e-session 572

Innovative therapeutic approaches for rare tumors of the head and neck cancers

Expert: **Dr Barbara Vischioni**, CNAO Foundation, Pavia, Italy

Discussant: **Dr Carlo Resteghini**, National Cancer Institute - IRCCS Foundation, Milan, Italy

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Innovative therapeutic approaches for rare tumors of the head and neck cancers

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2021, May 13th
Barbara Vischioni MD, PhD
CNAO
National Center for Oncological Hadrontherapy

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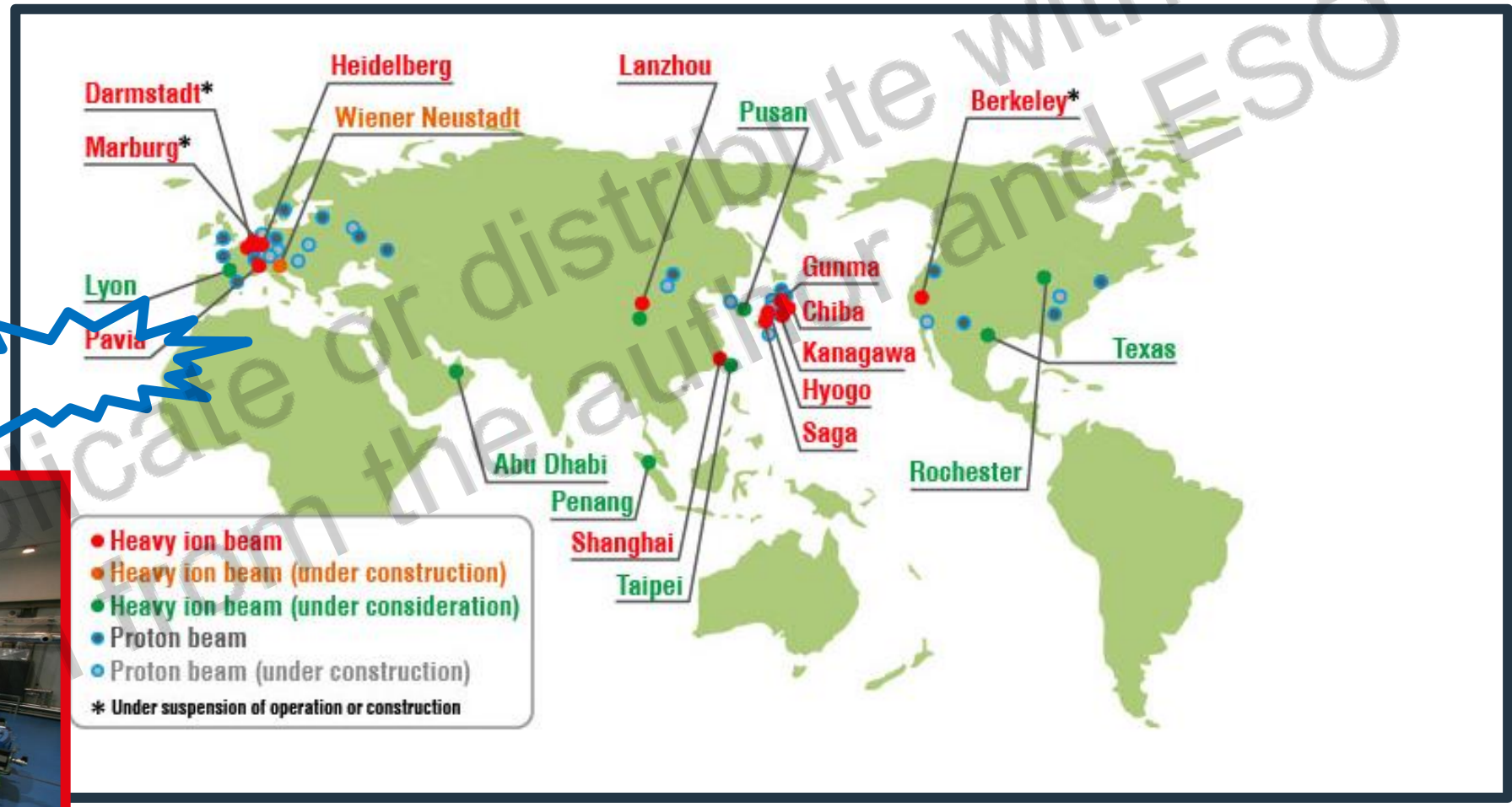
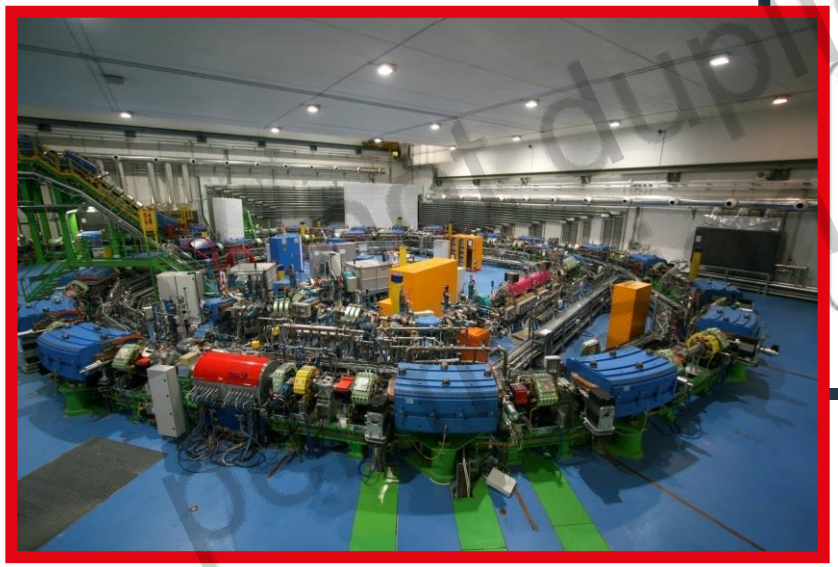
Charged particle therapy facilities around the world

AT CNAO BOTH PROTONS AND CARBON IONS BEAMS





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Rare tumors of the head and neck

According to

RARECARE definition (incidence < 6/100000 persons/year)

EC definition (prevalence < 5/10000)

- **Salivary gland tumors**

- **Sinonasal tumors**

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Outline

Salivary gland tumors

- Role of radiotherapy (RT) in locoregional disease
- What is particle therapy
- Evidence for salivary gland tumors treatment with carbon ions in Japan and Germany
- Recurrent disease

Sinonasal tumors

- Management and role of RT in locoregional disease
- Evidence in particle therapy for sinonasal tumors (protons and carbon ions)

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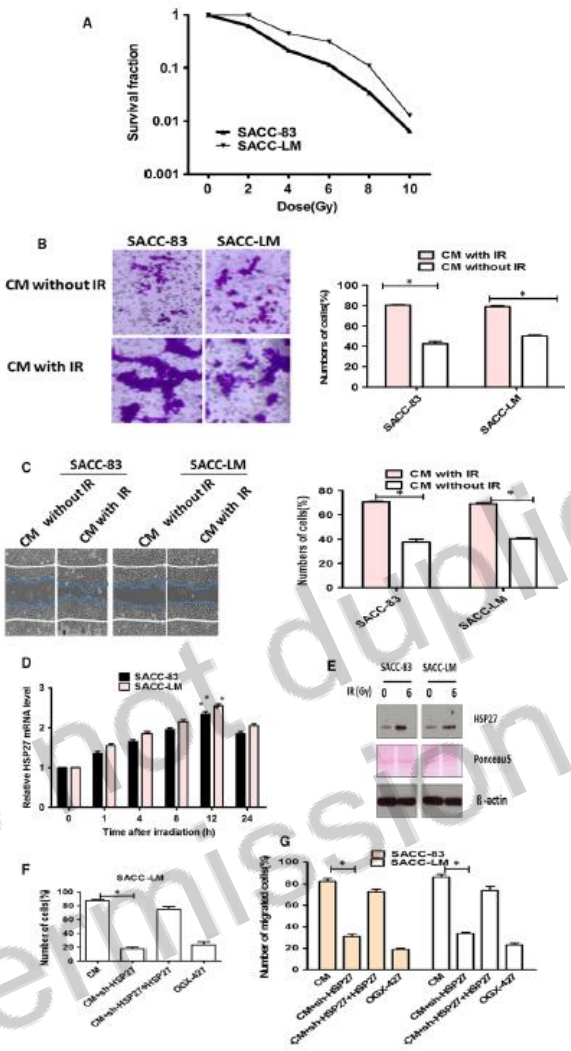
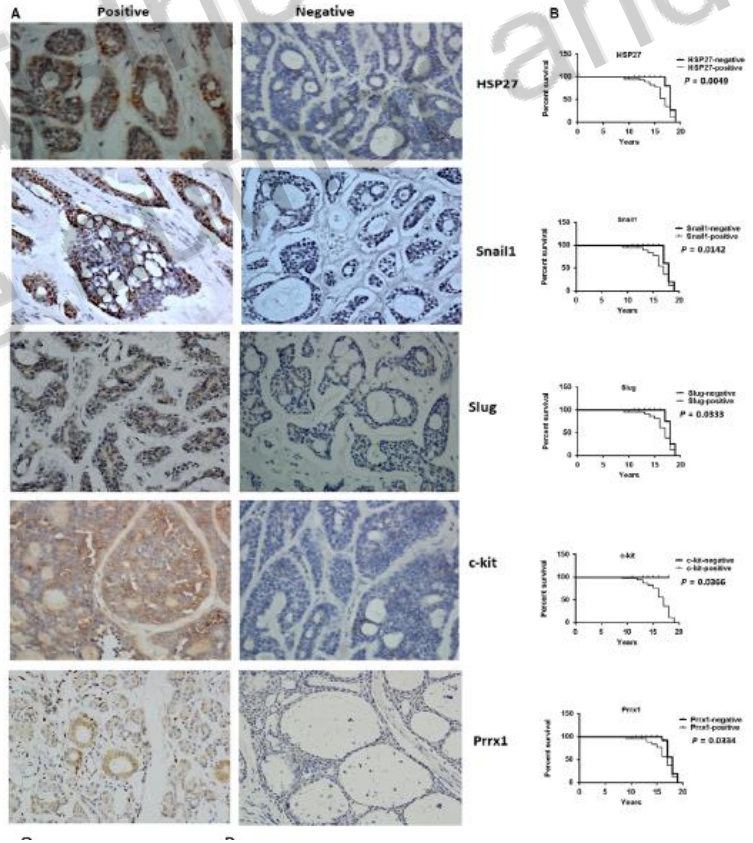
Salivary gland tumors and radioresistance



J. Cell. Mol. Med. Vol 22, No 4, 2018 pp. 2283-2298

HSP27 associates with epithelial–mesenchymal transition, stemness and radioresistance of salivary adenoid cystic carcinoma

Wei Chen [a, b, †], Xiaohua Ren [c, †], Jiashun Wu [a], Xiaolei Gao [a], Xiao Cen [a], Shasha Wang [a], Surui Sheng [a], Qianming Chen [a], Ya-jie Tang [d], Xin-hua Liang [a, *], Ya-ling Tang [a, e, *]



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Postoperative RT for Adenoid Cystic Carcinoma (ACC)

- Standard treatment: radical surgery + PORT

- PORT: significant impact on LC from retrospective series

rates of 95%, 86%, and 79% at 5-, 10-, and 15-years

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Balamucki CJ 2012; Mendenhall WM 2004; Garden AS, 1995; van Weert S, 2013;Ali S, 2017, Chen AM 2006, Gomez DR 2008, Oplatek A, 2010; Ellington CL, 2012; Prokopakis EP, 1999; Li Q 2011; Cordesmeyer R, 2016, Temelli O, 2017, Lee A 2017 Pakebayashi A, 2018; van Weert S, 2013; Ellington CL 2012 ; da Cruz Perez DE 2009 , Barret AW 2009

Definitive RT for unresectable SGCs

research article

Results of photon radiotherapy for unresectable salivary gland tumors: is neutron radiotherapy's local control superior?

Daniel E. Spratt[1], Lucas Resende Salgado[1], Nadeem Riaz[1], Michael G. Doran[1], Moses Tam[1], Suzanne Wolden[1], Evangelia Katsoulakis[1], Shyam Rao[1], Alan Ho[2], Richard Wong[3], Nancy Y. Lee[1]

[1] Department of Radiation Oncology, [2] Department of Medicine, [3] Department of Head and Neck Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Radiol Oncol 2014; 48(1): 56-61.

IMRT with doses ≥ 70 GY

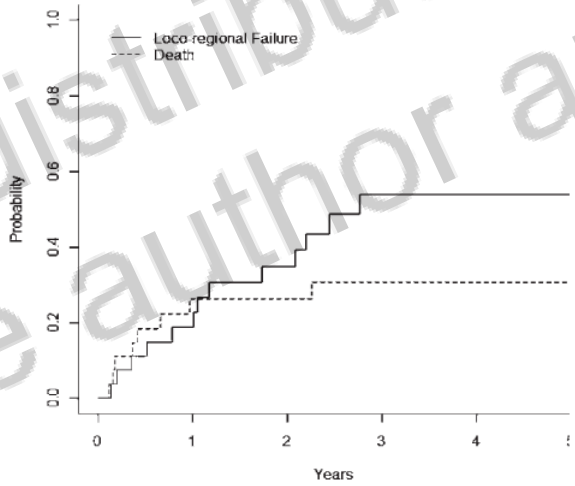

FIGURE 2. Loco-regional failure cumulative incidence for entire cohort with death as the competing risk.

5ys LC 50-55%

For unresectable SGC heavy particles or mixed beams (carbon ions with photons) are higly recommended

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Local control benefit with neutron treatment for unresectable malignant salivary gland cancers (SGCs)

Neutrons

Autore	*N.ro di pazienti*	*Tasso di controllo locoregionale (a 5 anni)*
Saroja et al., 1985	113	63 %
Catterall et Errington, 1987	65	77 %
Battermann et Mijnheer, 1986	32	66 %
Griffin et al., 1988	32	81 %
Duncan et al., 1987	22	55 %
Tsunemoto et al., 1989	21	62 %
Maor et al., 1981	9	6
Ornitz et al., 1989	8	3
Eichhorn, 1981	5	3
Skolyszewski, 1982	3	2
Schwarz, 1993	44	63 %
Breteau et al., 1993	21	57 %
Douglas et al., 1999	120	[illegible]
Total	495	64 %

RTOG-MRC Cooperative Randomized Study

Photon

Autore	*N.ro di pazienti*	*Tasso di controllo locoregionale (a 5 anni)*
Fitzpatrick et Theriault, 1986	50	12 %
Vikram et al., 1984	49	4 %
Borthne et al., 1986	35	23 %
Rafla, 1997	25	36 %
Fu et al., 1977	19	32 %
Stewart et al., 1968	19	47 %
Dobrowsky et al., 1986	17	41 %
Shidia et al., 1980	16	38 %
Elkon et al., 1978	13	15 %
Rossman, 1975	11	54 %
Piedbois et al., 1989	35	43 %
Buyn et al., 1980	23	22 %
Miglianico et al., 1987	21	62 %
Wang et al., 1991	24	[illegible]
Total	357	31 %


LBL-31422

Lawrence Berkeley Laboratory
UNIVERSITY OF CALIFORNIA

Accelerator & Fusion Research Division

DEC 1 6 1991

Presented at the NIRS International Workshop on Heavy Charged Particle Therapy and Related Subjects, Chiba, Japan, July 4-5, 1991, and to be published in the Proceedings

Future Biomedical Research at the Bevalac

J.R. Alonso, W.T. Chu, B. Feinberg, B.A. Ludewigt, T.R. Renner, and J.W. Staples

October 1991

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Prepared for the U.S. Department of Energy under Contract Number DE-AC03-76SF00098

Griffin et al, Int J Radiat Oncol Biol Phys, 1988

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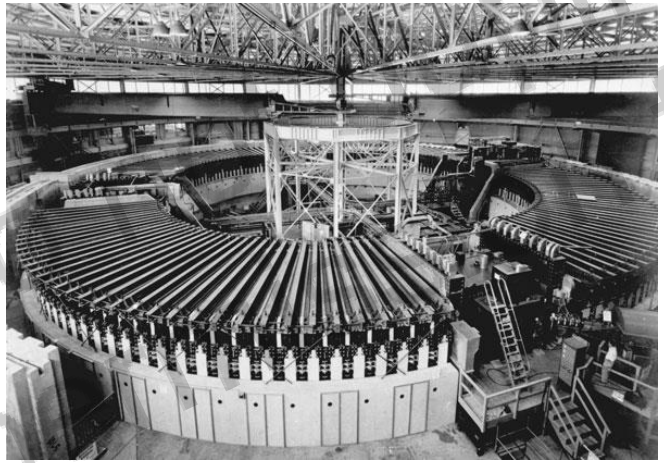
Clinical experience: definitive RT for unresectable SGCs

Neutron vs photon irradiation of inoperable salivary gland tumors: results of an RTOG-MRC Cooperative Randomized Study (prospectic phase III randomized trial)

LOCAL CONTROL in RTOG-MRC trial

	Fotoni	*Neutroni*
N.ro di pazienti	12	13
Tasso di controllo locoregionale		
A 1 anno	17 % ± 11	67 % ± 14
A 2 anni	17 % ± 11	67 % ± 14



	Photons	Neutrons
Hoarseness	0	1
Dysphagia	1	2
Dehydration	1	2
Malnutrition	1	2
Pain	0	3
Mucosal	1	3
Skin	2	2
Fibrosis	1	2
Necrosis	0	3
Xerostomia	2	1
Impaired taste	1	4
Other	0	1

Griffin et al, Int J Radiat Oncol Biol Phys, 1988

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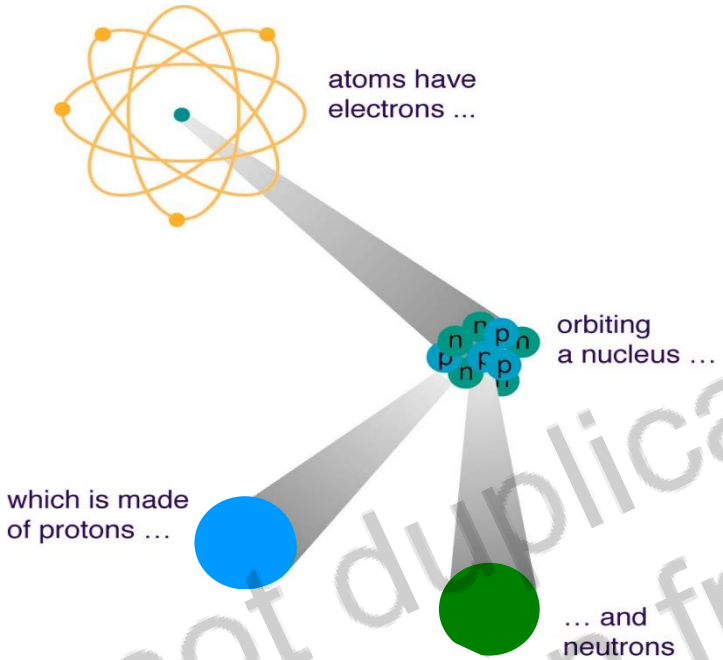
Particle therapy



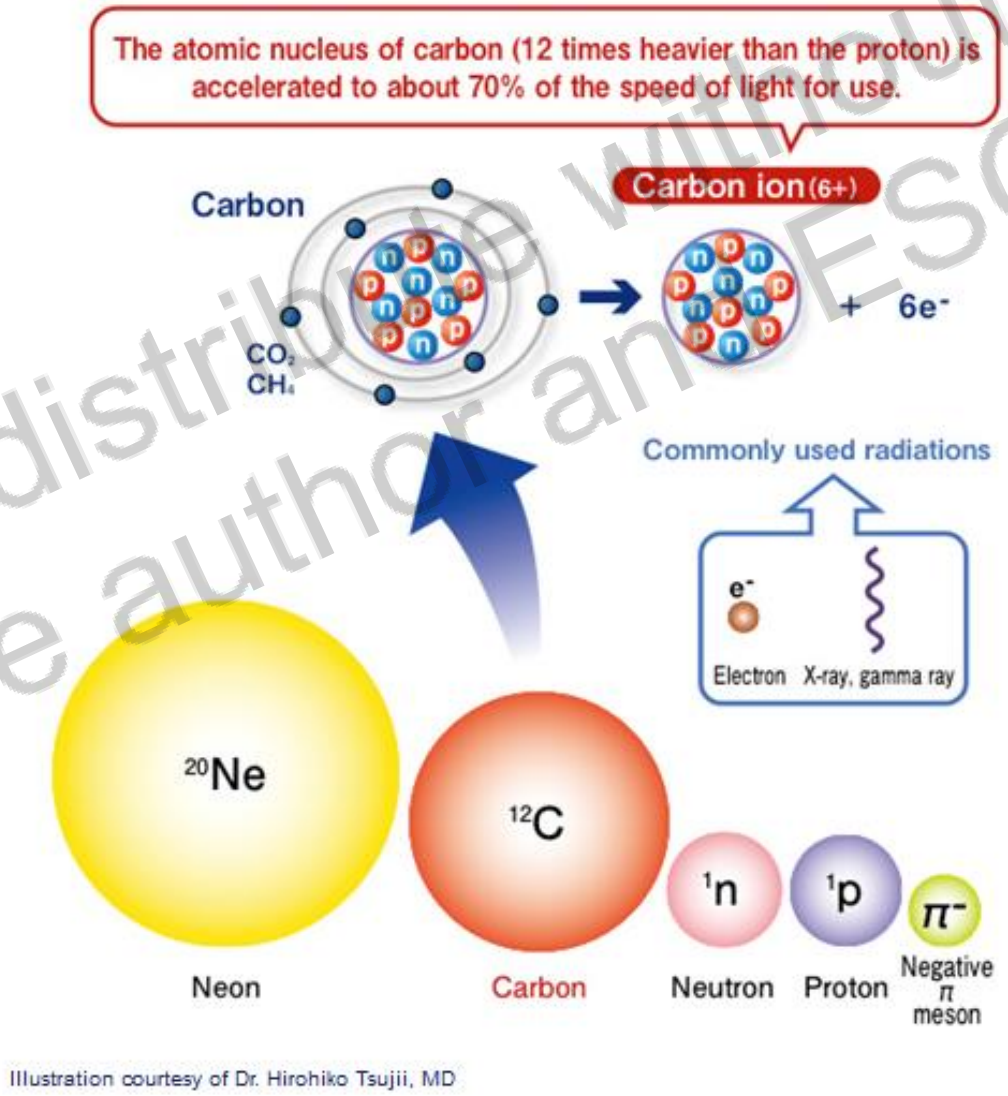


Illustration courtesy of Dr. Hirohiko Tsujii, MD

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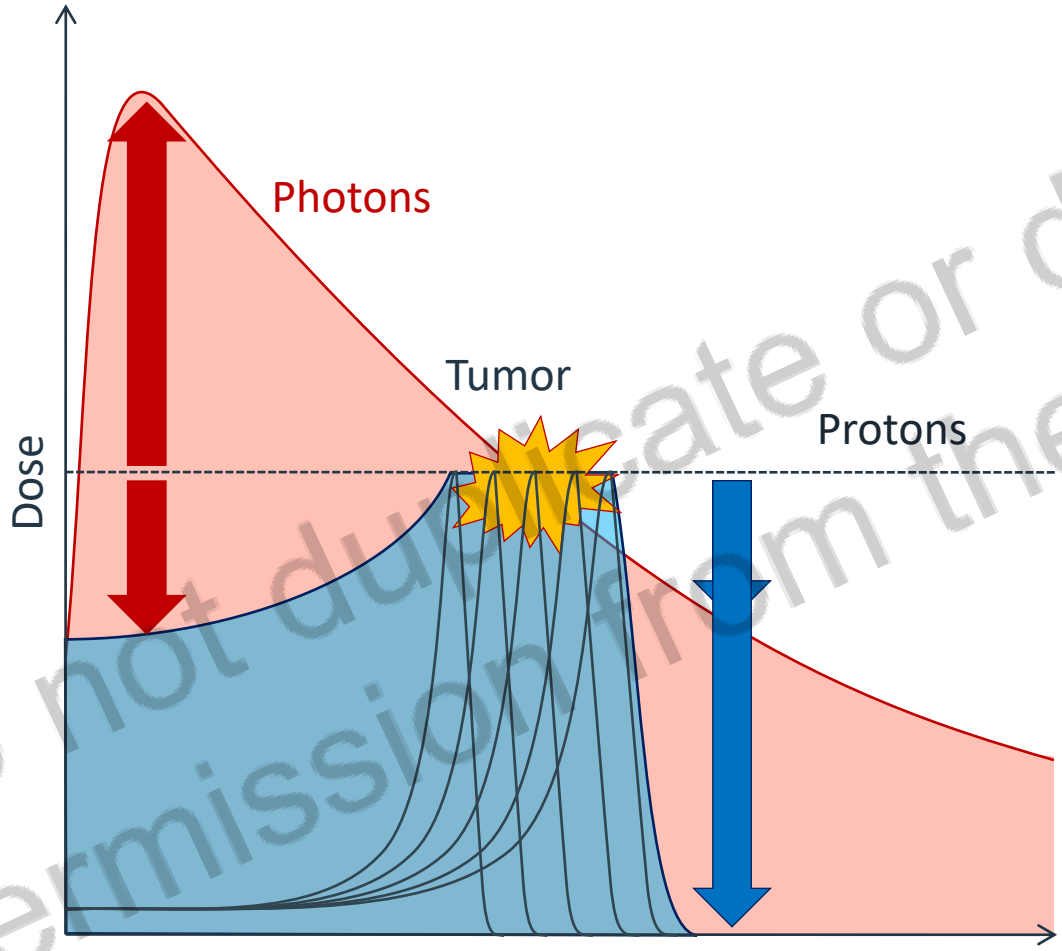
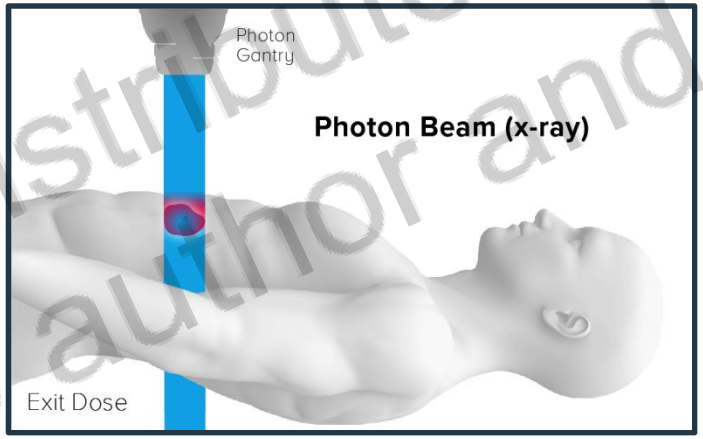
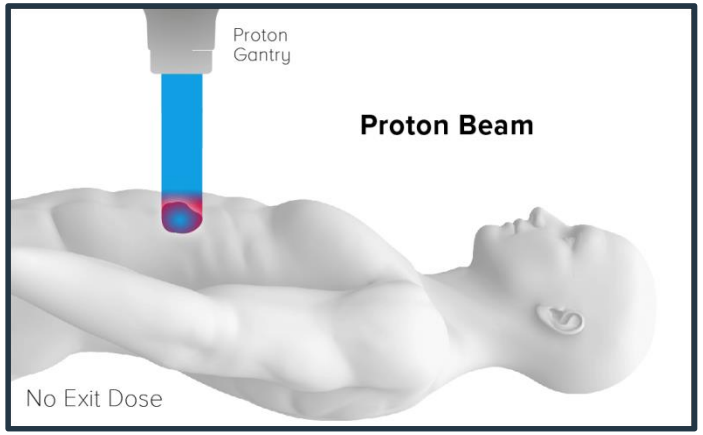
Dose shaping of hadrons







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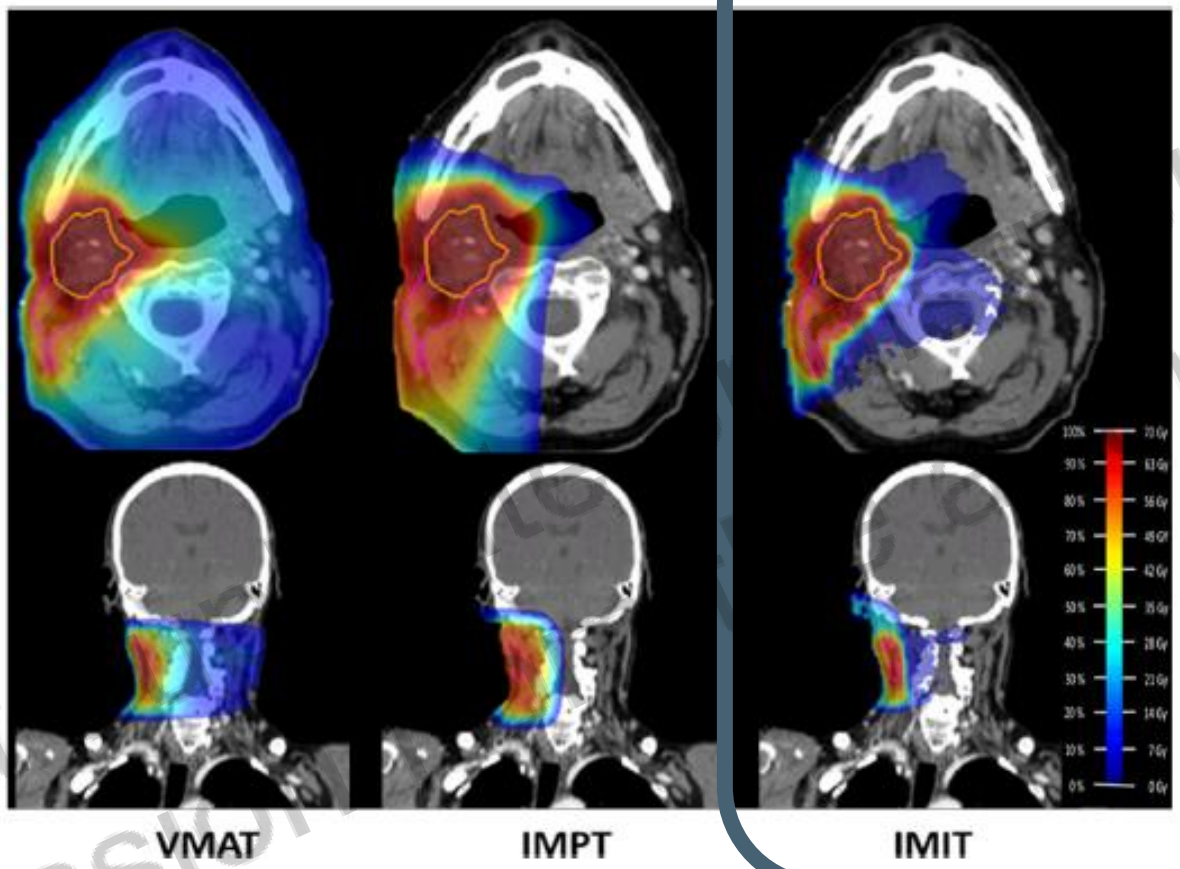
Dose shaping of hadrons

PHOTONS PROTONS CARBON IONS



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]

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OARs sparing and acute toxicity in proton beam therapy (PBT)

Radiotherapy and Oncology 118 (2016) 286–292

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Particle therapy in head and neck cancer

Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation ☆

Paul B. Romesser [a], Oren Cahlon [a,b], Eli Scher [a,c], Ying Zhou [d], Sean L. Berry [a], Alisa Rybkin [a], Kevin M. Sine [b], Shikui Tang [b], Eric J. Sherman [e], Richard Wong [f], Nancy Y. Lee [a,*]

[a] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York; [b] ProCure Proton Therapy Center, Somerset; [c] Rowan University School of Osteopathic Medicine, Stratford; [d] Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York; [e] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York; and [f] Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, United States

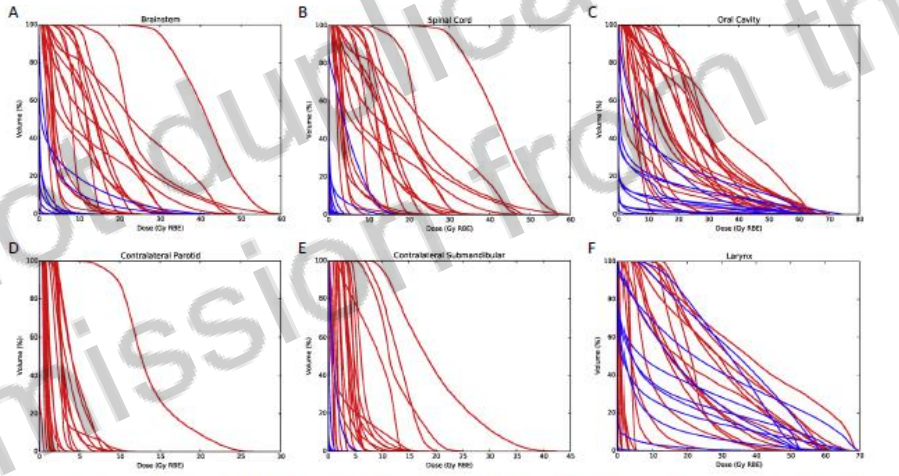

Fig. 1. Dose–volume histograms of organs at risk for proton (blue) and photon (red) patients: (A) brainstem, (B) spinal cord, (C) oral cavity, (D) contralateral parotid gland, (E) contralateral submandibular gland, (F) larynx. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Toxicity	IMRT ($N = 23$)	PBRT ($N = 18$)	P value
Dermatitis			
Grade 0	0 (0.0%)	0 (0.0%)	0.032
Grade 1	6 (26.1%)	0 (0.0%)	
Grade 2	9 (39.1%)	13 (72.2%)	
Grade 3	8 (34.8%)	5 (27.8%)	
Grade 4	0 (0.0%)	0 (0.0%)	
Mucositis			
Grade 0	3 (13.0%)	12 (66.7%)	0.005
Grade 1	8 (34.8%)	3 (16.7%)	
Grade 2	10 (43.5%)	3 (16.7%)	
Grade 3	2 (8.7%)	0 (0.0%)	
Grade 4	0 (0.0%)	0 (0.0%)	
Nausea			
Grade 0	7 (30.4%)	15 (83.3%)	0.003
Grade 1	3 (13.0%)	1 (5.6%)	
Grade 2	13 (56.5%)	2 (11.1%)	
Grade 3	0 (0.0%)	0 (0.0%)	
Dysgeusia			
Grade 0	4 (17.4%)	14 (77.8%)	<0.001
Grade 1	4 (17.4%)	3 (16.7%)	
Grade 2	15 (65.2%)	1 (5.6%)	
Dysphagia			
Grade 0	12 (52.2%)	15 (83.3%)	0.101
Grade 1	9 (39.1%)	2 (11.1%)	
Grade 2	2 (8.7%)	1 (5.6%)	
Grade 3	0 (0.0%)	0 (0.0%)	
Grade 4	0 (0.0%)	0 (0.0%)	
Fatigue			
Grade 0	2 (8.7%)	11 (61.1%)	0.002
Grade 1	19 (82.6%)	6 (33.3%)	
Grade 2	2 (8.7%)	1 (5.6%)	
Grade 3	0 (0.0%)	0 (0.0%)	

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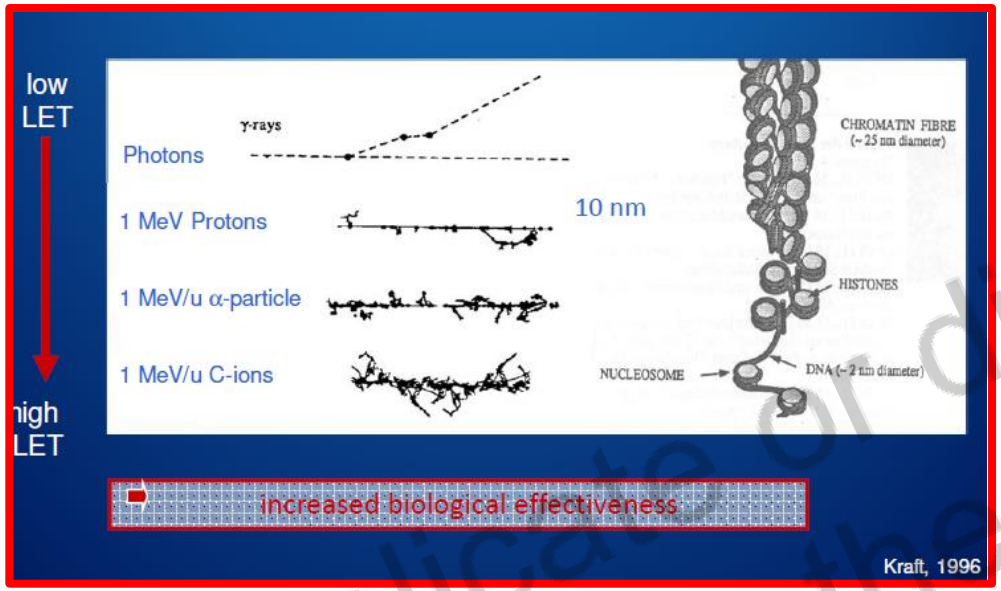
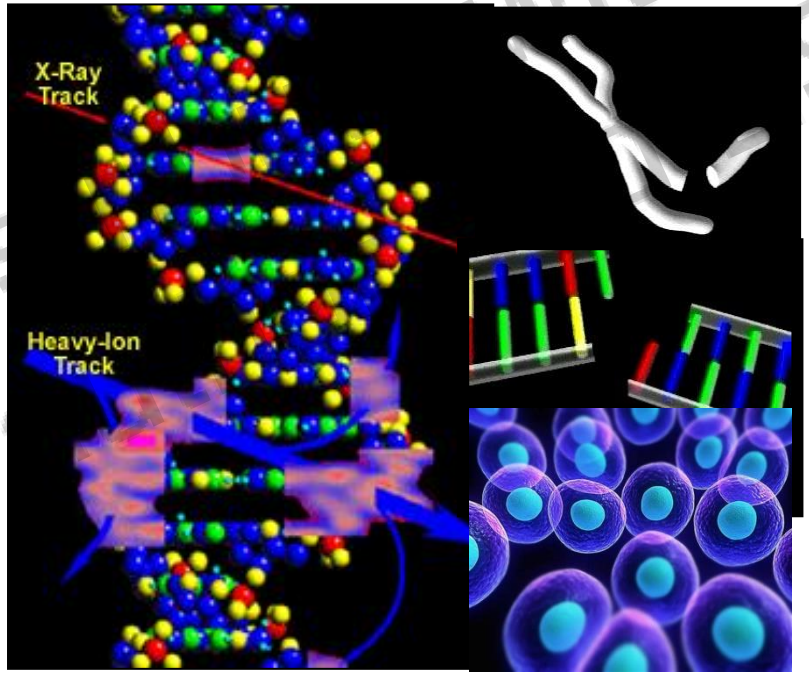
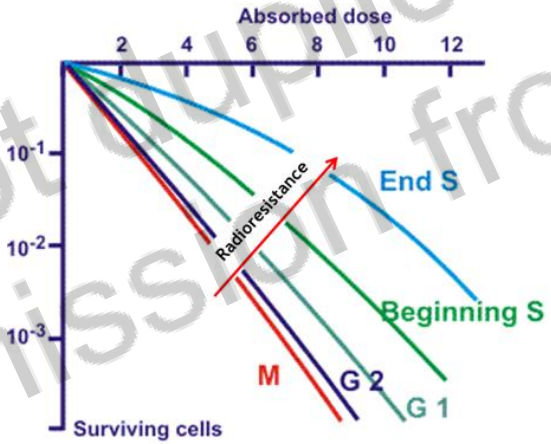
Higher biological effectiveness of carbon ions vs photon radiotherapy







Carbon ions: higher effectiveness on radioresistant clones

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CIRT outcome in locally advanced non-SCC HN tumors @ NIRS (National Institute for Radiological Sciences) Japan

Radiotherapy and Oncology 103 (2012) 32–37

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

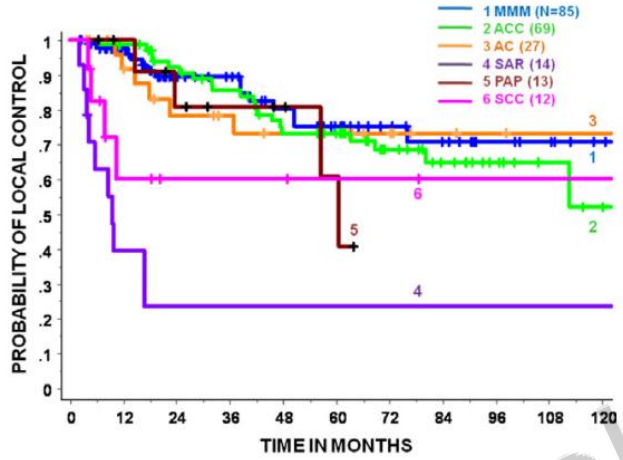
journal homepage: www.thegreenjournal.com

Carbon ion treatment of HNSCC

Results of carbon ion radiotherapy for head and neck cancer

Jun-etsu Mizoe[a,*], Azusa Hasegawa[a], Keiichi Jingu[a], Ryo Takagi[a], Hiroki Bessyo[a], Takamichi Morikawa[a], Morio Tonoki[b], Hiroshi Tsuji[a], Tadashi Kamada[a], Hirohiko Tsujii[a], Yoshitaka Okamoto[c], for Organizing Committee for the Working Group for Head Neck Cancer

[a] National Institute of Radiological Sciences, Chiba; [b] Department of Oral Surgery, Ichikawa; [c] Department of Otolaryngology, Chiba University, Chiba, Japan



MMM	85	63	48	41	33	26	19	15	9	7	3
ACC	69	65	57	50	41	36	24	15	9	5	3
AC	27	22	17	15	13	13	9	6	5	4	4
SAR	14	5	3	3	3	3	3	3	3	3	3
PAP	13	11	8	6	5	3	0	0	0	0	0
SCC	12	5	3	3	3	2	1	1	1	1	1

5ys local control:

Adenocarcinoma: 73%

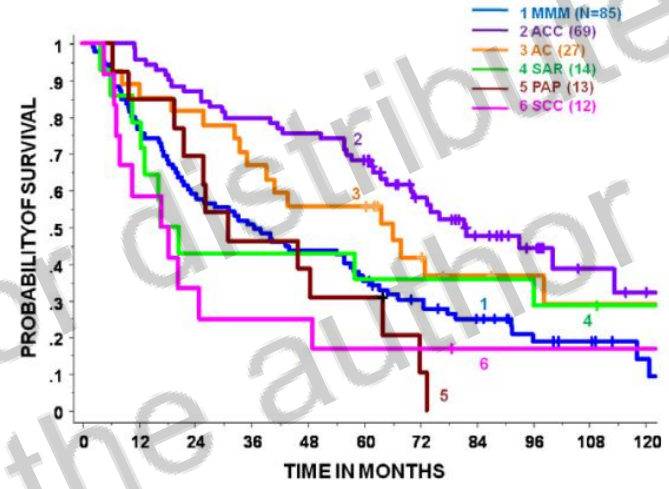
MMM: 75%

ACC: 73%

Papillary adenocarcinoma: 61%

SCC: 61%

Sarcoma 24: %



MMM	85	65	50	43	37	30	23	17	10	7	3
ACC	69	66	60	55	52	45	30	19	12	6	4
AC	27	24	22	18	15	15	9	6	5	4	4
SAR	14	11	6	6	6	5	5	5	5	4	3
PAP	13	11	9	6	5	4	1	0	0	0	0
SCC	12	7	4	3	3	2	2	1	1	1	1

5y sopravvivenza:

Adenocarcinoma: 56%

ACC: 68%

Sarcoma: 36%

MMM: 35%

Papillary adenocarcinoma: 31%

SCC: 17%

CIRT dose 64 GyRBE in 16 fraction

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Comparison of CIRT treatmet data in ACC

Institutions	No. of patients	Treatment	5-year local control (%)	5-year overall survival (%)	Late ≥GIII injury
Iowa, 2009 (34)	54	Surgery alone	72	85	—
	10	Photon alone	27	25	—
Florida, 2004 (35)	101	Photon alone	56	57	12.9%
MGH, 2006 (36)	23	Proton ± surgery	93	77	17%
Heidelberg, 2001 (37)	29	Neutron ± surgery	75	59	19%
GSI, 2005 (33)	34	Photon alone	25 (4 years)	78 (4 years)	<5%
	29	Photon + carbon boost	78 (4 years)	76 (4 years)	
NIRS, 2011 (32)	151	Carbon alone (all pats)	74	72	None
	32	Carbon alone (T1–T3)	96	92	
	119	Carbon alone (T4 or recurrences)	71	69	

Tsujii H and Kamada T, Jpn J Clin Oncol, 42: 670-685, 2012

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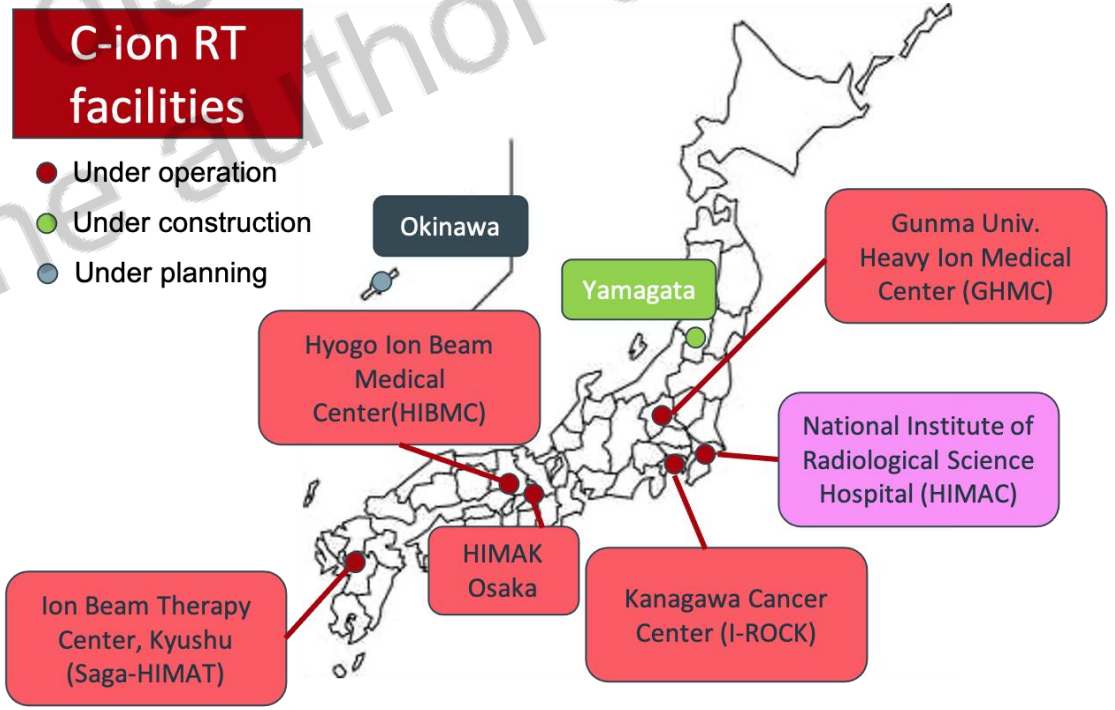
Japan Carbon-ion Radiation Oncology Study Group (J-CROS)

A retrospective multicenter study of carbon-ion radiotherapy for head and neck cancere except sarcoma: Japan Carbon-Ion Radiation Oncology Study Group (1402 HN)

AIM

To evaluate the efficacy and safety of CIRT for patients with head and neck cancer except sarcoma treated with CIRT in Japan

- 2003-2014
- unresected pts or unfit for surgery
- radical intent
- N0-N1



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J-CROS (Japan Carbon ion Radiation Oncology Group) Study 1402 HN (2003-2014) 908 pts enrolled

Received: 13 January 2018 | Revised: 21 February 2018 | Accepted: 24 February 2018
DOI: 10.1111/cas.13558

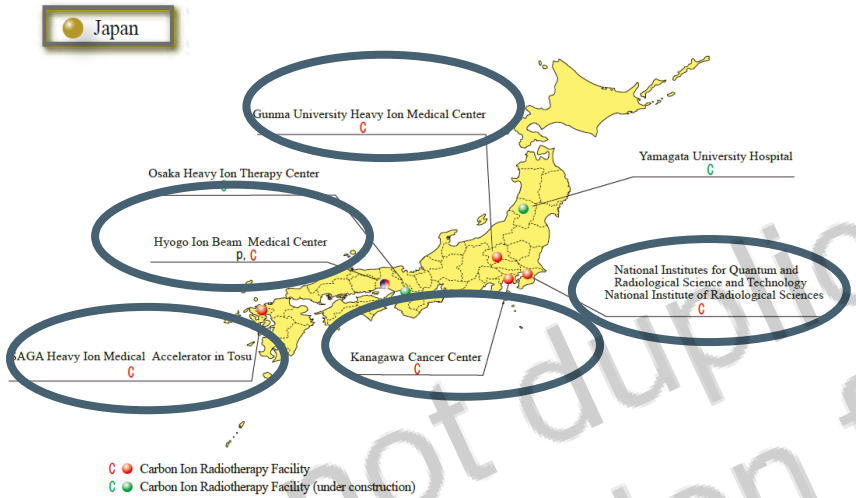
ORIGINAL ARTICLE

WILEY Cancer Science

A retrospective multicenter study of carbon-ion radiotherapy for major salivary gland carcinomas: Subanalysis of J-CROS 1402 HN

Kazuhiko Hayashi[1] | Masashi Koto[1] | Yusuke Demizu[2] | Jun-ichi Saitoh[3] | Hiroaki Suefuji[4] | Tomoaki Okimoto[2] | Tatsuya Ohno[3] | Yoshiyuki Shioyama[4] | Ryo Takagi[5] | Hiroaki Ikawa[1] | Kenji Nemoto[6] | Takashi Nakano[3] | Tadashi Kamada[1] | the Japan Carbon-Ion Radiation Oncology Study Group

69 pts
3 ys LC 81%



- unresected pts or unfit for surgery
- radical intent
- N0-N1

International Journal of Radiation Oncology biology • physics
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Clinical Investigation

Definitive Carbon-Ion Radiation Therapy for Locally Advanced Sinonasal Malignant Tumors: Subgroup Analysis of a Multicenter Study by the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS)

Masashi Koto, MD, PhD,* Yusuke Demizu, MD, PhD,† Jun-ichi Saitoh, MD, PhD,‡ Hiroaki Suefuji, MD, PhD,§ Hiroshi Tsuji, MD, PhD,* Tomoaki Okimoto, MD, PhD,† Tatsuya Ohno, MD, PhD,‡ Yoshiyuki Shioyama, MD, PhD,§ Hiroaki Ikawa, DDS, PhD,* Kenji Nemoto, MD, PhD,‖ Takashi Nakano, MD, PhD,‡ and Tadashi Kamada, MD, PhD,* the Japan Carbon-Ion Radiation Oncology Study Group

458 pts
2 ys LC 79.6%

Accepted Manuscript

A Multicenter Study of Carbon-ion Radiotherapy for Adenoid Cystic Carcinoma of the Head and Neck: Sub-analysis of the Japan Carbon-ion Radiation Oncology Study Group (J-CROS) Study (1402 HN)

Nor Shazrina Sulaiman, MD, PhD, Yusuke Demizu, MD, PhD, Masashi Koto, MD, PhD, Jun-ichi Saitoh, MD, PhD, Hiroaki Suefuji, MD, PhD, Hiroshi Tsuji, MD, PhD, Tatsuya Ohno, MD, PhD, Yoshiyuki Shioyama, MD, PhD, Tomoaki Okimoto, MD, PhD, Takashi Daimon, PhD, Kenji Nemoto, MD, PhD, Takashi Nakano, MD, PhD, Tadashi Kamada, MD, PhD

289 pts
2 ys LC 88%

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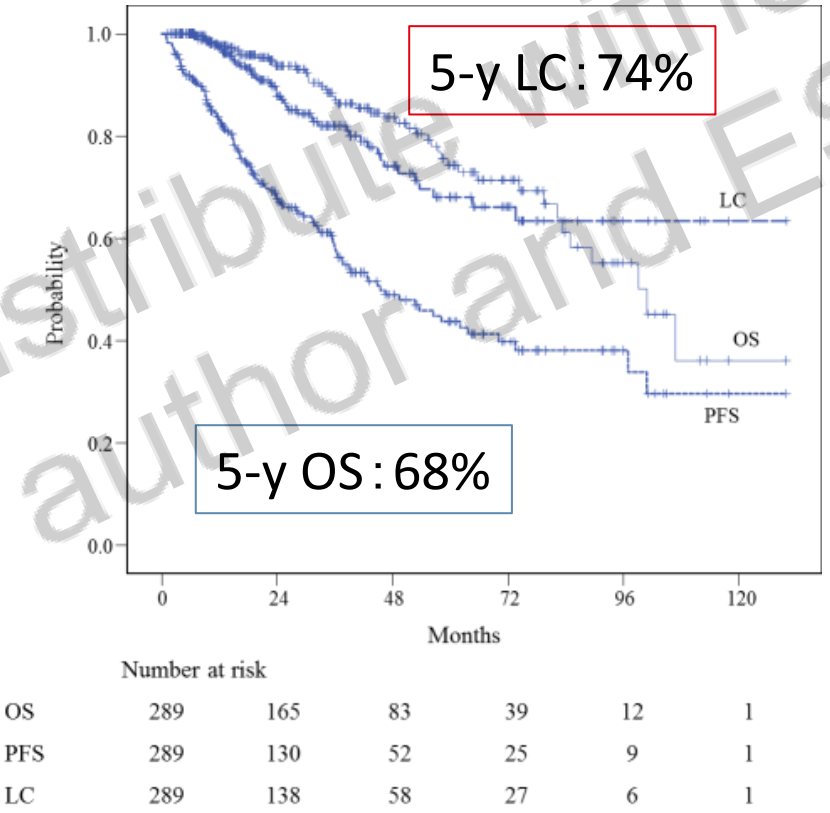
ACC and CIRT in Japan (J-CROS-1402)

No of patients		289
Gender	Male	105 (36%)
	Female	184 (64%)
Age	Median	68
Site	Sinonasal cavity	122 (42%)
	Pharynx	55 (19%)
	Oral cavity	33 (12%)
	Salivary glands	35 (12%)
	Others	44 (15%)
T classification	T1	15 (5%)
	T2	22 (8%)
	T3	45 (16%)
	T4	200 (69%)
	Unclassified	7 (2%)
N classification	N0	277 (96%)
	N1	12 (4%)
Tumor status	Naive	234 (81%)
	Recurrence	55 (19%)



Sulaiman et al. Int J Radiat Oncol Biol Phys. 2018

Late toxicity: 2 G5 (hemorrhage)
14 G4 (visual, brain)

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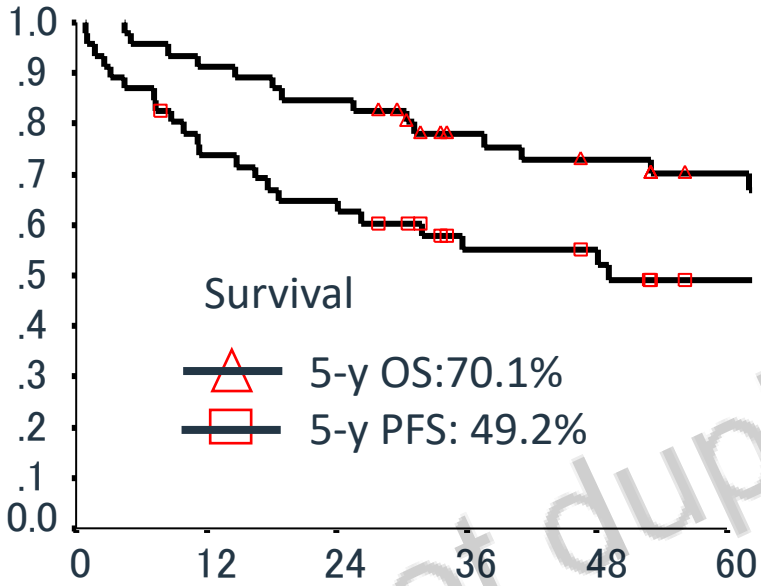
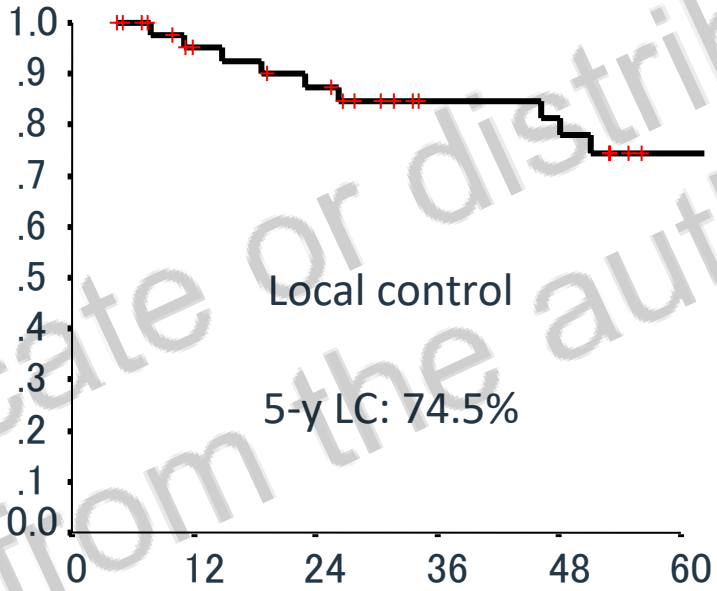
Parotid gland carcinoma and CIRT (NIRS data)

46 patients

Median follow up time: 62 months





16 ACC
8 MEC
8 adenocarcinoma
14 others

T2 3
T3 18
T4a 8
T4b 17

25 unresected
20 local recurrence after surgery
1 R2

83% of patients could maintain facial nerve function after C-ion RT!

Koto M, et al. Head Neck. 2017; 39:724-729

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CIRT for ACC @ HIT (Germany)

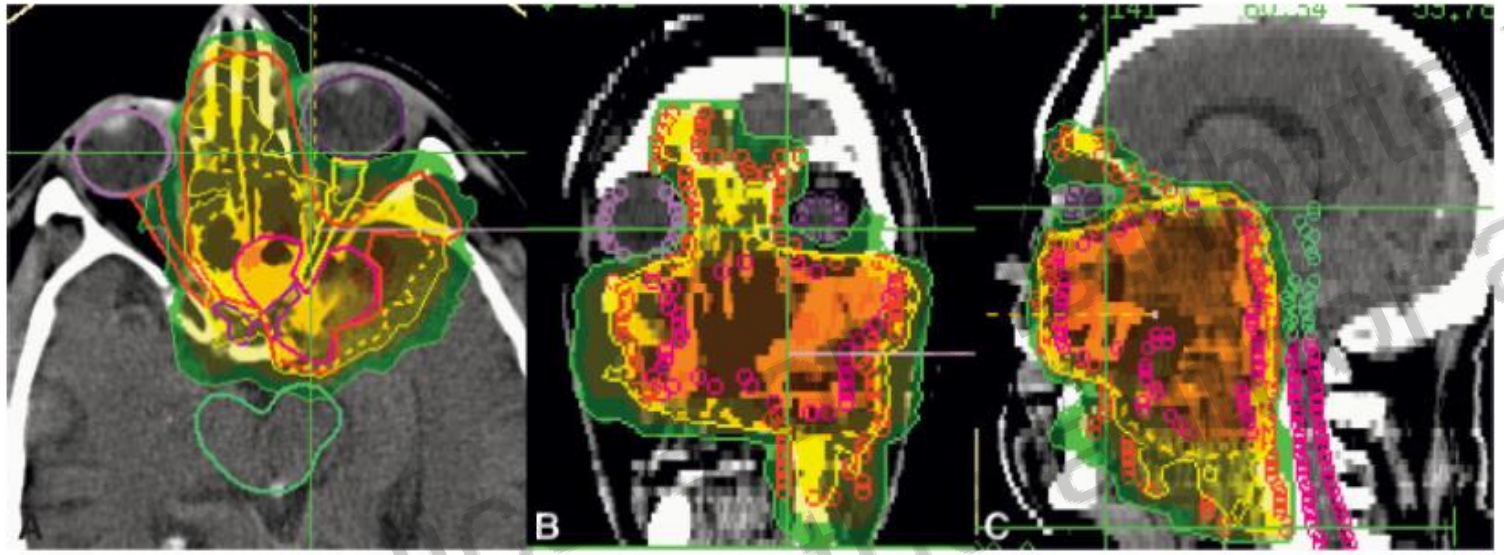

FIGURE 1. (A) Axial, (B) coronal, and (C) sagittal (C) views of a dose distribution (sum plan) consisting of a photon intensity-modulated radiation therapy plan (54.0 gray [Gy]) to the clinical target volume (CTV) and a carbon ion boost plan (18 cobalt gray equivalent [GyE]) to the macroscopic tumor volume (GTV). The Maximum dose was 78.17 GyE. Dotted yellow line: 60-GyE isodose line; fine yellow line: 54-GyE isodose line; fine green line: 39-GyE isodose line; thick red line: CTV; thick pink line: GTV.

Schulz-Ertner D et al, Cancer 2005

Feasibility data published in 2011: "Carbon ion therapy for advanced sinonasal malignancies: feasibility and acute toxicity", Jensen et al.

Mixed beam regimen: Median CIRT dose was 24 GyRBE, median IMRT dose was 50 Gy (according to COSMIC trial). The total dose of 74 GyRBE corresponds to a biological effective dose of 80 Gy BED

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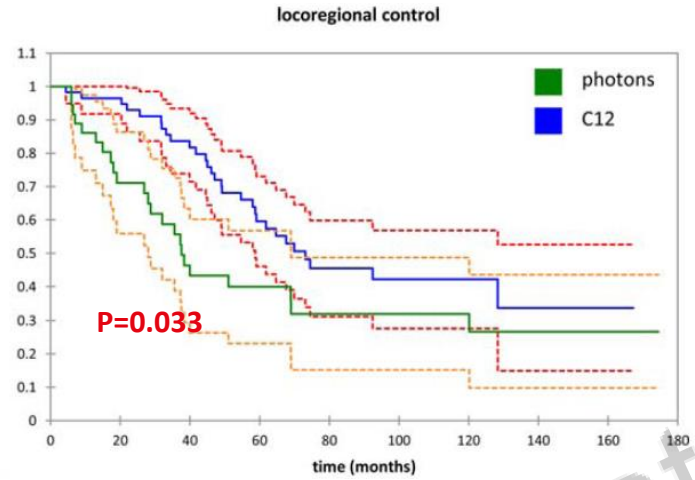
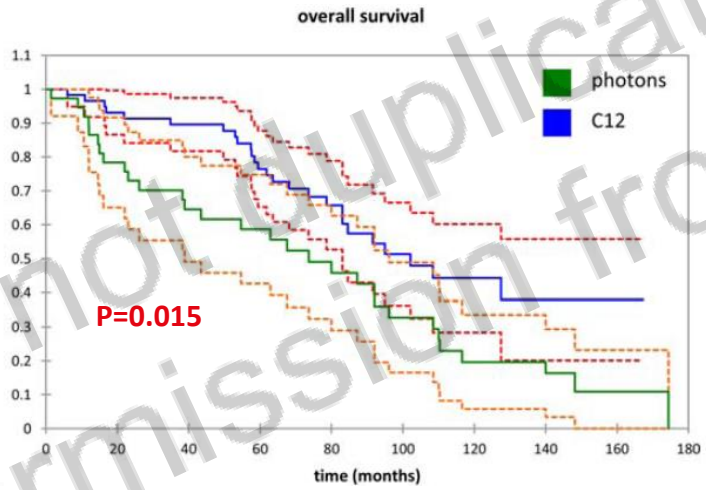
CIRT for ACC @ HIT (Germany)





METHODS
- R2 or unresected
- 58 ACC with C12 boost and IMRT vs 37 with photons (IMRT or FSRT)
- Median F/U =74 months in the C12 vs 63 in the photon group

RESULTS
- 5 ys LC in C12 vs photon: 59.6% vs 39.9%
- 5 ys PFS in C12 vs photon: 48.4% vs 27%
- 5 ys OS in C12 vs photon: 76.5% vs 58.7%

Most of recurrences in field→need for dose escalation

COSMIC trial with C12 boost dose increased up to 24 GyRBE started in 2010 *(Jensen et al, IJROBP, 2015)*

Jensen et al, Cancer 121:3001-9, 2015

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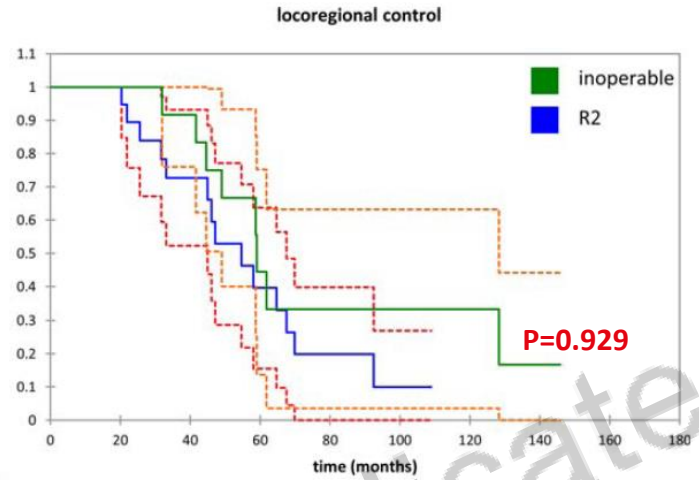
CIRT for ACC @ HIT (Germany)



No difference in LC in R2 vs unresected tumors

In T4 tumors, the necessity of extensive and potentially mutilating surgical procedures should be discussed with the patient where definitive radiotherapy may be a good alternative.

This data was confirmed also in the larger ACC series published in 2015 from the same group on all 309 ACC pts treated at GSI and HIT in their 15 years experience with raster scanning *(Jensen et al, Rad Oncol 2015)*.

Jensen et al, Cancer 121:3001-9, 2015

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CIRT for ACC @ HIT (Germany)

cancers

MDPI

Article

Intensity Modulated Radiotherapy (IMRT) + Carbon Ion Boost for Adenoid Cystic Carcinoma of the Minor Salivary Glands in the Oral Cavity

67 pts: surgery → PORT (Carbon boost)
R2: 7% only
Median follow up 40 mesi
Median 5 years OS and LDFS 85% e 75%

Characteristics	No of Patients
irradiation	
photons + carbon ions	67
median IMRT dose	Gy (range)
	50 (48–56)
median C12 dose	
	24 (18–24)
median dose of cervical lymphatic drainage	
	50 (48–56)
cumulative dose (IMRT + C12)	
	74 (68–74)

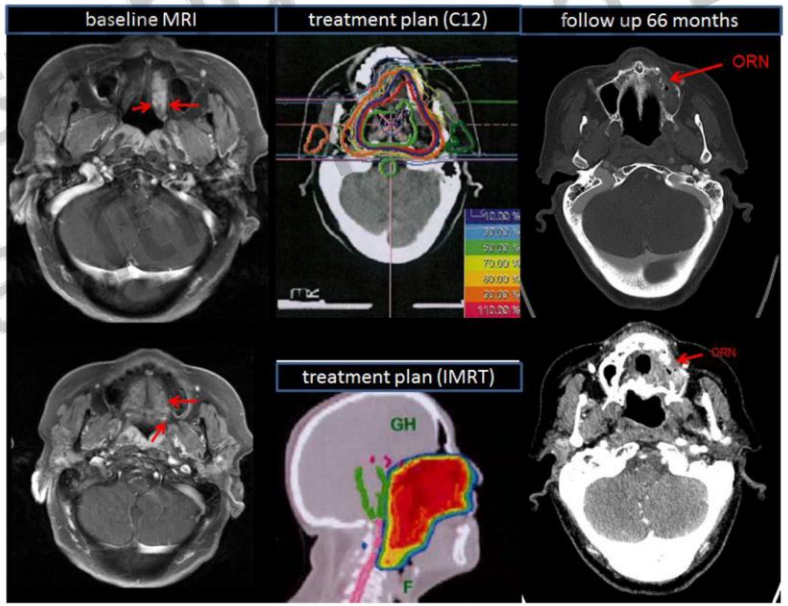

Figure 4. Radiation-induced osteoradionecrosis of the upper jaw: baseline MRI scan (left side) and follow-up CT scan (right side) of a patient who undergone surgery of adenoid cystic carcinoma of hard palate and additive bimodal radiotherapy. 66 months after RT, there was increased soft tissue as well as erosion of the posterior wall of the left side of maxilla. In comparison with the initially-treated radiation plan, the lesion occurred in an irradiated region of the hard palate at the edge of the 95%-isodose (middle up: carbon ion isodose plan alone, middle down: IMRT isodose plan alone). Abbreviations: radiotherapy (RT), computed tomography (CT), magnetic resonance imaging (MRI), intensity modulated radiotherapy (IMRT), carbon ions (C12).

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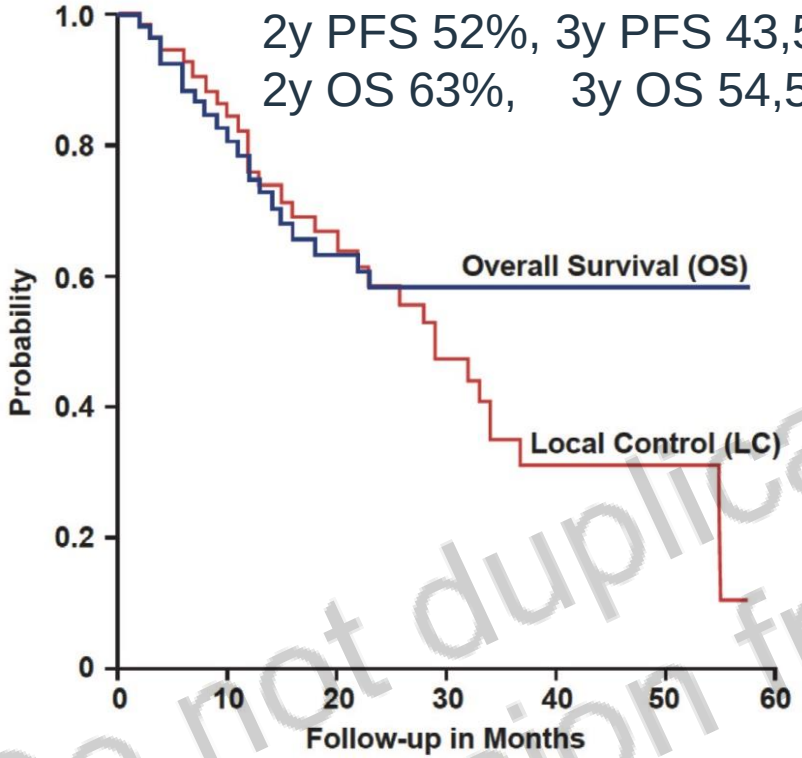
CIRT in recurrent ACC @ CNAO (Italy)

2y PFS 52%, 3y PFS 43,5%
2y OS 63%, 3y OS 54,5%



Numbers at risk

OS	51	45	34	30	30	30
LC	51	46	35	25	16	16

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.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

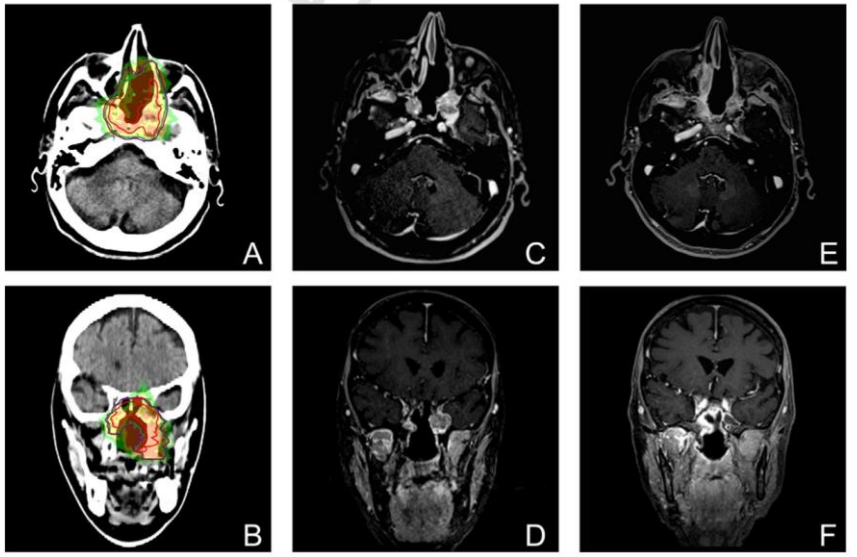
journal homepage: www.thegreenjournal.com

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]

[a] *Radiation Oncology Clinical Department, National Center for Oncological Hadrontherapy (CNAO), Pavia, Italy;* [b] *Radiation Medicine, Albert B. Chandler Hospital, University of Kentucky, USA;* [c] *Section of Radiological Sciences, University of Messina;* [d] *Radiation Oncology Department, Vito Fazzi Hospital, Lecce, Italy;* [e] *Radiation Oncology Department, Osaka Heavy Ion Therapy Center, Japan; and* [f] *Department of Radiotherapy, European Institute of Oncology, Milan, Italy*



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Outline

Salivary gland tumors

- Role of radiotherapy (RT) in locoregional disease
- What is particle therapy
- Evidence for salivary gland tumors treatment with carbon ions in Japan and Germany
- Recurrent disease

Sinonasal tumors

- Management and role of RT in locoregional disease
- Evidence in particle therapy for sinonasal tumors (protons and carbon ions)

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Sinonasal tumor management

- Usually managed with surgery

- Radiotherapy used in postoperative setting with schemes and results depending on stage, histology, margin status, grading (poor quality evidence)

- Importance of new high precision RT tecniques

CLINICAL INVESTIGATION Head and Neck

CARCINOMAS OF THE PARANASAL SINUSES AND NASAL CAVITY TREATED WITH RADIOTHERAPY AT A SINGLE INSTITUTION OVER FIVE DECADES: ARE WE MAKING IMPROVEMENT?

ALLEN M. CHEN, M.D.,* MEGAN E. DALY, M.D.,* M. KARA BUCCI, M.D.,¶ PING XIA, PH.D.,* CLAYTON AKAZAWA, C.M.D.,* JEANNE M. QUIVEY, M.D.,* VIVIAN WEINBERG, PH.D.,† JOAQUIN GARCIA, M.D.,‡ NANCY Y. LEE, M.D.,‖ MICHAEL J. KAPLAN, M.D.,# IVAN EL-SAYED, M.D.,§ DAVID W. EISELE, M.D.,§ KAREN K. FU, M.D.,* AND THEODORE L. PHILLIPS, M.D.*

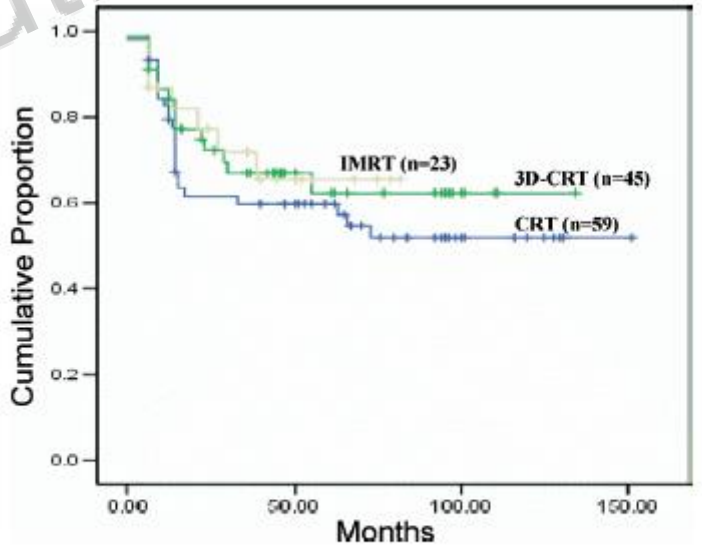

Fig. 2. Local control according to radiotherapy technique: conventional radiotherapy (CRT) vs. three-dimensional radiotherapy (3D-CRT) vs. intensity-modulated radiotherapy (IMRT).

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In locally advanced sinonasal tumors

- Radical radiotherapy treatment in unresectable patients often with addition of chemotherapy
- Histology driven chemotherapy and neoadjuvant chemotherapy improve prognosis

Author, year	Histology	Stage	Patients (*n*)	Chemotherapy	2 year OS (%)	2 year DFS (%)	ORR (%)	Comments
Lorusso et al., 1988 [16]	SCC, SNUC, Adenocarcinoma, SmCC	III, IV	16	5FU + cisplatin ± methotrexate; doxorubicin; bleomycin	–	–	82	1 death for gastrointestinal bleeding
Bjork et al., 1992 [17]	SCC, PNET, Anaplastic	I, III, IV	12	Cisplatin + 5FU	91	83	70	pCR in 8/12 (66%) pts
Lee et al., 1999 [18]	SCC, SNUC, Mucoepidermoid	III, IV	19	Cisplatin + 5FU	73 (5 year)	67 (5 year)	87	pCR in 5/16 (31%) pts
Licitra et al., 2003 [19]	Adenocarcinoma, SCC	I–IV	49	PFL	69 (3 year)	–	43	8 cardiologic treatment-limiting toxicities; 2 deaths from thromboembolic events; pCR in 8/49 (16%) pts
Hanna et al., 2011 [20]	SCC	III, IV	46	Cisplatin + taxanes ± ifosfamide/5FU	67	–	67	–

Bossi et al, Cancer Treatment Reviews 2015

- Multimodality treatment gives better resullts in prognosis

Eur Arch Otorhinolaryngol (2013) 270:293–299
DOI 10.1007/s00405-012-2008-5

HEAD AND NECK

Combined-modality treatment improved outcome in sinonasal undifferentiated carcinoma: single-institutional experience of 21 patients and review of the literature

Abrahim Al-Mamgani · Peter van Rooij · Robert Mehilal · Lisa Tans · Peter C. Levendag

	UVA (*p* value)	MVA (OR and *p* value)
T-stage (T4 vs. T3)	**0.02**	**36 (0.002)**
N-stage (N+ vs. N0)	0.99	
Tumor site (ethmoid vs. maxillary)	0.68	
Dural or intracranial extension (yes vs. no)	**0.005**	NS
Surgery (no vs. yes)	**0.02**	NS
Treatment modalities (two vs. three)	**0.004**	**55 (0.0003)**
RT technique (2D and 3DCRT vs. IMRT)	0.17	
RT dose (≤60 Gy vs. >60 Gy)	0.76	

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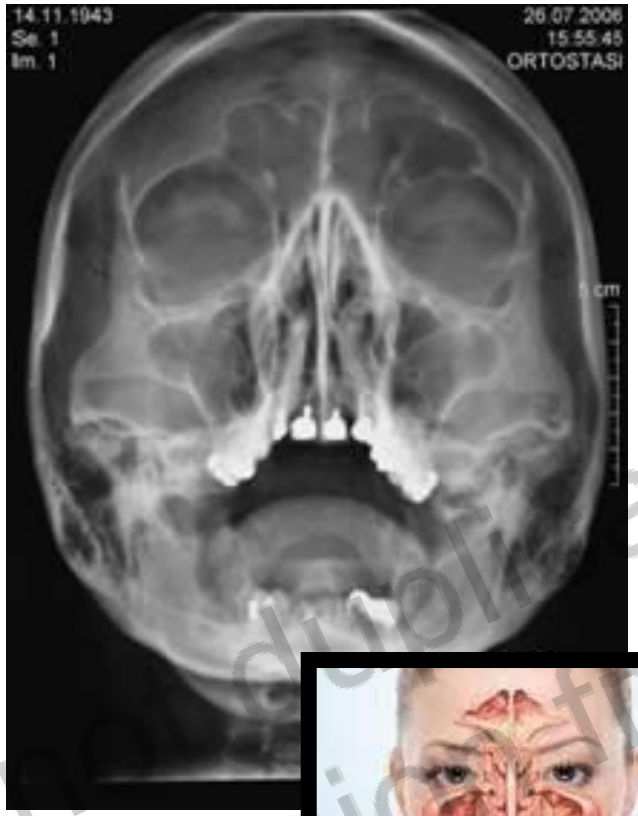
Rationale for the use of protons vs CIRT in sinonasal tumor treatment



	Radio-sensitivity
Squamous Cell Carcinoma (SCC) (90%)	+++
Undifferentiated Carcinoma	++++
Adenocarcinoma	++
Adenoid-cystic carcinoma Mucosal Melanoma	+

RADIORESISTANCE

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Rationale for the use of protons vs CIRT in sinonasal tumor treatment

- Protons→to spare toxicity and dose escalate

- Carbon ions→to increase effectiveness and cure rate

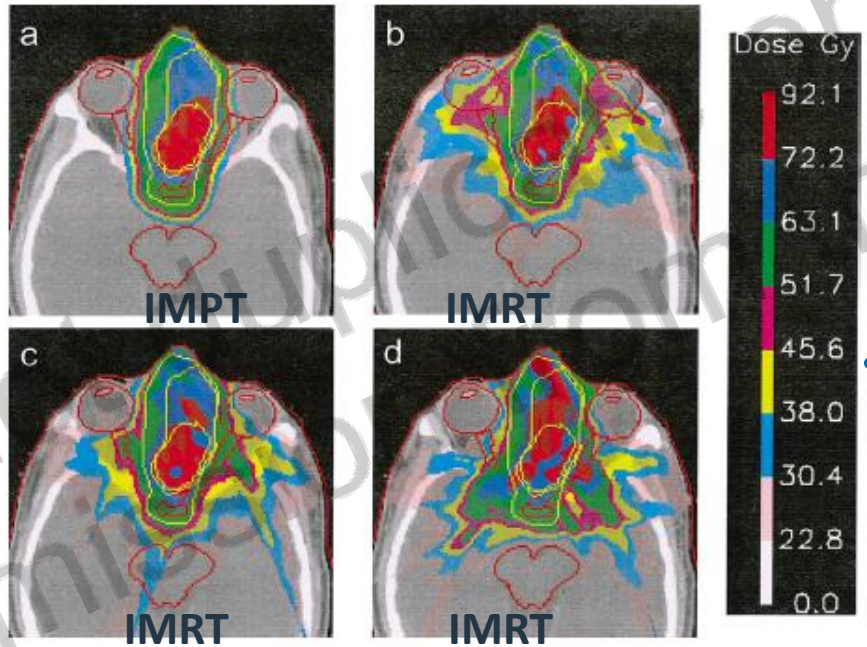

Fig. 5. Dose distributions for (a) P1, (b) X1, (c) X2 and (d) X3 at the level of the globes.

DIFFICULT LOCATION IN HEAD AND NECK

Lomax et al, Radiother Oncol, 2003

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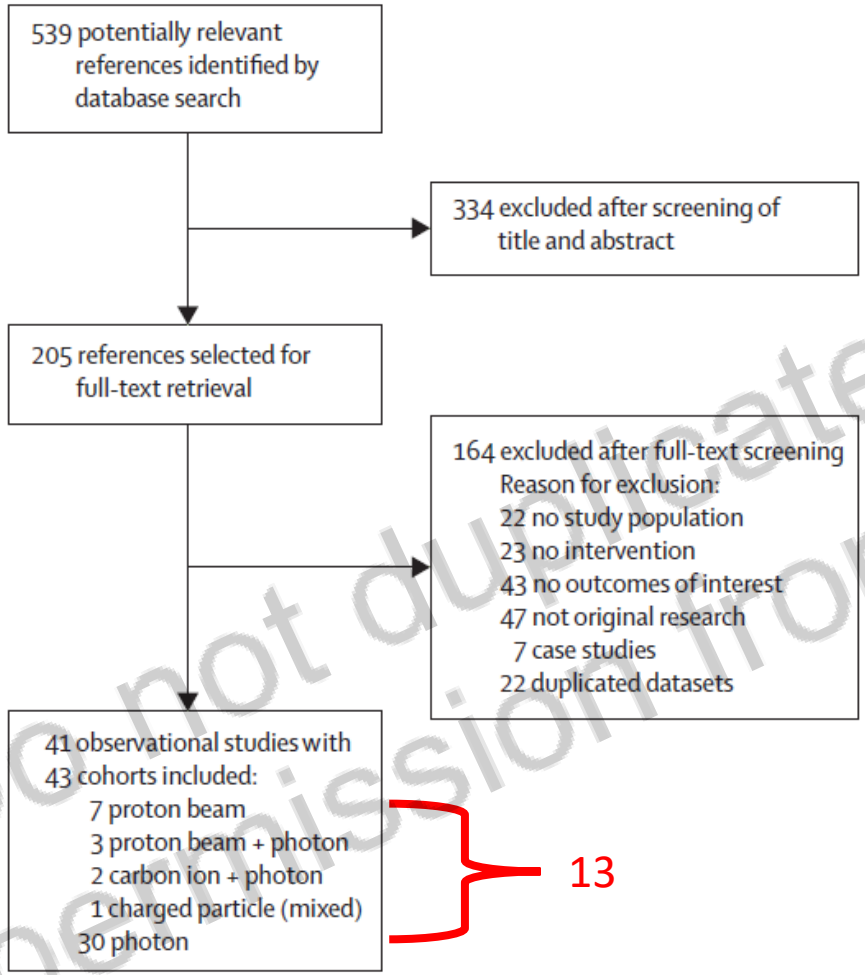
Can particle therapy improve LC and survival in sinonasal tumors?

Lancet Oncol 2014; 15: 1027–38



Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis

Samir H Patel, Zhen Wang, William W Wong, Mohammad Hassan Murad, Courtney R Buckey, Khaled Mohammed, Fares Alahdab, Osama Altayar, Mohammed Nabhan, Steven E Schild, Robert L Foote

	Charged particle therapy	Photon therapy	p
Cohorts (n)	13	30	..
Patients (n)	286	1186	
Treatment-naive patients (%)	80%	85%	0·10
Age (years)	57·7 (range 44–73)	59·2 (range 45–73)	0·61
Men (%)	57%	64%	0·28
Patients with advanced tumour (%)*	63%	57%	0·55
Patients with high-risk histological type (%)†	27%	50%	0·06
Median (range [IQR]) radiation dose (GyE)‡	60·1 (48–69 [55–67])	61·4 (31–70 [60–67])	0·66
Median (range [IQR]) follow-up (months)	38 (5–73 [23–55])	40 (14–97 [28–52])	0·72

1472 pts

RBE=relative biological effectiveness. *Included stage IV or Kadish stage C. †Included squamous-cell carcinoma, sinonasal undifferentiated carcinoma, and poorly differentiated or undifferentiated. ‡GyE=RBExGy; RBE of proton beam is 1·1; RBE of carbon ion is 3.

Table 2: Baseline characteristics of charged particle therapy cohorts and photon therapy cohorts

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	Cohorts (n)	Patients (n)	Event rate (95% CI)	I^2	Relative risk (95% CI)	p	NNT* (95% CI)
Overall survival†							
CPT	10	242	0·66 (0·56–0·79)	77·5%	1·27 (1·01–1·59)	0·037	7·09 (3·57–480·55)
Photon therapy	26	1120	0·52 (0·46–0·60)	86·0%	--	--	--
5-year overall survival							
CPT	6	146	0·72 (0·58–0·90)	80·1%	1·51 (1·14–1·99)	0·0038	4·12 (2·37–15·60)
Photon therapy	15	779	0·48 (0·40–0·57)	84·1%	--	--	--
Disease-free survival†							
CPT	3	78	0·67 (0·48–0·95)	79·4%	1·51 (1·00–2·30)	0·052	--
Photon therapy	8	411	0·44 (0·35–0·56)	76·5%	--	--	--
5-year disease-free survival							
CPT	2	58	0·80 (0·67–0·95)	41·6%	1·93 (1·36–2·75)	0·0007	2·60 (1·74–5·15)
Photon therapy	6	341	0·41 (0·30–0·56)	80·9%	--	--	--
Locoregional control†							
CPT	10	208	0·76 (0·68–0·86)	54·0%	1·18 (1·01–1·37)	0·031	8·55 (4·40–143·44)
Photon therapy	14	736	0·65 (0·59–0·71)	60·3%	--	--	--
5-year locoregional control							
CPT	3	58	0·66 (0·43–1·02)	81·2%	1·06 (0·68–1·67)	0·79	--
Photon therapy	8	546	0·62 (0·55–0·71)	73·0%	--	--	--

I^2≥50% suggests high heterogeneity across studies. CPT=charged particle therapy. NNT=number needed to treat. *Calculated when the difference between CPT and photon therapy was significant. †At longest duration of complete follow-up.

Table 3: **Comparison of primary outcomes for charged particle therapy cohorts and photon therapy cohorts**

OS

5 ys OS

5 ys DFS

LRC

Lancet Oncol 2014; 15: 1027–38

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Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis

Samir H Patel, Zhen Wang, William W Wong, Mohammad Hassan Murad, Courtney R Buckey, Khaled Mohammed, Fares Alahdab, Osama Altayar, Mohammed Nabhan, Steven E Schild, Robert L Foote

TOXICITY

Lancet Oncol 2014; 15: 1027–38

	Event rate (95% CI)	I^2	p
Eye			
CPT	0·19 (0·08–0·45)	85·3%	0·12
Photon therapy	0·43 (0·24–0·75)	97·3%	..
Head and neck			
CPT	0·54 (0·24–1·24)	96·5%	0·30
Photon therapy	0·87 (0·62–1·22)	95·6%	..
Nasal			
CPT	0·07 (0·01–0·55)	52·7%	0·66
Photon therapy	0·12 (0·04–0·37)	76·6%	..
Ear			
CPT	0·20 (0·09–0·47)	34·7%	0·56
Photon therapy	0·14 (0·06–0·32)	82·9%	..
Neurological			
CPT	0·20 (0·13–0·31)	0·0%	0·0002
Photon therapy	0·04 (0·02–0·08)	0·0%	..
Miscellaneous			
CPT	0·41 (0·17–1·02)	70·5%	0·78
Photon therapy	0·49 (0·24–1·00)	93·4%	..
Haematological			
CPT	2·31 (1·59–3·36)	-	0·40
Photon therapy	1·92 (1·55–2·37)	-	..

I^2 >50% suggests high heterogeneity across studies. Toxic effect group definitions are listed in the appendix (p 10). The difference between treatment event rates was not calculated because of under-reporting of toxic effects in the included studies. CPT=charged particle therapy.

Table 5: Comparison of toxic effect event rates for charged particle therapy and photon therapy

- PT studies more detailed on toxicity vs photon (92% *vs* 57%; p=0·03).
- Challenging cases sent to PT instead of photons
- Higher biological and phyiscal doses delivered in PT studies compared to photon

Conclusion:

Need for international PT registers for comparison or randomized trials

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Proton therapy for sinonasal cancers

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 1 Studies Evaluating Proton Therapy for Sinonasal Malignancies

References	Type	Accrual	Pts (*n*)	Technique	Comp photon,	CCT, %	S, %	Histology	Follow-up (median)	Outcomes	Late toxicity	% G3+
Resto et al[50]	Retro	1991-2002	102	PSPT	No	4	100	Various	61 mo	5-y; LC 95%, 82%, and 87%, OS 90%, 53%, and 49% for complete resection, partial resection, and biopsy only	Not reported.	ND
Nakamura et al[75]	Retro	1999-2012	42	PSPT	No	26	0	ENB	69 mo	5-y; OS/PFS: 100/80% for Kadish A, 86/65% for Kadish B, 76/39% for Kadish C	6 pts with G3-4 (ipsilateral visual impairment, 3; bilateral visual impairment, 1; liquorrhea, 1; cataract, 1).	14%
Russo et al[76]	Retro	1991-2008	54	PSPT	No	39	69	SCC	82 mo	5-y; LRC 73%, OS, 47%,	9 pts with G3 and 6 with G4. Mostly wound site issues (eg, fistulas). No G5.	16%
Dagan et al[77]	Retro	2007-2013	84	PSPT	No	75	74	Various	32 mo	3-y; LC 83%, NC 94%, freedom from DM 73.2%, OS 68%	G3-5: overall 24%. CNS necrosis: G2 in 11%, G3 in 4% and G5 in 1 pt. G3-4 bone or soft tissue necrosis in 7 pts. 3 pts died of Tx-related complications (G5).	24%
Nakamura et al[78]	Pro	2009-2011	26	PSPT	No	100	0	Various	ND	3-y; OS 58%	G4: 2 pts (osteonecrosis, retinopathy); G3: 4 pts (cataract: 2, mucositis/dermatitis: 2).	15%
McDonald et al[51]	Retro	2010-2014	14 + 26	PSPT	Yes	75	ND	Various	ND	ND	More feeding tubes and more morphine used in IMRT group (but more NPC in IMRT group and more paranasal in proton group).	BETTER PSPT
Zenda et al[54]	Pro	2008-2012	32	PSPT	No	0	0	Mel	36 mo	1-y; LC 76%3-year; OS 46%, PFS 36%	No late G3+ toxicity reported.	0%
Zenda et al[79]	Retro	1999-2008	90	PSPT	No	12	18	Various	57 mo	5-y; OS 64%, PFS 44%	Late toxicity G3 in 17 pts (19%), G4 in 6 pts (7%; encephalomyelitis infection 2, optic nerve disorder 4).	25%
Linton et al[80]	Retro	2004-2012	26	PSPT	No	0	77	ACC	25 mo	2-y; LC 95%, OS 93% (not previously irradiated)	Late toxicity G3 in 2 pts, G4 in 1, and G5 in 1 (after reirradation).	15%
Takagi et al[81]	Retro	2002-2012	40	PSPT	No	0	0	ACC	38 mo	5-y; OS 63%, PFS 30%, LC 76%	36 G3+ events in 21 pts (26%). G+ in 24 pts, mostly osteonecrosis, G4 in 9 pts (mostly vision loss) and G5 in 3 (NP ulcers). Not separated according to proton or carbon ion therapy.	26%

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Can particle therapy improve LC and survival in sinonasal tumors?

Anti-Tumour Treatment

Systematic review and meta-analysis of radiotherapy in various head and neck cancers: Comparing photons, carbon-ions and protons

Bram L.T. Ramaekers [a,*], Madelon Pijls-Johannesma [a,e], Manuela A. Joore [b,c,f,g], Piet van den Ende [a,e], Johannes A. Langendijk [d,h], Philippe Lambin [a,e], Alfons G.H. Kessels [c,g,i], Janneke P.C. Grutters [b,f,i]

Cancer Treatment Reviews 37 (2011) 185–201

Treatment	Outcome (95% CI)	Comparison	Difference (95% CI)	I^2	*P*-value[a]
Nasopharyngeal carcinoma					
	3Y LC				
IMRT	0.947 (0.923 to 0.970)				
Protons[b]	0.920 (0.743 to 1.000)	Protons – IMRT	−0.027 (−0.232 to 0.178)	19.0%	0.780
	3Y OS				
IMRT	0.897 (0.862 to 0.933)				
Protons[b]	0.740 (0.471 to 1.000)	Protons – IMRT	−0.157 (−0.473 to 0.158)	67.5%	0.298
	3Y LC *corrected for the year of publication*				
IMRT	0.946 (0.927 to 0.966)				
Protons[b]	0.898 (0.695 to 1.000)	Protons – IMRT	−0.048 (−0.252 to 0.156)	0.0%	0.609
Oropharyngeal carcinoma					
	2Y LC				
IMRT	0.947 (0.898 to 0.995)				
Protons[b]	0.960 (0.878 to 1.000)	Protons – IMRT	0.013 (−0.105 to 0.132)	0.0%	0.782
	2Y DFS				
IMRT	0.865 (0.812 to 0.918)				
Protons[b]	0.810 (0.662 to 0.958)	Protons – IMRT	−0.055 (−0.159 to 0.269)	49.9%	0.570
Paranasal and sinonasal carcinoma					
	5Y LC				
IMRT	0.662 (0.516 to 0.809)	Carbon-ions – IMRT	−0.172 (−0.600 to 0.256)		0.327
Protons	0.878 (0.755 to 1.000)	Protons – IMRT	0.216 (0.025 to 0.407)		0.035[c]
Carbon-ions[b]	0.490 (0.210 to 0.770)	Protons – carbon-ions	0.388 (−0.033 to 0.809)	0.0%	0.063
	5Y DFS				
IMRT	0.535 (0.162 to 0.907)				
Protons	0.609 (0.326 to 0.891)	Protons – IMRT	0.074 (−0.393 to 0.542)	78.2%	0.682
	5Y OS				
IMRT	0.516 (0.154 to 0.878)				
Protons	0.705 (0.414 to 0.995)	Protons – IMRT	0.188 (−0.276 to 0.653)	73.2%	0.323
Mucosal malignant melanoma					
	5Y OS				
Photons	0.252 (0.212 to 0.291)				
Carbon-ions	0.437 (0.316 to 0.558)	Carbon-ions – photons	0.185 (0.058 to 0.313)	51.7%	0.007[c]
Adenoid cystic carcinoma					
	5Y LC				
Photons	0.753 (0.635 to 0.870)	Carbon-ions – photons	0.061 (−0.249 to 0.371)		0.675
Protons[b]	0.930 (0.797 to 1.000)	Protons – photons	0.177 (−0.252 to 0.607)		0.386
Carbon-ions	0.691 (0.405 to 0.978)	Protons – carbon-ions	0.239 (−0.264 to 0.741)	93.7%	0.322
	5Y OS				
Photons	0.731 (0.674 to 0.789)	Carbon-ions – photons	−0.027 (−0.203 to 0.149)		0.752
Protons[b]	0.770 (0.639 to 0.901)	Protons – photons	0.039 (−0.233 to 0.310)		0.769
Carbon-ions	0.704 (0.538 to 0.871)	Protons – carbon-ions	0.066 (−0.248 to 0.379)	77.8%	0.666
	5Y OS *corrected for the percentage of operated patient*				
Photons	0.728 (0.672 to 0.784)				
Protons	0.893 (0.611 to 1.000)	Protons – photons	0.165 (−0.124 to 0.455)	73.6%	0.245

Methods: 74 IMRT vs 12 particles studies in HN pts

5 ys LC better for paranasal sinus treated with protons vs IMRT

5 ys OS better for MMM treated with CIRT vs IMRT

Conclusion:

- CIRT advantage for radioresistant ca
- Need for international PT registers for comparison

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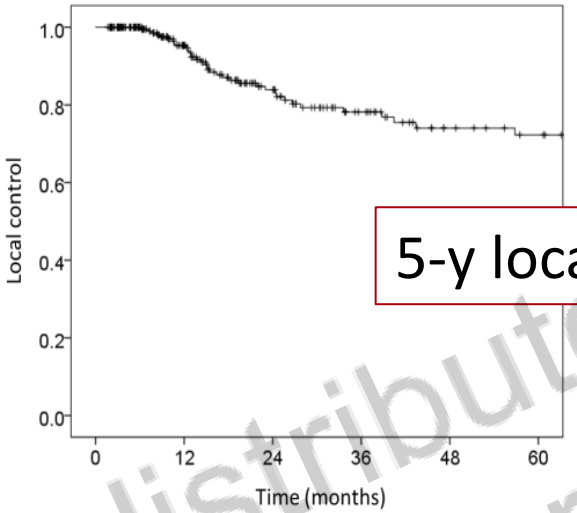
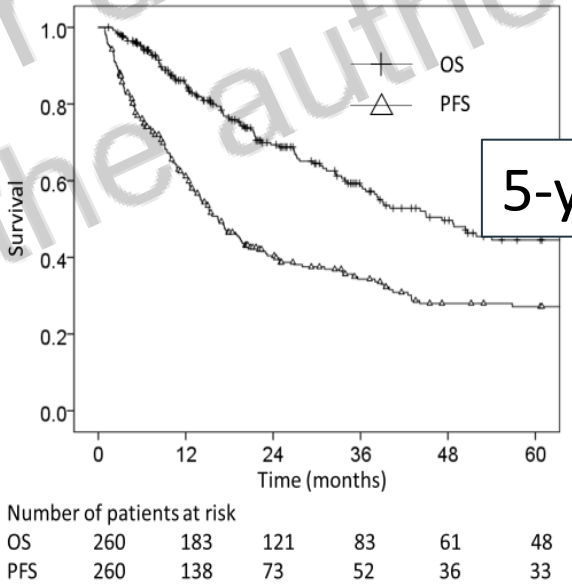
Mucosal melanoma and CIRT (J-CROS-1402)

No of patients		260
Gender	Male	111 (43%)
	Female	149 (57%)
Age, years	median	68
Primary sites	Sinonasal cavity	221 (85%)
	Oral cavity	27 (10%)
	Pharynx	12 (5%)
T classification	T3	86 (33%)
	T4a	147 (57%)
	T4b	27 (10%)
N classification	N0	251 (97%)
	N1	9 (3%)
Tumor status	Naive	224 (86%)
	Rec.	36 (14%)



5-y local control (LC) : 72. 3%



5-y overall survival (OS) : 44.6%

Koto M, et al. Int J Radiat Oncol Biol Phys. (2017) 97:1054-1060

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Comparison of CIRT with conventional RT for mucosal melanoma

	3-y OS	5-y OS	> Grade 4 toxicity
C-ion RT[4] （n=260）	58.6%	44.6%	2.7%
X-ray (n=31)[1]	33%	n.a.	6.5%
X-ray (n=11)[2]		13%	n.a.
X-ray (n=28)[3]		18%	n.a.
Surgery		25－46%	

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1. Wada H, et al. Int J Radiat Oncol Biol Phys. 2004;59:495-500.
2. Krengli M, et al. Int J Radiat Oncol Biol Phys 2006;65:751-759.
3. Gilligan D, Slevin NJ. Br J Radiol 1991;64:1147-1150.
4. Koto M, et al. Int J Radiat Oncol Biol Phys. (2017) 97:1054-1060.

Take home messages

• Carbon ion therapy can improve local control especially in non-radiosensitive tumors such as salivary gland tumors and malignant melanoma

• Proton therapy has the potential to improve local control in dose escalation studies with acceptable side effects

• No guidelines are available to help clinicians in the choice between IMRT and particle therapy, particularly as regards to protons. For nonradioresistant or relatively radioresistant tumors, such as SCC, SNUC, and neuroendocrine sinonasal carcinomas, for which the first goal is to reduce the risk of neurological radiation-induced adverse effects while achieving similar tumor control as compared to IMRT, NTCP based approach should be implemented to address patients to the proper treatment

• Large prospective studies or international registries should be designed to face efficacy and toxicity clinical issues.

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