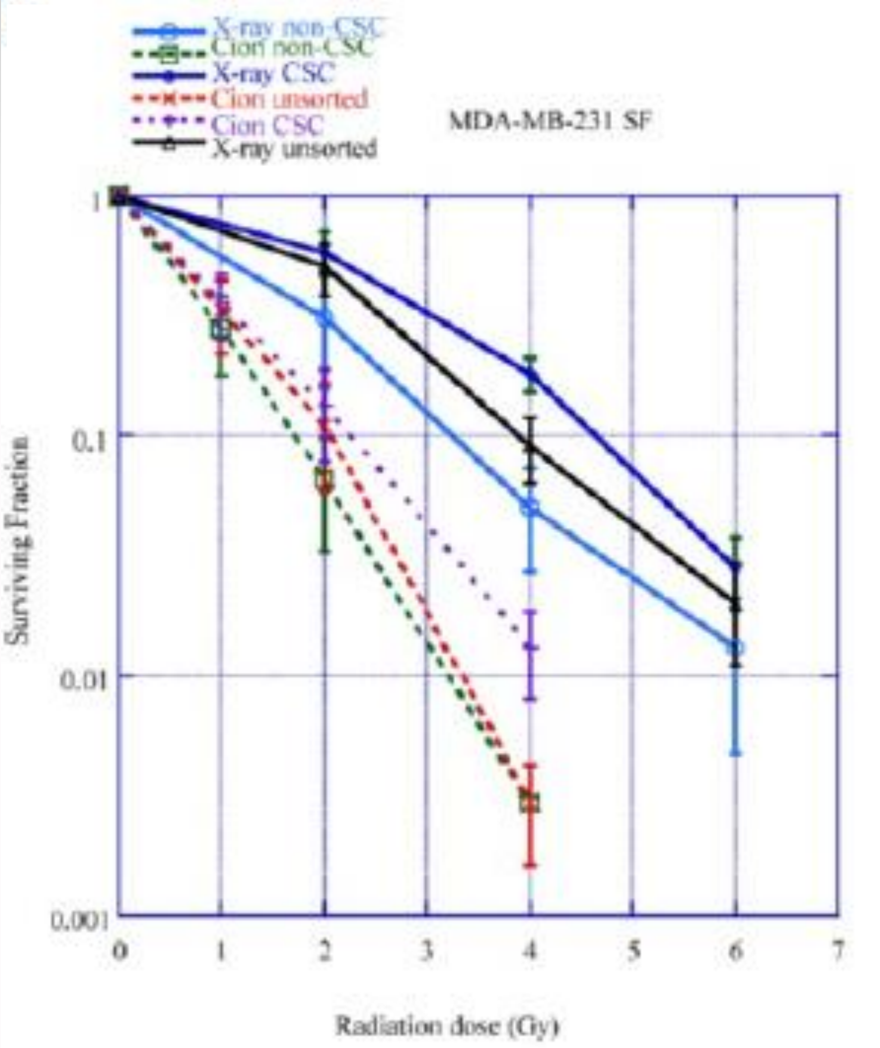


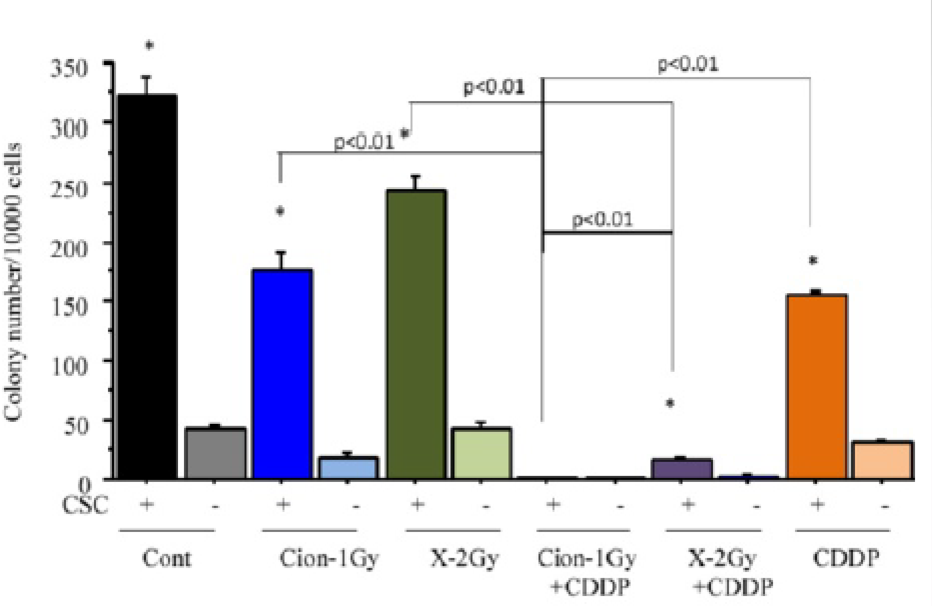


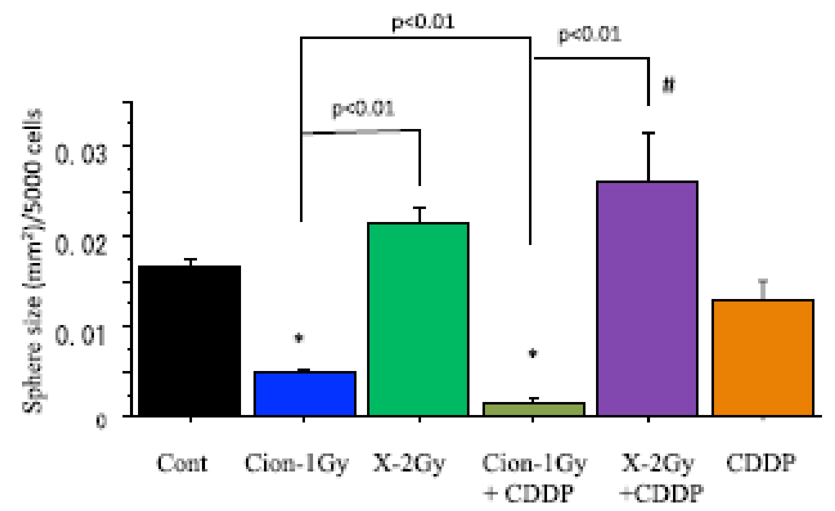
LOCs
Local Oxygenation Changes

Antonovic L et al, J Radiat Res 2015

Carbon ion beam combined with cisplatin effectively disrupts triple negative breast cancer stem-like cells *in vitro*

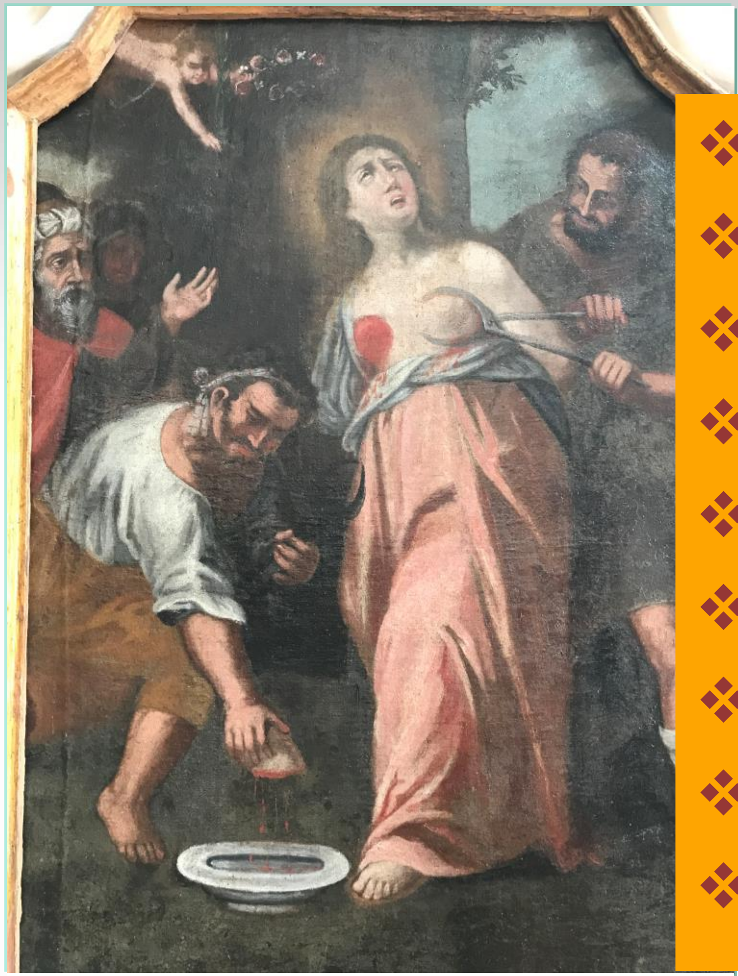






Sai S et al, Mol Cancer 2015

CIRT for breast cancer

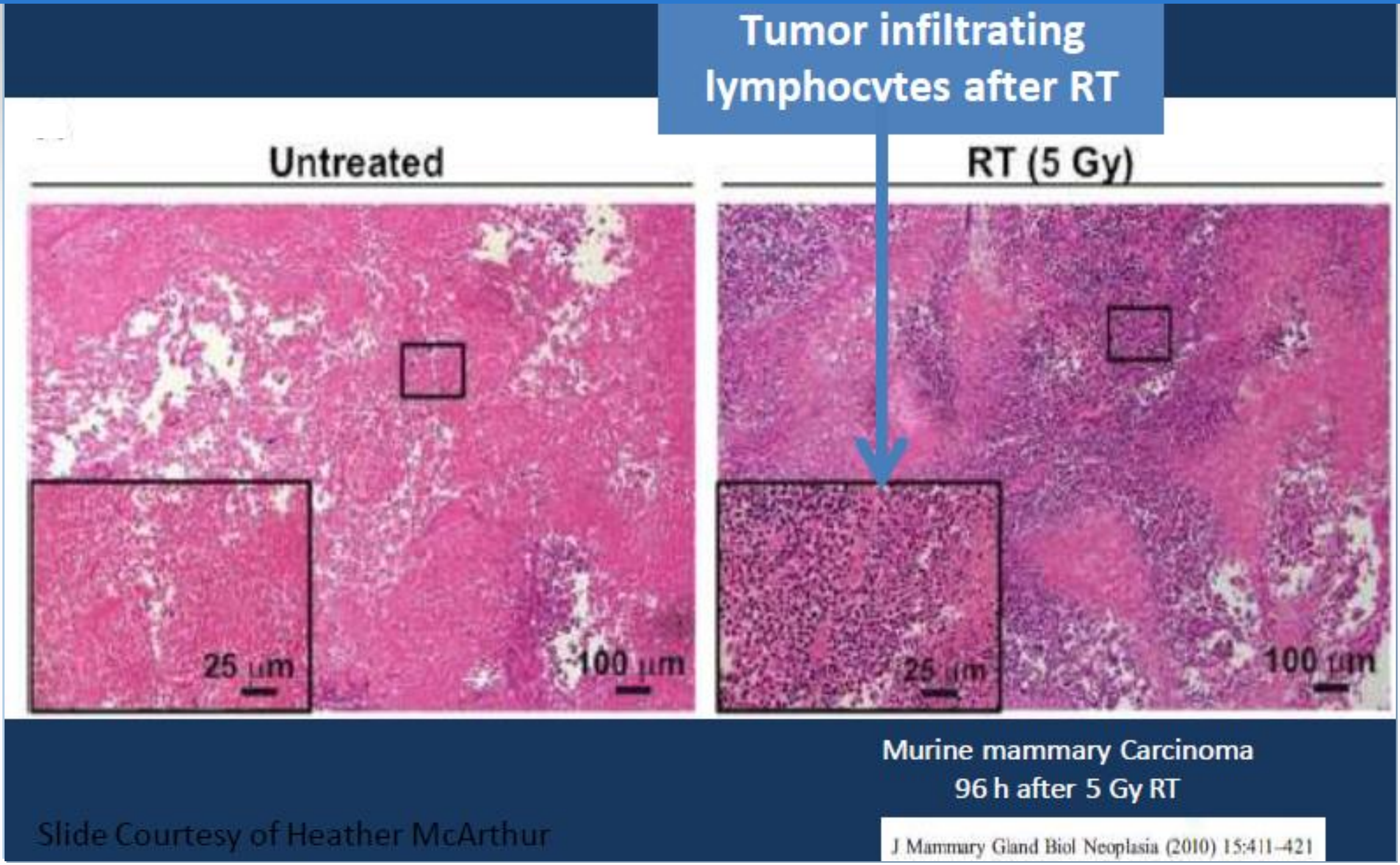


Anonimous,
San Francesco Church, Matera, Italy

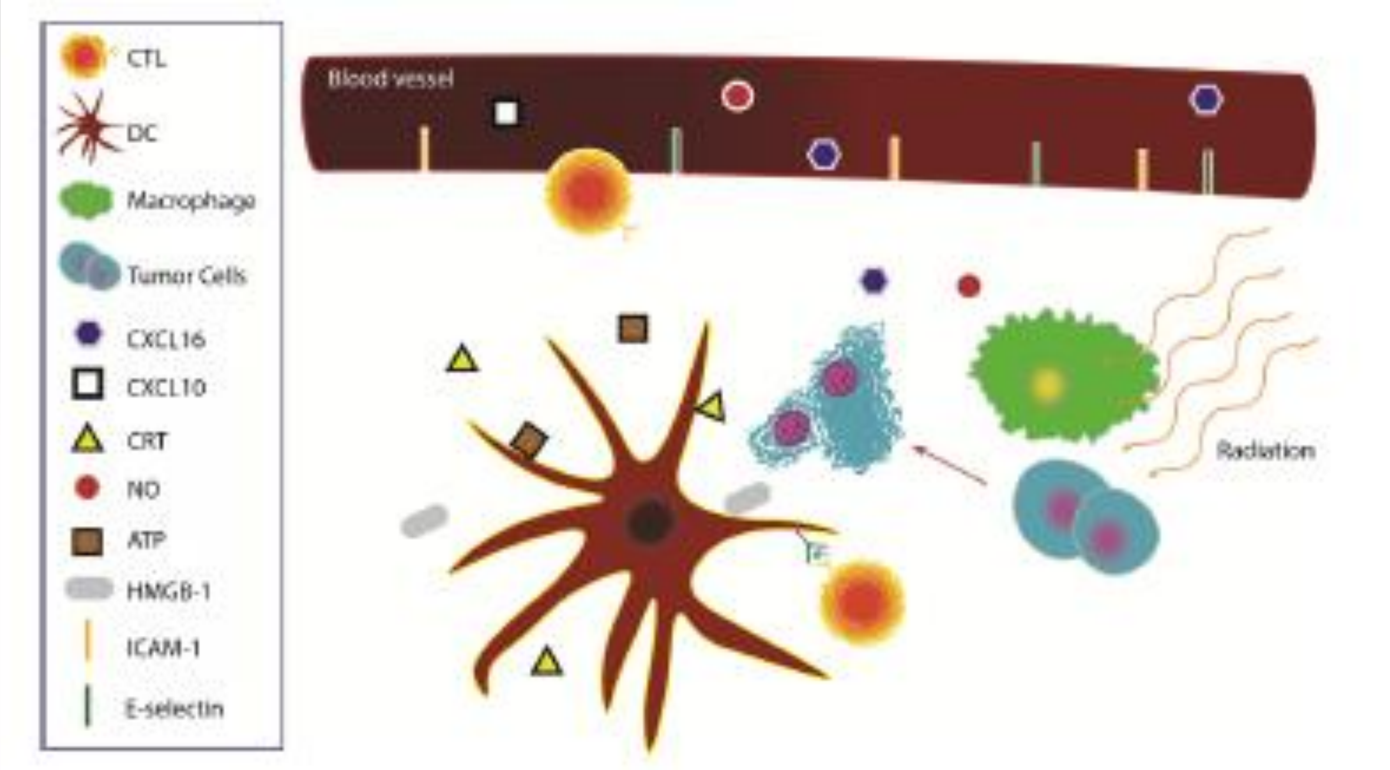
- IDC, T1N0M0, age ≥ 60 year old
- ER+, HER2-, no LVI, no EIC
- 48.0 GyE, 52.8 GyE, 60.0 GyE
- Four fractions in a week
- 12.0 GyE, 13.2 GyE, 15.0 GyE
- Surgery 90 days after
- 14/21 pCR (66%)
- 0ne PD
- No G3 skin toxicity

Karasawa K et al, Int J Radiat Oncol Biol Phys, 96:25 suppl 2016

RT is immunogenic

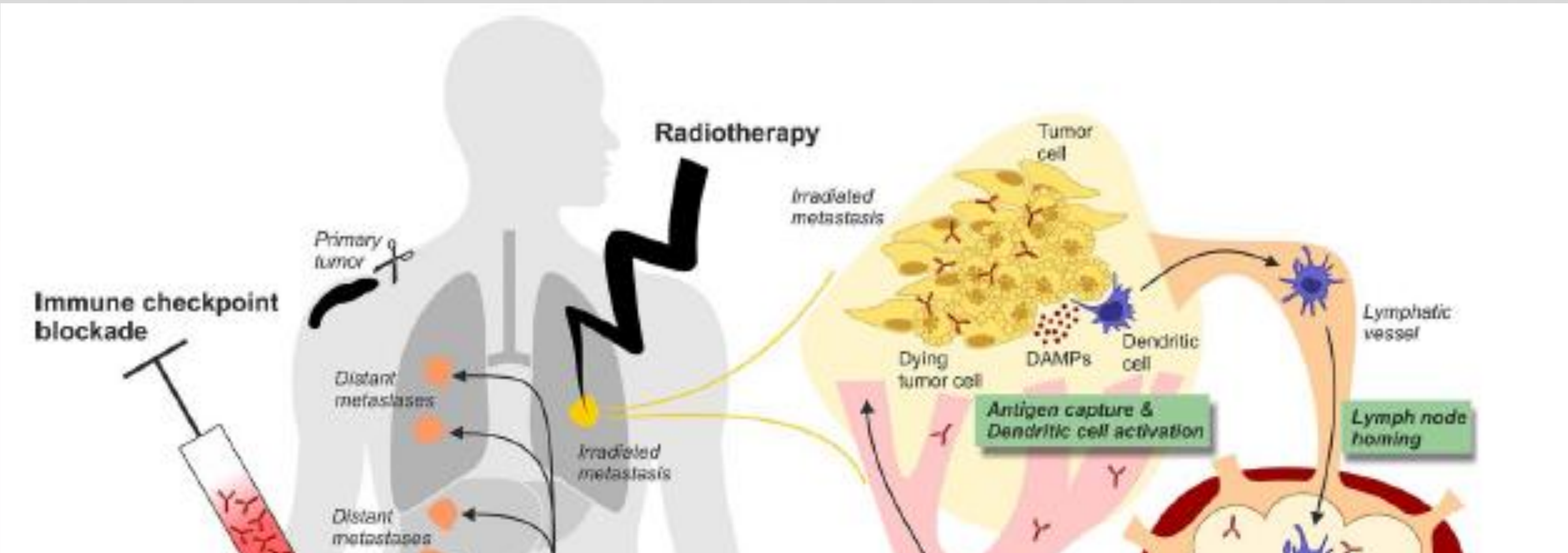


Immunogenic cell death



Localized RT induces cell death and release of immunogenic factors, which subsequently triggers the release of a number of endogenous damage-associated molecular patterns (DAMPs)

RT-induced ascopal effects and out-of-field lesion regression



Cytotoxic T Lymphocyte Antigen 4 (CTLA-4)
Ipilimumab
Anti-Programmed Cell Death 1 (PD-1)
Programmed Death-Ligand 1 PD-L1)
Nivolumab/Pembrolizumab

Thank You very much !!!!