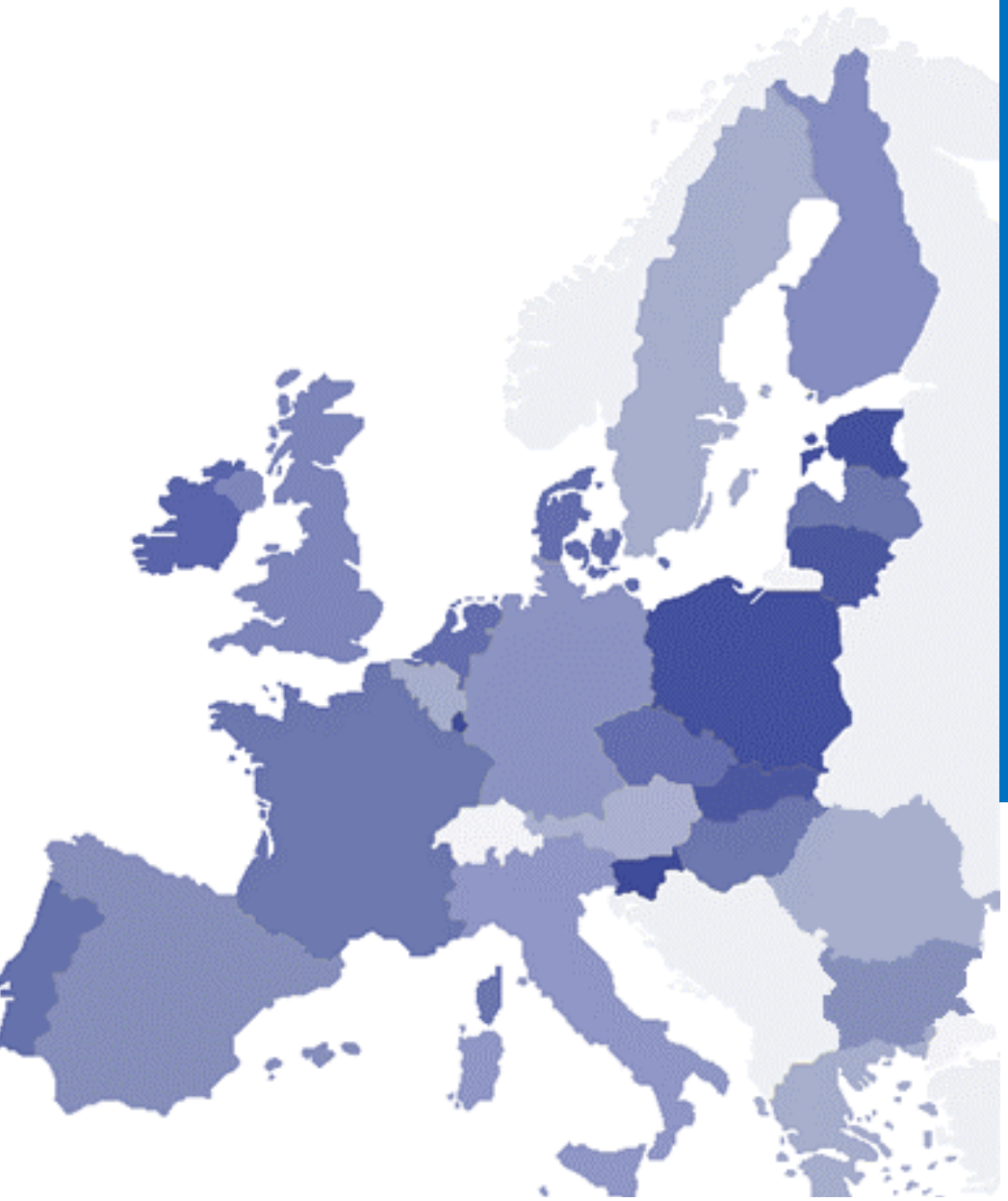


European Results or Progresses (HIRO and CNAO)

ENLIGHT

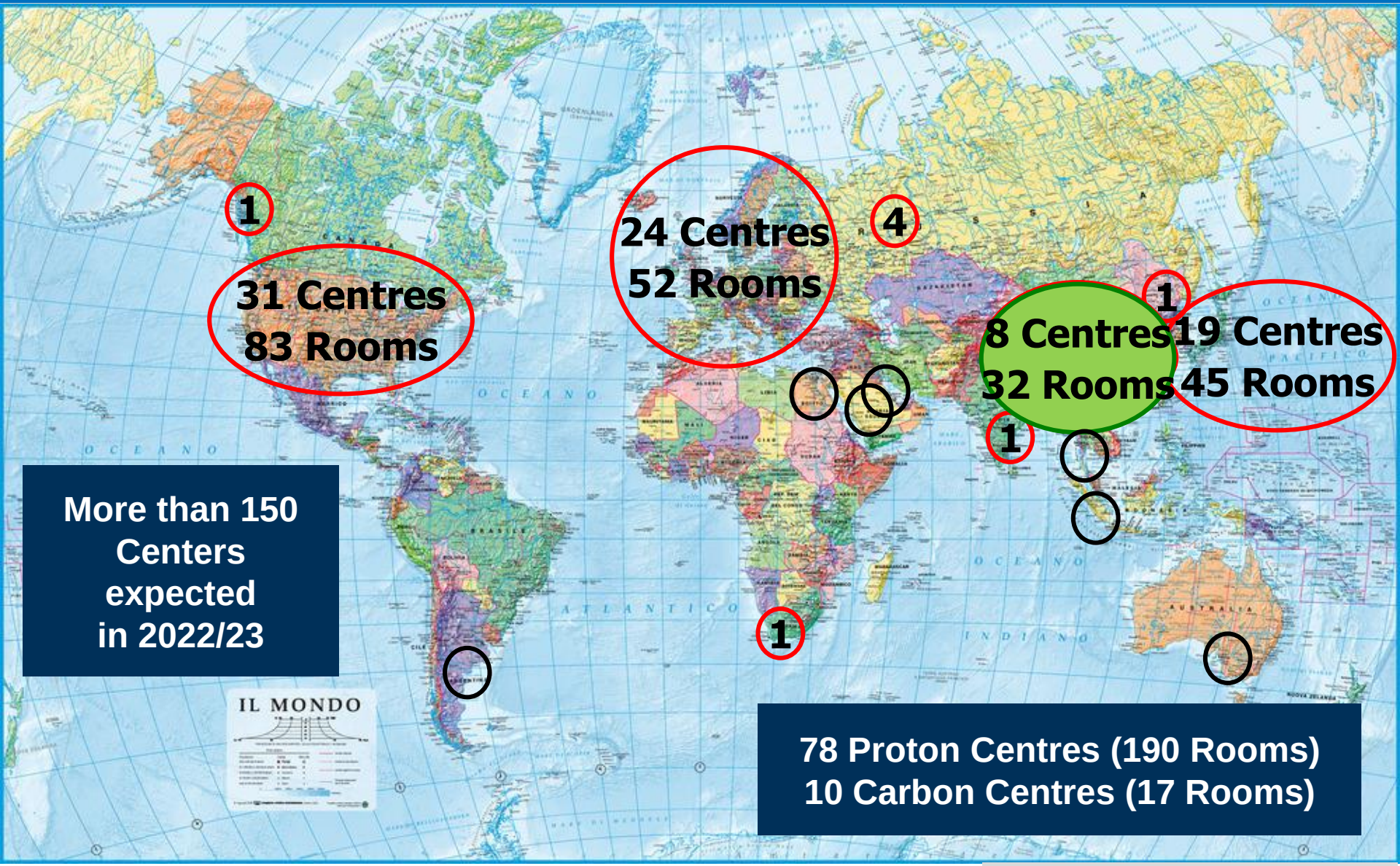
Roberto Orecchia

Centro Nazionale di Adroterapia Oncologica (CNAO) Pavia, Italy

Sistema Sanitario Regione Lombardia

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

Hadrontherapy (I)

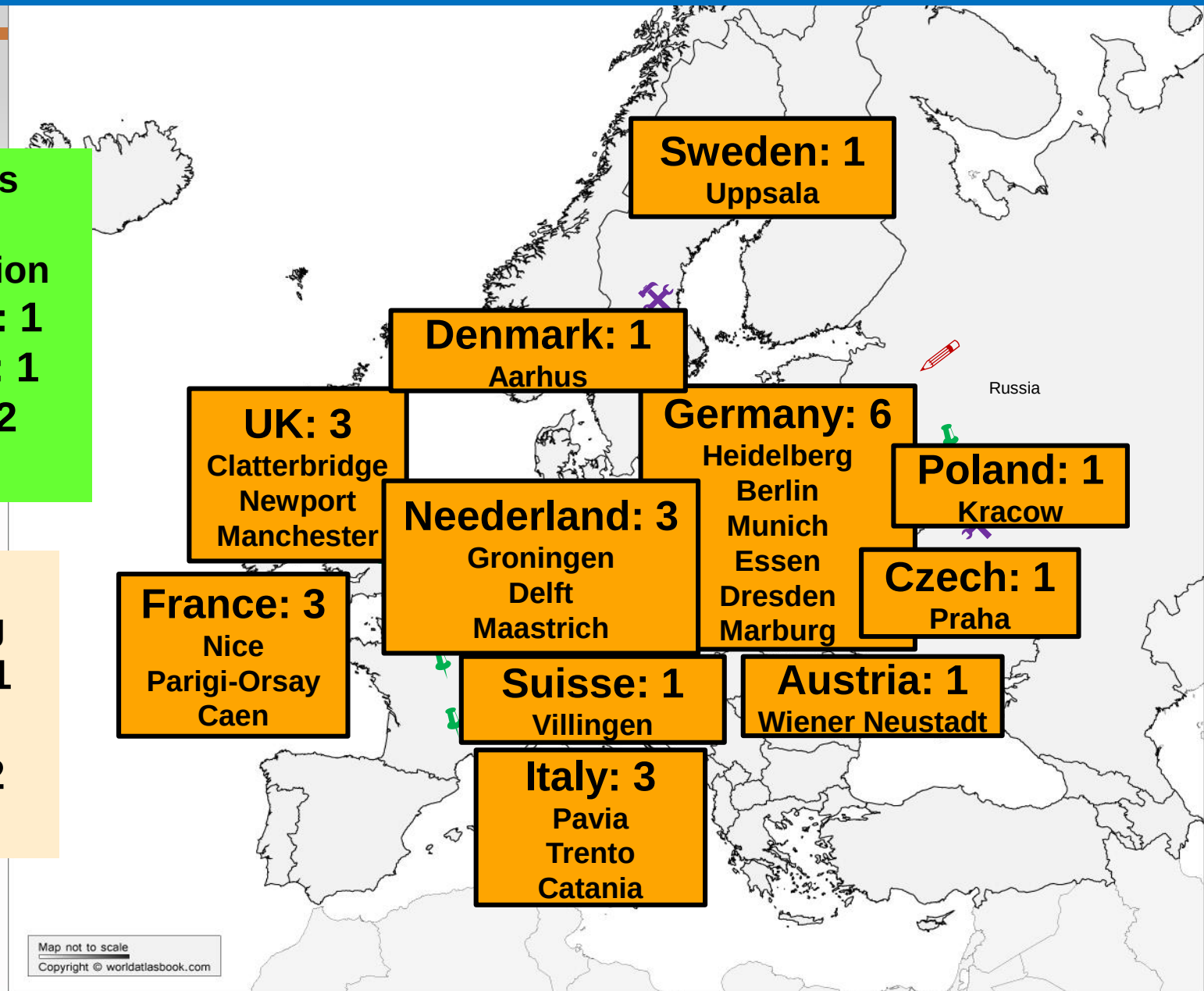


PTCOG web-site, April 2019

Hadrontherapy (II)

8 centers under construction
Belgium: 1
Slovack: 1
Spain: 2
UK: 4

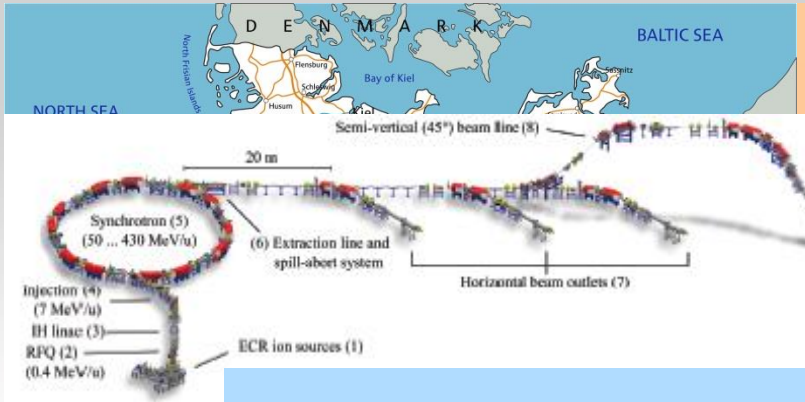
6 centers in planning
Belgium: 1
Italy: 1
Norway: 2
Suisse: 2



Hadrontherapy (III)

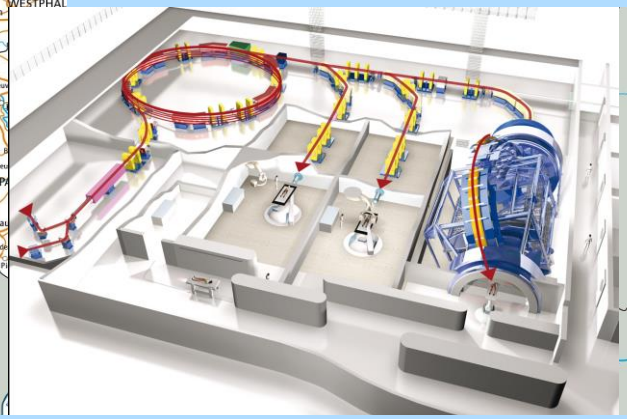
Country	Number Inhabitants	Room/Number Inhabitants
Denmark	5.770.000	1.900.000
Czech Rep	10.580.000	2.100.000
Suisse	8.500.000	2.200.000
Austria	8.800.000	2.900.000
Neederlands	17.100.000	3.400.000
Germany	82.800.000	5.900.000
UK	66.000.000	6.000.000
France	67.000.000	11.000.000
USA	327.900.000	3.900.000
Japan	127.000.000	2.800.000
Italy	60.060.000	12.000.000

Hadrontherapy (IV)



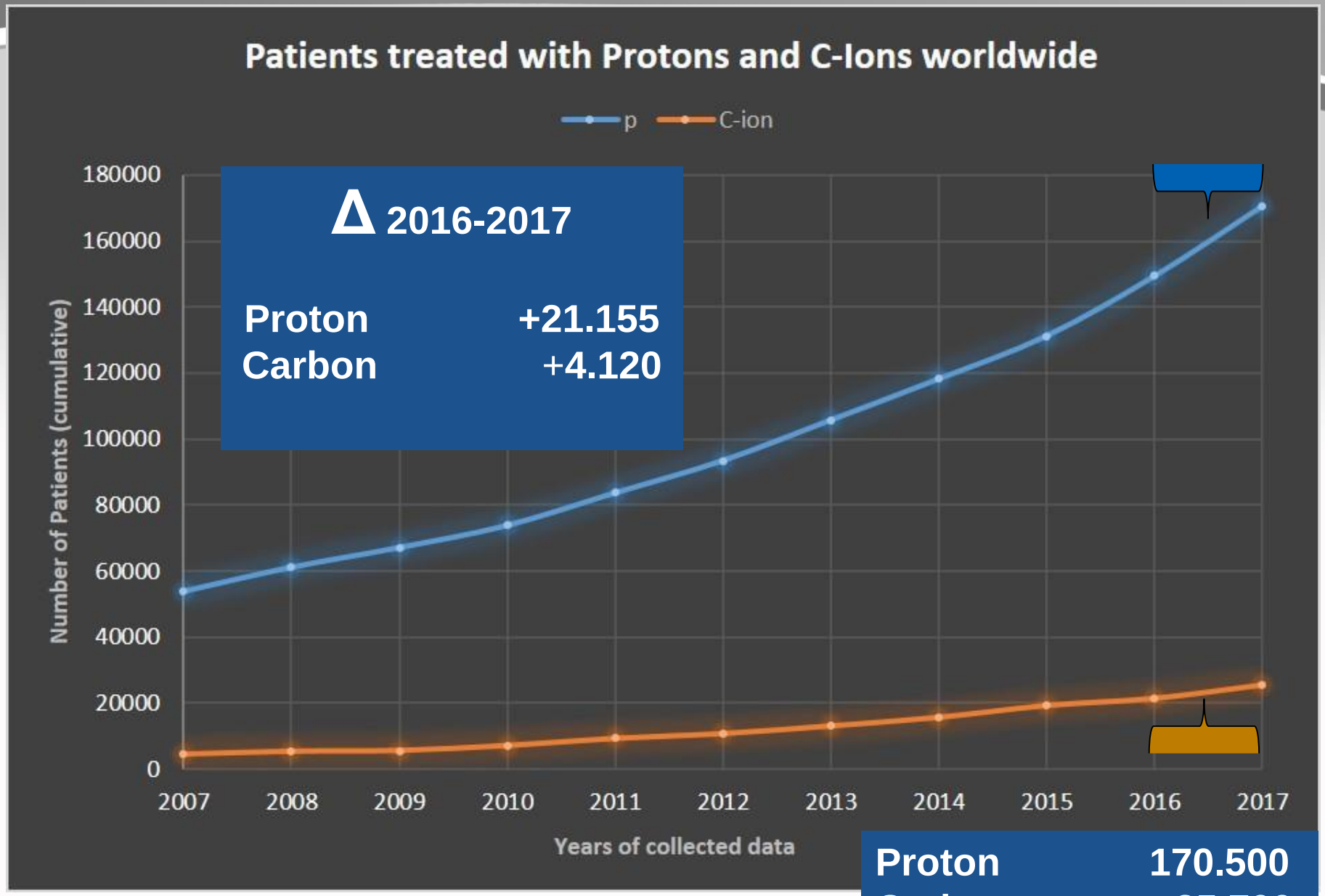
MIT Marburg

MedAustron
Wiener Neustadt



HIT Heidelberg

CNAO Pavia



Proton	170.500
Carbon	25.700
Helium	3500
Total	≈ 200.000

PTCOG web-site, April 2019

CIRT Clinical Trials (I)

63 clinical trials

The vast majority of the 63 trials were nonrandomized (84%)

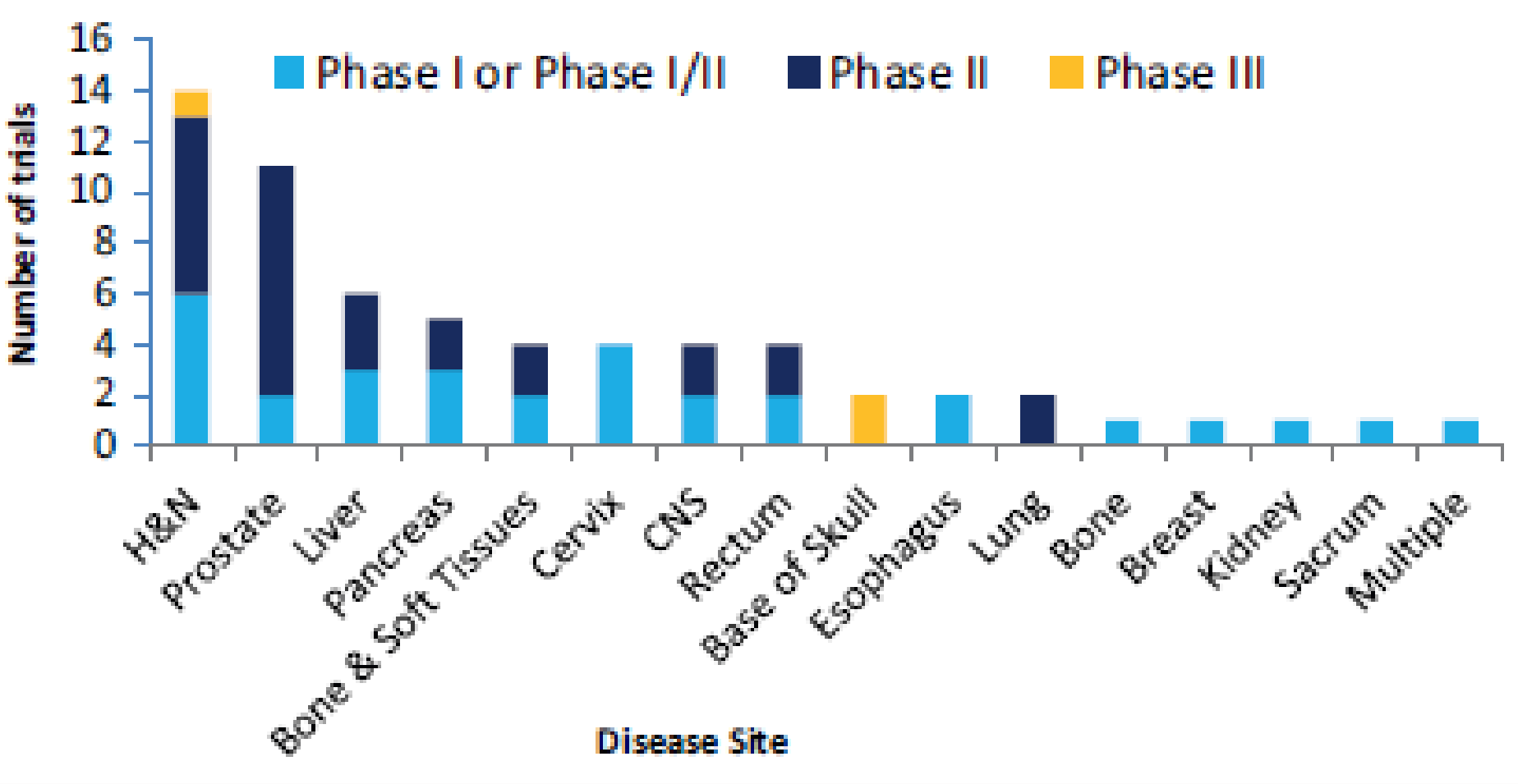
The median intended enrollment was 47 participants (from 6 to 689)

The trials with nonrandom allocation had a lower median enrollment goal of 40 participants compared with the larger median enrollment of 152 participants for those with random allocation

Nearly all of the clinical trials recruited adults only (54 trials; 86%) or recruited adults and pediatric patients (8 trials; 13%), and 1 trial (2%) exclusively studied children

Most trials were conducted in Japan (38 trials; 60%), followed by Germany (16 trials; 25%), China (7 trials. 11%), and Italy (1 trial; 2%). One trial (2%) of radioresistant head and neck (H&N) tumors was developed in France

CIRT Clinical Trials by tumor site



Lazar AA et al. Cancer 2018

CIRT Clinical Trials (II)

The primary endpoint for the majority of clinical trials (32 of 63; 51%) was adverse events (13 trials) or toxicity and/or dose response (19 trials), followed by LC in 15 trials (24%), PFS in 9 trials (14%), and OS in 7 trials (11%).

Of the 10 randomized trials, 1 phase II trial (10%) included OS as the primary endpoint, 2 (20%) used PFS as an endpoint, 4 (40%) used an adverse event or toxicity and/or a dose-response endpoint, and 3 (30%) focused on LC

The 10 randomized clinical trials, 30% were classified as phase III, and those phase III trials represented 5% (n = 3 of 63 trials) of all trials involving CIRT.

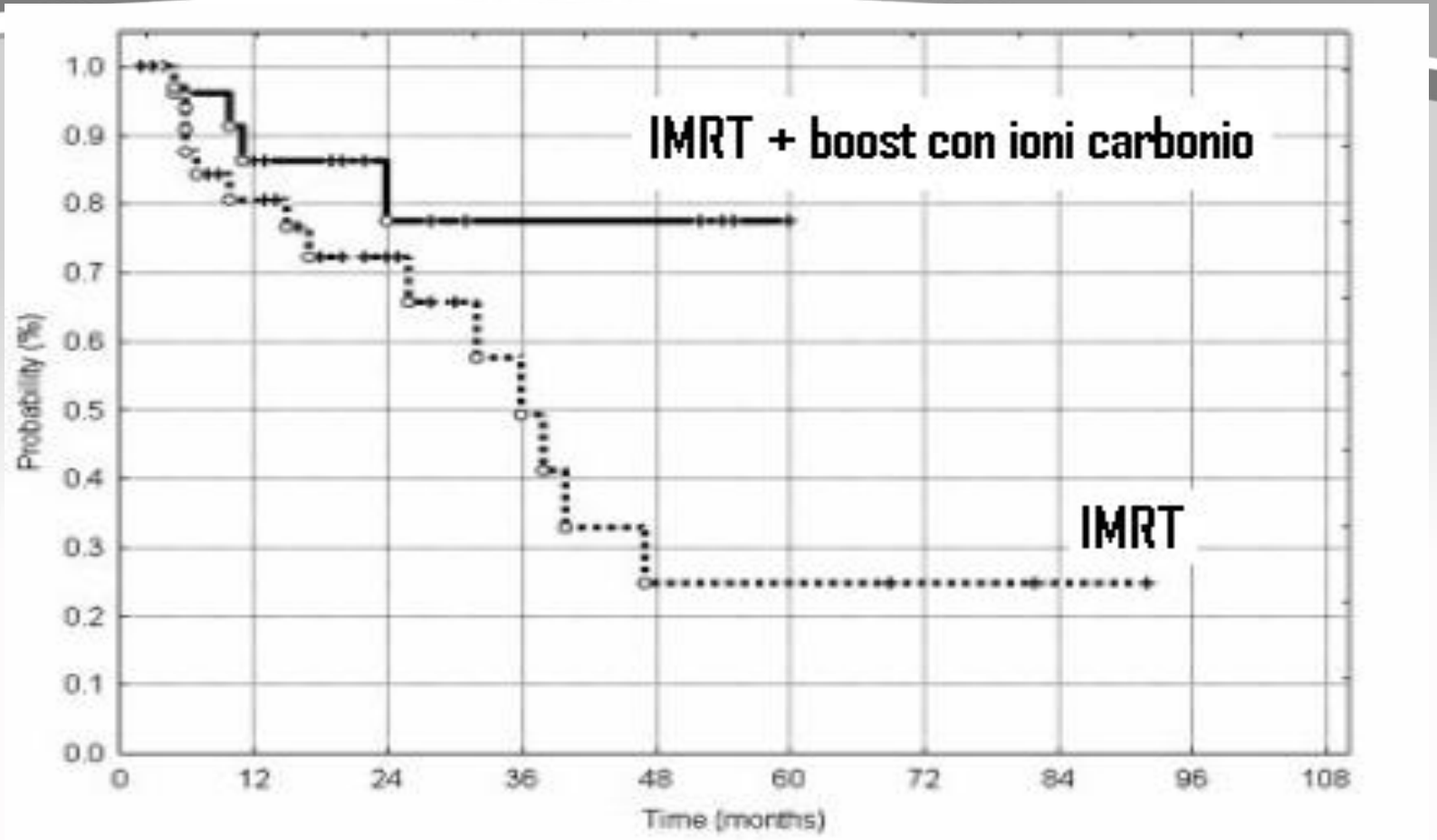
Two nonrandomized trials and a single randomized trial were considered completed, whereas 49% were still recruiting participants. Nine trials (14%) were not yet recruiting, 7 trials (11%) were no longer recruiting, 9 trials (14%) had unknown recruitment status, and 3 trials (5%) were terminated before completion

Some ongoing CIRT Clinical Trials

Table Ongoing Randomized Clinical Trials Comparing C-ions to Either Protons or Photon Therapy

Brief Title	ID	Sponsors	Phase	Condition	Arm 1	Arm 2
Trial of proton vs carbon ion radiation therapy in patients with chondrosarcoma	NCT01182753	Heidelberg University, Germany	III	Low and intermediate grade chondrosarcoma of the skull base	Protons	C-ions
Randomised trial of proton vs carbon ion radiation therapy in patients with chordoma	NCT01182779	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	C-ions
C-ion radiotherapy for glioblastoma	NCT01165671 CLEOPATRA	Heidelberg University, Germany	II	Primary glioblastoma	Protons **	C-ions **
Ion prostate irradiation	NCT01641185 IPI	Heidelberg University, Germany	II	Prostate cancer	Protons	C-ions
Ion irradiation of sacrococcygeal chordoma	NCT01811394 ISAC	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	C-ions
Randomized C-ions vs IMRT for radioresistant tumors	NCT02838602 ETOILE	Lyon University Hospitals, France	III	Adenoid cystic carcinoma and sarcomas	IMRT	C-ions
Prospective trial comparing carbon ions to IMRT in pancreatic cancer	BAA-N01C M51007–51	NCI, USA	I/III	Locally advanced pancreatic cancer	x-rays*	C-ions*
Prospective multicenter randomized trial of carbon ion vs conventional radiotherapy for pancreas cancer	CIPHER	Toshiba and UT Southwestern, Dallas, TX	III	Locally advanced pancreatic cancer	x-rays*	C-ions*

Durante M & Debus J, Sem Radiat Oncol 2018



GSI, Darmstadt. Adenoid Cystic Carcinoma (ACC)

IMRT vs. IMRT + carbon ion boost

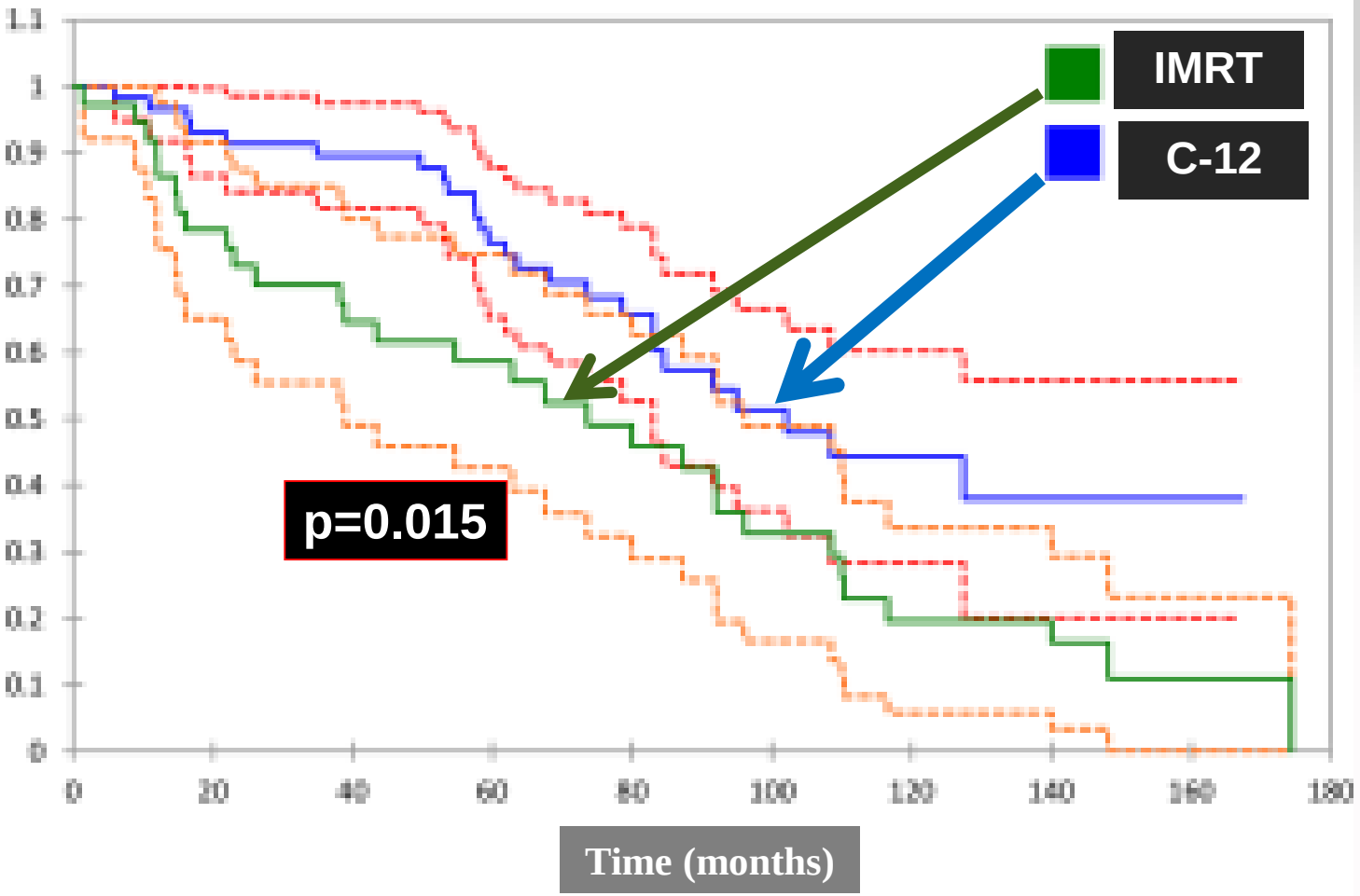
LC at 4 years 77.5% vs. 24.6%

Schulz-Ertner et al, IJROBP 2003

ACC. Long-term OS

GSI/HIT

10-year Overall Survival

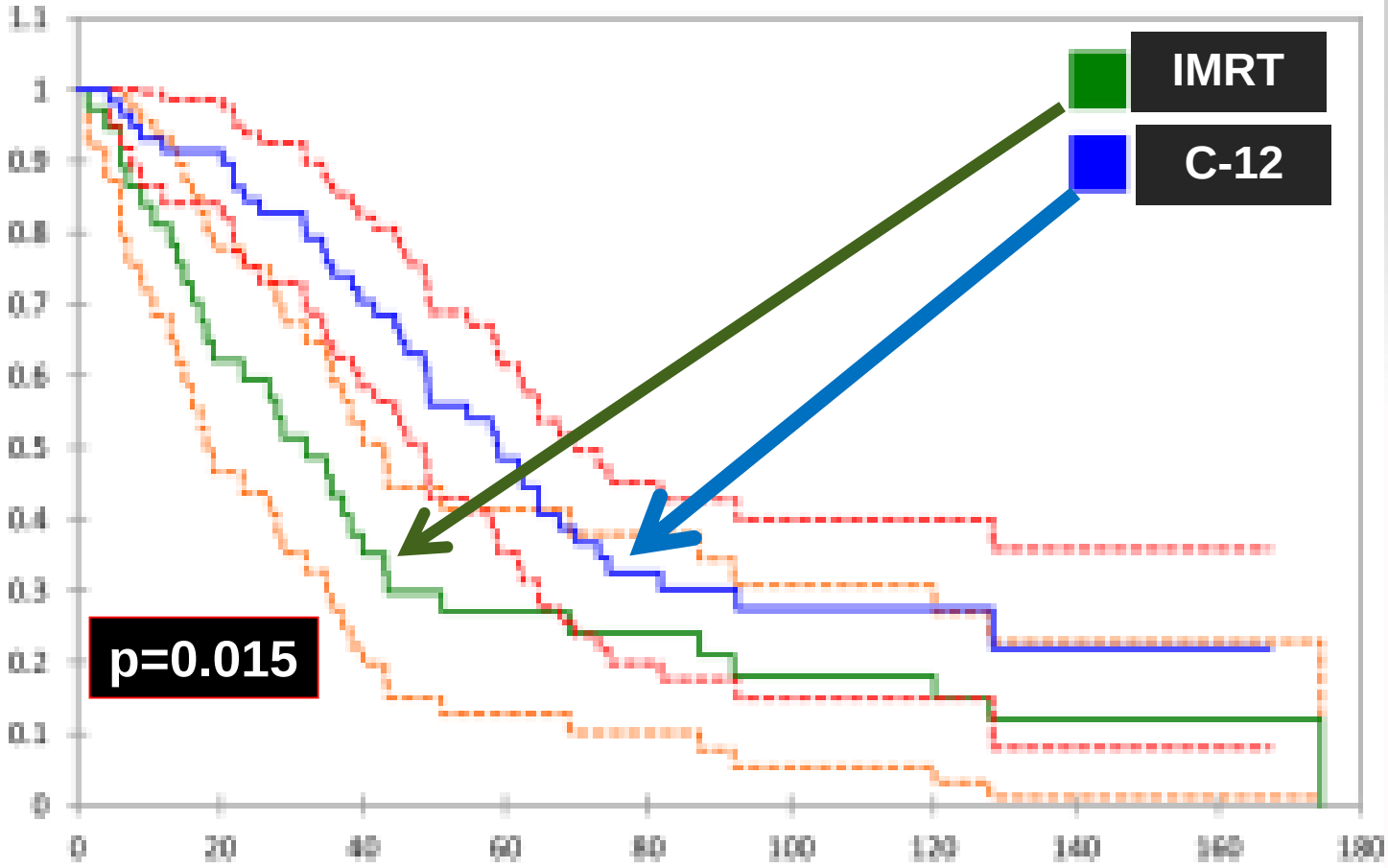


Jensen A et al, Cancer 2014; Jensen A et al, Radiother Oncol 2015

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

Raster-scanned carbon ion therapy for malignant salivary gland tumors: acute toxicity and initial treatment response

Alexandra D Jensen[1*], Anna V Nikoghosyan[1], Swantje Ecker[2], Malte Ellerbrock[2], Jürgen Debus[1], Klaus K Herfarth[1] and Marc W Münter[1]

Background and purpose: To investigate toxicity and efficacy in high-risk malignant salivary gland tumors (MSGT) of the head and neck. Local control in R2-resected adenoid cystic carcinoma was already improved with a combination of IMRT and carbon ion boost at only mild side-effects, hence this treatment was also offered to patients with MSGT and microscopic residual disease (R1) or perineural spread (Pn+).

Methods: From November 2009, all patients with MSGT treated with carbon ion therapy were evaluated. Acute side effects were scored according to CTCAE v.4.03. Tumor response was assessed according to RECIST where applicable.

Results: 103 patients were treated from 11/2009 to 03/2011, median follow-up is 6 months. 60 pts received treatment following R2 resections or as definitive radiation, 43 patients received adjuvant radiation for R1 and/or Pn+. 16 patients received carbon ion treatment for re-irradiation. Median total dose was 73.2 GyE (23.9 GyE carbon ions + 49,9 Gy IMRT) for primary treatment and 44.9 GyE carbon ions for re-irradiation. All treatments were completed as planned and generally well tolerated with no > CTC°III toxicity. Rates of CTC°III toxicity (mucositis and dysphagia) were 8.7% with side-effects almost completely resolved at first follow-up.
47 patients showed good treatment responses (CR/PR) according to RECIST.

Conclusion: Acute toxicity remains low in IMRT with carbon ion boost also in R1-resected patients and patients undergoing re-irradiation. R2-resected patients showed high rates of treatment response, though follow-up is too short to assess long-term disease control.

Jensen A et al. Radiat Oncol 2011

COSMIC phase 2 trial, 54 pts

- **At 3-years,**

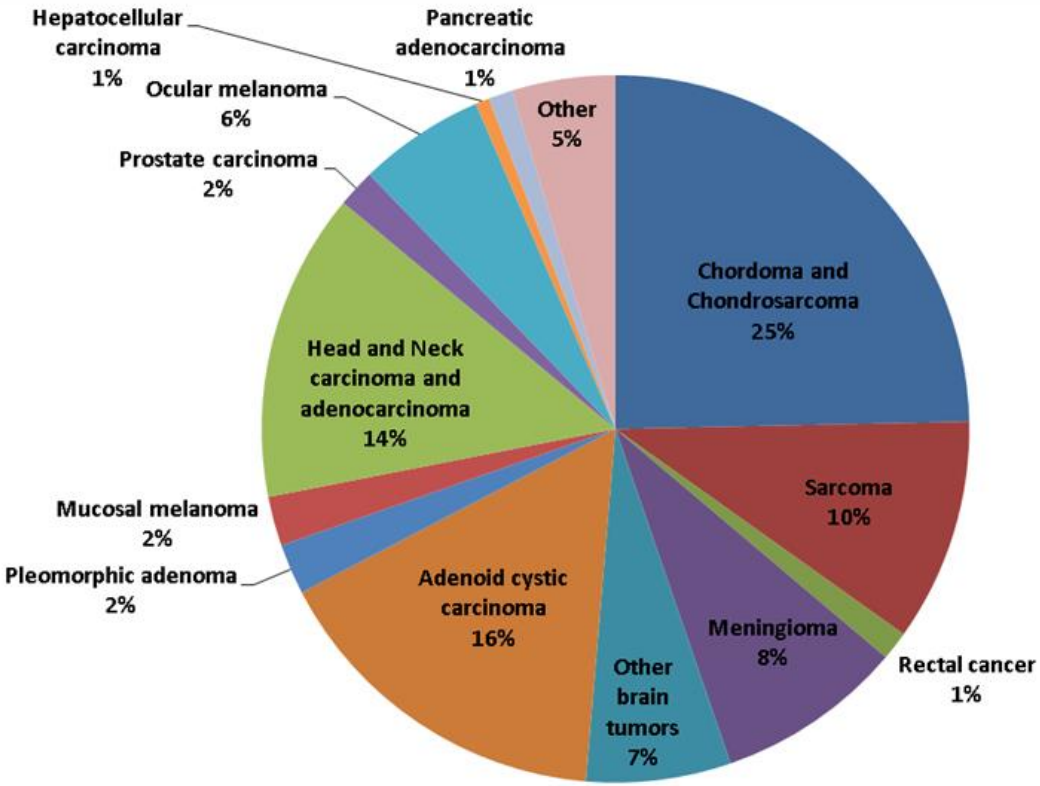
  LC 81.9%, PFS 57.9%, OS 78.4%

- **G3 Mucositis 26%**

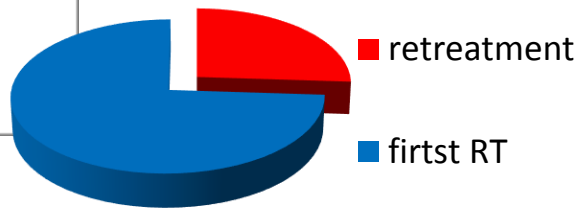
- **One G4 ICA hemorrhage, hearing impairment 25%, hearing loss 2%, adverse eye effects (no loss) 20%, one necrosis**

Jensen A et al, IJROBP 2015

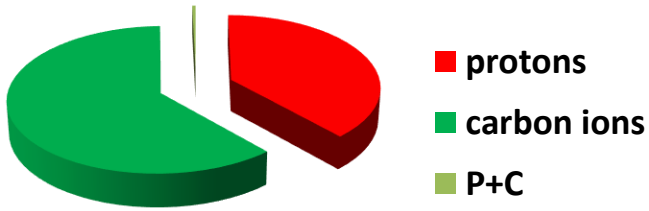
CNAO clinical experience



Total number of patients 2250



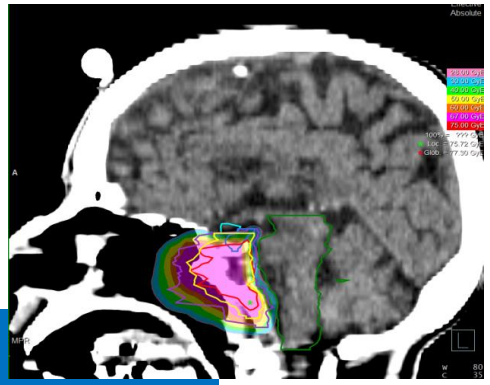
- **Radioresistant tumors**
- **Complex shape tumors**
- **Located close to critical structures**



Skull Base Chordomas

135 patients

RT Timing:	At primary diagnosis	79 %	(107/135)
	At recurrence	21%	(28/135)
Intent of RT treatment			
	Exclusive RT	4 %	(5/135)
	Post-operative RT	96%	(130/135)



Surgery 130 pts		
Macroscopic complete resection	15%	(19/130)
Macroscopic incomplete resection	85%	(111/130)

Proton	74 Gy (RBE) /37 fx/ 65 pts
Carbon ions	70.4 Gy(RBE) /16 fx/ 70 pts

Median volume GTV = 7.05 cc (0 – 99.3, range)

Median GTV carbon ions RT 12,9 cc ; Median GTV proton RT 4,5 cc

Brain involvement (abutment/compression)	Yes: 23 %	No: 77 %
Optic pathways involvement (abutment/compression)	Yes: 8 %	No: 92 %

Skull Base Chordomas

FU = 44 months (6 – 87, range)

Local Control (LC):

Protons	3 yrs LC 89 % 5 yrs LC 84 % 5 yrs - LC 100 % (19 pts with macroscopic complete resection)
Carbon ions	3 yrs LC 77 % 5 yrs LC 71 %

Overall Survival (OS):

Protons :	3 yrs LC 93 % 5 yrs LC 83 %
Carbon ions :	3 yrs LC 90 % 5 yrs LC 82 %

Skull Base Chordomas

Particle RT treatment failures

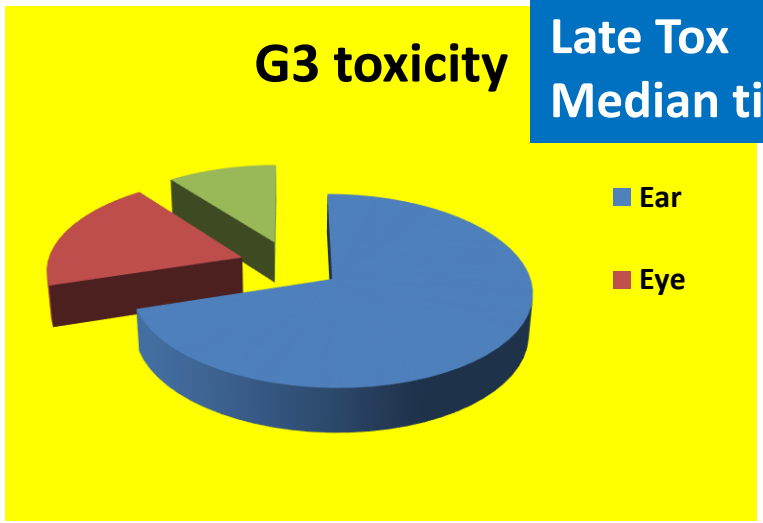
CARBON IONS RT 13/65 (21%) 11/13 in patients with brainstem/optic pathways involvement (abutting/compression)

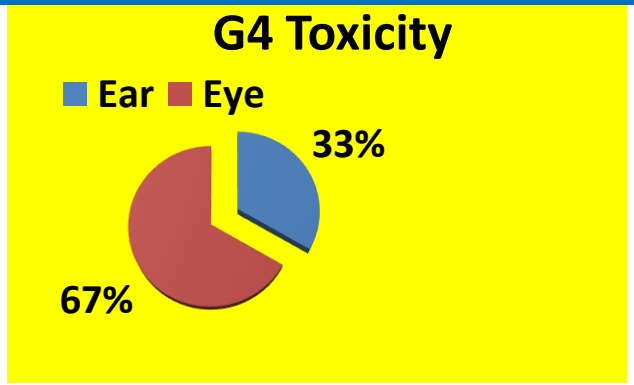
PROTON RT 8/70 (11%) 7/8 in patients with brainstem/optic pathways involvement (abutting/compression)

Acute Tox G ≥ 3 = 0

Late Tox G ≥ 3 = 11% (16 / 135) G3 = 13 ; G4 = 3

Median time to tox G ≥ 3 = 21 months (8 – 44, range)





Contents lists available at ScienceDirect

Radiotherapy and Oncology

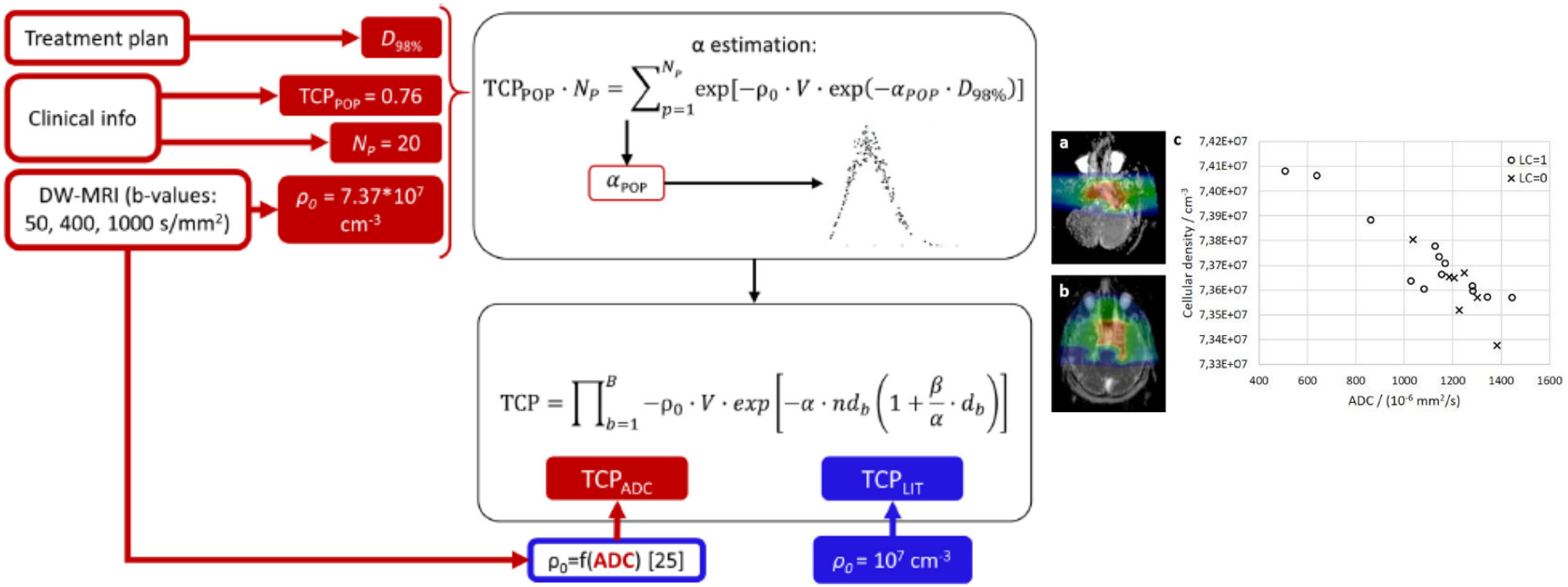
journal homepage: www.thegreenjournal.com

Original Article

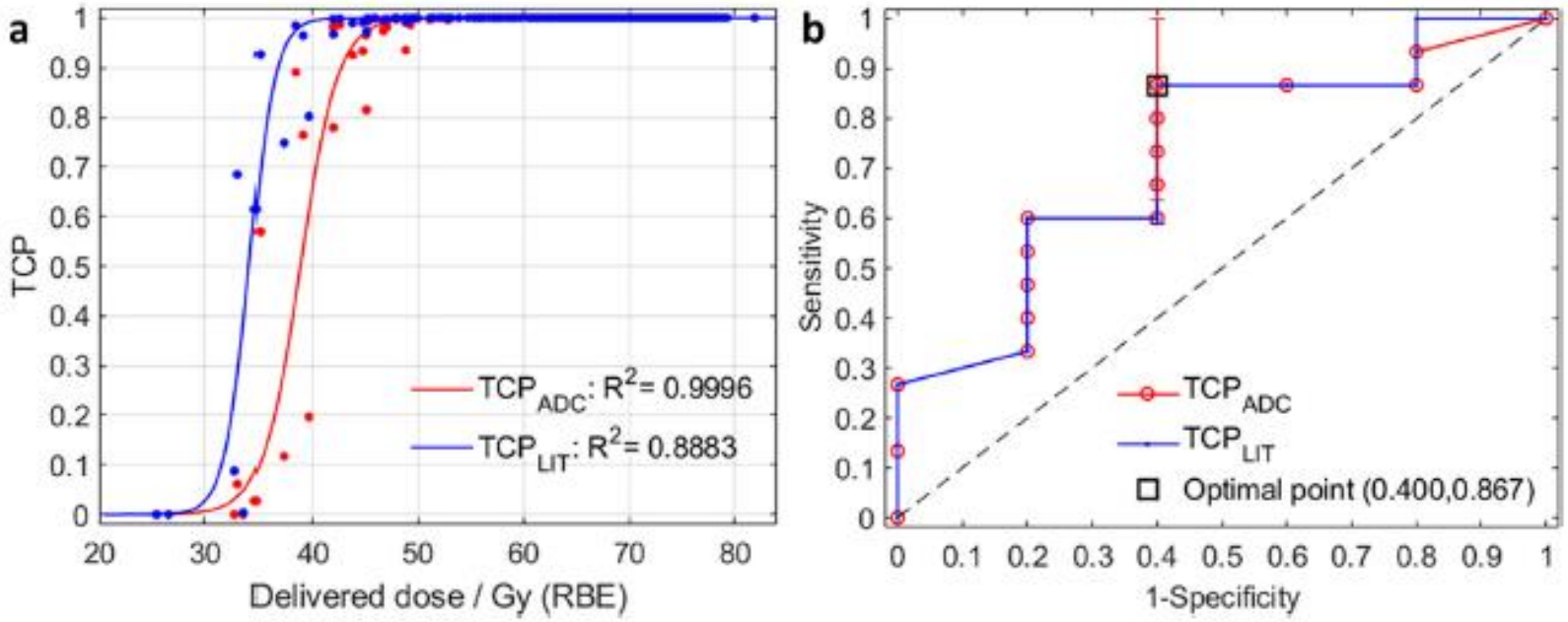
MRI-based tumour control probability in skull-base chordomas treated with carbon-ion therapy

Giulia Buizza [a,*], Silvia Molinelli [b], Emma D'Ippolito [b], Giulia Fontana [b], Andrea Pella [b], Francesca Valvo [b], Lorenzo Preda [b,c], Roberto Orecchia [b], Guido Baroni [a,b], Chiara Paganelli [a]

Purpose: To derive personalized tumour control probability (TCP) models, using diffusion-weighted (DW-) MRI for defining initial tumour cellular density in skull-base chordoma patients undergoing carbon-ion radiotherapy (CIRT).



Materials and methods: 67 patients affected by skull-base chordoma were enrolled for a standardized CIRT treatment (70.4 Gy (RBE) prescription dose). Local control information was clinically assessed. For 20 of them, apparent diffusion coefficient (ADC) maps were computed from DW-MRI and then converted into cellular density. Radiosensitivity parameters (α, β) were estimated from the available data through an optimization procedure, taking advantage of a relationship observed between local control and the dose received by at least the 98% of the gross tumour volume. These parameters were fed into two poissonian TCP models, based on the LQ model, being the first (TCP_{LIT}) computed from literature parameters and the second (TCP_{ADC}) enriched by a personalized initial cellular density derived from ADC maps.
Results: The inclusion of the cellular density derived from ADC into TCP_{ADC} yielded slightly higher dose values at which TCP = 0.5 (D_{50} = 38.91 Gy (RBE)) with respect to TCP_{LIT} (D_{50}34.16 Gy (RBE)). This suggested a more conservative approach, even if the prognostic power of TCP_{ADC} and TCP_{LIT}, tested with respect to local control, was equivalent in terms of sensitivity (0.867) and specificity (0.600).



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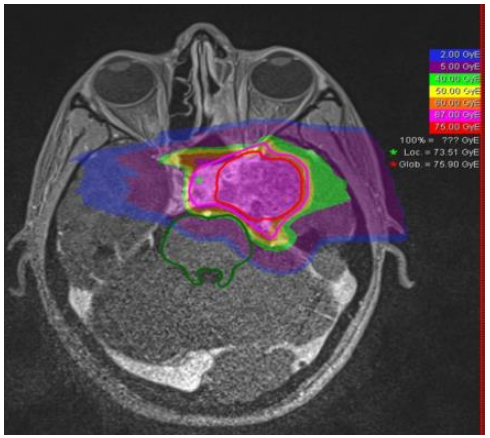
Skull Base Chondrosarcomas

35 patients



Intent of RT treatment

Exclusive RT:	51% (18/35)
Post-operative RT:	49% (17/35)

Proton	74 Gy (RBE) /37 fx/ 18 pts
Carbon ions	70.4 Gy(RBE) /16 fx/ 17pts

Median gross tumor volume (GTV) 16,4 cc (1,64 – 28,28, range)

Median follow-up 34 months (range, 5-70)

Local Control : 97%. (1-y, 3-y, and 5-y LC rates 100%, 96%, and 96%)

Overall Survival : 97%, 93% and 93% ,respectively

No pts developed late G4 treatment-related toxicity

G3 late toxicity: 2 (5.7%) of pts:

1 pz hearing impairment (expected)

1 pz optic neuropathy (sight reduction) (expected)

PT in Skull Base Chordomas and Chondrosarcomas

	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)
Munz et al, 1999							5 yrs: 73 (C) 5 yrs: 98 (CS)	41 (1-254)
Igaki 2004							3 yrs: 67.1 (C) 5 yrs: 46.0	69.3 (14.6-123.4)
Noel 2005					(1 - 125 cm3)	(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. (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)

Proton. 5-y Local Control

Chordoma 59-81%
Chondrosarcoma 79-98%

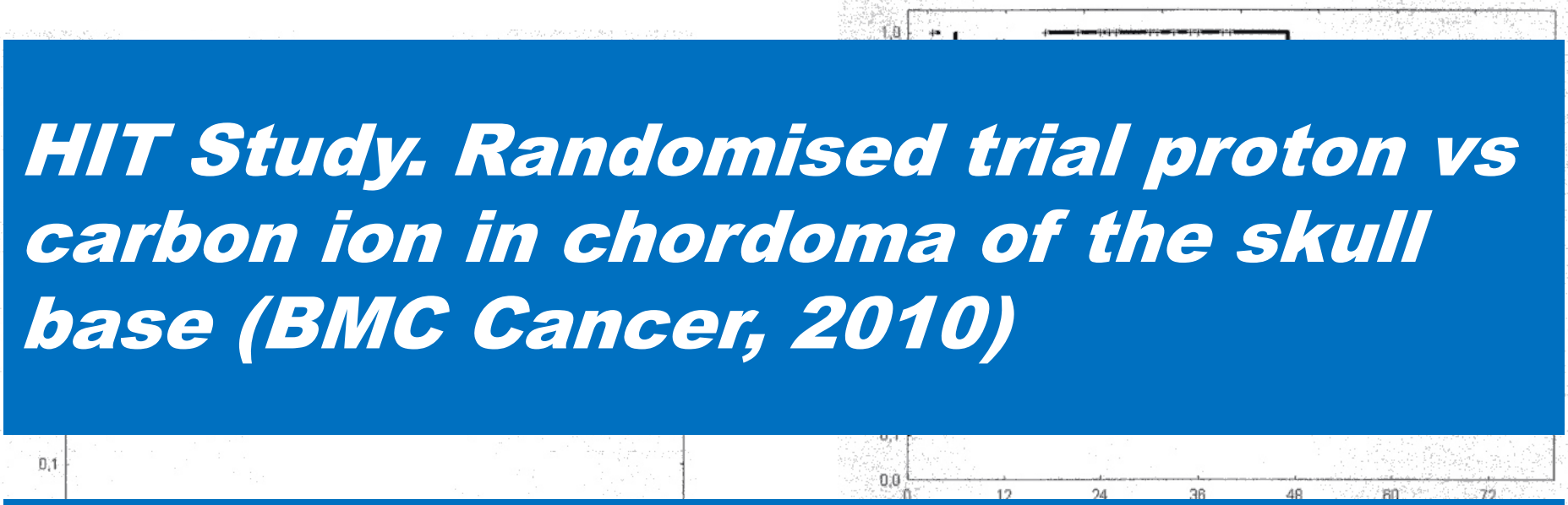
CIRT in Skull Base Chordomas and Chondrosarcomas

Mizoe et al, 2009	Chordoma	Carbon 60.8GyEq	LC 85% (5y) LC 64% (10y) OS 88% (5y) S 67% (10y)
Uh			LC 72% (5y) C 54% (10y) S 85% (5y) OS 75% (10y)
Uhl et al, 2014	Chondrosarcoma	Carbon 60 GyEq	LC 88% (5y) LC 88% (10y) OS 96% (5y) OS 79% (10y)

Carbon. 5-y Local Control

Chordoma 85-88%
Chondrosarcoma 88%

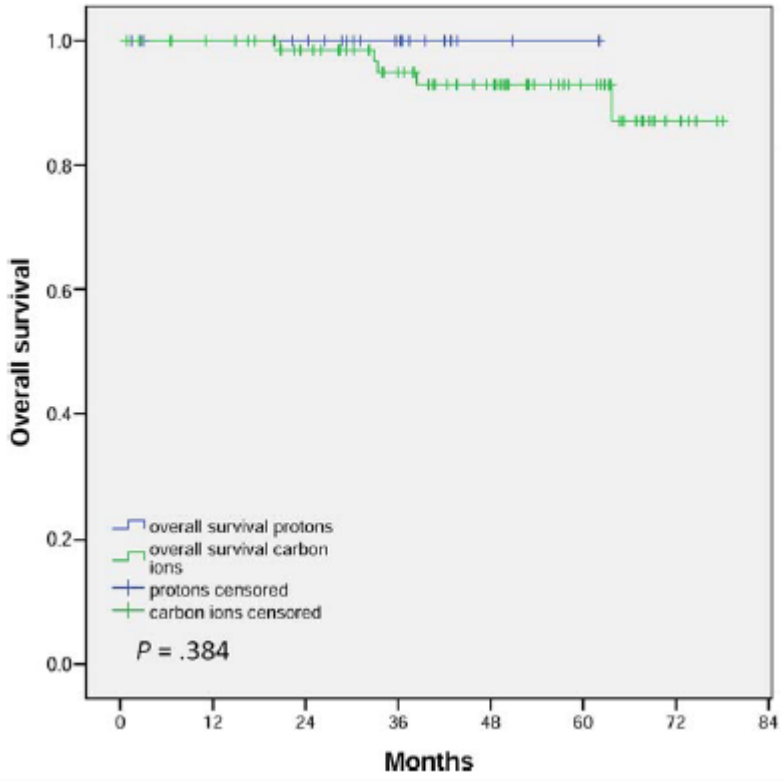
GSI pilot project → 1997-2001

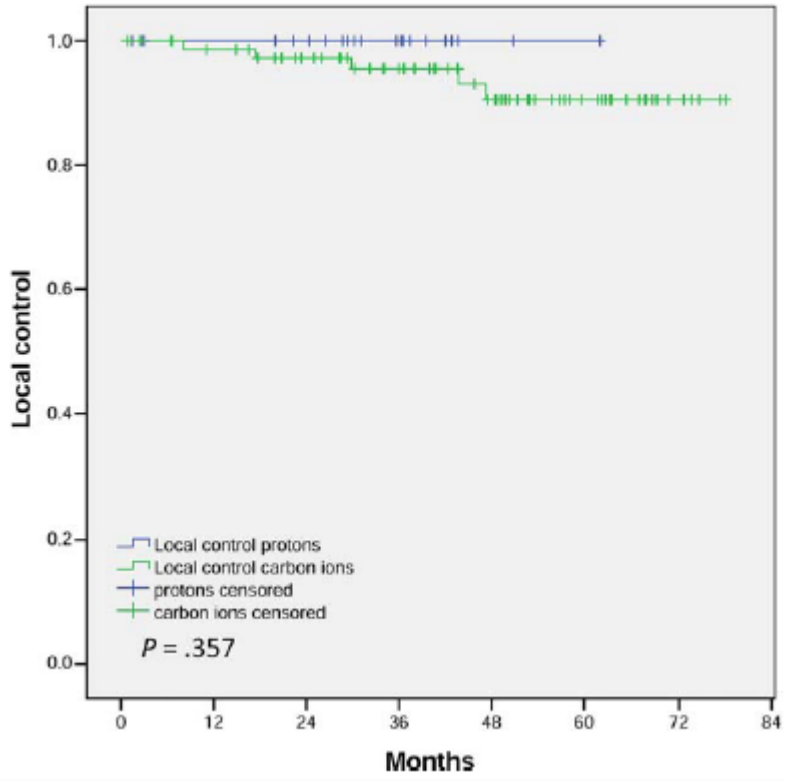


HIT Study. Randomised trial proton vs carbon ion in chordoma of the skull base (BMC Cancer, 2010)

HIT Study. Randomised trial proton vs carbon ion in low and intermediate grade chordrosarcoma of the skull base (BMC Cancer, 2010)

High Control Rates of Proton- and Carbon-Ion–Beam Treatment With Intensity-Modulated Active Raster Scanning in 101 Patients With Skull Base Chondrosarcoma at the Heidelberg Ion Beam Therapy Center





ND for subgroup analysis by:

age, clinical target volume, primary or recurrent tumor, sex, changes in double vision

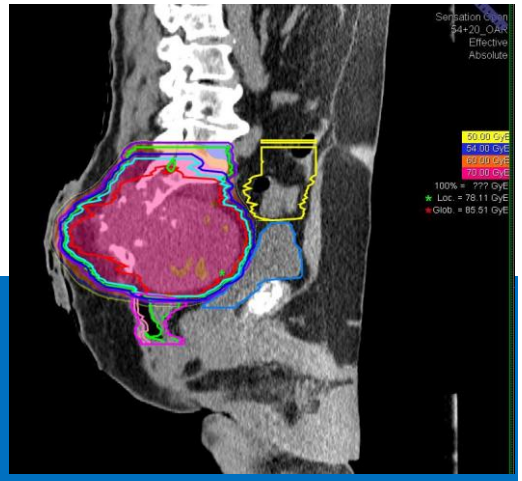
Mattke M et al, Cancer 2018

Sacral Chordomas

59 patients

Surgery Unresectable : 59/59

Carbon ions 70.4 -73,6 Gy(RBE) /16 fx



Median follow-up 25 months (range, 12-67 months)

Local Control : PR 60%
SD 26%
PD 14%

Late toxicity	Skin	Urinary	GI	Neuropathy
G0	38,6%	87,8%	92,2%	52,6%
G1	35,1%	8,8%	8,8%	26,3%
G2	22,8%	3,5%	---	21,1%
G3	3,5%	---	---	---

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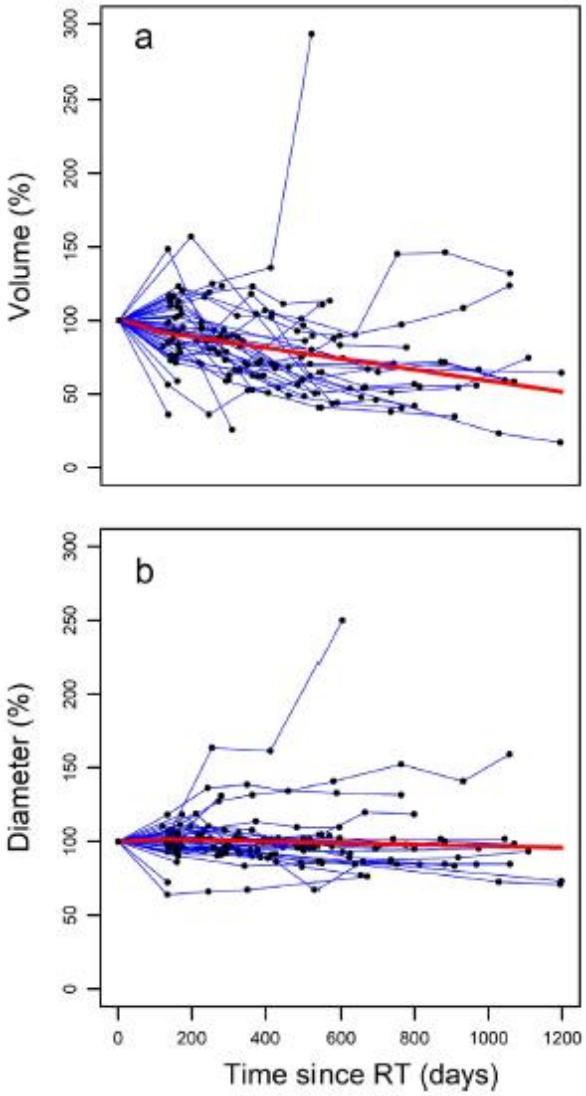
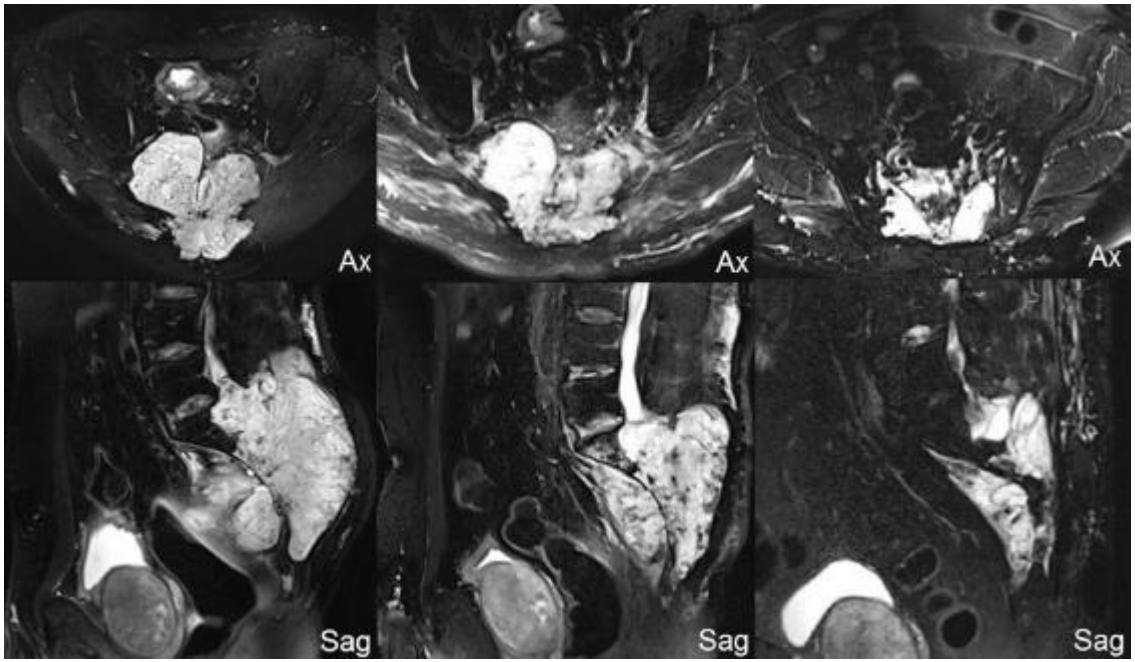
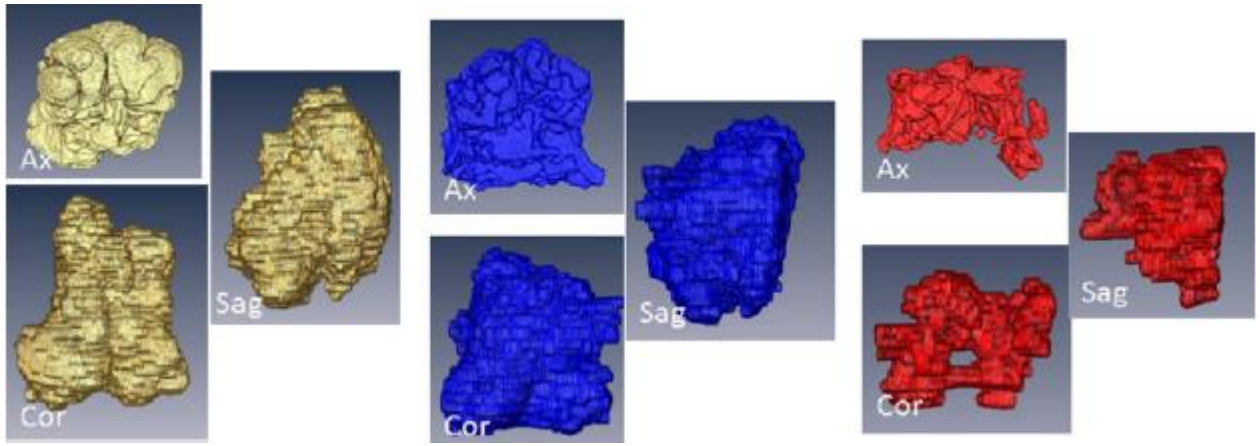
Original article

MRI evaluation of sacral chordoma treated with carbon ion radiotherapy alone

Preda L et al, 2018

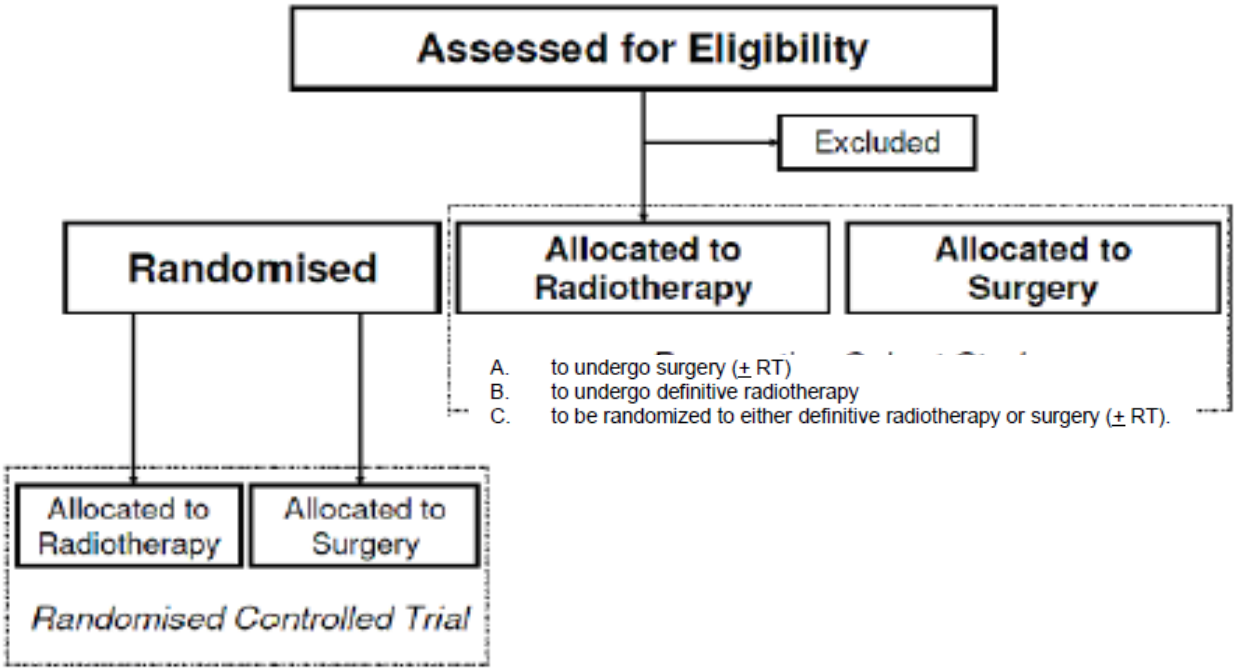






SAcral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO)

Schematic flow-chart



31 patients enrolled from February 2017
23 patients in ARM B C-12 @ CNAO

European Review for Medical and Pharmacological Sciences 2019; 23: 4002-4009

Carbon ions therapy as single treatment in chordoma of the sacrum. Histologic and metabolic outcome studies

G. EVANGELISTI[1], M.R. FIORE[3], S. BANDIERA[1], G. BARBANTI BRODANO[1], S. TERZI[1], M. GIROLAMI[1], V. PIPOLA[1], A. RIGHI[6], C. NANNI[2], S. FANTI[2], R. GHERMANDI[1], S. MOLINELLI[3], R. ORECCHIA[4], S. BORIANI[5], A. GASBARRINI[1]

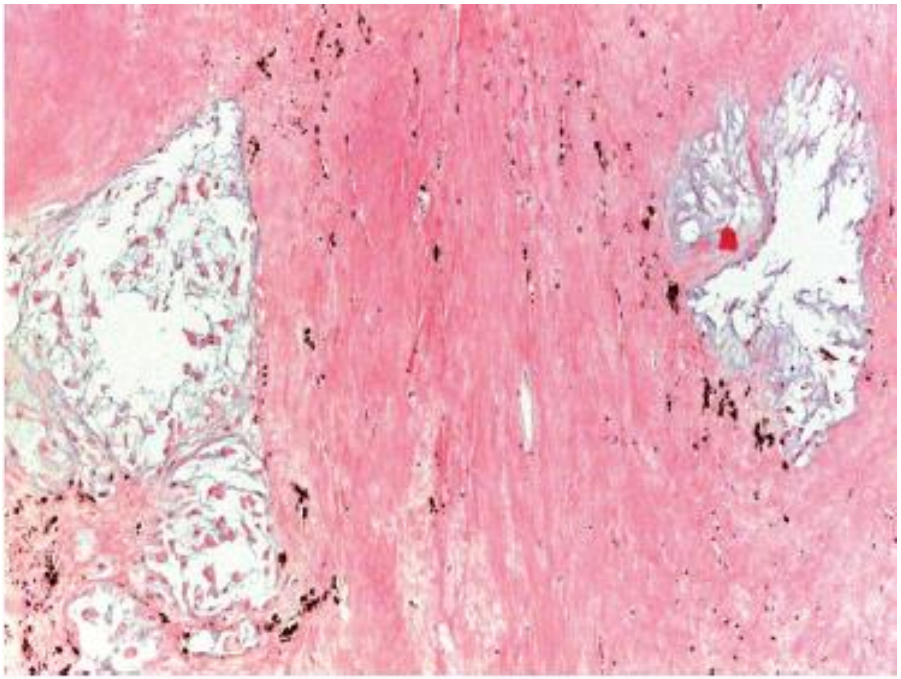


Figure 3. An example of chordoma post-CIRT with tumoral necrosis, fibrosclerosis associated with emosiderotic deposits without foci of viable chordoma (10X of original magnification).

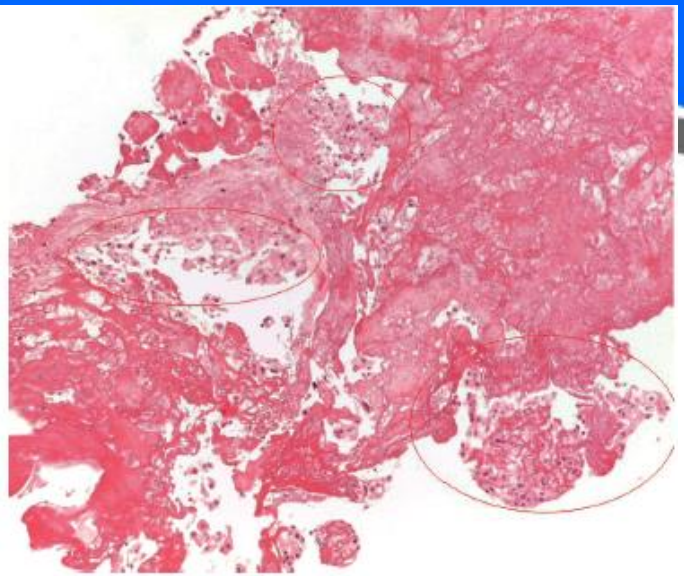


Figure 2. An example of chordoma post-CIRT where areas of necrosis and of fibrosclerosis are evident in the context of vital chordoma (circles) (10X of original magnification).

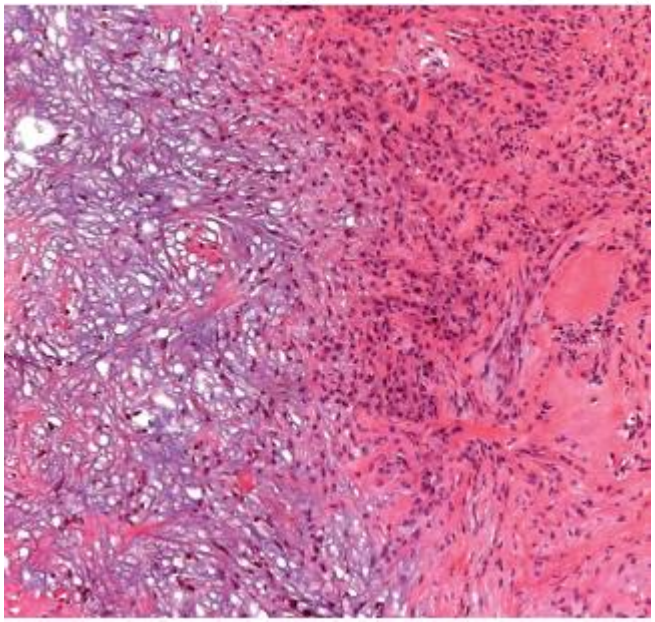


Figure 4. Dedifferentiated chordoma. **A**, On histology, typical features of chordoma with foci of necrosis and of fibrosclerosis is evident on the left with a change to an undifferentiated spindle cell sarcoma on the right (10x of original magnification).

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Characteristic	N=18
Mean age (range)	64.7 (83-43)
Male	12 (66.7%)
Female	6 (33.3%)
Spacer placement	3 (16.7%)
Proximal tumor extension	L5: 1 pts S1-S2: 10 pts S3-S4 or below: 7 pts

Toxicity

Eight patients out of 18 (44%) developed late neuropathy; of these 62.5% (5 patients) experienced mild paresthesia (G1 neuropathy), 37.5% (3 patients) developed a mild or severe pain (G2-G3) after CIRT.

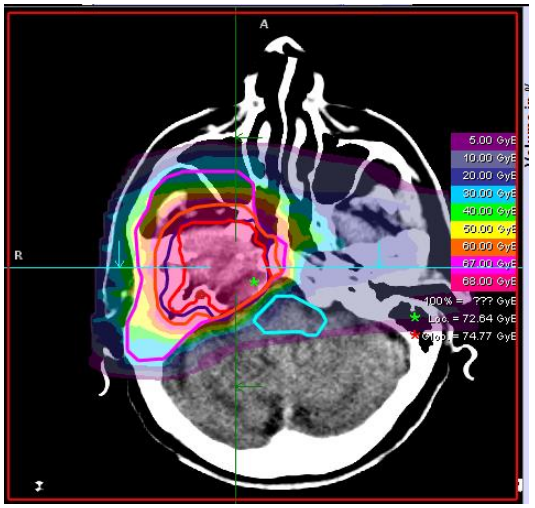
Six (33.3%) patients developed skin reactions; among these 5 developed erythema (G1) while 1 developed fibrosis (G2=1). One (5.5%) patient developed mild and sporadic urinary incontinence (G1), while 1 recovered from mild urinary incontinence. One (5.5%) patient developed late gastrointestinal toxicity (G2).

RESULTS: All histological analysis but 2 reported signs of necrosis and of fibrosclerosis after CIRT. One of these 2 patients turned into a dedifferentiated chordoma. Radiological partial response (PR) was observed in 10 patients (56.3%) and stable disease (SD) in 5 patients (28.3). Two patients (11%) had a local relapse.

The overall survival rate was 100% at 24 months. FDG PET CT after CIRT showed uptake decreasing compared with the baseline exam in all but one patient.

Adenoid Cystic Carcinoma (ACC)

128 patients



RT Timing:	At primary diagnosis	86% (110/128)
	At recurrence:	14% (18/128)
Intent of RT treatment		
	Exclusive RT:	38% (49/128)
	Post-operative RT:	62% (79/128)

Surgery	
Biopsy :	49/128
Macroscopic complete resection :	1/128
Macroscopic incomplete resection :	78/128

Carbon ions 68,8 Gy(RBE) /16 fx/4 fx/wk

PFS a 12 and 24 months was 81% and 67%

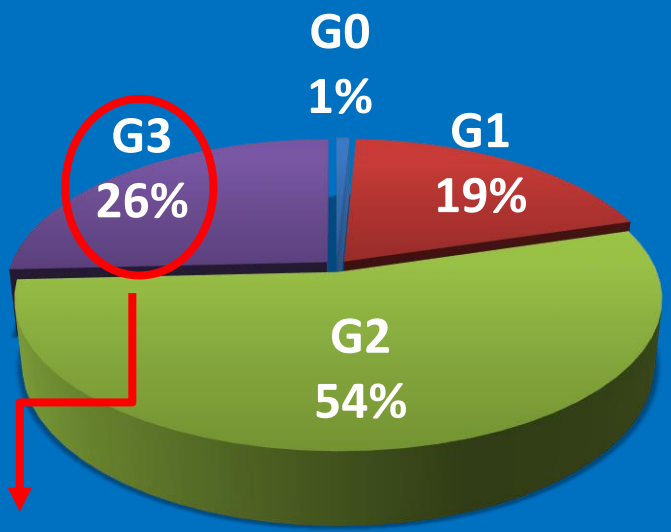
Distant Metastasis Free Survival 12 and 24 months 86% and 81%

OS at 12 and 24 months: 95% and 85%

Median OS time: 24 months

Adenoid Cystic Carcinoma (ACC)

Acute toxicity

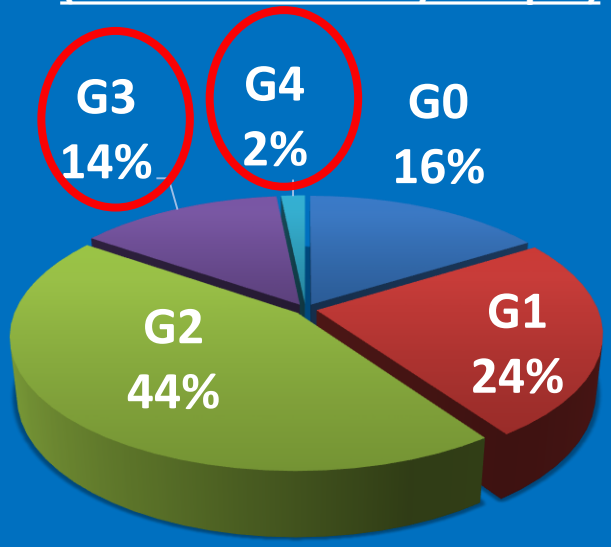


n 31 mucositis
n 2 hearing impairment
n 2 dermatitis (erythema)
n 1 bleeding, protective tracheotomy

No G4

Late toxicity

(evaluable for 124/128 pts)



n 17 G3: 3 visual loss (expected tox)
5 hearing loss (expected tox)
3 bone necrosis
3 soft tissue necrosis
2 neuropathy
1 mucositis

2 pts G4: 1 bleeding requiring surgery
1 epidural abscess

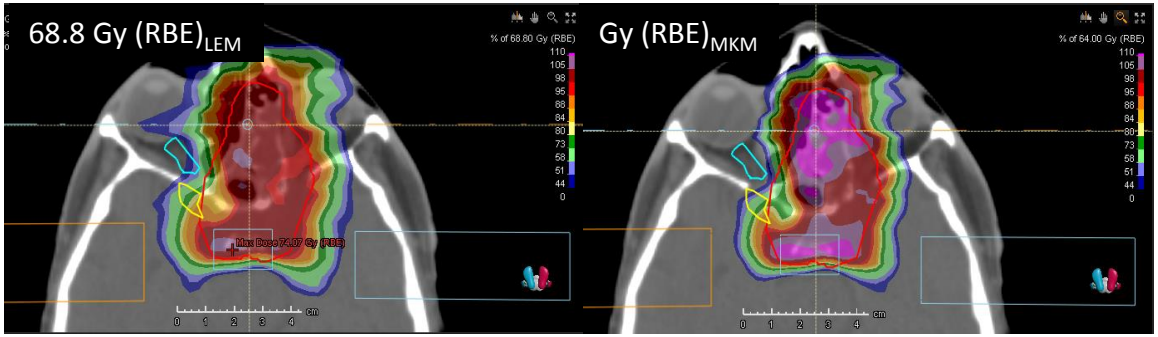
Adenoid Cystic Carcinoma (ACC)

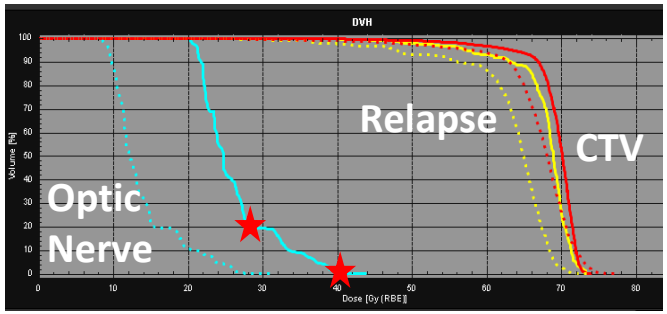
Patterns of failure

14 relapses close to OARs

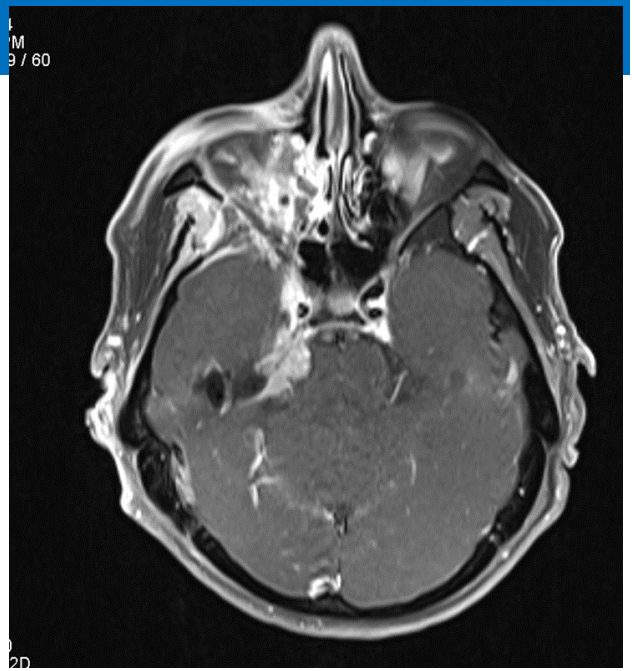
- **9 pts with a relapse close to the spared Optic Nerve**
- **(2 expected visual loss cases - G3)**

5 pts with a relapse close to the brain stem

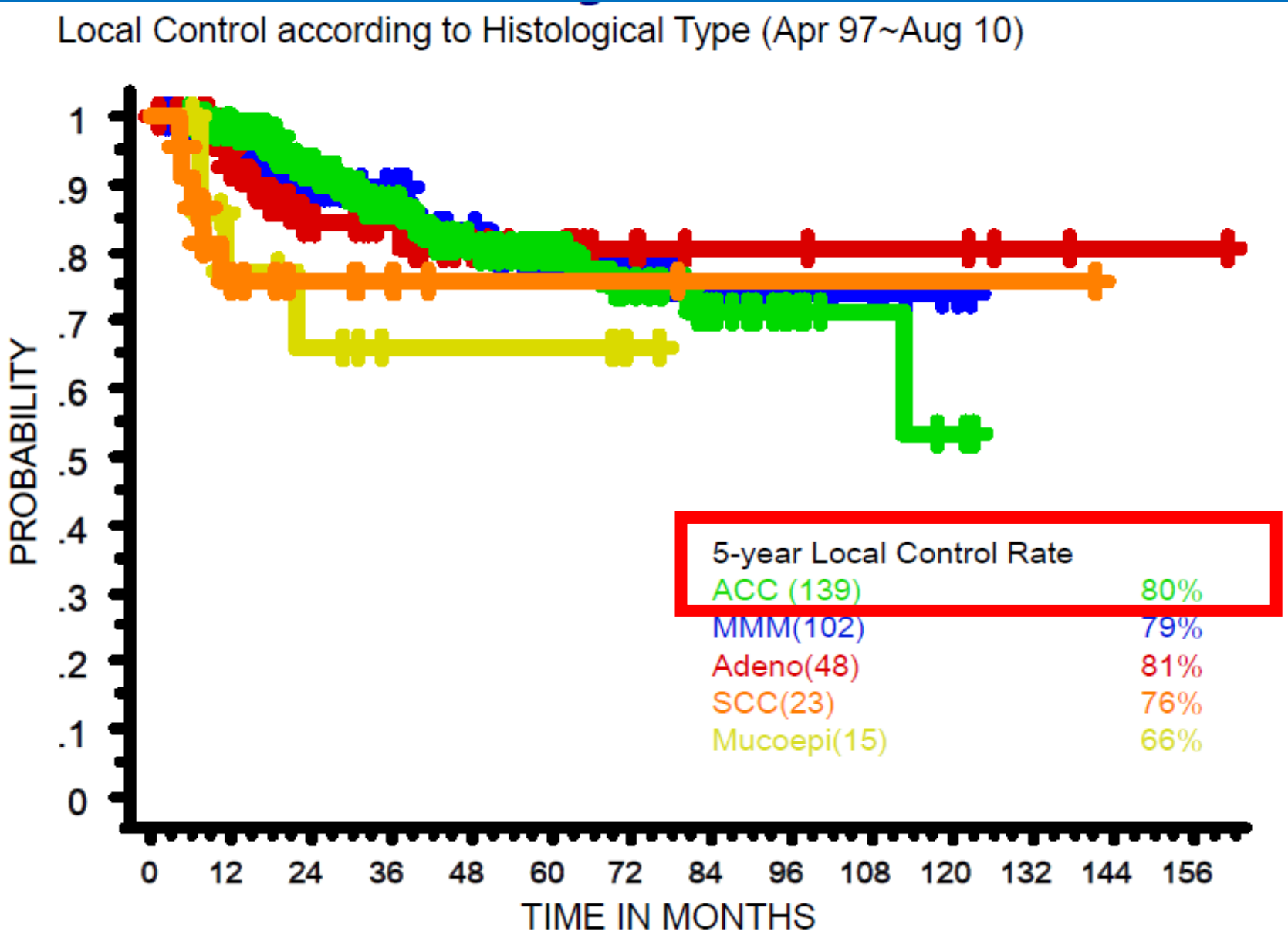




LEM ——
MKM - - -



ACC. Carbon ion RT at NIRS



IOP Publishing Physics in Medicine and Biology
Phys. Med. Biol. 57 (2012) 7543–7554 doi:10.1088/0031-9155/57/22/7543

Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy

Piero Fossati[1,2,4,5], Silvia Molinelli[1], Naruhiru Matsufuji[3], Mario Ciocca[1], Alfredo Mirandola[1], Andrea Mairani[1], Junetsu Mizoe[1,3], Azusa Hasegawa[3], Reiko Imai[3], Tadashi Kamada[3], Roberto Orecchia[1,2,4] and Hirohiko Tsujii[3]

Prescription doses (GyE)

(16 fractions, 4 fractions per week)

Indication	NIRS dose	CNAO dose						
		Opposed ports		Orthogonal ports		Single port		
		quadratic errors		quadratic errors		quadratic errors		MC
		Cubes	Spheres	Cubes	Spheres	Cubes	Spheres	Spheres
Head and neck non mesenchymal cancer	3.60	4.20	4.15	4.20	4.15	4.20	4.15	4.19
Skull base chordoma and hondrosarcoma	3.80	4.35	4.30	4.35	4.30	4.35	4.30	4.33
Head and neck non mesenchymal cancer	4.00	4.50	4.40	4.50	4.45	4.50	4.45	4.47
Spinal chordoma and chondrosarcoma	4.20	4.65	4.60	4.70	4.60	4.70	4.60	4.64
Head and neck sarcoma	4.40	4.80	4.70	4.80	4.70	4.80	4.70	4.75
Bone and soft tissue sarcoma	4.40	4.80	4.75	4.80	4.75	4.80	4.75	4.78

RBE-weighted dose in carbon ion therapy for ACC patients: impact of the RBE model translation on treatment outcomes
Molinelli S et al, PTCOG 2019, Abstract *(250)*
Submitted for publication

Plans of 78 ACC patients, treated with a LEM-optimization, were exported for recalculation with a modified Microdosimetric Kinetic Model (mMKM) -system, currently in use in Japanes centers. LEM prescription doses ranged from 68.8 Gy(RBE) to 65.6 Gy(RBE) in 16 fractions. D_{RBE} to 95%, 50% and 2% ($D_{V\%}$) of the CTV, were criteria to assess dose variations between LEM- and mMKM-computations. Selected cases included patients presenting tumor relapse, contoured on the follow-up MR scan, to analyze the relapse location with respect to CTV and OARs and D_{RBE} distributions.

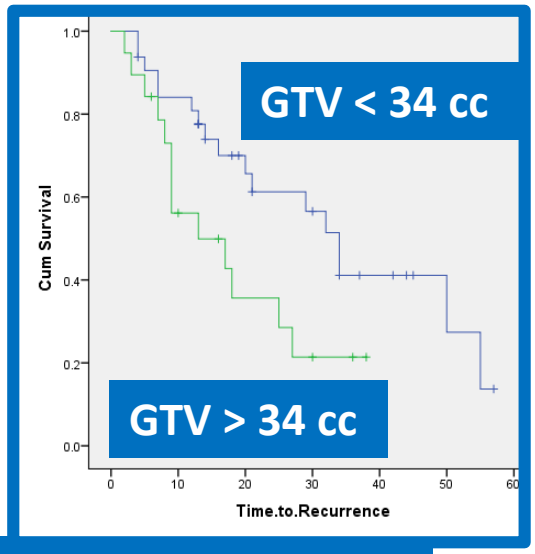
The mMKM analysis showed that conversion factors correctly acted on $D_{50\%}$, but allowed the generation of low and high D_{RBE} regions due to the steeper mMKM-RBE variation along the beam path. Recurrences were mainly (63%) detected in a poor CTV coverage region, in the original plan, due to OARs sparing to an mMKM level substantially lower than expected.

D_{RBE} deviations between LEM- and mMKM-plans were significantly higher in regions where steep dose gradients were applied to spare OARs, than in the target region. New constraints have been defined for optic pathways and brainstem to improve target coverage with no expected increase in tissue complications.

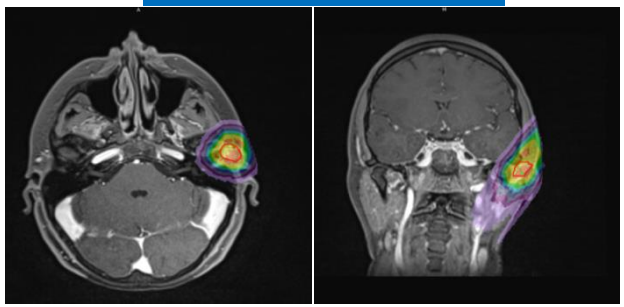
ACC. Re-treatment

51 pazienti

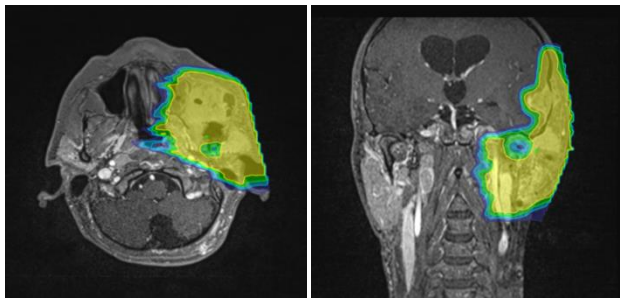
T-Stage	n	%
rcT2	1	2%
rcT3	5	10%
rcT4a	26	51%
rcT4b	19	37%



CIRT 60 GyE



CIRT 48 GyE



Prior RT dose median 60 Gy (24 – 78 Gy, range)
In-field recurrences 82 %
Median GTV 29 cc (1.75-205.54 cc)
Re-RT Carbon Ions median 60 Gy RBE (46,8 – 74 GyE)

Acute toxicity G3 : 3.5%	3-yr PFS 43.5%
Late toxicity G3 : 17%	3-yr OS 54.5%

Ongoing trial

PROTOCOL

Randomized study comparing the carbon ion radiotherapy with conventional radiation treatments including proton therapy - for the treatment of radioresistant tumors. PHRC ETOILE-ULICE

Ongoing trial

Study Protocol SINTART1 — 26 February 2013

Multidisciplinary approach for poor prognosis sinonasal tumors: Phase II study of chemotherapy, surgery, photon and heavy ion radiotherapy integration for more effective and less toxic treatment in operable patients.

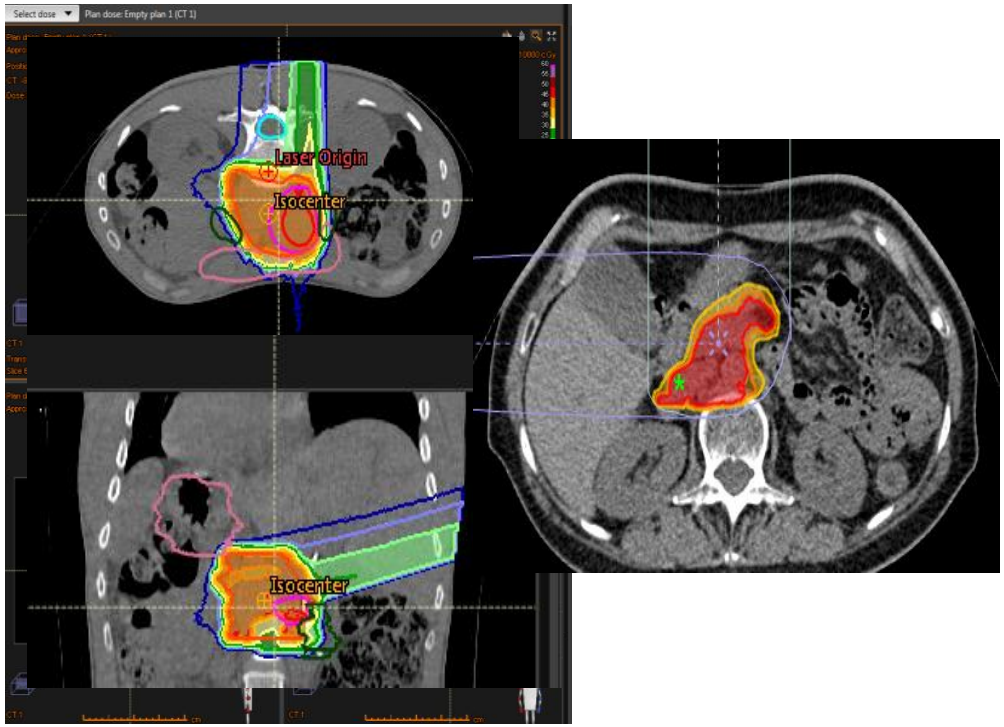
Study Protocol SINTART2 — 26 February 2013

Multidisciplinary approach for poor prognosis sinonasal tumors: Phase II study of chemotherapy, photon and heavy ion radiotherapy integration for more effective and less toxic treatment in inoperable patients.

Pancreatic cancer

16 Patients after chemotherapy (Gem/Gemox/Folfirinox)

CIRT: 57.6 GyE (12 fx)



Età (mediana, range)	71 (43-78)
cT3 cT4 pT3	1 11 4
N1 N0	9 7
M1	2 -Peritoneum -Liver

1-y LPFS: 71%

MDFS median	11 months (4-55 m)
OS median	12 months (5-55 m)

Toxicity: G2 – G3 0%

Morphological Analysis of Amoeboid-Mesenchymal Transition Plasticity After Low and High LET Radiation on Migrating and Invading Pancreatic Cancer Cells.
Facoetti A et al. Anticancer Res 2018 Aug; 38(8):4585-4591

Cell migration and invasion are fundamental components of tumor cell metastasis that represent the biggest threat to the survival and quality of life of cancer patients. There is clear evidence that ionizing radiation can differently modulate migration and invasiveness of cancer cells depending on the cell lines, the doses and the radiation types investigated. This suggests that motile cells are able to adopt different migration strategies according to their molecular characteristics and external signals.

In this study, a morphological analysis was performed on pancreatic cancer Aspc-1 cells to evaluate the amoeboid-mesenchymal mobility transition in several experimental conditions considering the role played by factors released by normal and tumor cells, in basal conditions and after low and high Linear Energy Transfer (LET) irradiation.

The migratory behavior of Aspc-1 cells is modulated by factors released by normal fibroblasts and tumor cells, and this is in turn modulated by both the radiation dose and the radiation quality

Evidence of 68Ga-DOTA-NT-20.3 Uptake in Pancreatic Adenocarcinoma AsPC-1 Cell Line - in vitro Study.

Marenco M et al. Curr Pharm Biotechnol 2018; 19(9):754-759

Neurotensin receptors are overexpressed in several cancer types including pancreatic ductal adenocarcinoma. Three NTR subtypes have been cloned: NTR-1, NTR-2 and NTR-3. The most expressed NTR-1 is not present in normal pancreatic tissue and has a low expression in chronic pancreatitis

Objective of this study was to test in vitro affinity of the new 68Ga labelled neurotensin analogue DOTA-NT-20.3 on the human pancreatic ductal adenocarcinoma cell line AsPC-1

For the preparation of 68Ga-DOTA-NT-20.3, 68GaCl3 solution and 50 µg of precursor water dissolved were used in an automatic synthesis module. The labeled compound was added to cell culture flask and incubated at 37°C. At various time points after tracer addition up to 80min, cells were recovered, rinsed and counted for radioactivity

Labeling yield was ≥98 %. The molar ratio between labelled and total peptide was about 1/400. AsPC-1 cell line showed rapid uptake of the tracer including surface and internalized binding, tending to a plateau phase 80 min after tracer addition (11%/200.000 cells). The Kd (7.335 pmol) and Bmax (90.52 kBq) value indicated high tracer affinity for AsPC-1cell line. The new tracer 68Ga-DOTA-NT-20.3 can be a suitable candidate for the clinical use in patients with pancreatic ductal adenocarcinoma.

Ongoing trial

UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

NCI CCC

CIPHER: A Prospective, Multi-Center Randomized Phase 3 Trial of Carbon Ion versus Conventional Photon Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer

- **Move forward with phase III trials**

Although there are modest numbers of trials involving CIRT that have been completed in recent times or are currently being conducted a minority are randomized, a smaller minority are phase III trials, and even fewer involve an OS primary endpoint

Despite recent international consensus for a model-based approach to particle-beam therapy that includes patient selection, nonrandomized trials based on highly selected patients are inadequate for providing high-level evidence for the efficacy of CIRT required to justify the construction of new facilities

Registration type trials

Clinical research progresses would involve Germany, Italy, and/or Japan: the countries with the largest current activity in CIRT

Furthermore, even when the same CIRT dose is prescribed in a trial from Japan or a European site, the tumors (and normal tissues) may be receiving different carbon doses because of facility-dependent protocols and assumptions in the biologic models used for treatment planning of effective doses.

Thus, going forward, a consensus on dose prescription have to be reached, capturing detailed dosimetric and clinical information so that clinical outcomes can be used to adjudicate these differences of opinion

We must now

- Support efforts by facilitating patient accrual to phase III randomized trials
- Improve collaboration between several national and international investigators
- Improving survival and LC of selected cancers, ranging from rare to common, is the target of CIRT
- A registry have to create, to facilitate definitive comparisons