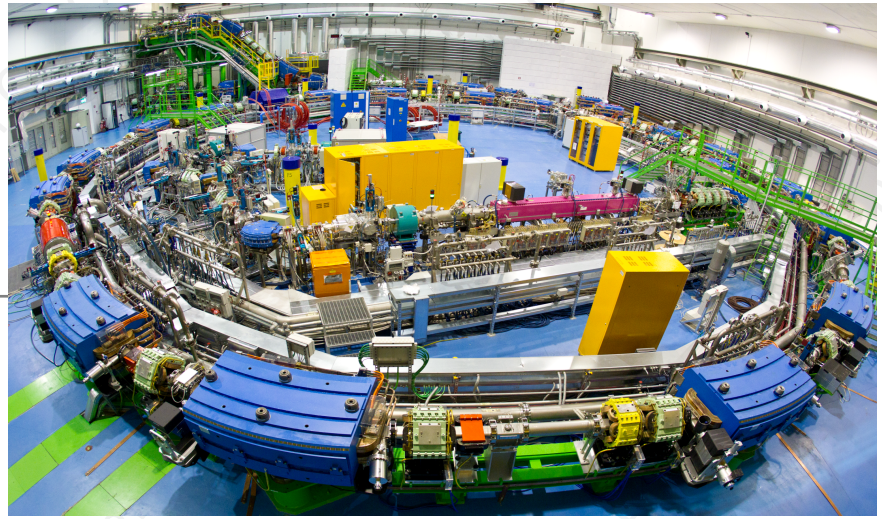
REIRRADIATION FOR HEAD AND NECK TUMORS WITH PARTICLE RADIOTHERAPY



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REIRRADIATION FOR HEAD AND NECK CANCERS

- ✓ approximately 40% of patients will develop a second cancer or **locoregional recurrence**.
- ✓ **locoregional recurrence** is the most common cause of death in head and neck cancer,

LOCAL TREATMENT plays an important role

- ➢ Alternative options: **surgery** or **systemic therapy** (especially in the era of immunotherapy)
- ➢ No randomised evidence to guide management
- ➢ Several options largely reported from single institution studies
- ➢ Risk of life-threatening complications after reRT (or at least those that significantly affect the quality of life)

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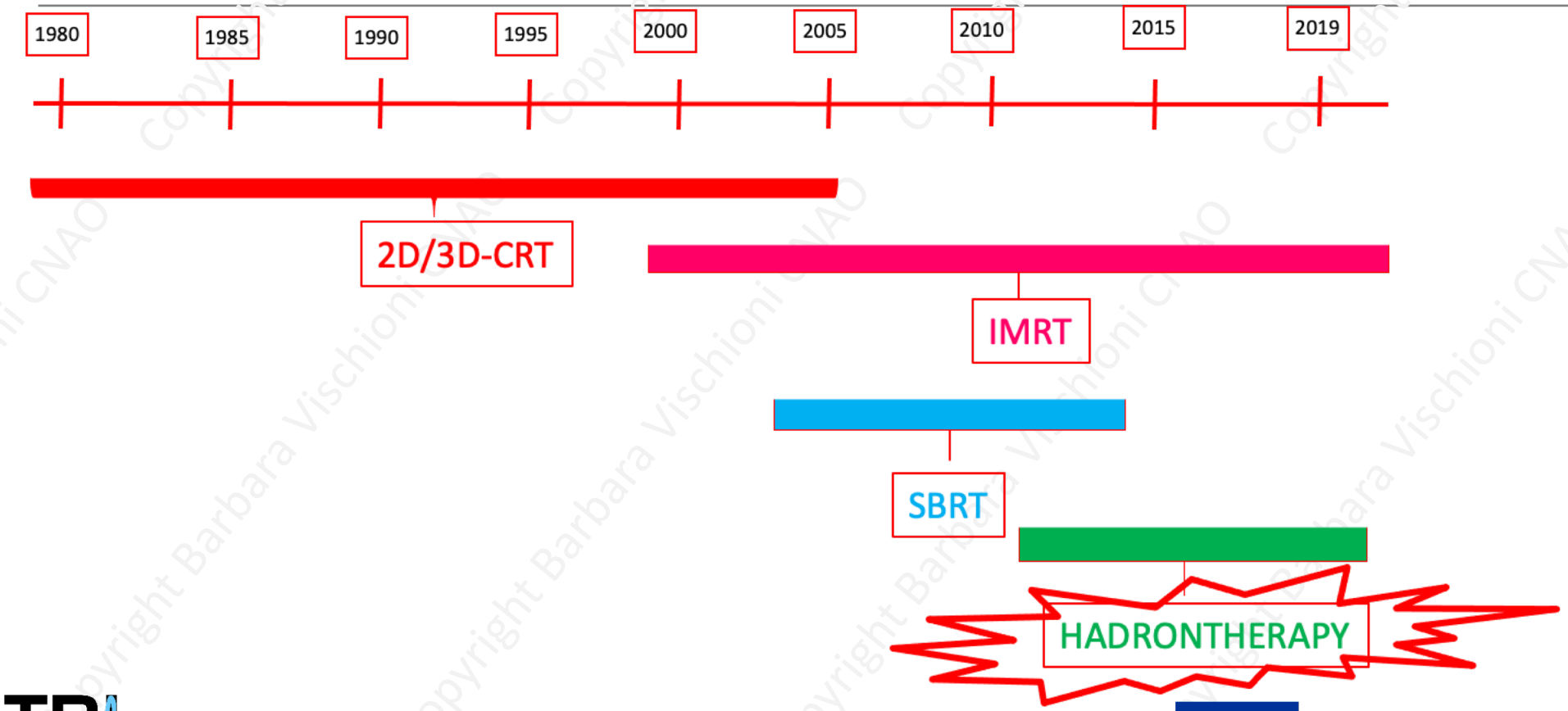
Evolution of radiation oncology



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Recurrent disease and radiation oncology

Issues for reirradiation in tumors of the head and neck region

→ sensitive OARs essentials for vital function

→ Usually already received high doses in previous curative treatment

→ New radiotherapy course needs high doses if curative intent since relapse probably arises from selection of radioresistant clones after first radiotherapy course

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Recurrent disease and radiation oncology

3D CRT

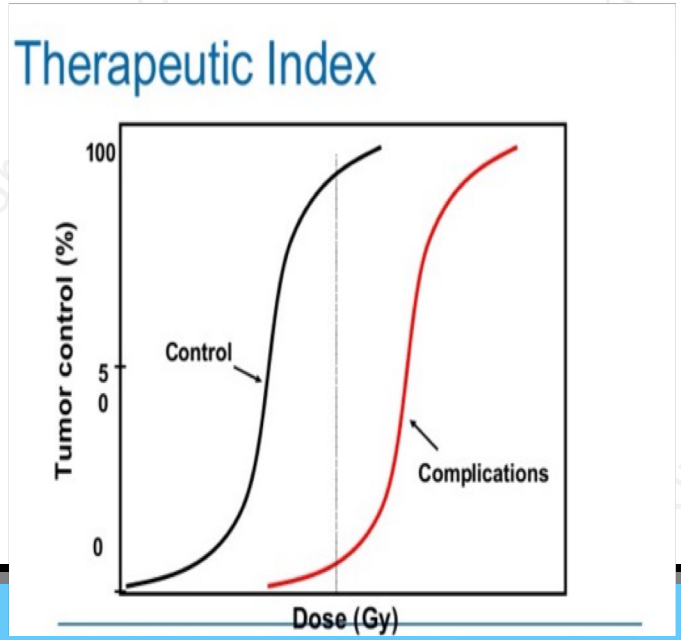
→ better local control

→ lower toxicity

IMRT

→ Possibility to combine chemotherapy to improve overall survival

SBRT / Hadrontherapy or particle therapy



Treatment Cost: side effects
Tretment Benefit: tumor control

- Interval from 1st RT
- Late effects from previous RT
- Previous dose exposure
- Age
- Stage TNM
- Site
- Recurrence or second primary

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Reirradiation in head and neck tumors with curative intent when…

"In general, the reirradiated population of head and neck cancer patients described in current literature represents a diverse but highly selected group of patients treated in centers where there is high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment is curative and surgery is not an option, reirradiation strategies can be considered for patients who: develop locoregional failures or second primaries at ≥6 months after the initial radiotherapy; can receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully analyzed through review of dose-volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: Outcomes and analyses. Int J Radiat Oncol Biol Phys 2016;95:1117-1131.)

- In centers of high expertise where it is possible to manage acute and long term toxicities
- At least 6 months after initial RT
- Possibility to receive additional doses of RT of at least 60 Gy
- Consider protons when normal tissue constraints cannot be met by photons

Takiar et al. 2016

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Particle or photon radiotherapy in the recurrent setting

Strahlenther Onkol (2017) 193:525–533
DOI 10.1007/s00066-017-1129-6

ORIGINAL ARTICLE

Reirradiation for recurrent head and neck cancers using charged particle or photon radiotherapy

Hideya Yamazaki[1,2] · Yusuke Demizu[3] · Tomoaki Okimoto[3] · Mikio Ogita[4] · Kengo Himei[5] · Satoaki Nakamura[1] · Gen Suzuki[1] · Ken Yoshida[6] · Tadayuki Kotsuma[6] · Yasuo Yoshioka[7] · Ryoongjin Oh[8]

Multicentric retrospective study (Japan)

Between 2000 and 2010.

26 pts charged particle radiotherapy (CP): (17 carbon and 9 proton)
150 pts photons (117 CBK/36 IMRT).

Higher prescribed doses in CP than photon RT

CP for younger pts and non-SCC

1-year OS:
67.9% for CP
54.1% for photon radiotherapy ($p = 0.15$)

Prognostic factors for better OS:
- Primary site (nasopharynx) $p<0.001$
- GTV < 40 cc $p<0.001$
- Prescribed dose (EQD2) > 40 Gy

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Particle or photon radiotherapy in the recurrent setting

Table 3 Toxicity of reirradiation

Grade	Photon radiotherapy			CP		
0–2	113	(75%)	–	14	(54%)	–
3	21	(14%)	Ulceration and bleeding (2) Necrosis (soft tissue 2, bone 3) Fistula (7) Visual disturbance and lateral lobe necrosis (1) Edema (4) Abscess (2)	5	(19%)	Nerve palsy (2) Mucosal ulceration (2) Skin ulceration (1)
4	2	(1%)	Bleeding and temporal lobe necrosis (1) Soft tissue damage with pain (1)	3	(12%)	Visual disturbance (2) Soft tissue necrosis (1)
5	13	(9%)	Bleeding (10) Ulceration (1) Mucositis (1) Trismus and abscess (1)	4	(15%)	Bleeding (2) Skin/bone necrosis and infection (1) Soft tissue necrosis and infection (1)

CP Charged particle

Conclusion

CP provided suprior survival outcomes when compared to the outcomes with photon radiotherapy. Small-volume nasopharyngeal cancer treated with a higher prescribed dose was associated with longer survival. Younger patients with a larger PTV may experience grade 3 or worse toxicity.

Significant predictors of grade 3 or worse toxicity @MVA:

Younger age (<64 y) p= *0.01*
Primary site (nasopharynx) p= 0.05
PTV volume > 40 cm ^{3} p=0.022

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Agenda

- Rational for differential use of protons and carbon ions for reirradiation (reRT)
- When proton and when carbon ions for reRT
- reRt at cnao (salivary, sinonasal)
- Toxicity (with a focus on carotid toxicity)
- Vademecum for reRT

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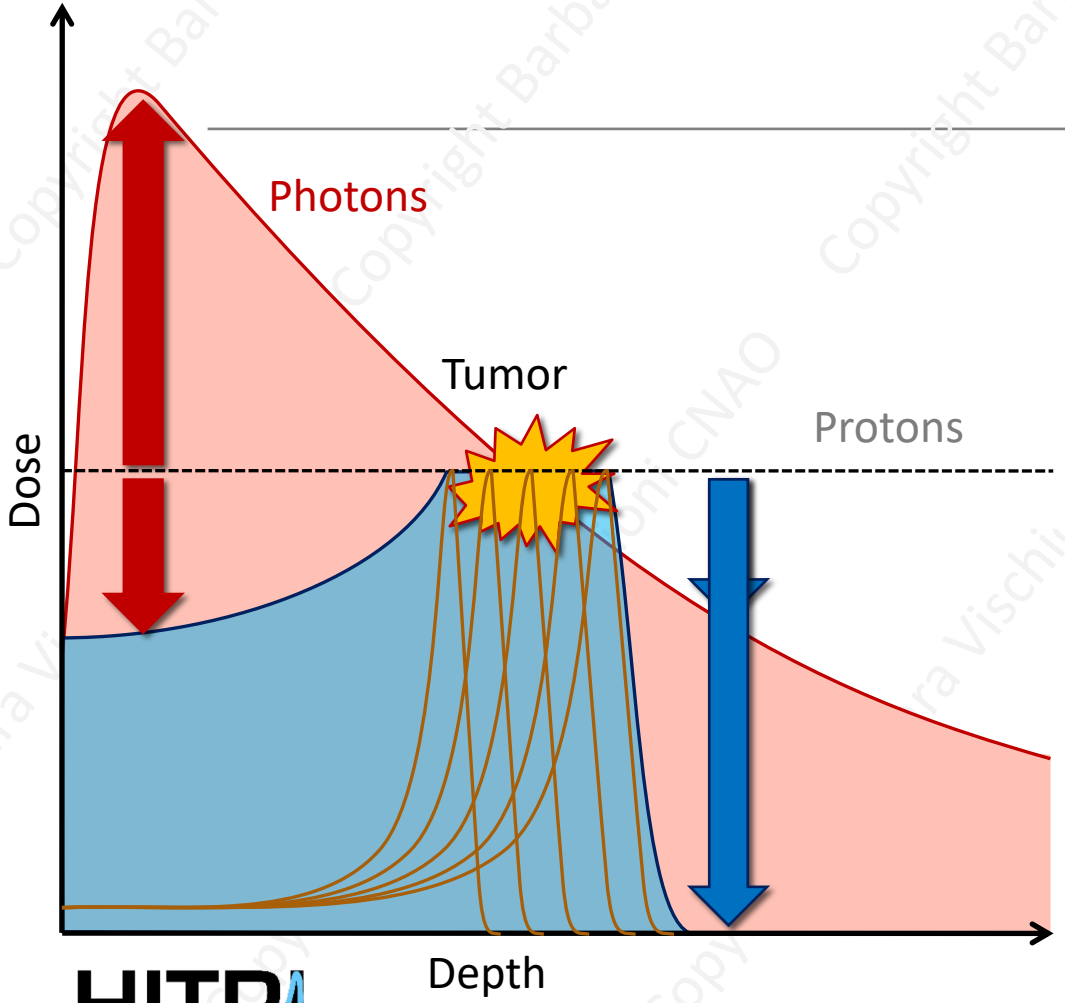
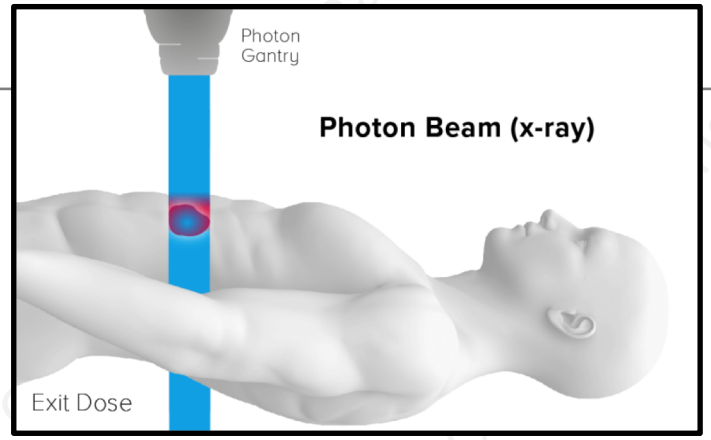
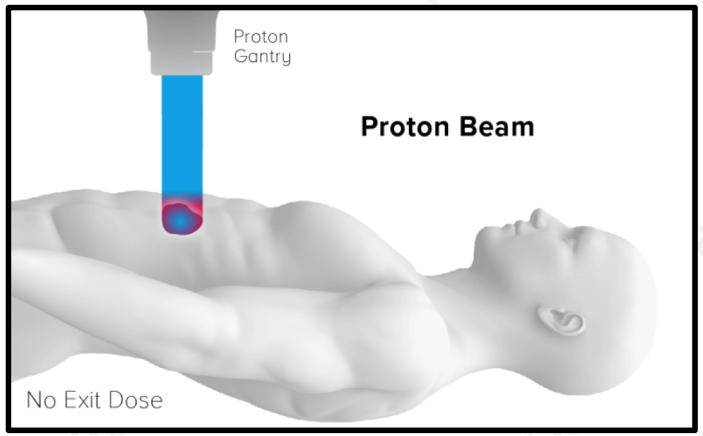
Dose shaping with particle therapy







Protons and carbon ions:

Lower dose-bath then conventional radiotherapy

Lower toxicity due to better dosimetry

Dose escalation

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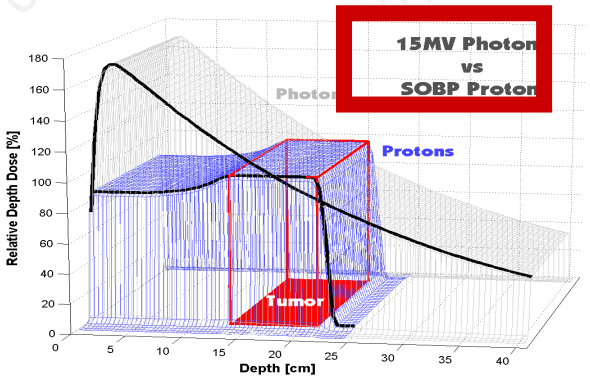
Biological properties of carbon ions

Carbon ions:

Higher efficacy on radioresistant clones

Higher efficacy in radioresistant tumors



1. Physical selectivity
- Bragg Peak has High-LET components.

2. Radiobiological effect at the peak for carbon ions

- RBE increases with depth.

- Peak to plateau ratio of the "biologically equivalent dose" is larger than other ion species

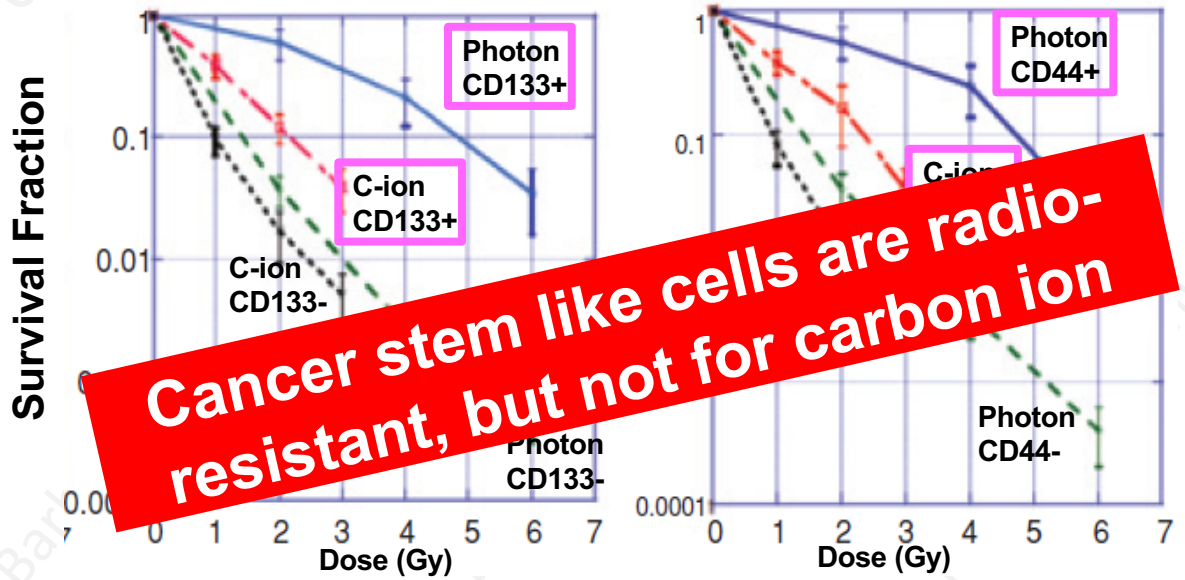
- Increased efficiency against hypoxic cells (OER)

- Increased efficiency against cells in a resistant phase of the mitotic cycle

- Little repair possibility of irradiated cells.

- Increased efficiency against cancer stem like cells

Cui X, et al. Cancer Res. 2011



Cancer stem like cells are radio-resistant, but not for carbon ion

CD133+, CD44+ : stem–like cell property

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

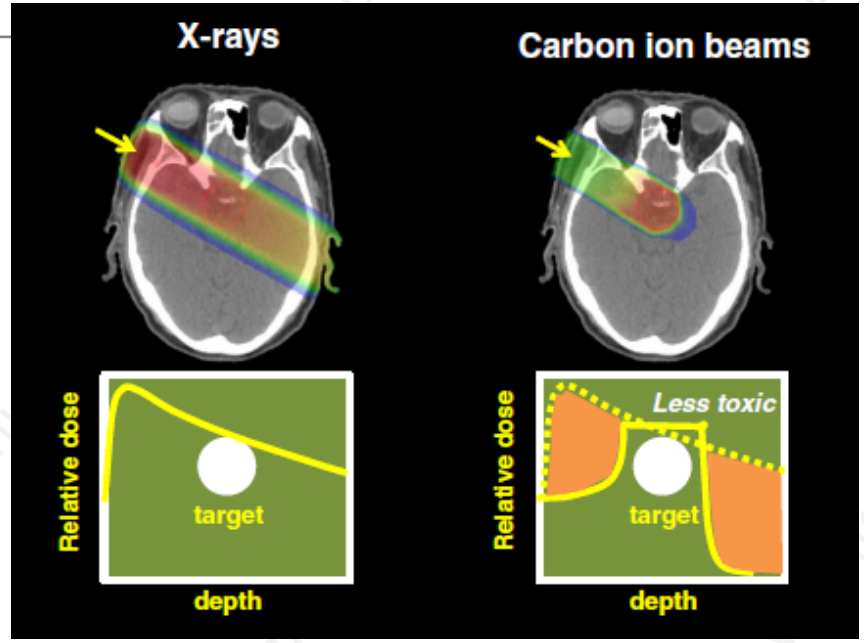
Experience with hadrontherapy for head and neck tumors in the real world

- Protons (PT): good dosimetry to spare OARs

→ difficult location

- CIRT: good dosimetry and high RBE (Relative Biological effectiveness)

→ radioresistant tumors and difficult location



Different indications for PT vs CIRT:

- CIRT in radioresistant tumors, unresectable or unfit for surgery

- Protons for radiosensitive tumors, in postoperative cases (R0 or R1) or in definitve setting to reduce toxicity (in young patients , in cases of carotid tumor invasion or post surgical flap insertion)

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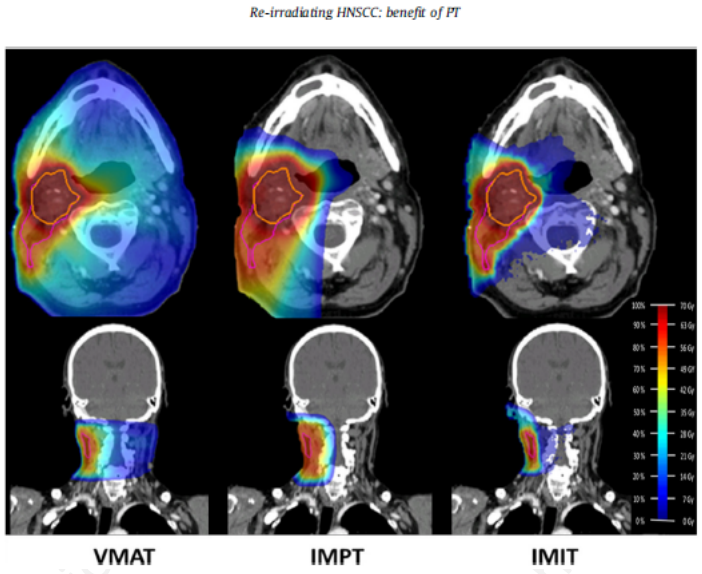
Benefit of particle therapy in *in silico* studies



Original article

Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric *in silico* ROCOCO trial

Daniëlle B.P. Eekers [a,*], Erik Roelofs [a], Urszula Jelen [b,1], Maura Kirk [c], Marlies Granzier [a], Filippo Ammazzalorso [b,1], Peter H. Ahn [c], Geert O.R.J. Janssens [d], Frank J.P. Hoebers [a], Tobias Friedmann [b,1], Timothy Solberg [c], Sean Walsh [a], Esther G.C. Troost [a,e,f,g], Johannes H.A.M. Kaanders [d], Philippe Lambin [a]

Table 2
Mean doses (SD) of selected dosimetric parameters for organs at risk and target volume in Gy(E) for IMPT and IMIT compared to VMAT after scaling to the mean CTV70 Gy doses of 70 Gy.

D_{mean} (Gy)	VMAT	IMPT	IMIT
Arytenoid ipsi & bilateral	34.5 (24.4)	27.3 (24.9)	20.6 (24.9)[a]
Arytenoid contralateral	17.6 (13.2)	2.3 (4.2)[a]	1.1 (0.9)[a]
Base of tongue	32.1 (19.4)	25.5 (23.3)	18.8 (21.7)[a]
Carotid ipsi- & bilateral	35.0 (17.1)	35.9 (19.4)	31.9 (19.8)[a]
Carotid contralateral	12.9 (8.4)	2.0 (4.5)[a]	0.83 (1.4)[a]
Body	5.9 (2.8)	3.9 (2.1)[a]	2.7 (1.5)[a]
Jugular ipsi- & bilateral	29.6 (20.2)	29.0 (22.5)	24.6 (22.8)[a]
Jugular contralateral	10.4 (6.6)	0.97 (3.0)[a]	0.57 (1.6)[a]
Larynx	34.1 (18.0)	27.2 (18.4)[a]	20.3 (17.5)[a]
Mandible	16.1 (12.7)	11.5 (11.5)[a]	8.2 (11.0)[a]
Oral cavity	14.9 (14.3)	9.0 (13.7)[a]	7.6 (14.6)[a]
Parotid ipsi- & bilateral	16.0 (15.2)	16.3 (16.6)	13.5 (14.5)[a]
Parotid contralateral	4.4 (2.1)	<0.01 (0.02)[a]	0.038 (0.13)[a]
Sterno cleido mastoid ipsi- & bilateral	31.2 (17.1)	30.9 (20.5)	26.3 (19.5)[a]
Sterno cleido mastoid contralateral	11.4 (6.8)	1.6 (3.0)[a]	0.64 (1.4)[a]
Submandibular gland ipsi- & bilateral	35.4 (20.0)	35.9 (20.2)	29.2 (18.5)[a]
Submandibular gland contralateral	16.3 (9.3)	0.64 (1.7)[a]	0.73 (1.2)[a]
Swallowing muscle total	31.9 (21.5)	25.1 (21.5)[a]	18.9 (21.1)[a]
Thyroid	30.9 (25.2)	29.8 (25.2)	25.9 (24.4)[a]
Vertebrae	18.1 (7.6)	10.8 (6.8)[a]	5.8 (4.2)[a]
CTV_{54Gy}	60.9 (2.7)	61.7 (2.7)[a]	61.3 (2.5)
CTV_{70Gy}	70.0 (<0.01)	70.0 (<0.01)	70.0 (<0.01)

Overall mean dose benefit comparing IMPT to VMAT = 40%
Overall mean dose benefit comparing IMIT to VMAT = 54%

D_2 (Gy)	VMAT	IMPT	IMIT
Brainstem	8.2 (7.9)	2.7 (5.3)[a]	1.3 (2.5)[a]
Spinal cord	16.6 (4.7)	6.7 (5.7)[a]	4.8 (3.2)[a]
V_{95} (%)	VMAT	IMPT	IMIT
CTV_{54Gy}	99.5 (0.6)	99.7 (0.4)	100.0 (0.02)[a]
CTV_{70Gy}	98.9 (2.5)	99.9 (0.3)	99.9 (0.2)

[a] Is significant ($P < 0.02$).

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Which particle?
Experience with proton therapy for reirradiation of head and neck tumors

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation

Vivek Verma [a], Jean-Claude M. Rwigema [b], Robert S. Malyapa [c], William F. Regine [c], Charles B. Simone II [c,*]

[a] Department of Radiation Oncology, University of Nebraska Medical Center, Omaha; [b] Department of Radiation Oncology, Mayo Clinic, Scottsdale; and [c] Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, USA

In summary, based on the preponderance of the available data, we posit that PBT may be the safest option to reirradiate patients with locoregional recurrences, and thus PBT may be the best approach for offering select patients a new chance of cure. How-

grade 3 toxicity and achievement of longer-term OS. PBT for H&N malignancies shows appropriate local/locoregional control and favorable toxicity profiles versus historical photon-based methods, including low (9–10%) rates of feeding tube placement. PBT for recurrent lung cancer can achieve favorable survival

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Experience with proton therapy for reirradiation of head and neck tumors

ELSEVIER

Seminars in RADIATION ONCOLOGY

Proton Therapy for Head and Neck Cancers

Pierre Blanchard, MD, PhD,*,† Gary Brandon Gunn, MD,* Alexander Lin, MD,‡ Robert L. Foote, MD,§ Nancy Y. Lee, MD,¶ and Steven J. Frank, MD*

Table 3 Studies Evaluating Proton Therapy for Head and Neck Reirradiation

References	Accrual	Technique	Type	Pts (n)	S, %	CCT, %	Histology	Follow-up (median)	Outcomes	Toxicity
McDonald et al[86]	2004-2014	PSPT	Retro	61	47.5	29	SCC (32) Other (29)	29 mo	2 y; LF 19.7%, OS, 32.7%,	8 G3 (bone and soft tissue necrosis); 3 G4 (2 unilateral blindness, 1 soft tissue necrosis); 3 treatment-related deaths (G5) (1 acute and 2 late)
Phan et al[59]	2011–2015	PSPT ($n = 15$), IMPT ($n = 45$)	Pro	60	58	73	SCC (40) Other (20)	13.6 mo	1 y; LRFFS 68.4%, OS, 83.8%	Acute G3+ toxicity 30%, including 22% feeding tubes; 1-y G3+ toxicity 16.7%; 3 treatment-related deaths (G5)
Romesser et al[58]	2011-2014	PSPT	Retro	92	39	39	SCC (52) Other (40)	13.3 mo	1 y; LRF 25.1%, OS, 65.2%	G3+ late toxicity: 6 pts (8.7%) for skin and 4 pts (7.1%) for dysphagia. 1 death during treatment (progression) and 2 G5 late bleeding
Hayashi et al[60]	2009-2013	PSPT	Pro	25	46	IA	SCC (25)	24 mo	2 y; LF 30%, OS, 46%,	1 pt with late G4. No G5. Patients were a mix of previously irradiated pts and pts with recurrence after single-modality surgery, for whom side effects may have been underestimated.

CCT, concomitant chemotherapy; Comp, comparison; G, grade; IMPT, intensity-modulated proton therapy; LF, local failure; LRF, locoregional failure; LRFFS, locoregional failure-free survival; OS, overall survival; Pro, prospective study; pts, patients; PSPT, passive scattered proton therapy; Retro, retrospective study; SCC, squamous cell carcinoma.

HITRI Heavy Ion Therapy Research Integration

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Comparison with recent IMRT photons H&N reirradiation studies

2 ys late toxicity 32-46%

- Carotid rupture 2%
- Feed tube dependence 57%
- Fistula 5%

Study	RT Technique	Patient Numbers (% SCC)	Median Follow-up (months)	2-Yr LRC	2-Yr OS	Late G3 or higher Toxicity	Median CTV Volume (range)	Predictors of Increased Toxicity
Langer et al, 2007, RTOG 99-11 [18]	IMRT & 3DCRT	105 (≥77% SCC)	24	30%*	26%	Pharynx 18%*, Fibrosis 16%*, ORN 5%*, CAR 2%*		
Lee et al, 2007, MSKCC [9]	IMRT & 3DCRT	105 (86% SCC) (34% Surgery)	35	42% 52% (IMRT)	37%	15% G3-4* Brain Necrosis 4%* pharynx 4%*, trismus 3%*		
Popovtzer et al. 2009 [25]	IMRT & 3DCRT	66 (>90% SCC) (61% Surgery)		29%	40%	(29% G3+)		
Biagioli et al, 2007 [31]	IMRT	41 (85% SCC) (42% Surgery)	14	n/a	49%	11% G3-5* Fistula 5%* CAR 2%* Esophagus 2%*		
Sulman et al. 2009, MDACC [10]	IMRT	74 (77% SCC) (27% Surgery)	25.4	64%	58%	ORN 5%* Esophagus 4%* Brain Necrosis 1%*		
Sher et al. 2010, Dana-Farber [8]	IMRT	35 (>90% SCC) (49% Surgery)	27	67%	48%	46% G3+ *		
Chen et al, 2011 [32]	IMRT	21		65%	40%	FT dependent 57%*		
Kharofa et al, 2012, Medical College of Wisconsin [26]	IMRT	38 (100% SCC) (34% Surgery)	14	--	49%	Fistula 5%* CAR 2%* Esophagus 2%*		
Dupres et al. 2014, Belgium [20]	IMRT	84 (77% SCC) (22% Surgery)	18.5	48%	32%	2-Year 27%		
Takiar et al. 2015, MDACC [11]	IMRT	207 (84% SCC) (51% Surgery)	25.1	65% 59% (SCC)	57% 51% (SCC)	2-Year 32%	71.5 ± 98.3 cm^3	CTV1 Vol ≥ 50 cm^3 Concurrent Chemotherapy
Current Study	Proton	60 (67% SCC) (58% Surgery)	13.6	72.8% (62.1% SCC)	69.7% (60.2% SCC)	2-Year 26.0%	46.8 ± 57.7 cm^3	CTV1 Vol ≥ 50 cm^3

Abbreviations: CAR, carotid artery rupture; SCC, squamous cell carcinoma; ORN, osteoradionecrosis
In parentheses, ( ), toxicity reported as incidence rate and non-actuarial

Phan et al, 2016

5 ys LRC 72%
2 ys late tox 26%

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Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Experience with proton therapy for reirradiation of head and neck tumors

JAMA Network Open

Original Investigation | Oncology

Evaluation of Proton Therapy Reirradiation for Patients With Recurrent Head and Neck Squamous Cell Carcinoma

Anna Lee, MD, MPH; Robbie Woods, MB, MD; Amgad Mahfouz, MD; Sarin Kitpanit, MD; Olivia Cartano; Nader Mohamed, BA; Irini Youssef, MD; Kathryn Marqueen, MD; Kevin Sine, BS; Dennis Mah, PhD; Brian Neal, PhD; Kaveh Zakeri, MD, MAS; Jung J. Kang, MD, PhD; Nadeem Riaz, MD, MS; Yao Yu, MD; Sean M. McBride, MD, MPH; Linda D. Chen, MD; C. Jillian Tsai, MD, PhD; Daphna Y. Gelblum, MD; Robert H. Press, MD; Loren S. Michel, MD; Eric J. Sherman, MD; David Pfister, MD; Lara A. Dunn, MD; Alan L. Ho, MD, PhD; James Fetten, MD; Richard J. Wong, MD, PhD; Jay O. Boyle, MD; Bhuvanesh Singh, MD, PhD; Jennifer R. Cracchiolo, MD; Ian Ganly, MD, PhD; Marc A. Cohen, MD, MPH; Nancy Y. Lee, MD

242 pts-retrospective cohort study
Median interval from first RT 22 months
Median prior RT dose 69,96 Gy

Median PT reRT dose

70 Gy fractionated cohort

1-year LC was 71.8%
1-year OS was 66.6%

Salvage surgery prior to PT-ReRT and PT-ReRT dose were associated with improved LC

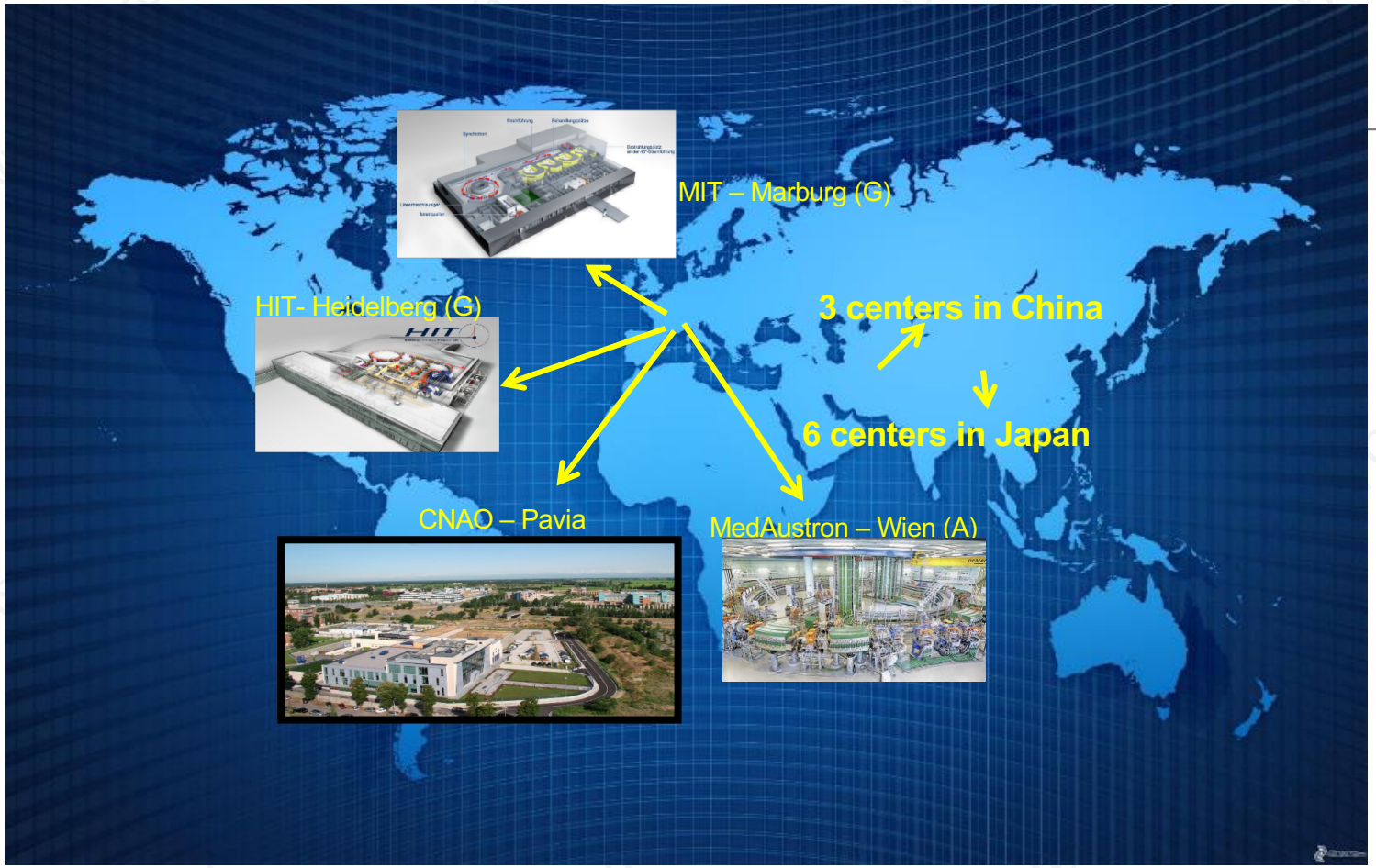
The toxic effects observed in the current study were not low, and because **longer survival was observed compared with our IMRT experience**, it is probable that patients are surviving long enough to develop late effects that would not have been seen previously.

HITRI Heavy Ion Therapy Research Integration

79 potential grade 3, 4 G4, and 5 G5 late toxic effects (CBS).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Hadrontherapy centers in the world



130 clinical facilities of protons and 13 centers of carbon ions in the world

6 multi-particle (protons and carbon ions)

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Which particle?
Experience with carbon ions for reirradiation of head and neck tumors

Jensen, 2011

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Particle beam radiotherapy

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

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

Combs, 2011

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Carbon ion radiotherapy

Carbon ion radiotherapy performed as re-irradiation using active beam delivery in patients with tumors of the brain, skull base and sacral region

Stephanie E. Combs [a,*], Adriana Kalbe [a], Anna Nikoghosyan [a], Benjamin Ackermann [c], Oliver Jäkel [b,c], Thomas Haberer [c], Jürgen Debus [a]

[a] Department of Radiation Oncology, University Hospital of Heidelberg, Heidelberg, Germany; [b] Department of Medical Physics, German Cancer Research Center (dkfz), Heidelberg, Germany; [c] Heidelberger Ionenstrahl Therapiezentrum (HIT), Heidelberg, Germany

28 patients:
16 base of skull chordoma
2 base of skull chondrosarcoma

Median dose re RT: **51 GyE** (3 Gy/fr)
LC: 92 % 2y e 64% 3y

4 ACC
1 SCC
3 high grade meningioma
1 sacral chordoma
1 sacral chondrosarcoma

Median dose re RT: **18 GyE boost**(3 Gy/fr)

No acute nor late severe toxicity (> G2)

HITRI
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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Carbon ion experience @ HIT for head and neck reirradiation

Radiotherapy and Oncology 114 (2015) 182–188

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Adenoid cycstic carcinoma

Re-irradiation of adenoid cystic carcinoma: Analysis and evaluation of outcome in 52 consecutive patients treated with raster-scanned carbon ion therapy

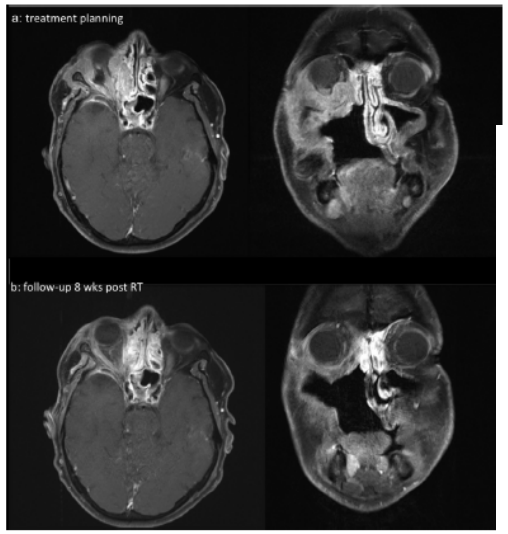
Alexandra D. Jensen[a,*], Melanie Poulakis[a], Anna V. Nikoghosyan[a], Naved Chaudhri[b], Matthias Uhl[a], Marc W. Münter[a], Klaus K. Herfarth[a], Jürgen Debus[a]

[a] Dept of Radiation Oncology, University of Heidelberg; and [b] Dept of Medical Physics, Heidelberg Ion Beam Therapy Center, Germany

Conclusion: Despite high applied doses, C12 re-irradiation shows moderate side-effects, response rates even in these heavily pre-treated patients are encouraging and present a good alternative to palliative chemotherapy. Though most local recurrences occur within the high-dose area, further dose escalation should be viewed with caution.

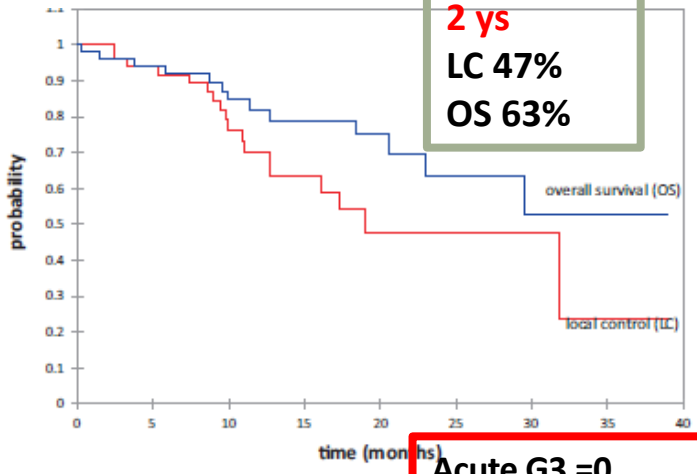
→4 mixed beam (C12 + IMRT)

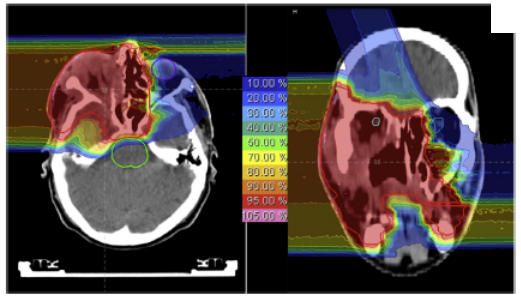
51 Gy E



1y
LC 70%
OS 81%

2 ys
LC 47%
OS 63%





Acute G3 =0
Late G3 = 5,8 (CNS necrosis, osteoradionecrosis)
G4 = 3,8 ica blow-out

HITRI
Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Carbon ion experience @ HIT for head and neck reirradiation

Tumor histology		
ACC	124	54.1
HNSCC	60	26.2
Adenocarcinoma	19	8.3
Other	26	11.4
Tumor site		
Salivary glands	55	24.0
Nasopharynx	52	22.7
Paranasal sinuses	49	21.4
Lip and oral cavity	23	10.0
Oropharynx	14	6.1
Hypopharynx	5	2.2
Other	31	13.6
Salvage surgery before CIR		
Yes	39	17.0
No	190	83.0
Salvage surgery resection status (n = 39)		
R0	3	7.8
R1	11	28.2
R2	20	51.3
Rx	5	12.8
TNM stage reirradiation		
T1	8	3.5
T2	20	8.7
T3	19	8.3
T4	143	62.5
TX	39	17.0
N0	159	69.4
N1	5	2.2
N2	24	10.5
N3	1	0.4
NX	40	17.5
M1	48	21.0
M0	181	79.0

Heavy Ion Therapy Research Integration

Carbon Ion Reirradiation for Recurrent Head and Neck Cancer: A Single-Institutional Experience

Thomas Held, MD,*,†,‡ Paul Windisch, MD,*,†,‡ Sati Akbaba, MD,*,†,‡ Kristin Lang, MD,*,†,‡ Rami El Shafie, MD,*,†,‡ Denise Bernhardt, MD,*,†,‡ Peter Plinkert, MD,§ Steffen Kargus, MD,‖ Stefan Rieken, MD,*,†,‡,¶,#,** Klaus Herfarth, MD,*,†,‡,¶,#,** Jürgen Debus, MD, PhD,*,†,‡,¶,#,** and Sebastian Adeberg, MD*,†,‡,¶,#,**

International Journal of Radiation Oncology biology • physics

229 patients
2010-2017
51 median GyRBE
28.5 mo follow up
Retrospective

Table 3 Multivariable analysis for local progression-free survival

Variable	HR	95% CI	*P* value
Age (y)	0.990	0.971-1.009	.287
Sex (female vs male)	1.013	0.629-1.630	.959
KPS (%)	0.989	0.964-1.016	.428
Total dose CIR (≥51 vs <51 Gy [RBE])	0.441	0.245-0.792	.006*
RT interval (≥12 vs <12 mo)	0.284	0.116-0.697	.006*
Tumor histology (ACC vs other)	0.488	0.297-0.802	.005*
Planning target volume (cm^3)	1.006	0.998-1.002	.500
Tumor resection before CIR (yes vs. no)	0.802	0.408-1.577	.522

Abbreviations: ACC = adenoid cystic carcinoma; CI = confidence interval; CIR = carbon ion reirradiation; KPS = Karnofsky performance score; PTV = planning target volume; RBE = relative biological effectiveness; RT = radiation therapy.
* $P < .05$ statistically significant.

Selection of patients for carbon ion
Better LC for ACC compared to other histologies

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Carbon ion experience in Japan for head and neck reirradiation after photon radiotherapy (J-CROS study)

Multicenter study of re-irradiation using carbon-ions for head and neck malignancies after photon radiotherapy

Daiki Takahashi[1] | Yusuke Demizu[1,2] | Masashi Koto[3] | Nobuteru Kubo[4] | Hiroaki Suefuji[5] | Hiroaki Ikawa[3] | Tatsuya Ohno[4] | Yoshiyuki Shioyama[5] | Tomoaki Okimoto[1] | Hiroshi Tsuji[3] | the Japan Carbon-Ion Radiation Oncology Study Group

- 56 pts 2003-2019
- Previous photon RT
- Tumors mainly located sinonasal cavity and orbit
- Most common histology SCC

CIRT fractionation schemes

Dose fractionation (Gy [RBE]/number of fractions)	
57.6/16	23 (41.1)
60.8/16	7 (12.5)
64/16	5 (8.9)
70.4/16	4 (7.1)
60/30	4 (7.1)
57.6/12	3 (5.4)
Others	10 (17.9)

Results: The 2-year local control, progression-free survival, and overall survival rates were 66.5%, 36.9%, and 67.9%, respectively. The median follow-up time was 28 months. Two patients (3.6%) developed grade ≥ 3 acute toxicities, and 14 (25.0%) developed grade ≥ 3 late toxicities. A single patient had confirmed grade 5 dermatitis with infection.

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Carbon ion experience in Japan for head and neck reirradiation after photon radiotherapy (J-CROS study)

Study	Modality	Study design	*n*	Median follow up periods (month)	Treatment methods (%)	SCC (%)	OS (%): year	LC (%: year)	Proportion of patients with severe late toxicities (%)
Our study	Carbon	M	56	28	RT (98.2) and CCRT (1.8)	19.6	67.9: 2y	66.5: 2y	25.0: Grade ≥ 3
Held et al.[9]	Carbon	S	229	28.5	RT	26.2	59.2: 1.5y	44.7: 1.5y	14.5: Grade ≥ 3
Held et al.[14]	Carbon	S	32	18.1	RT	0	77.4: 1y	66: 1y	0: Grade ≥ 3
Gao et al.[10]	Carbon	S	141	14.7	RT and CCRT	75.3	95.9: 1y	84.9: 1y	approximately 10
Spencer et al.[15]	Photon	M	79	—	CCRT	77.2	15.2: 2y	—	—
Ward et al.[16]	Photon (IMRT)	M	412	10.4	RT (25) and CCRT (75)	—	40.0: 2y	—	—
Romesser et al.[17]	Proton	M	92	10.4	RT (52.2) and CCRT (47.8)	56.5	65.2: 1y	—	7.2: Grade 4 2.9: Grade 5
Phan et al.[18]	Proton	S	60	13.6	RT (26.7) and CCRT (73.3)	66.7	69.0: 2y	—	20.0: Grade 3

Abbreviations: CCRT, concurrent chemoradiotherapy; IMRT, intensity-modulated radiotherapy; LC, local control; M, multi-institution; *n*, number of patients; OS, overall survival; PFS, progression-free survival; RBE, relative biological effectiveness; RT, radiotherapy; S, single-institution; SCC, squamous cell carcinoma.

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Carbon ion experience in Japan after carbon ions for head and neck reirradiation

Radiotherapy and Oncology 136 (2019) 148–153

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Feasibility of Re-irradiation using carbon ions for recurrent head and neck malignancies after carbon-ion radiotherapy

Kazuhiko Hayashi [a,b], Masashi Koto [a,*], Hiroaki Ikawa [a], Yasuhito Hagiwara [a], Hiroshi Tsuji [a], Kazuhiko Ogawa [b], Tadashi Kamada [a]

[a] Hospital of the National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Sciences and Technology, Chiba, Japan; [b] Department of Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

Retrospective
48 patients retreated with CIRT from 2007 to 2016
After previous CIRT

Histology:
21 pts (43.8%) MMM
17 (35.4%) ACC
6 (12.5%) bone and soft tissue sarcomas,
4 (8.3%) other disease types.

Tumor recurrence site
paranasal cavity (n = 18, 37.5%),
nasal cavity (n = 9, 18.8%),
Nasopharynx (n = 4, 8.3%),
orbit (n = 3, 6.3%),
cavernous sinus (n = 3, 6.3%),
other sites (n = 11, 22.9%).

Median dose of initial CIRT 57.6 GyRBE
Median dose at re-irradiation 54.0 GyRBE
No concurrent chemotherapy.

Median FU 27.1 months.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Carbon ion experience in Japan after carbon ions for head and neck reirradiation

Table 2
Toxicity.

Grade	2	3	4	5
Acute				
Mucositis	14	4	0	0
Dermatitis	1	1	0	0
Conjunctivitis	1	0	0	0
Nausea	1	0	0	0
Middle ear inflammation	1	0	0	0
Hearing impaired	1	0	0	0
Late				
Central nervous system necrosis	7	1	1	1
Optic nerve disorder	0	2	9	0
Infection	7	6	1	0
Arterial injury	0	0	1	0
Cataract	0	1	0	0
Osteonecrosis	7	0	0	0
Trismus	4	1	0	0
Dysphagia	1	1	0	0
Mucositis	4	0	0	0
Middle ear inflammation	2	0	0	0
Hearing impaired	1	0	0	0
Soft tissue necrosis	1	0	0	0
Central hypothyroidism	1	0	0	0

Acute ≥ G3 in 10.4%

Late ≥ G3 in 18 pts (37.5%)
50% expected visual loss for relapse
proximity to optic nerve

1 pt G5 (CNS radionecrosis)

acute and late toxicity profiles comparable to those of proton therapy.

McDonald et al[86]	2004-2014	PSPT	Retro	61	47.5	29	SCC (32) Other (29)	29 mo	2 y; LF 19.7%, OS, 32.7%,	8 G3 (bone and soft tissue necrosis); 3 G4 (2 unilateral blindness, 1 soft tissue necrosis); 3 treatment-related deaths (G5) (1 acute and 2 late)
Phan et al[59]	2011–2015	PSPT ($n = 15$), IMPT ($n = 45$)	Pro	60	58	73	SCC (40) Other (20)	13.6 mo	1 y; LRFFS 68.4%, OS, 83.8%	Acute G3+ toxicity 30%, including 22% feeding tubes; 1-y G3+ toxicity 16.7%; 3 treatment-related deaths (G5)
Romesser et al[58]	2011-2014	PSPT	Retro	92	39	39	SCC (52) Other (40)	13.3 mo	1 y; LRF 25.1%, OS, 65.2%	G3+ late toxicity: 6 pts (8.7%) for skin and 4 pts (7.1%) for dysphagia. 1 death during treatment (progression) and 2 G5 late bleeding
Hayashi et al[60]	2009-2013	PSPT	Pro	25	46	IA	SCC (25)	24 mo	2 y; LF 30%, OS, 46%,	1 pt with late G4. No G5. Patients were a mix of previously irradiated pts and pts with recurrence after single-modality surgery, for whom side effects may have been underestimated.

→ Worse toxicity if CIRT after CIRT compared to CIRT after photon *(personnal communication)*

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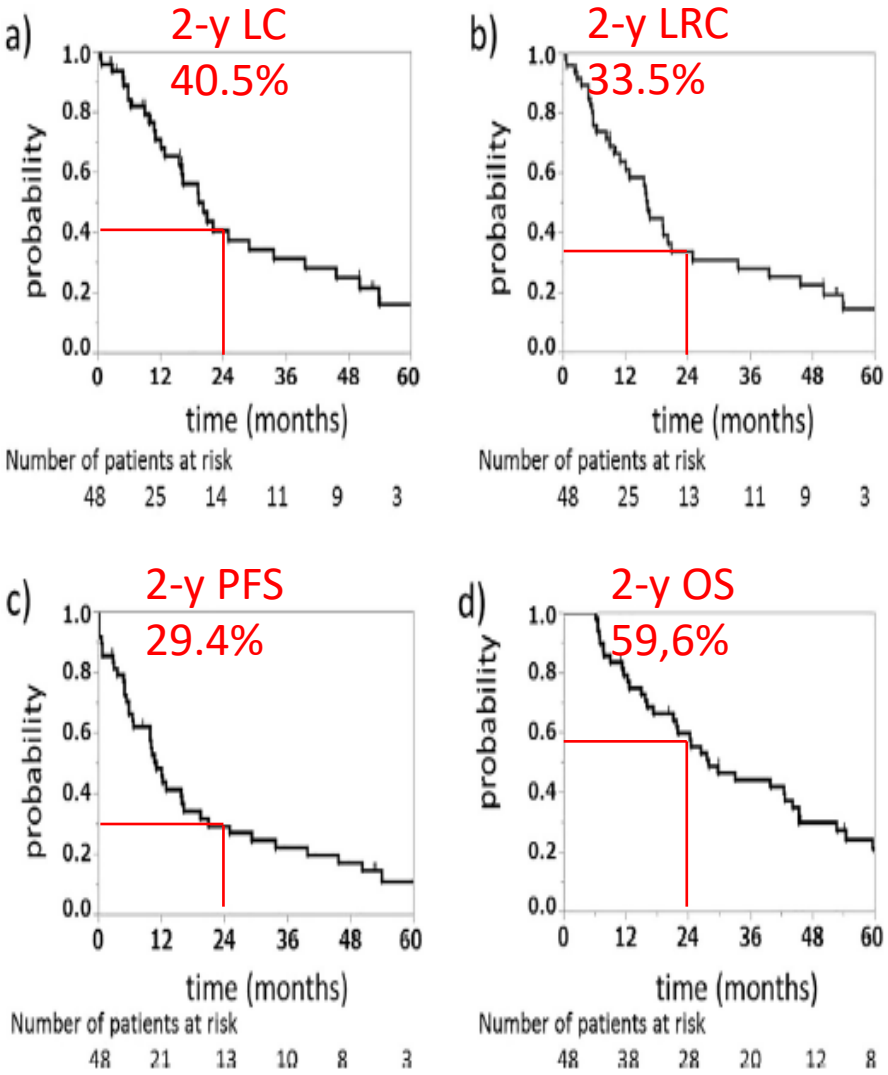
Carbon ion experience in Japan after carbon ions for head and neck reirradiation



Significant predictors @ MVA:

Site of failure at reirradiation
(in-field vs marginal recurrence)
2-y LC: 52.8% vs 28.2% (P = 0.030)
2-y PFS 38.6% vs 19.1% (P = 0.042)

Interval between initial CIRT and re-CRT
(<24 months vs >24 months)
2-y PFS 20.8% vs 38.3%, (P = 0.036)
2-y OS 37.5% vs 82.7% (P = 0.002)

In conclusion, our findings suggest that re-irradiation with CIRT is a reasonable treatment option with tolerable toxicity for recurrent head and neck malignancies after initial CIRT. In future, large-scale multicenter trials are warranted.

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Carbon ion experience @ SPHIC (China) for head and neck reirradiation

Tumor sites		
Nasopharynx	114	78.1
Nasal cavity or paranasal sinuses	12	8.2
Oropharynx	5	3.4
Salivary glands	4	2.7
Skull base	1	0.7
Larynx and hypopharynx	2	1.4
Other	3	2.1
Histology		
Squamous cell carcinoma (including poorly or un-differentiated)	110	75.3
Adenoid cystic carcinoma	10	6.8
Mucoepidermoid carcinoma	3	2.1
Adenocarcinoma	3	2.1
Spindle cell sarcoma	1	0.7
Osteosarcoma	1	0.7
Rhabdomyosarcoma	2	1.4
Pleomorphic sarcoma	1	0.7
Parotid mixed tumor	1	0.7
Primitive neuroectodermal tumor	1	0.7
Radiation induced secondary primary malignancy	8	5.5
Recurrent T stage*		
rT1	19	13.6
rT2	15	10.7
rT3	41	29.3
rT4	52	37.1
rT0 (+retropharyngeal node)	13	9.3
Recurrence clinical stage*		
I	18	12.9
II	25	17.9
III	41	29.3
IVA/B	56	40.0
Time to recurrence		
≥3 years	69	48.9
<3 years	72	51.1
median (mo)	36	
range (mo)	11–257	
Original RT technique		
IMRT	129	91.5
Stereotactic radiosurgery	1	0.7
Not recorded	11	7.8
Pre-Salvage-PT therapy		
Surgery	23	16.3
Chemotherapy	64	45.4
None	54	38.3

Salvage Carbon-Ion Radiation Therapy For Locoregionally Recurrent Head and Neck Malignancies

Jing Gao[1,2], Jiyi Hu[1,2], Xiyin Guan[1,2], Jing Yang[1,2], Weixu Hu[1,2], Lin Kon

SCIENTIFIC REPORTS

Median time to locoregional recurrence 12.9 mo
Median incidence of LC and RC 84.9% vs 97.7%

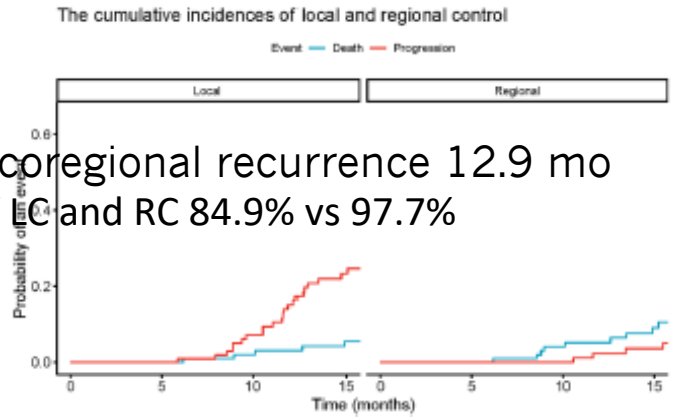

Figure 2. Cumulative incidence of local and regional failure with death as a competing risk.

141 patients
2015-2017
60 median GyRBE
14.7 mo follow up
Retrospective

	Grade 1or 2	Grade 3 or higher
Xerostomia	1 (0.7%)	1 (0.7%)
Mucosal necrosis	0	10 (7.1%) *
Temporal lobe necrosis	8 (5.7%)	1 (0.7%)
Hearing loss	1 (0.7%)	0
Cranial neuropathy	1 (0.7%)	3 (2.1%)

Table 3. Type and frequency of late toxicities. *Including 4 died of hemorrhage secondary of mucosal necrosis.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Carbon ion experience @ SPHIC (China) for nasopharyngeal cancer reirradiation

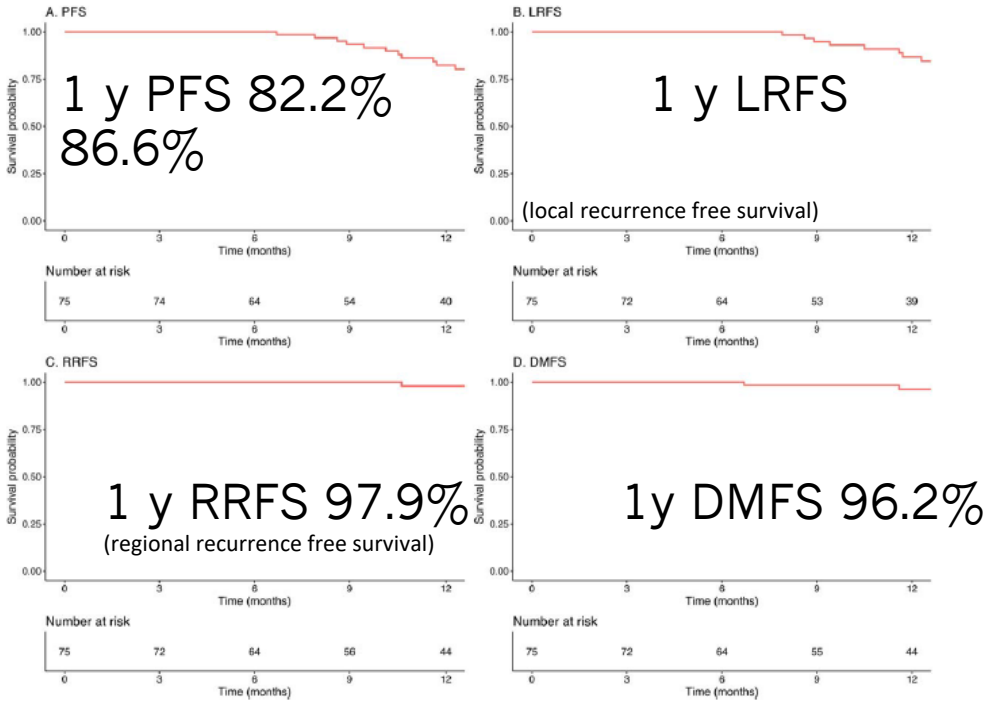

Figure 3. The 1-year (A) progression-free survival (PFS), (B) local recurrence-free survival (LRFS), (C) regional recurrence-free survival (RRFS), and (D) distant metastasis-free survival (DMFS) rates of patients with locoregionally recurrent nasopharyngeal carcinoma treated with intensity-modulated carbon ion radiotherapy.

Salvage Treatment Using Carbon Ion Radiation in Patients With Locoregionally Recurrent Nasopharyngeal Carcinoma: Initial Results

Jiyi Hu, MD, PhD[1]; Cihang Bao, MD[2]; Jing Gao, MD[1]; Xiyin Guan, MD[1]; Weixu Hu, MD[1]; Jing Yang, MD[1]; Chaosu Hu, MD[2]; Lin Kong, MD[2]; and Jiade J. Lu, MD, MBA [1]

75 patients
2015-2017
50-66 GyRBE
15 mo follow up

TABLE 2. Type and Frequency of Late Toxicities[a]

Toxicity	Grade 1 or 2 No. of Patients (%)	≥Grade 3 No. of Patients (%)
Nasopharyngeal mucositis[b]	0	7 (9.3%)[b]
Temporal lobe necrosis	7 (9.3%)	1 (1.3%)
Xerostomia	1 (1.3%)	1 (1.3%)
Hearing loss	1 (1.3%)	0
Cranial nerve neuropathy	1 (1.3%)	0

[a] Toxicities were graded according to the Radiation Therapy Oncology Group criteria.
[b] All necrosis initiated at the tumor bed without evidence of mucosal necrosis or erythema. One patient died of hemorrhage (grade 5).

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Carbon ion experience @ SPHIC (China) for nasopharyngeal cancer reirradiation

Journal of Cancer 2016, Vol. 7 774

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2016; 7(7): 774-783. doi: 10.7150/jca.14399

Research Paper

Phase I/II Trial Evaluating Carbon Ion Radiotherapy for Salvaging Treatment of Locally Recurrent Nasopharyngeal Carcinoma

Lin Kong[1], Jiyi Hu[2], Xiyin Guan[2], Jing Gao[2], Rong Lu[3], Jiade J. Lu[2]✉

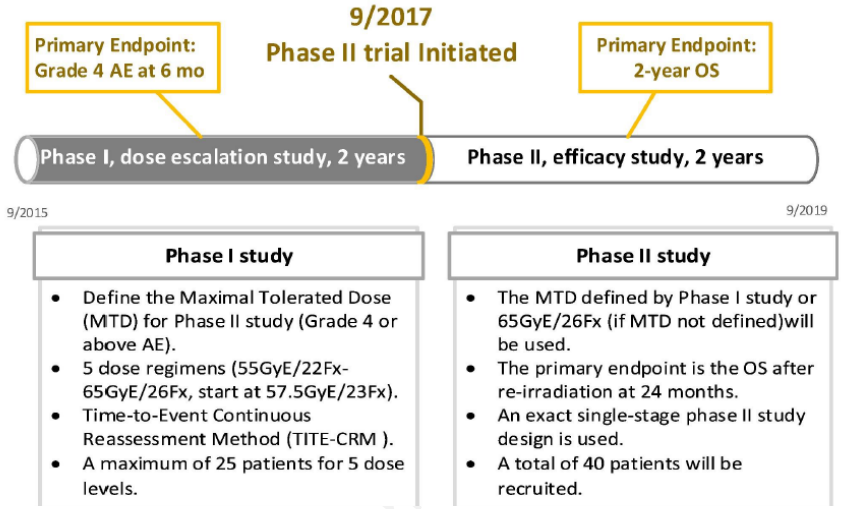
Kong et al. Chin J Cancer (2016) 35:101
DOI 10.1186/s40880-016-0164-5

Chinese Journal of Cancer

STUDY PROTOCOL Open Access

Phase I/II trial evaluating concurrent carbon-ion radiotherapy plus chemotherapy for salvage treatment of locally recurrent nasopharyngeal carcinoma

Lin Kong[1], Jing Gao[2], Jiyi Hu[2], Weixu Hu[2], Xiyin Guan[2], Rong Lu[3] and Jiade J. Lu[2,4*]

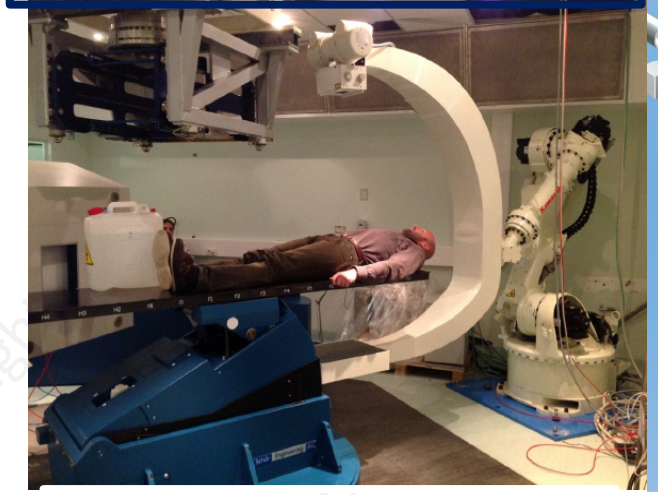


HITRI Heavy Ion Therapy Research Integration

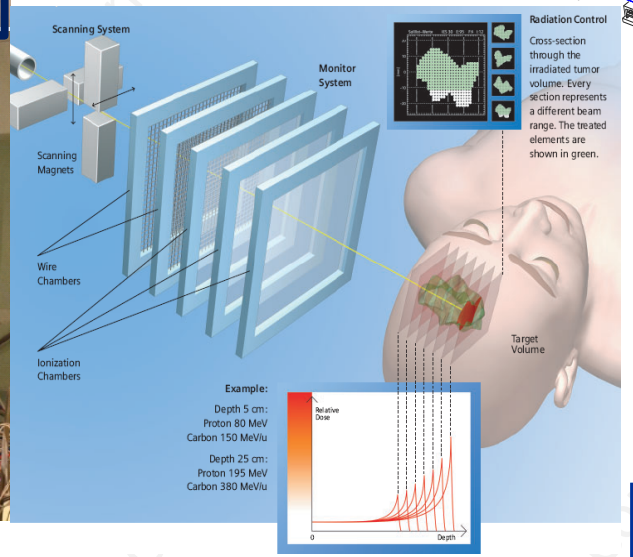
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

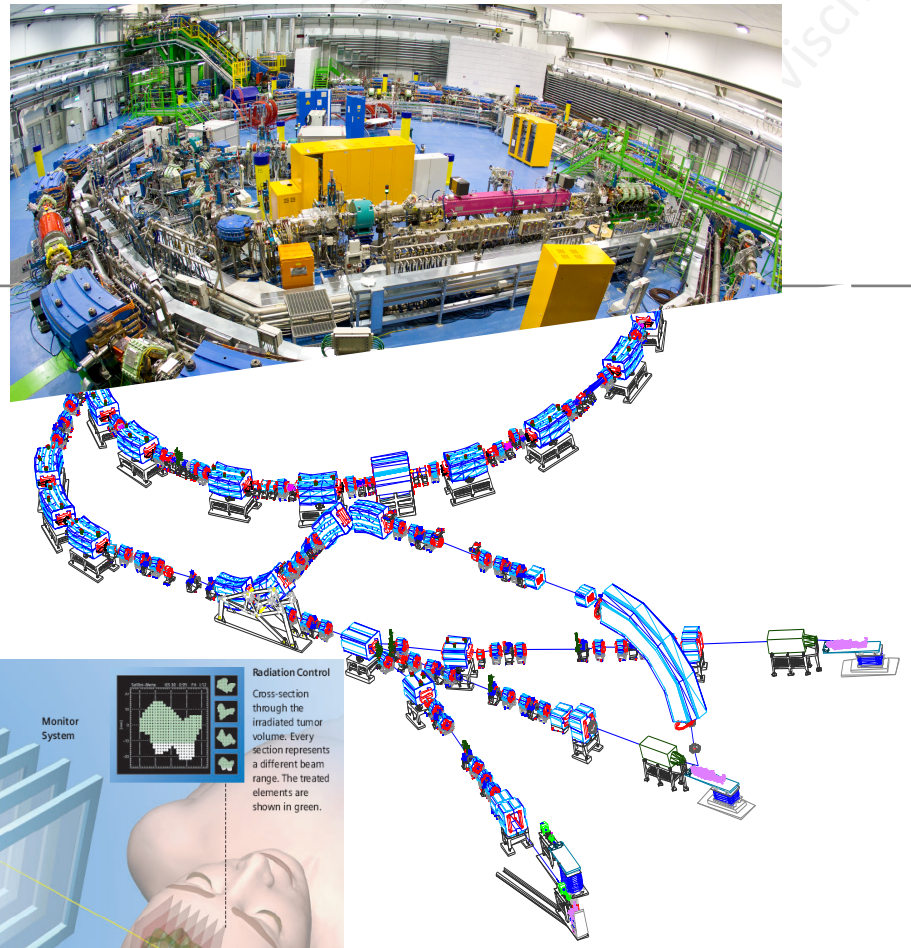
CNAO
National Center for Oncological Hadrontherapy experience in head and neck reirradiation

6-DoF Robotic couch



in room 3D imaging





Protons /Carbon Ions

3 treatment rooms
50 pts/day

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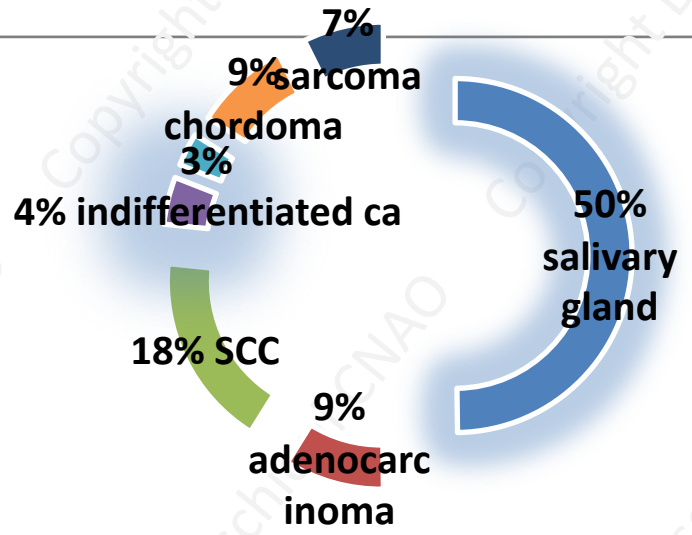
Reirradiation experience @CNAO in head and neck tumors



- SCC, not radioresistant tumors
- Previous surgery
- Good PS but fragile patient (for comorbidities)

→ **PROTONS**

Radioresistant histologies

→ **CARBON IONS**

HITRI
Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

CIRT reirradiation for recurrent salivary gland tumors @ CNAO

52 pts

Patients and treatment characteristics	N (%)
Sex	
Male	27 (53)
Female	24 (47)
Prior surgery	
None	1 (2)
One	10 (19.6)
Two	23 (45.1)
Three	10 (19.6)
Four	7 (11.7)
Histology	
Adenoid cystic carcinoma	38 (74.5)
Mucoepidermoid carcinoma	6 (11.8)
Myoepithelial carcinoma	3 (5.8)
Carcinoma ex pleomorphic adenoma	2 (3.9)
Mucinous adenocarcinoma	1 (2)
Ductal adenocarcinoma	1 (2)
Site of retreatment	
Parotid	17 (33.3)
Nasal cavity	5 (9.8)
Nasopharynx	3 (5.9)
Mandible	2 (3.9)
Maxillary sinus	5 (9.8)
Hard palate	3 (5.9)
Ethmoid	3 (5.9)
Para-pharyngeal space	3 (5.9)
Oropharynx	1 (2)
Lacrimal gland	2 (3.9)
Soft palate	1 (2)
Tongue	1 (2)
Retromolar trigone	1 (2)
Pterygopalatine fossa	4 (7.8)
Reirradiation stage	
rcT2	1 (2)
rcT3	5 (9.8)
rcT4a	26 (51)
rcT4b	19 (37.2)
rcN0	46 (90.2)
rcN1	4 (7.8)
rcN2b	1 (2)
M0	45 (88.2)
M1	6 (11.8)
Prior RT courses	
One	46 (90.1)
Two	5 (9.9)
CIRT fractionation scheme	
3.0 Gy [RBE]/fr × 15 fr	1 (2)
3.0 Gy [RBE]/fr × 16 fr	3 (5.8)
3.0 Gy [RBE]/fr × 18 fr	10 (19.6)
3.0 Gy [RBE]/fr × 19 fr	1 (2)
3.0 Gy [RBE]/fr × 20 fr	15 (29.4)
3.0 Gy [RBE]/fr × 22 fr	2 (3.9)
3.75 Gy [RBE]/fr × 16 fr	1 (2)
4.0 Gy [RBE]/fr × 14 fr	1 (2)
4.0 Gy [RBE]/fr × 15 fr	6 (11.7)
4.0 Gy [RBE]/fr × 16 fr	1 (2)
4.3 Gy [RBE]/fr × 16 fr	9 (17.6)
5.0 Gy [RBE]/fr × 12 fr	1 (2)

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Original Article

Reirradiation of salivary gland tumors with carbon ion radiotherapy at CNAO

B. Vischioni [a,*], B. Dhanireddy [a,b], C. Severo [a,c], M. Bonora [a], S. Ronchi [a], V. Vitolo [a], M.R Fiore [a], E. D'Ippolito [a], R. Petrucci [a], A. Barcellini [a], E. Ciurlia [a,d], A. Iannalfi [a], A. Hasegawa [a,e], S. Molinelli [a,e], A. Mirandola [a,e], F. Valvo [a], R. Orecchia [a,f]

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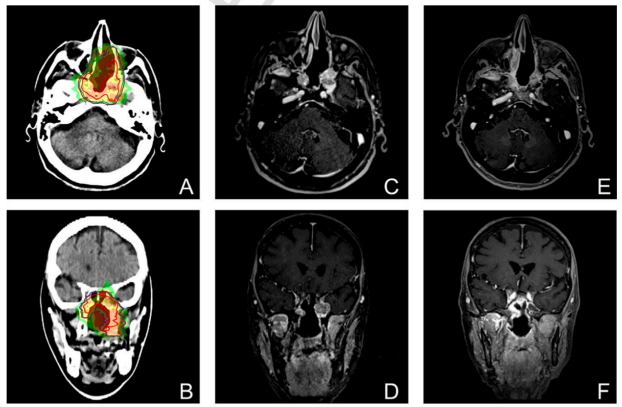

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

CIRT reirradiation for recurrent salivary gland tumors @ CNAO

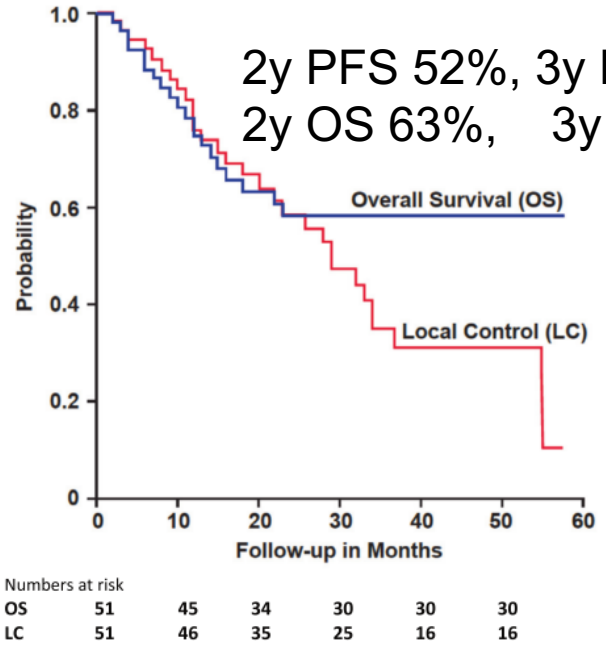

Fig. 2. Local control (LC) and overall survival (OS) following reirradiation with CIRT in a series of inoperable recurrent salivary gland tumors treated at CNAO.

Table 3
Multivariate analyses for prognostic value of major patients and treatment characteristics.

Model covariates		OS	PFS	LC
Gross tumor volume	HR	4.831	5.597	6.683
(<62 cc vs ≥62 cc)	(95% CI)	1.645–14.187	2.027–15.455	2.144–20.834
	P-value	0.004	0.0009	0.001
Nodal disease	HR	0.288	0.445	0.390
(N0 vs N+)	(95% CI)	0.031–2.690	0.110–1.793	0.088–1.741
	P-value	0.27	0.25	0.22
Re-radiation interval	HR	0.836	0.954	0.998
	(95% CI)	0.709–0.987	0.831–1.095	0.863–1.153
	P-value	0.03	0.50	0.98
Sex	HR	4.325	1.808	1.457
	(95% CI)	1.250–14.959	0.799–4.091	0.622–3.412
	P-value	0.02	0.16	0.39
M1 disease before CIRT	HR	0.156	0.740	0.863
	(95% CI)	0.018–1.361	0.245–2.238	0.282–2.640
	P-value	0.09	0.59	0.80
Age	HR	1.387	1.146	1.196
(<60 years vs ≥62 years)	(95% CI)	0.441–4.363	0.499–2.633	0.511–2.799
	P-value	0.58	0.75	0.68
CIRT radiation dose	HR	0.986	0.956	0.943
	(95% CI)	0.909–1.069	0.898–1.017	0.882–1.008
	P-value	0.73	0.16	0.09

Vischioni et al, 2020

Author	Particle	No patients (Histology)	Median FU	Outcomes	G3+ toxicities
Jensen et al. 2015	Carbon ions	52 (salivary glands)	14 months	1y LC 70%, 2y LC 47% 1y OS 81%, 2y OS 63%	No acute Late **G3 = 5,8%** **G4 = 3,8%** ica blow-out
Hayashi et al. 2019	Carbon ions	48 (miscellaneous)	27,8 months	2y LC 40,5% 2y PFS 29,4% 2y OS 59,6%	Late ≥ G3 in 37.5% 1 pt G5
Gao et al. 2019	Carbon ions	141 (miscellaneous)	14,7 months	1y LPFS 84,9% 1y OS 95,9%	≥ G3 in 7,1% (4 late G5 events)
CNAO	Carbon ions	52 (salivary glands)	23 months	2y PFS 52%, 3y PFS 43,5% 2y OS 63%, 3y OS 54,5%	Acute G3 = 3,9% Late G3 = 17,5% No G4

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CIRT reirradiation for recurrent sinonasal tumors @ CNAO

Article

Particle Reirradiation of Malignant Epithelial and Neuroectodermal Sinonasal Tumors: A Case Series from CNAO

Barbara Vischioni [1,*,†], Rossana Ingargiola [1,†], Maria Bonora [1], Sara Ronchi [1], Anna Maria Camarda [1], Stefania Russo [2], Eleonora Rossi [2], Giuseppe Magro [2], Alfredo Mirandola [2] and Ester Orlandi [1]

Table 1. Patients and tumor characteristics at the time of primary treatment.

Patients Characteristics	All Patients (n = 15)
Median age	58 (range 32–84)
Gender	
Males	13 (86.7%)
Females	2 (13.3%)
Histology	
ITAC	7 (46.7%)
SCC	2 (13.3%)
ONB	3 (20%)
SNUC	2 (13.3%)
Adenocarcinoma	1 (6.7%)
Stage (TNM VIII ed.)	
I	0
II	2 (13.3%)
III	7 (46.7%)
IV	6 (40%)
Site of primary tumor	
Nasal cavity	7 (46.7%)
Ethmoid sinus	6 (40%)
Maxillary sinus	2 (13.3%)
Primary treatment	
Surgery	2 (13.3%)
Surgery + RT	8 (53.3%)
Exclusive RT	5 (33.4%)
Type of first RT	
Photons	14 (93.3%)
Gammaknife	1 (6.7%)
First RT characteristics	
Median dose	60 Gy (range 20–70)
Median dose/fraction (fr)	2 Gy/fr (1.8–20)

Table 2. Patients and tumor characteristics at the time of particle re-RT.

Patients Characteristics	All Patients (15)
Median age	61.5 years (range 38–87)
Median time from first RT	37 months (range 10–213)
No. of relapses before the particle re-RT	
1	5 (33.3%)
2	7 (46.7%)
3	3 (20%)
Site of relapsed tumor at the particle re-RT	
Maxillary sinus	2 (13.3%)
Ethmoid sinus	4 (26.6%)
Nasal cavity	7 (46.7%)
Sphenoid sinus	1 (6.7%)
Retromolar trigone	1 (6.7%)
Pattern of failure after particle re-RT	
Infield	9 (60%)
Marginal	6 (40%)
Number of previous surgery	
0	2 (13.3%)
1	7 (46.7%)
2	5 (33.3%)
3	1 (6.7%)
Re-RT particle type	
PT	2 (13.3%)
CIRT	13 (86.7%)
Re-RT schedule	
Median dose	54 GyRBE (range 45–64)
Median dose/fr	3 GyRBE
Median EQD2 (α/β = 3)	61.2 Gy
Median GTV	36.41 cm^3 (3.4–122.89)
Median follow-up time	22 months (range 6–95)
Acute Toxicity	
G0	1 (6.7%)
G1-2	14 (93.3%)
G3-4	0
Late Toxicity	
G0	4 (26.6%)
G1-G2	10 (66.7%)
G3-G4	1 (6.7%)

1 y LC 44%

1 y OS 92.9%

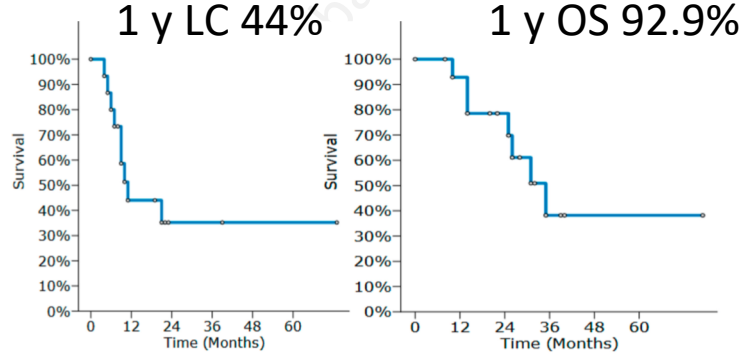

Figure 1. Kaplan–Meyer curve for local control (LC) in the series with patients at risk at 6, 12, 24, and 36 months of 13, 6, 2, and 2, respectively (**A**). Kaplan–Meyer curve for overall survival (OS) with patients at risk at 6, 12, 24, and 36 months of 15, 14, 9, and 3, respectively (**B**). Censored patients are marked with a circle.

Table 3. Acute and late toxicity details after particle re-RT.

	Number of Toxic Effects			
Grade of Toxic Effects	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ACUTE				
Mucositis	2	4	0	0
Dermatitis	6	3	0	0
Edema	0	1	0	0
Conjunctivitis	2	2	0	0
Neuropathy	0	2	0	0
Dry mouth	0	1	0	0
LATE				
Dry mouth	1	1	0	0
Dysphagia	1	1	1	0
Neuropathy	0	3	0	0
Brain necrosis	1	2	0	0
Periorbital edema	0	1	0	0
Dry Eye	1	0	0	0
Soft tissue necrosis	0	1	0	0
Hypopituitarism	0	1	0	0
Alopecia	1	0	0	0
Fibrosis	1	0	0	0
Trismus	1	0	0	0

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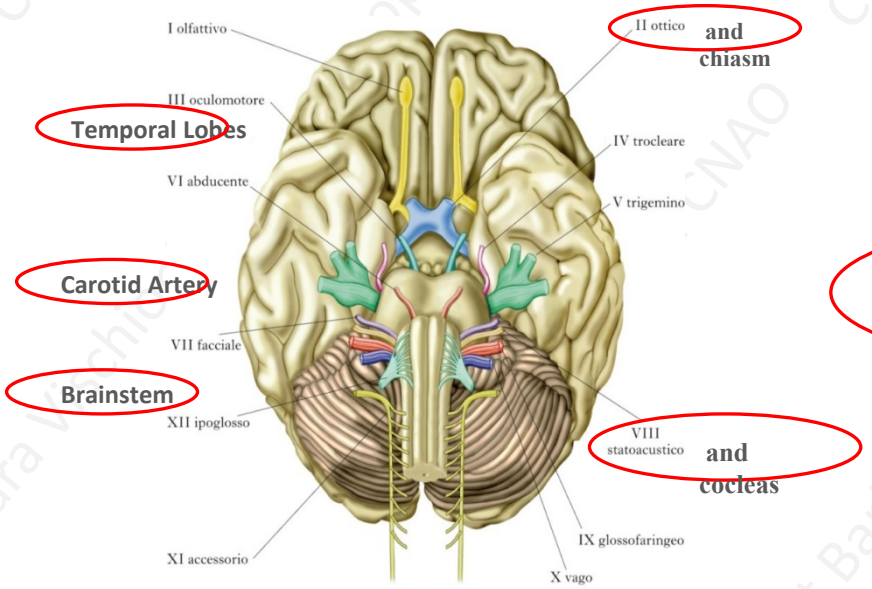
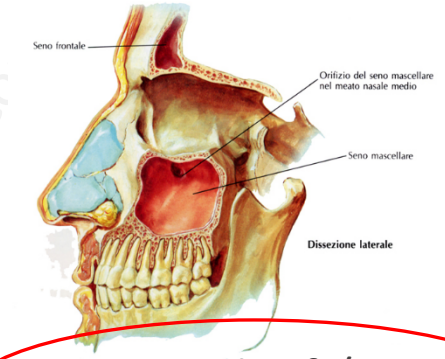
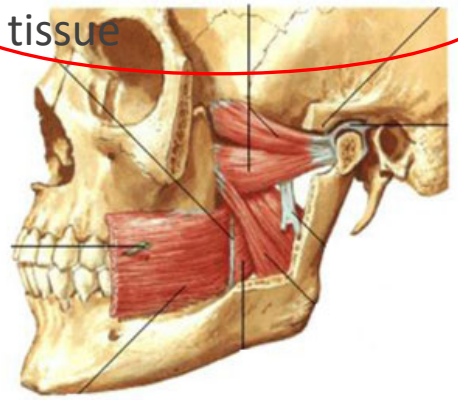
Late toxicity and reirradiation





Bones and soft/muscle tissue



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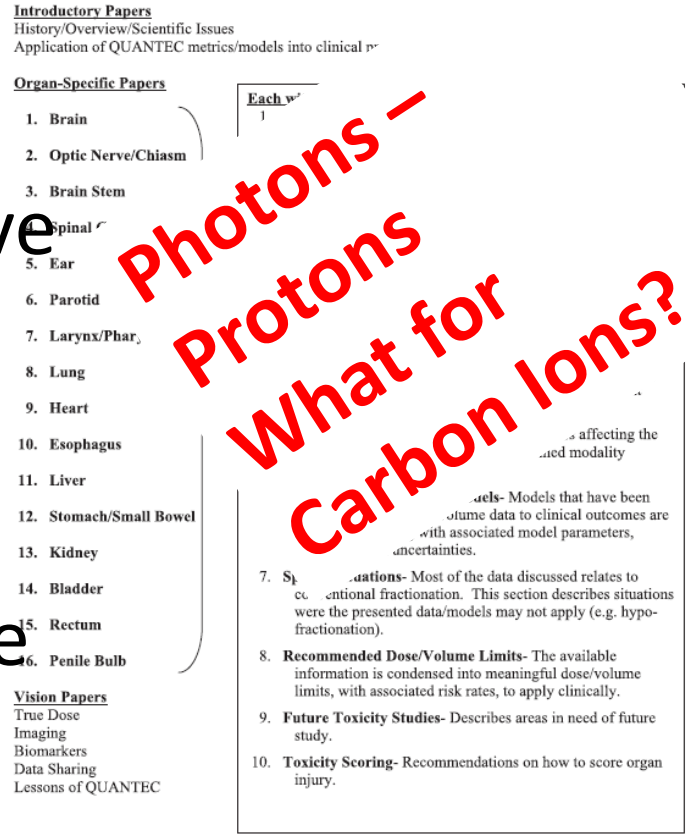
Normal

Tissue

Effect in the

Clinic



Introductory Papers
History/Overview/Scientific Issues
Application of QUANTEC metrics/models into clinical p

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal C**
5. **Ear**
6. **Parotid**
7. **Larynx/Phar**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each w
]

affecting the
ied modality

uels- Models that have been
olume data to clinical outcomes are
with associated model parameters,
ncertainties.

7. **S uations**- Most of the data discussed relates to
c ntional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Photons – Protons What for Carbon Ions?

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Late toxicity and reirradiation

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					

CTCAE scale to grade toxicity
Example of mucositis

Strahlenther Onkol 2014 · 190:686–691
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Active raster scanning with carbon ions

Reirradiation in patients with recurrent skull base chordomas and chondrosarcomas

Table 4 Cranial nerve status/side effects before and after treatment

Cranial nerve paresis/ side effect	Baseline (*n*)	Improvement (*n*)	Impairment (*n*)	New (*n*)
Nn. olfactorii	3	–	–	–
N. opticus	8	1	–	–
N. oculomotorius/ trochlearis	4	–	–	–
N. trigeminus	11	1	3	–
N. abducens	12	1	2	–
N. facialis	4	–	–	–
N. vestibulocochlearis	10	–	–	–
N. glossopharyngeus	5	–	–	–
N. vagus	4	–	–	–
N. hypoglossus	8	–	1	–
Loss of taste	5	–	–	–
Middle ear effusion	2	–	–	3
Pituitary deficiency	4	–	–	–
Hemiplegia	1	–	–	–
Focal epilepsy	1	–	–	–
Chronic cephalgia	5	1	–	–
Osteoradionecrosis	–	–	–	1
Temporal lobe reaction	–	–	–	5

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Late toxicity and reirradiation: Focus on carotid artery rupture

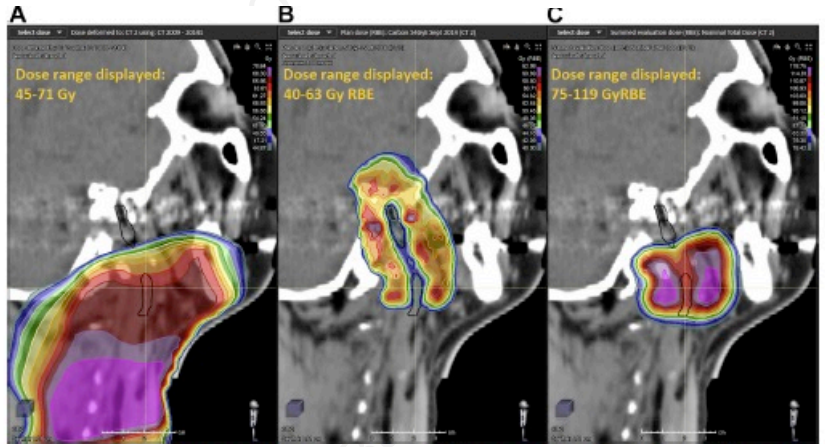
	Quality of Final Re-RT			P value
	All (n = 96)	Proton RT (n = 17)	CIRT (n = 79)	
Median age (range), y	61 (24-88)	55 (24-75)	63 (24-88)	
Sex, male:female	56:40	8:9	48:31	NS
Comorbidity, n (%)				
Hypertension	26 (27.0)	2 (11.8)	24 (30.4)	NS
Diabetes mellitus	6 (6.3)	2 (11.8)	4 (5.1)	NS
Cardiovascular disease	5 (5.2)	3 (17.6)	2 (2.5)	.037
Histology, n (%)				
Adenoid cystic carcinoma	28 (29.2)	0 (0.0)	28 (35.4)	.003
Squamous cell carcinoma	27 (28.1)	13 (76.5)	14 (17.7)	
Sarcoma	11 (11.5)	0 (0.0)	11 (13.9)	
Mucoepidermoid carcinoma	5 (5.2)	0 (0.0)	5 (6.3)	
Undifferentiated carcinoma	5 (5.2)	1 (5.9)	4 (5.1)	
Pleomorphic adenoma	5 (5.2)	0 (0.0)	5 (6.3)	
Adenocarcinoma	3 (3.1)	0 (0.0)	3 (3.8)	
Myoepithelial carcinoma	3 (3.1)	0 (0.0)	3 (3.8)	
Meningioma	3 (3.1)	1 (5.9)	2 (2.5)	
High grade glioma	2 (2.1)	2 (11.8)	0 (0.0)	
Other[a]	4 (4.2)	0 (0.0)	6 (7.8)	
Site of Primary Tumor, n (%)				
Parotid gland	18 (18.8)	0 (0.0)	18 (22.8)	.003
Paranasal sinuses	17 (17.7)	0 (0.0)	17 (21.5)	
Rhinopharynx	15 (15.6)	6 (35.3)	9 (11.4)	
Oropharynx	10 (10.4)	3 (17.6)	7 (8.9)	
Oral cavity	7 (7.3)	2 (11.8)	5 (6.3)	
Brain/meninges	5 (5.2)	3 (17.6)	2 (2,5)	
Nasal cavity	5 (5.2)	1 (5.9)	4 (5.1)	
Skull base	5 (5.2)	0 (0.0)	5 (6.3)	
Skin of scalp or face	4 (4.2)	1 (5.9)	3 (3.8)	
Submandibular gland	3 (3.1)	0 (0.0)	3 (3.8)	
Larynx	2 (2.1)	1 (5.9)	1 (1.3)	
Lacrimal gland	2 (2.1)	0 (0.0)	2 (2.5)	
Other[b]	3 (3.1)	0 (0.0)	3 (3.8)	
Site of Highest Dose to CA, n (%)				
Neck	50 (52.1)	9 (52.9)	41 (51.9)	NS
Skull base	34 (35.4)	4 (23.5)	30 (38.0)	
Sinus cavernosus	10 (10.4)	3 (17.6)	7 (8.9)	
Intracranial	2 (2.1)	1 (5.9)	1 (1.3)	
Tumor Involvement Grade, n (%)				
No involvement	24 (25.0)	6 (35.3)	18 (22.8)	NS
<1/3 of CA circumference	14 (14.6)	2 (11.8)	12 (15.2)	
≥1/3 < 2/3 of CA circumference	9 (9.4)	2 (11.8)	7 (8.9)	
≥2/3 of CA circumference	49 (51.1)	7 (41.2)	42 (53.2)	
Surgery, n (%)				
Any surgery	80 (83.3)	10 (58.8)	70 (88.6)	.007
Neck dissection	26 (27.1)	6 (35.3)	20 (25.3)	NS
In vicinity of highest dose to CA	46 (47.9)	5 (29.4)	41 (51.9)	NS
High-Risk Features[c], n (%)				
0 risk factors	28 (29.2)	8 (47.1)	20 (25.3)	NS
1 risk factor	41 (42.7)	6 (35.3)	35 (44.3)	
2 risk factors	27 (28.1)	3 (17.6)	24 (30.4)	

CA, carotid artery; CIRT, carbon ion radiation therapy; NS, not significant; RT, radiation therapy.
[a] Esthesioneuroblastoma, sinonasal carcinoma, carcinoma ex pleomorphic adenoma, oncocytoma.
[b] Mandible, hyoid bone, lymph node metastasis neck.
[c] Risk factors: Tumor involvement grade ≥2/3 and surgery in high-dose areas.

Risk of carotid blowout after reirradiation w particle therapy

Jon Espen Dale MD [a,*], Silvia Molinelli MSc [b], Elisa Ciurlia MD [b], Mario Ciocca MSc [b], Maria Bonora MD [b], Viviana Vitolo MD [b], Alfredo Mirandola MSc [b], Stefania Russo MSc [b], Roberto Orecchia MD [b,c], Olav Dahl PhD, MD [a,d], Piero Fossati MI

Advances in Radiation Oncology (2017) 2, 465-474



No vascular toxicity in patients reirradiated with carbon ions @ CNAO

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

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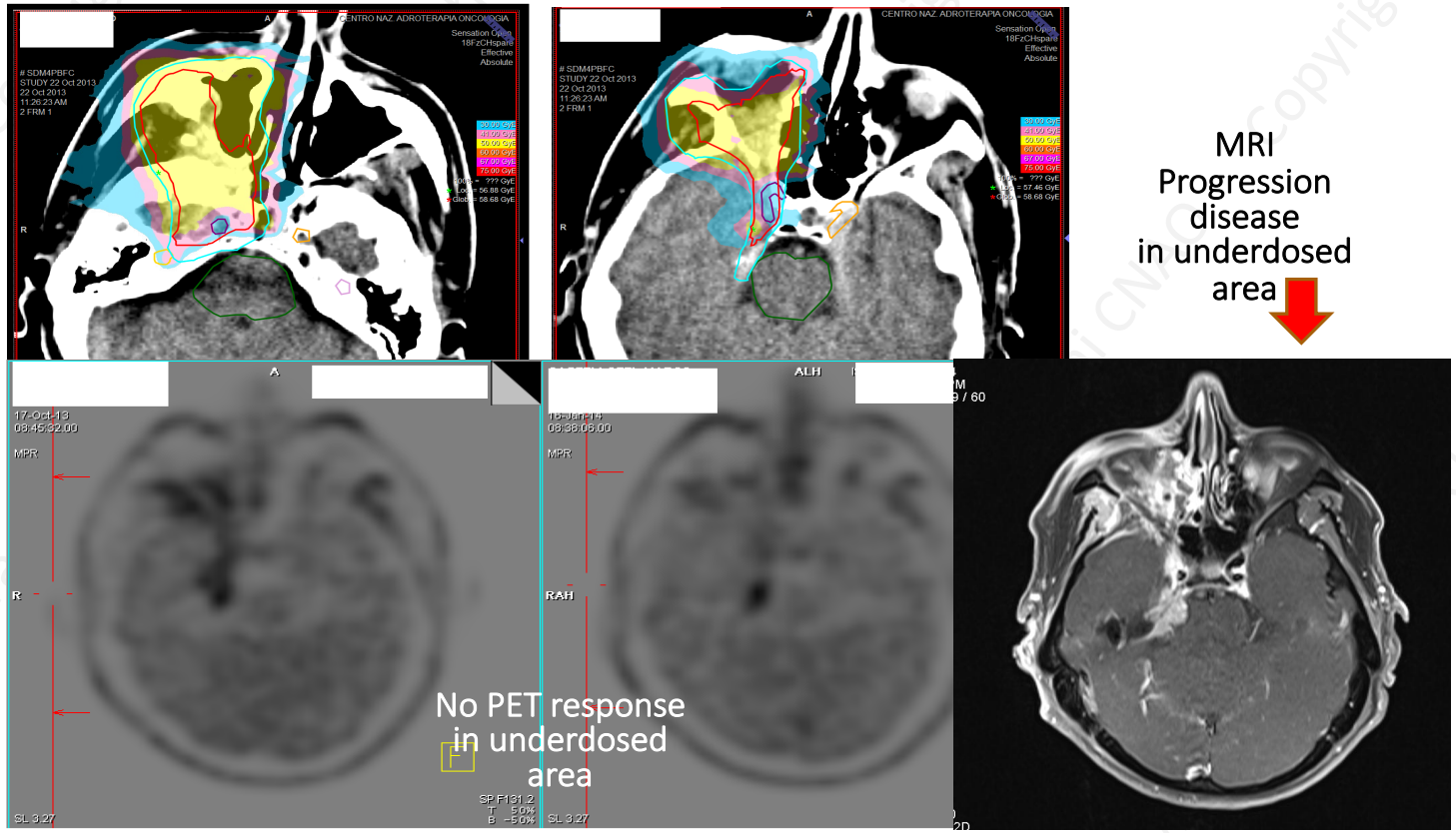
Late toxicity and reirradiation: risk of local progression in case of organ sparing

Selective Carotid Sparing



MRI
Progression
disease
in underdosed
area

54 Gy(RBE) to GTV
30 Gy (RBE) to ICA

Carotid blowout syndrome after reirradiation for head and neck malignancies: a comprehensive systematic review for a pragmatic multidisciplinary approach

Daniela Alterio [a,1], Irene Turturici [a,1], Stefania Volpe [a,b,*], Annamaria Ferrari [a], Samuel William Russell-Edu [c], Barbara Vischioni [d], Dikran Mardighian [e], Lorenzo Preda [f,g], Sara Gandini [h], Giulia Marvaso [a,b], Matteo Augugliaro [a], Stefano Durante [a], Simona Arculeo [a,b,3], Filippo Patti [a,b,3], Dario Boccuzzi [i], Alessia Casbarra [a,b], Anna Starzynska [j], Riccardo Santoni [k,2], Barbara Alicja Jereczek-Fossa [a,b,2]

Carotid coiling to increase dose prescription

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Take home messages

- Only small series (very heterogeneous in histologies and location in the head and skull base) with short follow up are available on particle reirradiated patients

- This is because hadrontherapy is a relative new type of treatment and there are only a few centers treating patients, especially with carbon ions (only 13) in the world. Prospective clinical trials or collaborative registries are needed to assess the benefit of particle therapy in reirradiation setting

- Data of patients reirradiated with protons compare well with IMRT. Carbon ion reirradiation is a valid option when surgery is not indicated for radioresistant tumors (nasopharynx?)

- Patient selection criteria are needed to address patients to reirradiation with protons or carbon ions (genetic signature, nomograms…).

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Vademecum for reRT

- multimodal imaging could be very useful to help define target volumes
- fusion of Digital Imaging and Communications in Medicine radiotherapy files to generate a sum plan (DICOM), is recommended if available in order to evaluate total cumulative doses and better optimize the reirradiation plan
- Active scanning and robust optimization

✓ There is little consensus on dose constraints to organs at risk in the reirradiation setting

✓ BED for OARs/cumulative doses

TABLE 2 | Dose constraints of OARs as proposed in the CARE trial by Held et al. (34).

Structures	Maximum Cumulative EQD2 (RT interval ≤24 months)	Maximum Cumulative EQD2 (RT interval >24 months)	Comments
Brain stem ($\alpha/\beta = 2$)	60	72 (≙+20%)	Maximum (surface)
Optic chiasm ($\alpha/\beta = 3$)	54	64.8 (≙+20%)	Maximum
Optic nerves ($\alpha/\beta = 3$)	54	64.8 (≙+20%)	Maximum
Spinal cord ($\alpha/\beta = 2$)	50	60 (≙+20%)	Maximum
Further OARs	ALARA		/

OAR, organ at risk; EQD2, equivalent dose in 2-Gy fractions; RT, radiotherapy; ALARA, as low as reasonably achievable.

Treatment tailored to the patient characteristics

Treatment consent

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