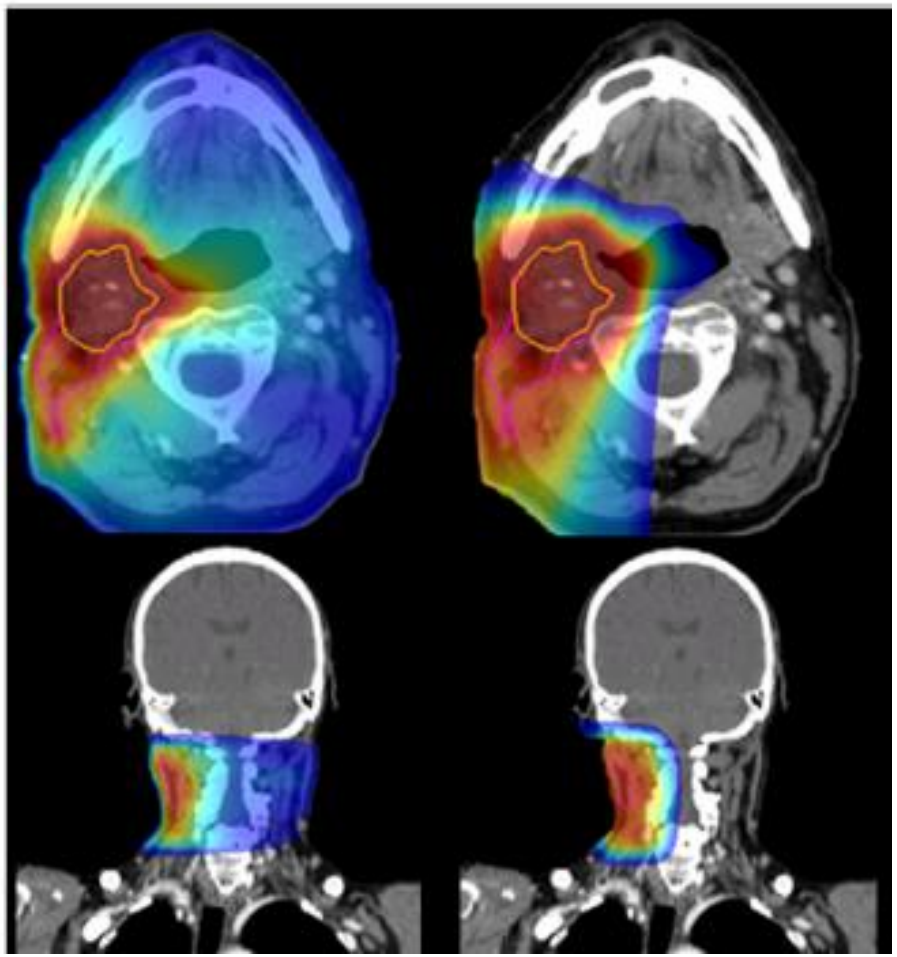
Session II: Clinical indications for proton and particle therapy. Existing clinical evidence and on-going clinical trials

25 May 2023
Workshop: Particle therapy - future for the Baltic States? State-of-play, synergies and challenges
Moderator: Dr. Erika Korobeinikova
Speaker: Dr. Anna Maria Camarda

PROTON THERAPY: dosimetric properties and physical selectivity



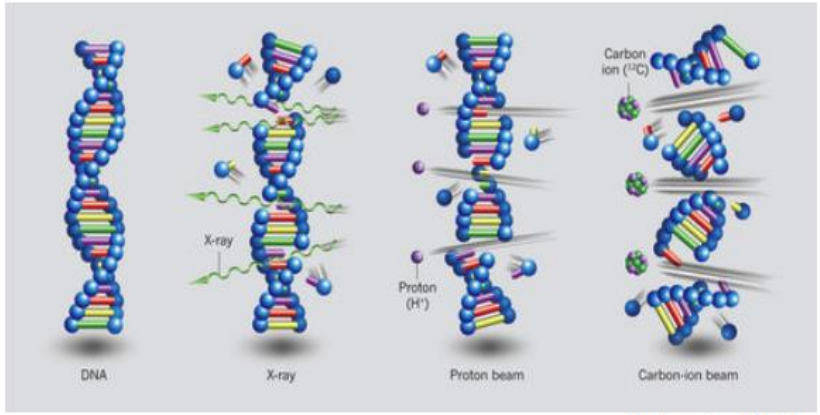
Photons **Protons**

Dose to OARs

- Potential optimization of local tumor probability by increasing dose to the tumor without increasing the dose to OAR
- No changes in dose prescription but reduction of the likelihood of radiation induced toxicity

CARBON ION THERAPY: 3Rs (Rare), Radioresistant, Recurrent

1.



Nature, April 2014

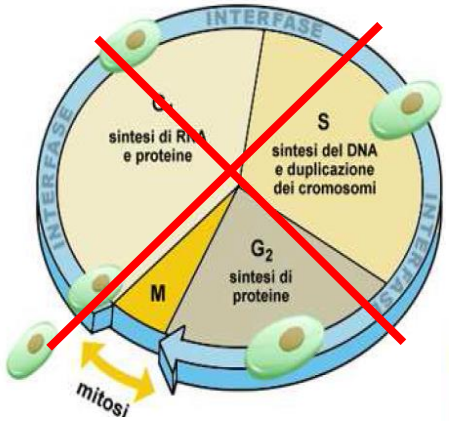
C-ions: High Linear Energy Transfer (LET) radiation

X-rays and protons cause similar DNA damage → similar tumor killing → Repair

Carbon ions cause complex DNA damage → greater tumor killing → **No Repair**

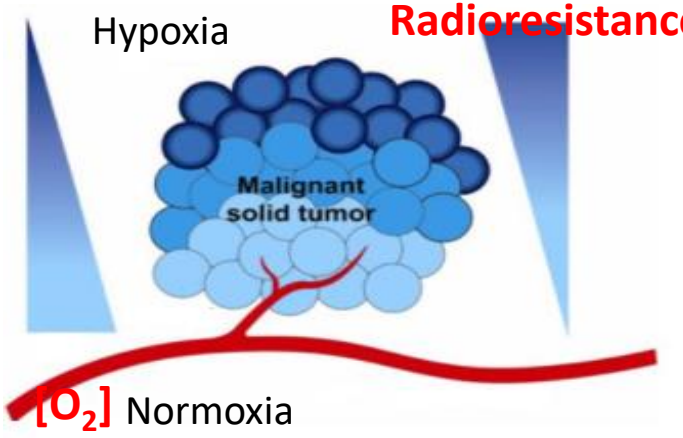
→ **High radiobiological effectiveness (RBE) > Effective for radioresistant tumors**

2.



Low cell-cycle dependence: increased lethality in the target because cells in radioresitant phase (S) are sensitized

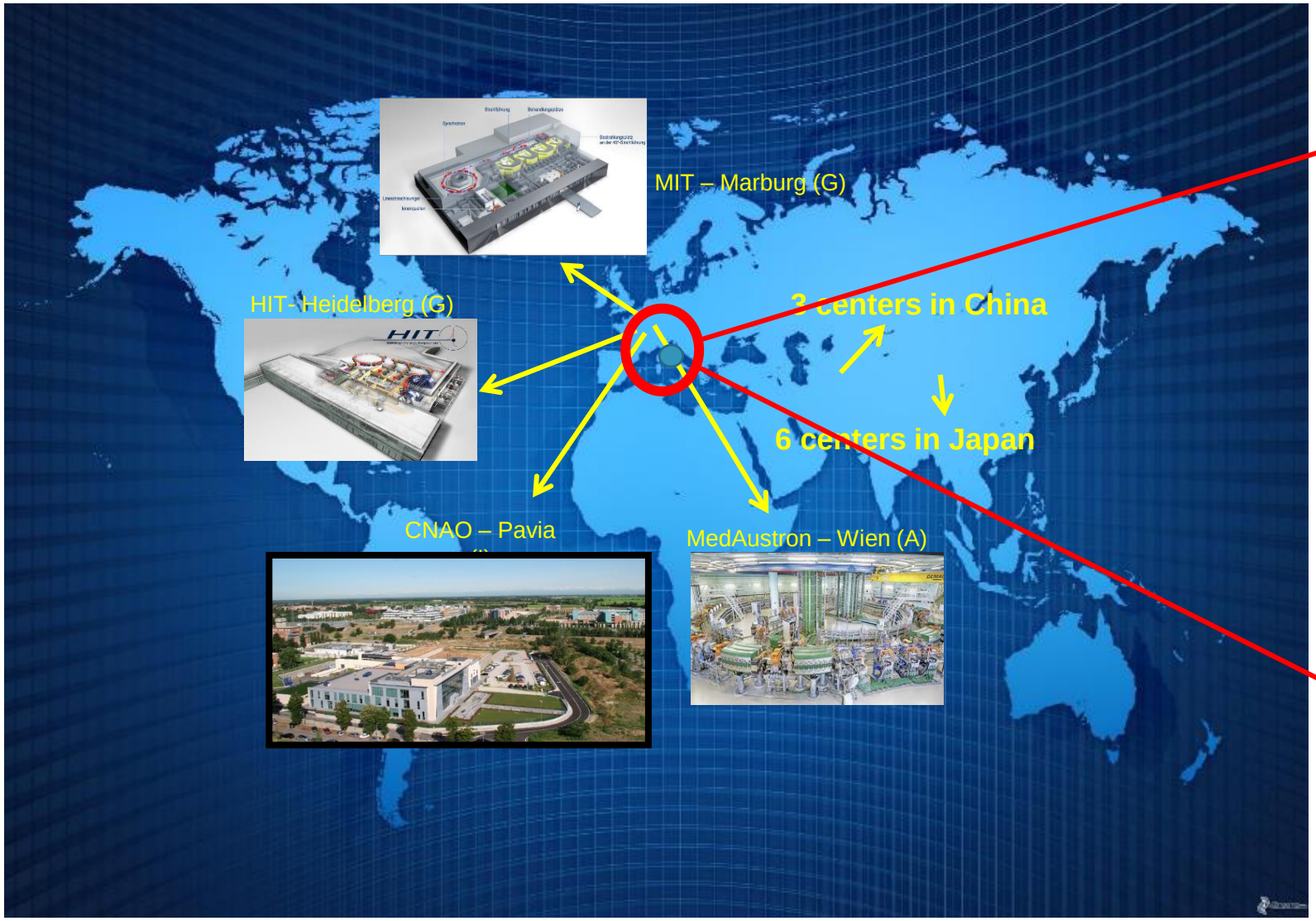
3.



Low OER:
Effective against hypoxic tumor cells

Tinganelli , Cancers, 2020

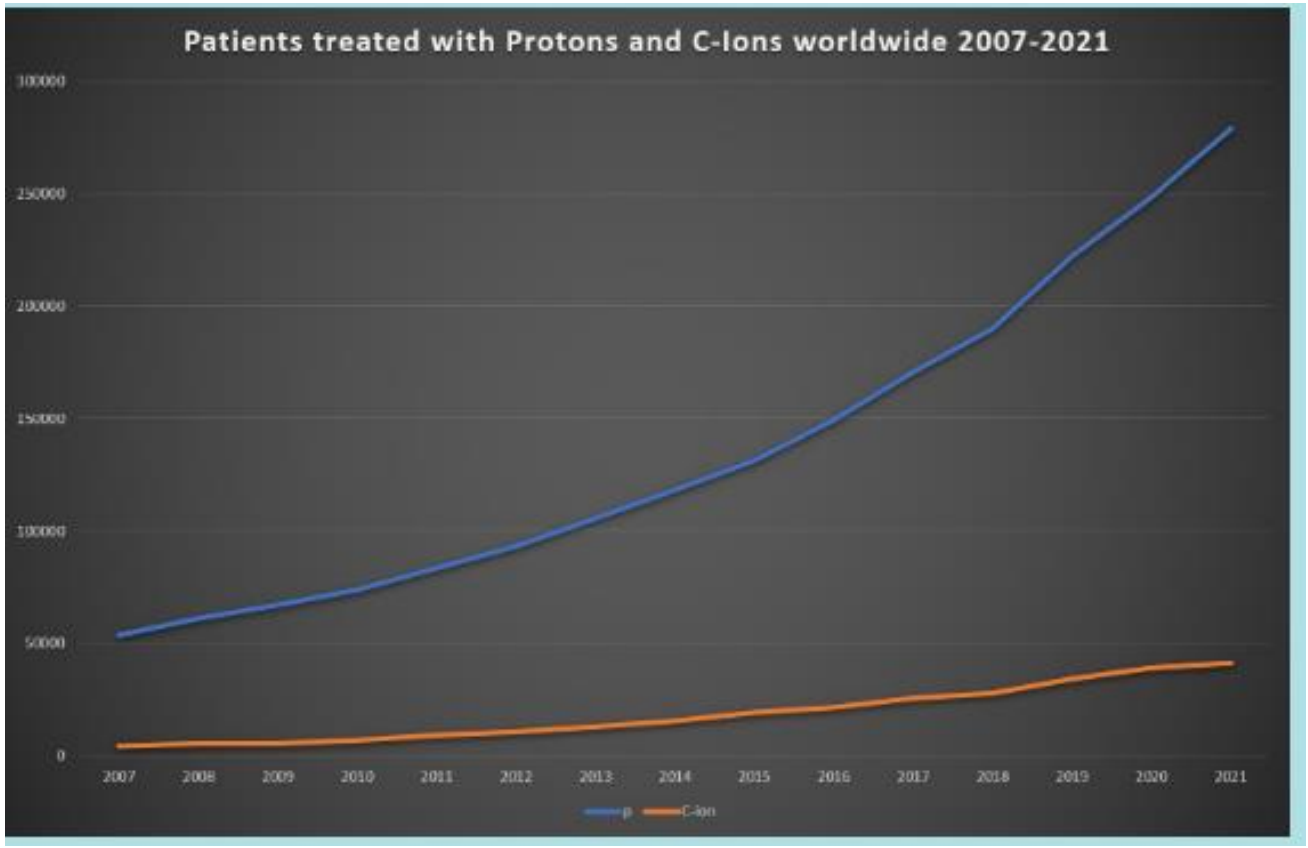
140 clinical facilities (operational phase) of protons and 13 centers of carbon ions in the world, 6 multi-particle (protons and carbon ions)



In Italy

- **Centro Nazionale di Adroterapia Oncologica CNAO; Pavia**
- **Centro di Protonterapia, Trento**
- **Centro di AdroTerapia ed Applicazioni Nucleari Avanzate, Catania**

Patients treated with Particle therapy worldwide (2007-2021)



PTCOG Website

Radiotherapy and Oncology 167 (2022) 7–13

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Current practice in proton therapy delivery in adult cancer patients across Europe

Makbule Tambas [a,*], Hans Paul van der Laan [a], Roel J.H.M. Steenbakkers [a], Jerome Doyen [b], Beate Timmermann [c,d], Ester Orlandi [e], Morten Hoyer [f], Karin Haustermans [g], Petra Georg [h], Neil G Burnet [i], Vincent Gregoire [j], Valentin Calugaru [k], Esther G.C. Troost [l,m,n,o,p,q,r], Frank Hoebers [s], Felipe A. Calvo [t], Joachim Widder [u], Fabian Eberle [v], Marco van Vulpen [w], Philippe Maingon [x], Tomasz Skóra [y], Damien C. Weber [z], Kjell Bergfeldt [aa], Jiri Kubes [ab], Johannes A. Langendijk [a]

Centres	Gantry (n)	Treatment start	Number of patients treated in 2020								Total (n)	Total (%)	N of tumor sites treated in that centre
			CNS	HNC	Prostate	Breast	Lung	GI	Lymphoma	GYN			
Centre_1	3	2012	110	50	500	150	30	50	60		950	22%	7
Centre_2	2	2018	100	120		60	80	50	10		420	10%	6
Centre_3	4	2013	308	50	30			11	15		414	10%	5
Centre_4	2	2014	300	10							310	7%	2
Centre_5	4	2011	170	90				2			262	6%	3
Centre_6	1	2019	41	15		40	90	23	5		214	5%	6
Centre_7	2	2018	72	30		86	10		2		200	5%	5
Centre_8	4	2015	153	6	13			13	10	2	197	5%	6
Centre_9	1	2014	70	10	80		10	20	5		195	5%	6
Centre_10	2	2015	115	38		2			39		194	5%	4
Centre_11	3	2019	69	61		39		3			172	4%	4
Centre_12	2(3)*	2016	60	80	10			10		2	162	4%	5
Centre_13	3	1984-2018	90	32					15		137	3%	3
Centre_14	2	2011, 2016	88	40							128	3%	2
Centre_15	1	2020	40	15	5	4	5	16	3	9	97	2%	8
Centre_16	3	2018	79								79	2%	1
Centre_17	1	1991, 2016	60								60	1%	1
Centre_18	1	2020	20	2							22	1%	2
Centre_19	1	2018	20								20	0%	1
Total (n)	*43*		1965	649	638	381	225	198	164	13	4233		
Total (%)			46%	15%	15%	9%	5%	5%	4%	0%		100%	
% of centras treating that tumor site			100%	84%	32%	37%	32%	53%	53%	16%			

CLINICAL INDICATIONS FOR PARTICLE THERAPY

USA: ASTRO PBT Model policy Group1

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of skull, including but not limited to:
  - Chordoma
  - Chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Hepatocellular cancer
- Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply
- Patients with genetic syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients
- Malignant and benign primary CNS tumors
- Advanced (eg, T4) and/or unresectable head and neck cancers
- Cancers of the paranasal sinuses and other accessory sinuses
- Non-metastatic retroperitoneal sarcomas
- Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)

UK

Pediatric tumor
Most pediatric tumors, malignant and benign
Adult
Base of skull tumors (radioresistant)
Spinal and paraspinal tumors (radioresistant)
Paranasal sinus tumors with base of skull involvement

JAPAN

PBT
Pediatric cancer
Bone and soft tissue sarcoma
Head and neck
Prostate
CIRT
Bone and soft tissue sarcoma
Head and neck
Prostate

WHAT ABOUT ITALY?

PATOLOGIE TUMORALI INSERITE NEI LEA

CONDROSARCOMI E CORDOMI DELLA BASE DEL CRANIO E DEL RACHIDE

TUMORI DEL TRONCO ENCEFALICO E DEL MIDOLLO SPINALE

SARCOMI DEI TESSUTI MOLLI

SARCOMI OSSEI INCLUSI OSTEOSARCOMI E CONDROSARCOMI

MENINGIOMI INTRACRANICI IN SEDI CRITICHE

TUMORI ORBITARI E PERIORBITARI INCLUSO IL MELANOMA OCULARE

CARCINOMI ADENOIDEO-CISTICI DELLE GHIANDOLE SALIVARI

TUMORI SOLIDI PEDIATRICI

TUMORI IN PAZIENTI AFFETTI DA SINDROMI GENETICHE

RITRATTAMENTI DI TUMORI IN SEDI GIÀ IRRADIATE

INDICATIONS for non-epithelial skull base tumors

General Treatment and Dosing Information - Chordoma

- Specialized techniques such as intensity-modulated RT (IMRT); particle beam RT with protons, carbon ions, or other heavy ions; or stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.

- Cranial (base of skull)
  - Resectable:[1]
    - Consider postoperative RT (>70 Gy) after R1/R2 resection using specialized techniques.
  - Unresectable:
    - Consider RT (>70 Gy) using specialized techniques.

General Treatment and Dosing Information - Chondrosarcoma

Dosing Prescription Regimen

- Low-grade and intracompartmental
  - Unresectable:
    - Consider RT (>70 Gy) with specialized techniques

- High-grade, clear cell, or extracompartmental
  - Resectable:[1]
    - Preoperative RT: Consider if positive margins are likely (19.8–50.4 Gy) followed by individualized postoperative RT with final target dose of 70 Gy for R1 resection and 72–78 Gy for R2 resection.
    - Postoperative RT: Consider, especially for high-grade/dedifferentiated subtype, 70 Gy for R1 and >70 Gy for R2 resection using specialized techniques.
    - Radiation is not needed for R0 resection; there should be no pre- or postoperative considerations.
  - Unresectable:
    - Consider RT (>70 Gy) with specialized techniques

Fractionation schedules with Particle Therapy in SB Chordoma: CNAO experience

Skull Base Chordoma:

- R0/R1 margins:

a) Proton Therapy: 74 Gy[RBE] CTV HR, 54 Gy[RBE] CTV LR (2 Gy [RBE]/fr).

- R2 or biopsy or recurrent disease after surgery:

a) Carbon Ions: 65,6 - 70,4 Gy [RBE] CTV HR, 36,9-39,6 Gy[RBE] CTV LR, 16 fractions (4,1-4,4 Gy[RBE]/fr). Fractionation schedule depends on extension of the disease and proximity to critical structures.

a) Proton Therapy: 74 Gy[RBE] CTV HR, 54 Gy[RBE] CTV LR (2 Gy [RBE]/fr).

Single institutional reports on PT and CIRT for CHORDOMA of the skull base

Author Year	Particle	Number of patients	Prescription dose (GyRBE)	Median time of follow-up (months)	LC (%)	OS (%)
Hug, 1999 (Loma Linda University)	Ph + Protons	33	71.9 (range 66.6 – 79.2)	32.2	3y: 67 5y: 59	3y: 87 5y: 79
Munzenrider, 1999 (Massachusetts General Hospital—Adults)	Ph + Protons	169	Range 66 - 83	41	5y: 73 10y: 54	5y: 80 10y: 54
Noel, 2005 (Centre de Protontherapie d'Orsay, France)	Ph + Protons	100	67 (range 60 – 71)	31	4y: 53	4y: 90
Mozoe, 2009	Carbon ions	33	Range 40 – 60.8	53 (mean)	5y: 85 10y : 64	5y: 88 10y : 67
Uhl, 2014	Carbon ions	155	60 (range 54 -70)	38	3y: 82 5y: 72 10y: 54	3y: 95 5y: 85 10y: 75
Weber, 2016 (Paul Sherer institute-Switzerland)	Protons	151	72.5	50 (mean)	5y: 78 7y: 70.9	7y: 72.9
Fung, 2018	Protons	106	Range 68.4 – 73.8	61	4y: 78.3 5y: 75.1	4y: 90.2 5y: 88.3
Iannalfi 2020 ° CNAO		**135**		44		
	Protons	**70**	74 (range 72 – 74)		3y: 89 5y: 84	3y: 93 5y: 83
	Carbon ions	**65**	70.4		3y: 77 5y: 71	3y: 90 5y: 82

Skull Base Chordomas

CNAO experience

135 patients

From November 2011 and December 2018

- CIRT (70.4 Gy RBE in 16 fr): 65 pts (unfavourable)
- PT (74 GyRBE in 37 fr): 70 pts

5-year LC:
71% in CIRT; 84% in PT.

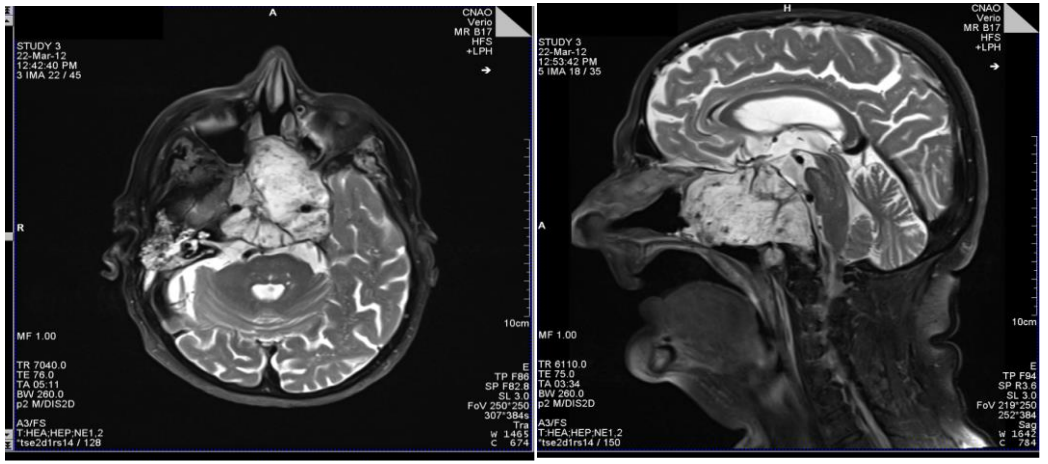
5-year OS:
82% in CIRT; 83% in PT.

On multivariate analysis, **gross tumor volume (GTV), optic pathways, and/or brainstem compression** and **dose coverage** are independent prognostic factors of local failure risk.

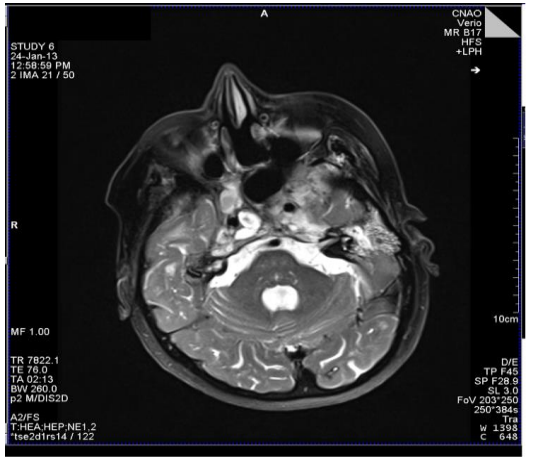
1348 Neuro-Oncology
22(9), 1348–1358, 2020 | doi:10.1093/neuonc/noaa067 | Advance Access date 20 March 2020

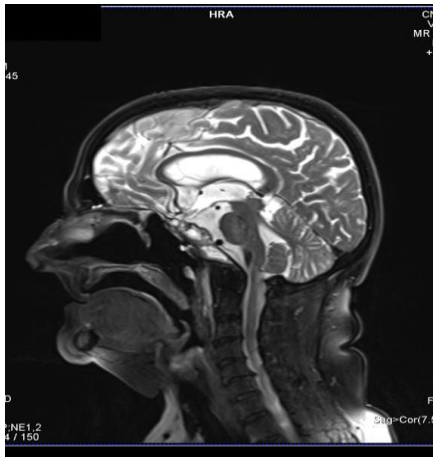
Iannalfi A, Neuro-Oncology 2020

Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy



10 months F-UP





Fractionation schedules with Particle Therapy in SB Chondrosarcoma: CNAO experience

Skull Base Chondrosarcoma Low grade (G1)

- R0 margins: no adjuvant RT.

- R1 margins:

a) Proton therapy: 70 Gy[RBE] CTV HR, 54 Gy[RBE] CTV LR (2 Gy [RBE]/fr).

- R2 or biopsy or recurrent disease after surgery:

a) Carbon Ions: 70,4 Gy [RBE] CTV HR, 36,9-39,6 Gy[RBE] CTV LR, 16 fractions (4,1-4,4 Gy[RBE]/fr). Fractionation schedule depends on extension of the disease and proximity to critical structures.

b) Proton Therapy: 70 Gy[RBE] CTV HR, 54 Gy[RBE] CTV LR (2 Gy [RBE]/fr).

Skull Base Chondrosarcoma Medium-High grade (G2-G3)

- R0/R1 margins:

a) Proton Therapy: 70 - 74 Gy[RBE] CTV HR, 54-56 Gy[RBE] CTV LR (2 Gy [RBE]/fr).

- R2 or biopsy or recurrent disease after surgery:

a) Carbon Ions: 70,4 - 76,8 Gy [RBE] CTV HR, 39,6-43,2 Gy[RBE] CTV LR, 16 fractions (4,4 - 4,8 Gy[RBE]/fr).

b) Proton Therapy: 70-78 Gy[RBE] CTV HR, 54 Gy[RBE] CTV LR (2 Gy [RBE]/fr). Evaluate if expected toxicity is high.

Single institutional reports on PT and CIRT for CHONDROSARCOMA of the skull base

Author Year	Particle	Number of patients	Prescription dose (GyRBE)	Median time of follow-up (months)	LC rate	Late Toxicity
Hug 1999	Protons	25	70.2* (median)	33.2*	3y LC: 94%	7% (G3-G4)
Munzenrider 1999 (Massachusetts General Hospital)	Protons	229	72* (mean)	41*	5y LC: 98%	-
Ares 2009	Protons	22	68.4 (median)	34 *	5y LC: 94%	6.2%
Fuji 2011	Protons	8	63* (median)	42*	3y LC: 86%	No G ≥3
Weber 2016 (Paul Sherer Institute-Switzerland)	Protons	71	72.5* (median)	50 *	5y LC: 93.6%	8.1 % (G3-G4)
Mattke 2018	Protons Carbon ions	22 79	70 (median) 60 (median)	30.7 43.7	4y LC: 100% 4y LC: 90.5%	No G ≥3
Holtzman 2019	Protons	43	73.8 (median)	44	4y LC: 89%	4.6 % (G3) + 9% G3 expected hear loss
Riva 2021 ° CNAO	Protons Carbon ions	**32** **16**	70 70.4	31 66	3y LC: 100% 3y LC: 94%	8% (G3) No G4-G5

Skull Base Chondrosarcomas

cancers

Riva et al. Sept 2021

Article

Particle Radiotherapy for Skull Base Chondrosarcoma: A Clinical Series from Italian National Center for Oncological Hadrontherapy

CNAO experience

48 patients

From September 2011 to July 2020

67% PT (70 GyRBE in 35 fractions)

33% CIRT (70.4 GyRBE in 16 fractions)

3-year LC : 98%.

2% G3 acute toxicity; 8% G3 late toxicity.

White-matter brain changes 46% patients, but only 7 needed steroids (G2). No patients had G3 brain toxicity.

No G4–5 complications

PT and CIRT appeared to be effective and safe treatments for patients with SB-CHS, resulting in high LC rates and an acceptable toxicity profile.

INDICATIONS FOR BRAIN TUMORS

PROTON THERAPY SPECIAL FEATURE: REVIEW ARTICLE

Proton therapy for brain tumours in the area of evidence-based medicine

[1,2,3]DAMIEN C WEBER, MD, [1]PEI S LIM, MD, [1]SEBASTIEN TRAN, MD, [1]MARC WALSER, MD, [1]ALESSANDRA BOLSI, PhD, [1]ULRIKE KLIEBSCH, PhD, [1]JÜRGEN BEER, MD, [1]BARBARA BACHTIARY, MD, [1,4]TONY LOMAX, PhD and [1]ALESSIA PICA, MD

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[4]Department of Physics, ETH, Zürich, Switzerland

2020

Advanced Drug Delivery Reviews 109 (2017) 26–44

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journal homepage: www.elsevier.com/locate/addr

Proton therapy – Present and future☆

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INDICATIONS FOR BRAIN TUMORS

2020

PROTON THERAPY SPECIAL FEATURE: REVIEW ARTICLE

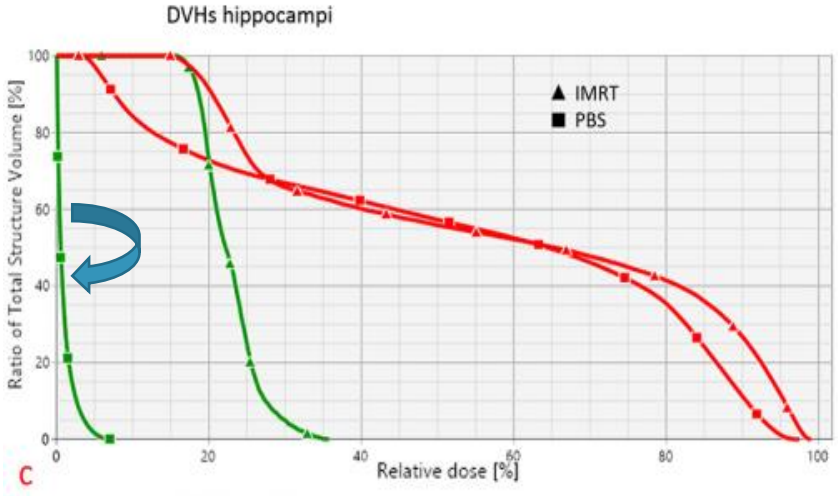
Proton therapy for brain tumours in the area of evidence-based medicine

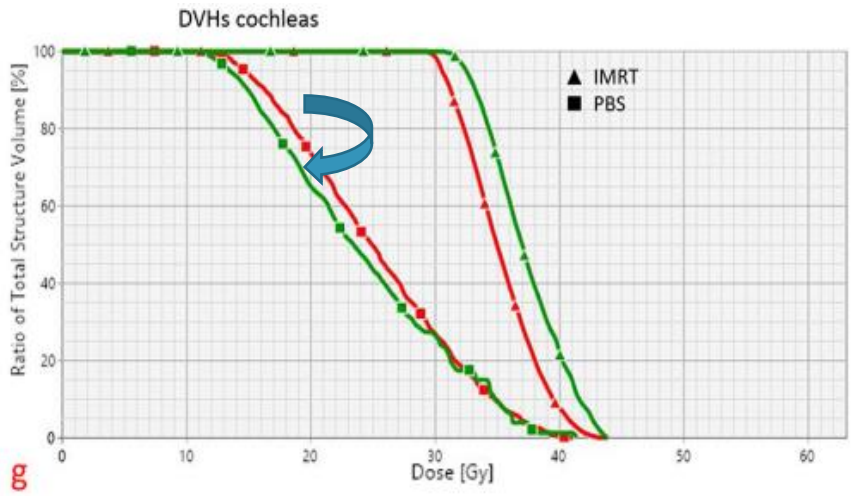
[1,2,3]DAMIEN C WEBER, MD, [1]PEI S LIM, MD, [1]SEBASTIEN TRAN, MD, [1]MARC WALSER, MD, [1]ALESSANDRA BOLSI, PhD, [1]ULRIKE KLIEBSCH, PhD, [1]JÜRGEN BEER, MD, [1]BARBARA BACHTIARY, MD, [1,4]TONY LOMAX, PhD and [1]ALESSIA PICA, MD

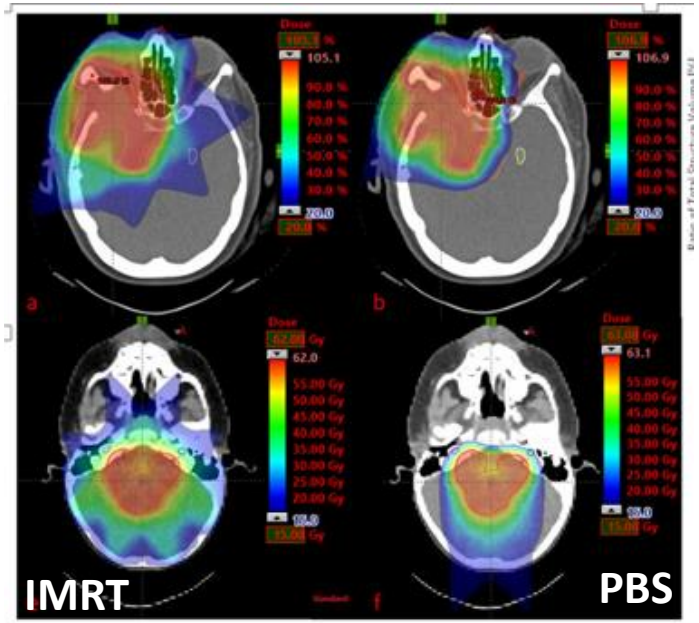
[1]Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland
[2]University of Bern, Bern, Switzerland
[3]University of Zürich, Zürich, Switzerland
[4]Department of Physics, ETH, Zürich, Switzerland

- Even for **very complex target volumes involving large parts of the brain**, such in whole ventricular RT for intracranial germ cell tumours, a dosimetric comparison study showed an approximately one-third reduction in integral dose to the brain, and also a better sparing of the circle of Willis with PT.

- **Decrease of dose** delivered with PT as opposed to IMRT to the **hippocampus and cochleas**' for a supra- and infratentorial tumor, respectively.



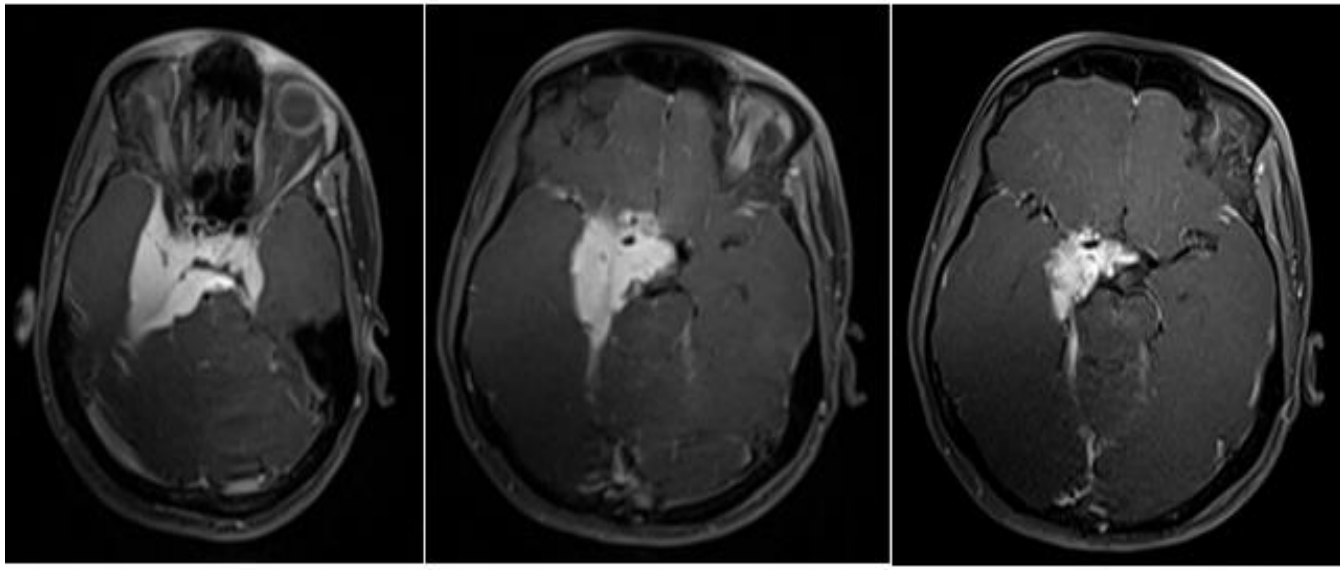




Preliminary evidence suggests that this PT dosimetric gain also translates into a clinical benefit such as, for example, **reduced neuro-cognitive disability and improved quality of life**.

Intracranial meningiomas in critical sites (close proximity to the optic pathways and brainstem)

- Total surgical resection is the treatment of choice for symptomatic/progressive meningioma.
- However, not all meningioma are suitable for surgery and therefore radiation therapy is often indicated.
- In particular, patients with residual non-benign, recurrent or high-grade tumours are candidates for radiation therapy.
- Large and complex shaped meningioma located close to brainstem, optical nerve, pituitary gland and cochlea may present however a therapeutic challenge and proton may provide dose escalation possibilities for non benign meningiomas.



CNAO

Weber et al. 2020

Indication/selection criteria for Particle therapy (RT naive patients)

Intracranial meningiomas

WHO I (histologically prove or radiologically presumed): Cases requiring conventional fractionation

- Confirmed RT indication regardless RT modality

Exclusive therapeutic option in unresectable tumors OR postoperative in uncompletely-resected tumors OR post-surgery recurrence

- Large/very large/giant sized (eventual extra-cranial involvement): often complex/irregular shaped tumors

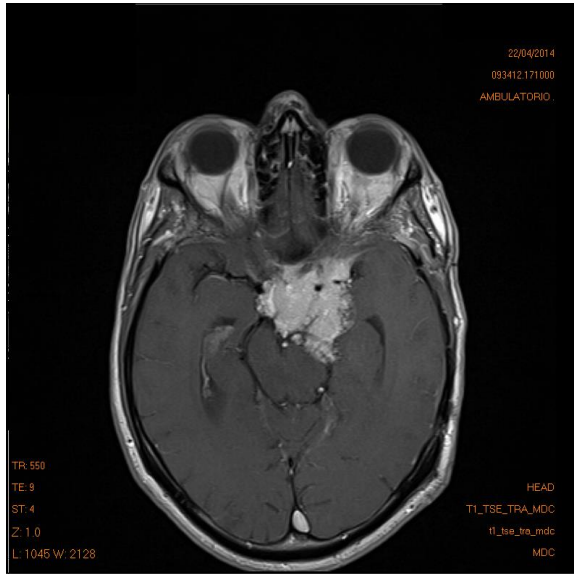
- Lesions located in close proximity of o directly involving critical organs at risk (optic-pathways and brainstem)

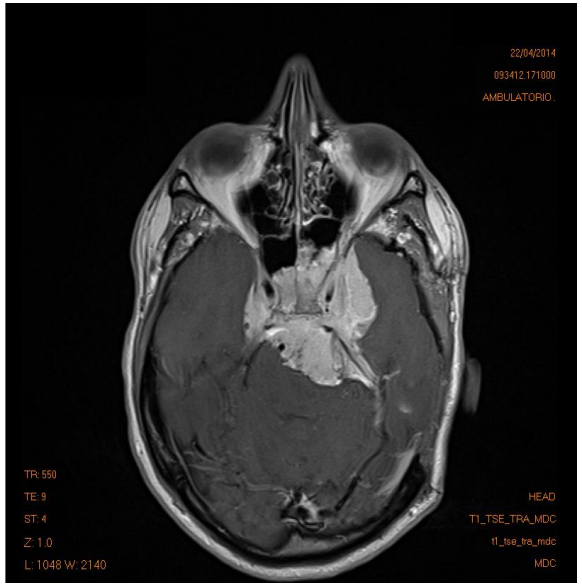
Particle Radiotherapy (exclusive proton or photon + proton):

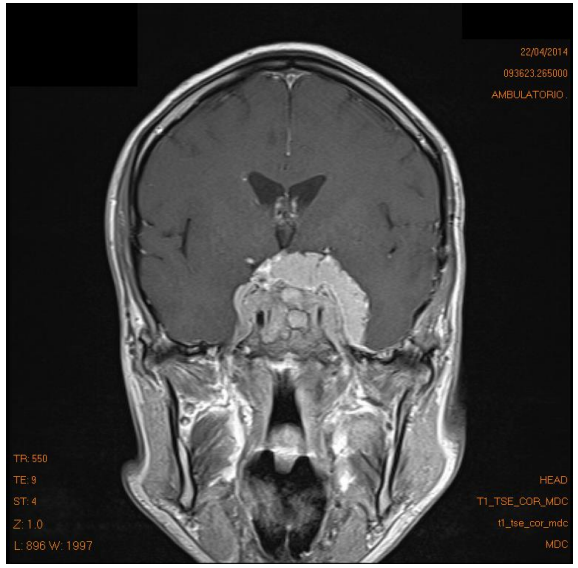
5-years Local Control → ≥ 95 %

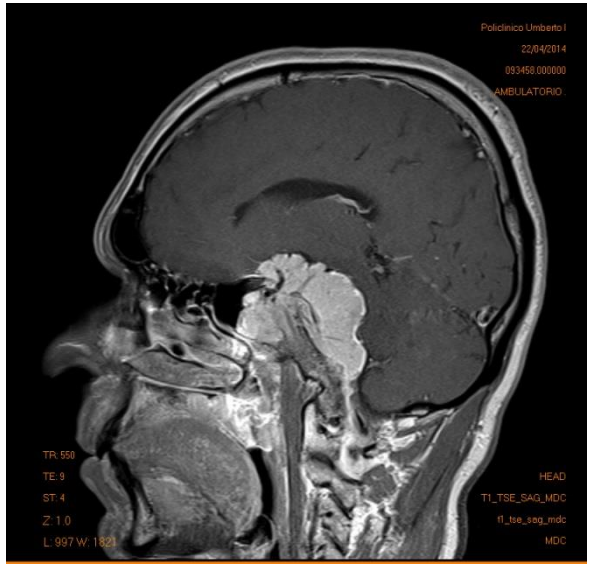
(Wenkel et al. 2000 ; Noel et al. 2005 ; Slater et al. 2012; Murray et al. 2017 ; El Shafie et al. 2018)

Skull base WHO-I Meningioma: Proton therapy at CNAO





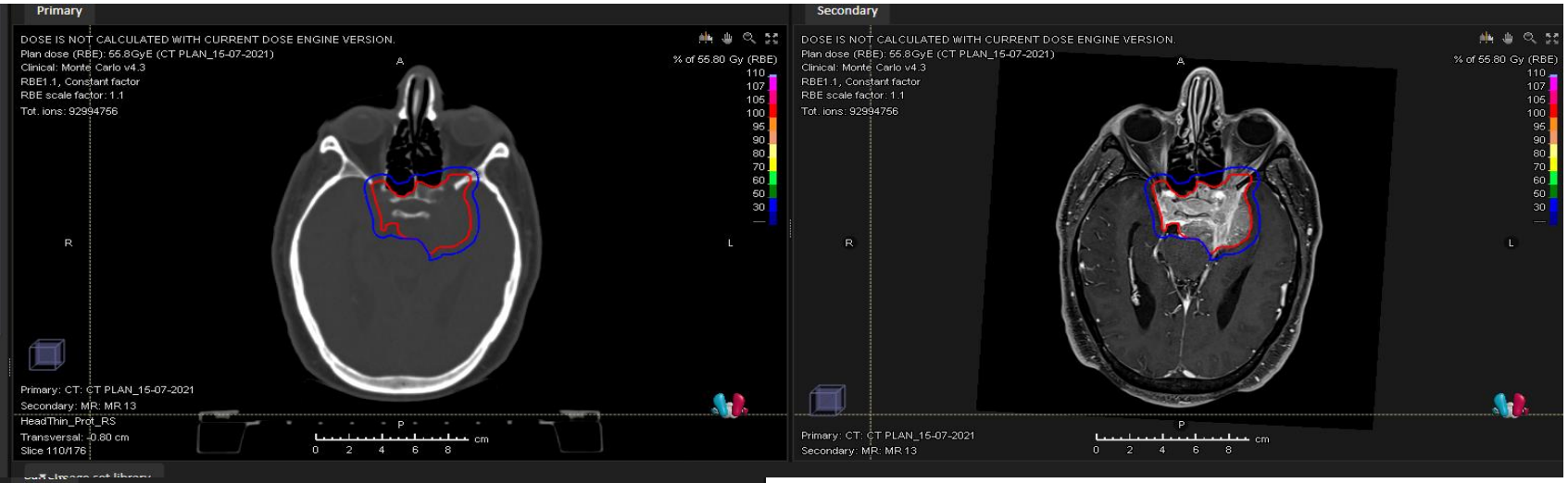


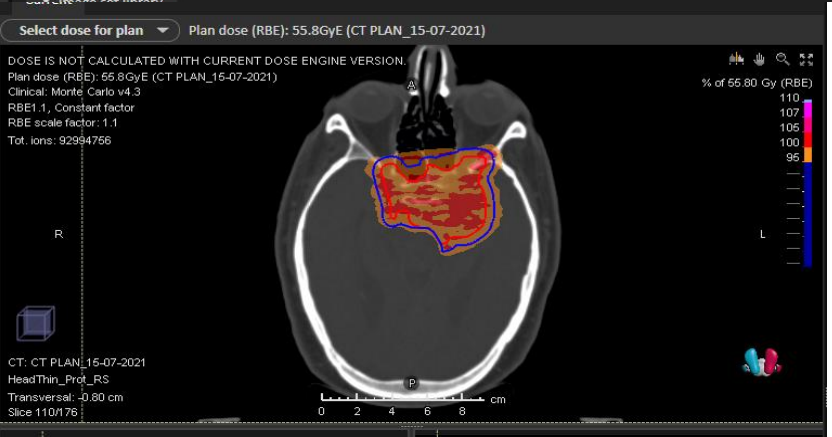


WHO II -WHO III Meningiomas (regardless tumor location)

Indication for First Radiotherapy (RT naive patients) regardless RT modality

- RT fractionated dose schedule should be adopted (EANO guidelines , 2021)
- HIGHER RT dose level (≥ 60 Gy) required



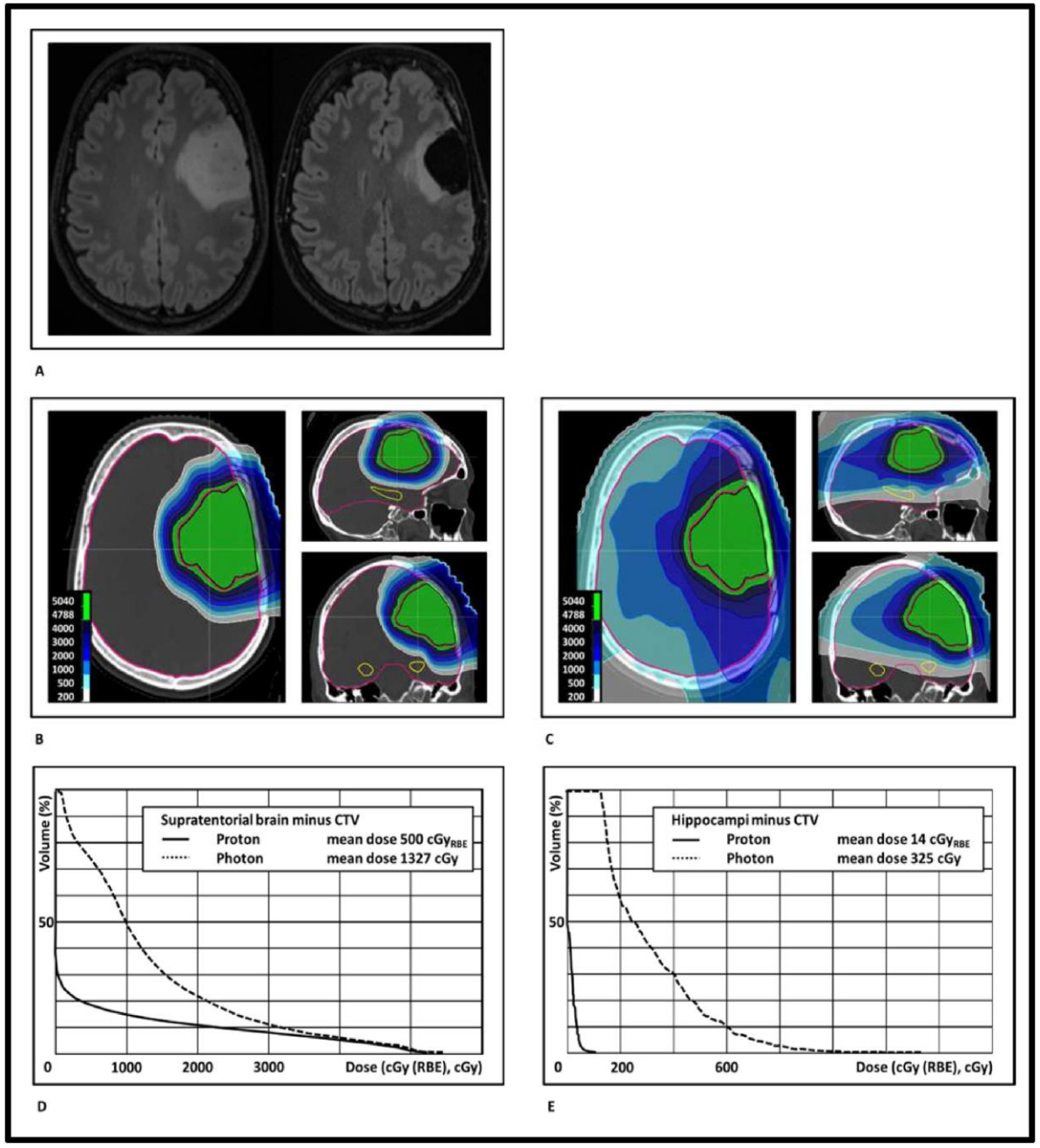


(Hug et al , 2000 ; Boskos et al , 2009 ; Kaur et al, 2014 ; Aizer et al, 2014; Jenkinson et al, 2014; Hwang et al, 2017 ; Weber et al 2018 ; Lee et al, 2019; Rogers et al, 2020)

Glioma tumors: any role for particle therapy?

- Proton therapy for low-grade gliomas has also been evaluated.
- Investigators from the MGH first utilized mixed photon/proton treatments for dose escalation studies including patients with grades II and III gliomas.
- Investigators from the University of Heidelberg, which employs scanning beam proton delivery technology, have also reported on 19 patients treated for lowgrade gliomas. Similar to photon-based treatments, their initial results suggest high rates of tumor control and acceptable toxicity rates
- in a recent study Shih, et al. reported results of a prospective trial, which enrolled patients with grade II gliomas and assessed cognitive function and quality of life following proton therapy
- With a median follow-up of 5.1 years, measures of cognitive function were stable to improved compared to the baseline

Mohan R et al. Adv Drug Deliv Rev. 2017
Fitzek MM et al. Int J Radiat Oncol Biol Phys. 2001
Hauswald H. et al. Radiat Oncol. 2012
Shih HA et al. Cancer. 2015



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Review Article

Proton therapy for selected low grade glioma patients in the Netherlands

Hiska L. van der Weide [a,*], Miranda C.A. Kramer [a], Daniel Scandurra [a], Daniëlle B.P. Eekers [b], Yvonne L.B. Klaver [c], Ruud G.J. Wiggenraad [c], Alejandra Méndez Romero [c,d], Ida E.M. Coremans [e], Liesbeth Boersma [b], Marco van Vulpen [c,d,e], Johannes A. Langendijk [a], On behalf ofthe Dutch Society for Radiation Oncology NVRO

[a] University of Groningen, University Medical Center Groningen, Department of Radiation Oncology; [b] Department of Radiation Oncology (Maastro), GROW School for Oncology, Maastricht University Medical Centre+; [c] Holland Proton Therapy Center, Delft; [d] Department of Radiation Oncology, Erasmus University Medical Center, Rotterdam; and [e] Department of Radiation Oncology, Leiden University Medical Center, the Netherlands

- ✓ Neurocognitive function is a difficult clinical endpoint to evaluate and quantify, and currently high-quality NTCP-models for NCF outcome, necessary to give clinical meaning to the superior dose distribution of protons, are lacking
- ✓ In the Netherlands, the most favourable LGG patients with an indication for radiotherapy are eligible for proton therapy.

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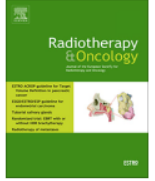


Review Article

Proton therapy for selected low grade glioma patients in the Netherlands

Hiska L. van der Weide [a,*], Miranda C.A. Kramer [a], Daniel Scandurra [a], Daniëlle B.P. Eekers [b], Yvonne L.B. Klaver [c], Ruud G.J. Wiggenraad [c], Alejandra Méndez Romero [c,d], Ida E.M. Coremans [e], Liesbeth Boersma [b], Marco van Vulpen [c,d,e], Johannes A. Langendijk [a], On behalf ofthe Dutch Society for Radiation Oncology NVRO

[a] *University of Groningen, University Medical Center Groningen, Department of Radiation Oncology;* [b] *Department of Radiation Oncology (Maastro), GROW School for Oncology, Maastricht University Medical Centre+;* [c] *Holland Proton Therapy Center, Delft;* [d] *Department of Radiation Oncology, Erasmus University Medical Center, Rotterdam; and* [e] *Department of Radiation Oncology, Leiden University Medical Center, the Netherlands*

- ✓ Eligibility criteria are:

(1) good prognosis, defined as an expected 10-year survival of 50% or higher;
(2) good clinical and neurocognitive status prior to radiotherapy, defined as a Karnofsky performance status of 80 or higher and iADL independent function;
(3) dose benefit of proton therapy over photon therapy, defined as more than 5% dose reduction to the supratentorial brain and/or both hippocampi outside the target volume

- ✓ In the coming years collaborative efforts will be made to prospectively evaluate and register NCF outcome data with the intention to develop NCFbased NTCP models to enable model-based selection in the future.

Table 1. Prospective trials and tumor registries currently accruing patients in Europe and in the United States for brain tumours

Tumor type	NCT number	Allocation	Activation (closed) [year]	# of patients	Age limit	Hypothesis	Primary endpoint	Total dose (dose per fx) [GyRBE]	status
Europe (lead)									
All brain tumorsa (*Dresden, D*)	02824731	Non-randomized Phase II	1997	418	no	rate of chronic 1 year toxicity: 15% lower with protons	Chronic toxicity @ 1 year and QoL	54-60(27-30)	accruing
WHO grade II/ WHO grade III and IDH mutated (*Essen, D*)	DRKS 00015160 NOA-25	prospective, randomized (Photons *vs* Protons)	2019	80	≥18 years	Less impairment of neurocognition after proton therapy when compared to photon radiotherapy	Neurocognition after 3 years	WHO II: 54 Gy (30 × 1,8 Gy) WHO III: 60 Gy (30 × 2 Gy) Or 59,4 Gy (33 × 1,8 Gy)	accruing
United States (lead)									
All brain tumors *Washington Uni. School of Medicine*	02559752	Non-randomized Phase II	2015	80	4–21 years	Testing as measured by an acceptance rate of 60% of eligible patients administered PT	Feasibility of obtaining serial computer-based neurocognitive testing for patients administered PT	NR	accruing
Craniopharyngioma *St Judes Children Hospital*	02792582	Non-randomized Phase II	1996	140	≤21 years	Increase of PFS @ 3 years compared to photon data	PFS @ 3 years	54 (1.8)	accruing
Meningioma (Recurrent) *Washington Uni. School of Medicine*	03267836	Phase Ib	2018	12	≥18 years	Proof of concept to demonstrate on-target effect of the PT-ICI	Immunogenicity as measured by changes of CD8+/ CD4 + TILs	20(5) with concomitant Avelumab	accruing
Meningioma (non-benign) *Mass. General Hospital*	02693990	Non-randomized Phase I/II	2016	60	≥18 years	Dose escalation	Assess Safety and Utility of Increased Dose IMPT (DLT)	Dose escalation 3 × 3 design	accruing
Low-grade brain tumours *Mass. General Hospital*	03286335	Observational study	2018	100	≥18 years	None (observational)	Tumor control @ 2 years	NR	accruing
Vestibular Schwannoma *Mass. General Hospital*	01199978	Observational study	2010	30	≥18 years	None (observational)	Incidence of late toxicity @ 2 year	54(27)	Accruing

Tum°r type	NCT number	All°cation	Activati°n (cl°sed) [year]	# °f patients	Age limit	Hyp°thesis	Primary endp°int	T°tal dose (d°se per fx) [GyRBE]	status
All brain tum°urs requiring CSA *Mass. General H°spital*	03281889	Feasibility	2018	20	3–18 years	T° assess if IMPT is feasible for CSA vertebral body sparing	Rate °f G3/4 haematological toxicity < 5% within 3 months	NR	Accruing
Recurrent Ependym°ma *St Judes Children H°spital*	02125786	N°n-Randomised Phase II	2014	99	1–21 years	T° assess if surgery and fractionated re-irradiation with either proton or photon is effective and safe	PFS and °S @ 3 years	NR	Accruing
Gli°blastoma *NRG °ncology*	02179086	Rand°mised Phase II	2014	606	≥18 years	D°se escalation with IMRT or PT is better than standard dose photon radiation therapy	°S dose escalation *vs* standard dose	NR	Accruing
IDH mutant Gli°ma (GII/III) *NRG °ncology*	03180502	Rand°mised Phase II	2017	120	≥18 years	PT will preserve c°gnition compared with IMRT	Change in c°gnition (CTB COMP scoreb) up t° 10 years	NR	Accruing
Medull°blastoma *St Judes Children H°spital*	01878617	Phase II	2013	625	3–39 years	Assess clinical and m°lecular risk directed therapy	PFS @ 2 years, neur°cognition @ baseline and 12 weeks	NR	Accruing
Brain tum°urs *May°*	03055364	°bservational study	2017	160	≥4 years	N°ne (observational)	C°gnitive performance change (CogState) within 12 months of radiotherapy	NR	Accruing
Meningi°ma (G II) *NRG °ncology*	03180268	Rand°mised Phase III	2017	148	≥18 years	°bservation *vs* adjuvant RT in the completely resected setting	PFS up t° 10 years	59.4 (1.8)	Accruing
Lept°meningeal metastases *MSKCC*	03520504	Phase I	2018	26	≥10 years	Identificati°n of safe and effective dose for PT in leptomeningeal metastases	Number °f patients with DLT	30 (3) °r 25 (2.5) CSA	Accruing

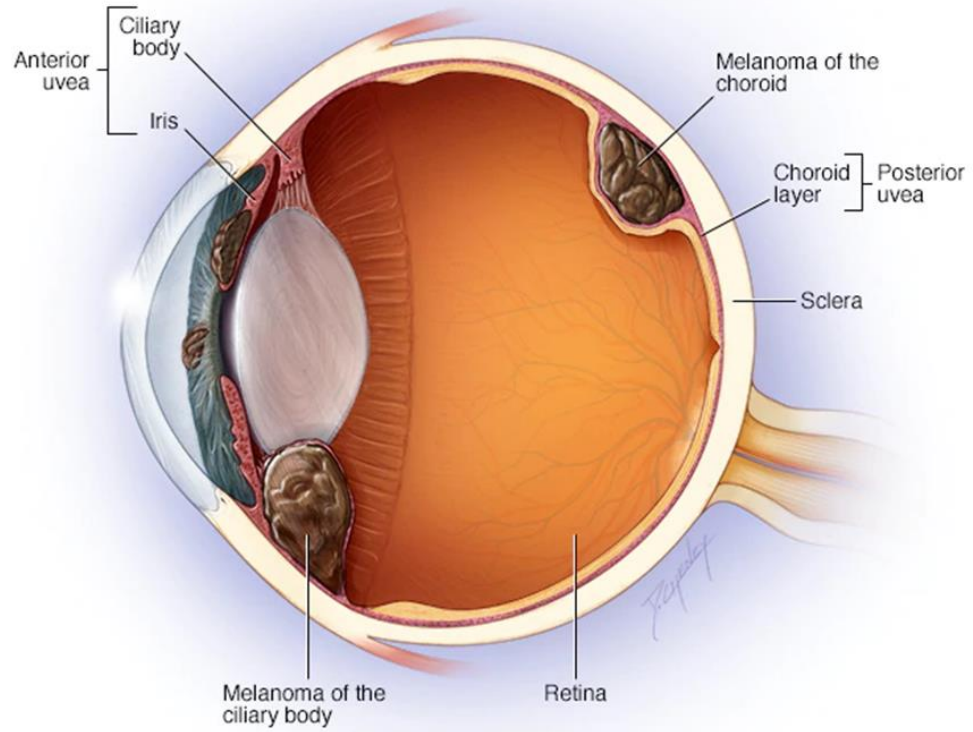
OCULAR MELANOMA

- Most common intraocular tumor in adults
- Rare malignancy arising within melanocytes of the uveal tract: iris, ciliary body and choroid.
- Historically, surgery has been the mainstay of treatment for primary melanoma.

From 1970s eye-preserving treatment modalities gradually replaced the radical approach.

The radiotherapy techniques of globe-conserving therapy:

- radiotherapy: plaque brachytherapy
- external beam radiotherapy with photons
- helium ions
- **PROTON RT**
- carbon ions RT



Critical Review

Charged Particle Radiation Therapy for Uveal Melanoma: A Systematic Review and Meta-Analysis

Particle therapy

- **6718 pts proton therapy**
- 623 helium ions therapy
- 116 received carbon ion therapy

Standard care group

1352 patients

- enucleation
- iodine-125 brachytherapy

Main findings

- **the risk of local recurrence was markedly lower with CPT**
- **lower incidence of cataract and radiation retinopathy with CPT.**
- **CPT was associated with a 47% reduction in the risk of enucleation , this reduction did not reach statistical significance**

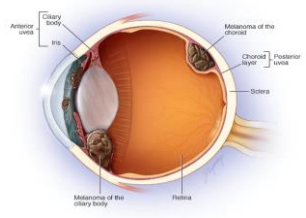
Ocular Melanoma

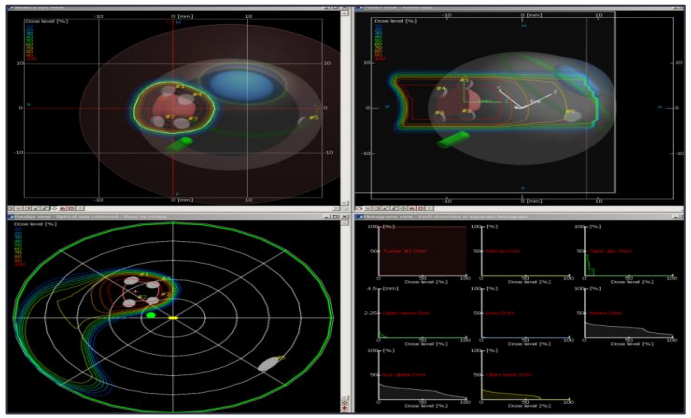
CNAO experience

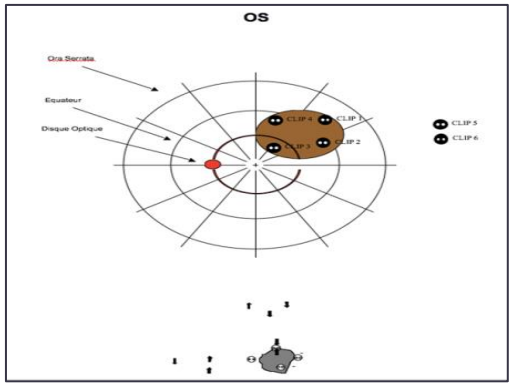
> 200 patients

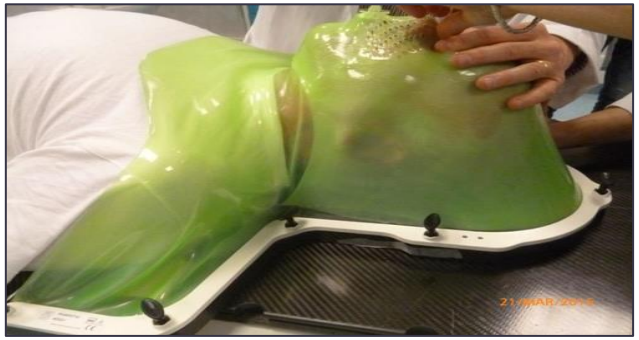
Protons: 60 GyE (4 fx)

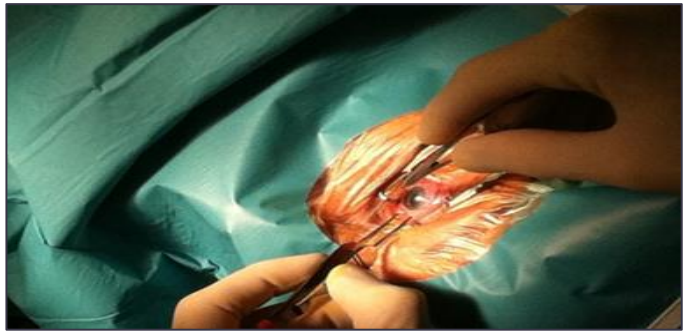
Local Control >95%
Eye preservation >90%
Visual function >45%

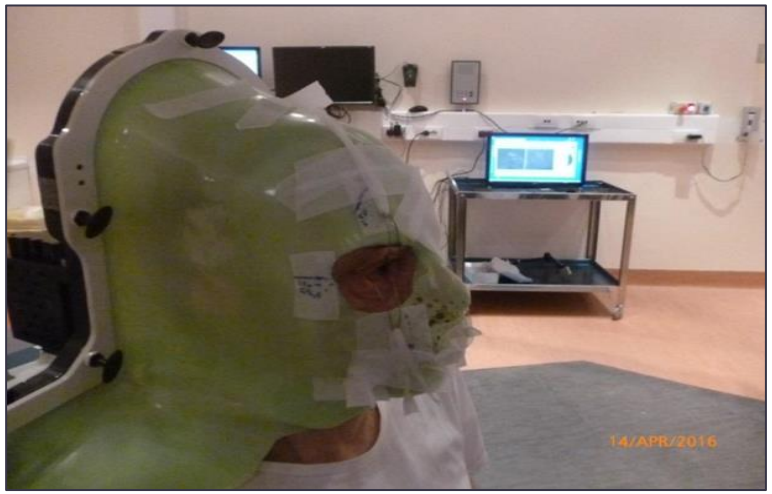


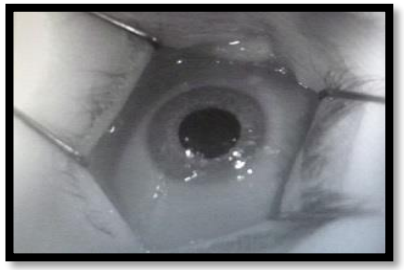












INDICATIONS FOR HEAD AND NECK CANCER

INDICATIONS FOR HEAD AND NECK CANCER

- The superior dosimetric conformity and organ-sparing capabilities appear to correspond with improved patient outcomes when compared with IMRT per the existing literature

- **Locally advanced Head and neck cancers**: IMPT, compared to VMAT, significantly reduced toxicities (feeding tube placement and dependence, narcotics use, xerostomia) and hospitalization (~30% to ~8%) within 60 days post-RT, improve QOL, better financial toxicity.

- Different indications for proton therapy vs CIRT. CIRT in radioresistant tumors, unresectable or unfit for surgery. Emerging evidence suggests to avoid demolitive surgery deemed to be R2 in favour of radical CIRT. Protons to reduce toxicity in tumors in difficult locations (orbit and paranasal tumors)

Table 3
Tumour-site specific factors considered while selecting patients for PT.

Tumour site	Factors
HNC	Good immobilization capacity of the patient during long treatment time Locally advanced HNC with primary tumour close to skull base Tumours of nasopharynx, salivary gland, and paranasal sinus tumours Unilateral tumours Dose reduction to the brain

PROTON THERAPY

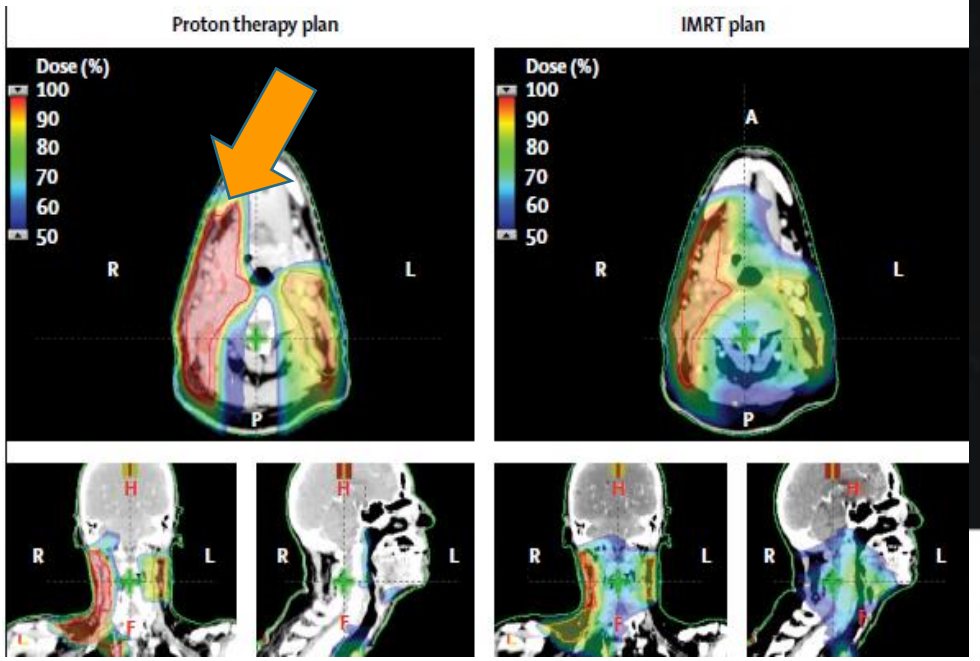
Table 1. Relevant findings and recommendations, by subsite/indication.

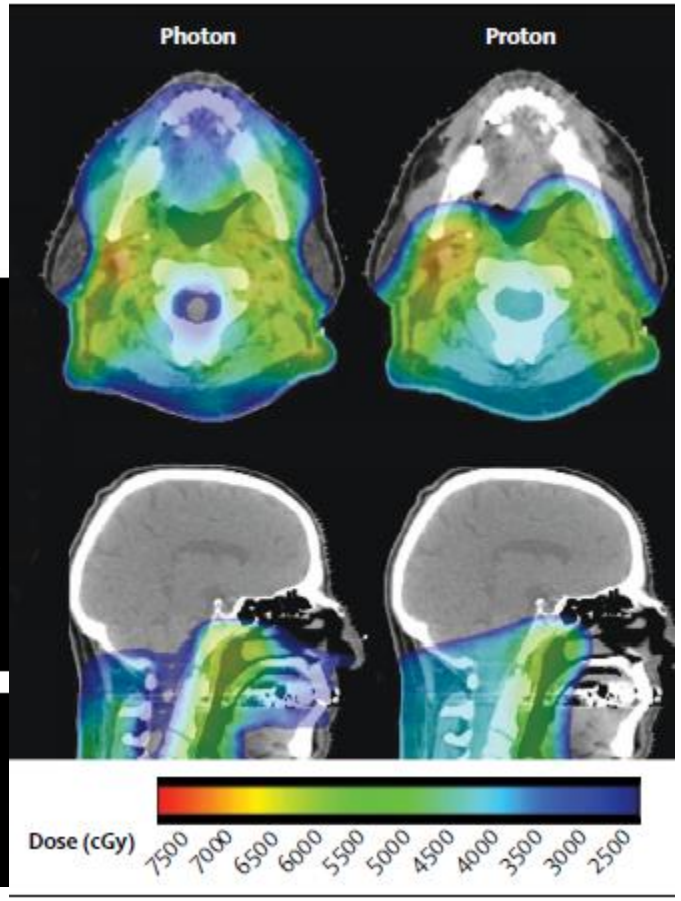
Subsite/ indication	Relevant findings	Recommendation
Nasopharynx	Nonrandomized, comparative data showing less toxicity with proton therapy.	Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location.
Reirradiation	Local regional and toxicity with proton therapy favorable when compared to historical controls. Clinical trials directly comparing proton therapy to IMRT currently enrolling.	Careful evaluation required for each patient to determine risks/benefits of reirradiation. Enrollment in clinical trial encouraged whenever possible.
Sinonasal	Systematic review/meta-analysis showing improved local regional control and disease-free survival with proton therapy over IMRT, but with greater risk of neurotoxicity.	Consider proton therapy whenever feasible. Most advanced treatment, imaging, and adaptation techniques should be used to minimize risk of neurotoxicity, given anatomic location.
Postoperative	Nonrandomized, comparative data showing less toxicity and improved patient-reported outcomes with proton therapy. Clinical trials directly comparing proton therapy to IMRT currently enrolling.	Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible.
Oropharynx	Nonrandomized, comparative data showing less toxicity and improved patient-reported outcomes with proton therapy. Model-based methods being used to select patients most appropriate for proton therapy. Clinical trials directly comparing proton therapy to IMRT currently enrolling.	Consider proton therapy whenever feasible. Enrollment in clinical trial encouraged whenever possible.

PTCOG Head and Neck Subcommittee Consensus Guidelines on Particle Therapy for the Management of Head and Neck Tumors
Lin et al. 2021

OROPHARYNGEAL CANCER

- sparing of multiple critical organs including the oral cavity (in particular the anterior mucosa) , major salivary glands and mandible; reduction or elimination of the dose to uninvolved controlateral oropharyngeal and nasopharyngeal mucosa.
- Mitigation of late toxicities in HPV + disease with good prognosis.





- A phase III randomized IMPT versus IMRT trial for **stage III-IVB oropharyngeal cancer** (NCT01893307) just completed accrual (N = 518), the results of which are awaited and expected to be more convincing

Perkins SM 2012, Zhang W, 2017, van de Water TA , 2011, 2012; Cozzi L 2001, Holliday EB 2016

Prospective registry

biology • physics
www.redjournal.org

2016

Clinical Investigation

Intensity Modulated Proton Therapy Versus Intensity Modulated Photon Radiation Therapy for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes

Terence T. Sio, MD, MS,*,† Huei-Kai Lin, MS,‡ Qiuling Shi, PhD,‡

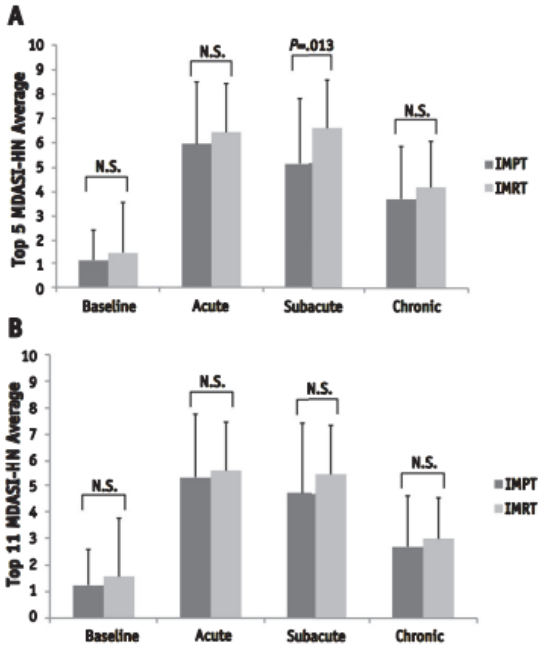


Fig. 2. Mean scores on the top 5 (A) and top 11 (B) items in the MD Anderson Symptom Inventory—Head and Neck (MDASI-HN) module for intensity modulated proton therapy (IMPT) versus intensity modulated (photon) radiation therapy (IMRT). All temporal phases are included. Error bars represent 1 standard deviation from mean values.

The top 5 symptoms were food taste problems, dry mouth, swallowing/chewing difficulties lack of appetite, and fatigue

According to the MDASI-HN, symptom burden was lower among the IMPT patients than among the IMRT patients during the subacute recovery phase after treatment

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Original Article

Intensity-modulated proton therapy for oropharyngeal cancer reduces rates of late xerostomia

Jianzhong Cao [a,b,1], Xiaodong Zhang [c,*], Bo Jiang [c], Jiayun Chen [c], Xiaochun Wang [c], Li Wang [d],

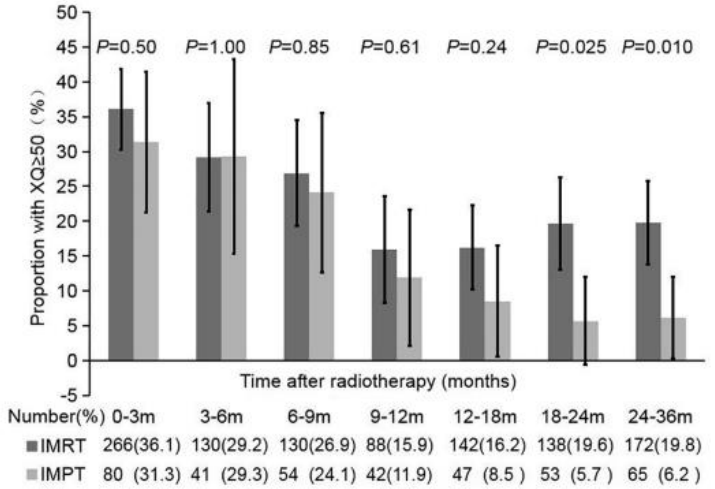


Fig. 1. The proportions of patients with moderate-severe xerostomia (XQs ≥ 50) in both treatment groups (IMRT and IMPT) at the indicated times after treatment. The total numbers of patients in each group are shown under the graph. The *p* values are for comparison of the proportions of patients with moderate-severe xerostomia in the two groups (chi-square test). The error bars indicate 95% confidence intervals.

IMPT was associated with less late xerostomia than was IMRT in OPC patients

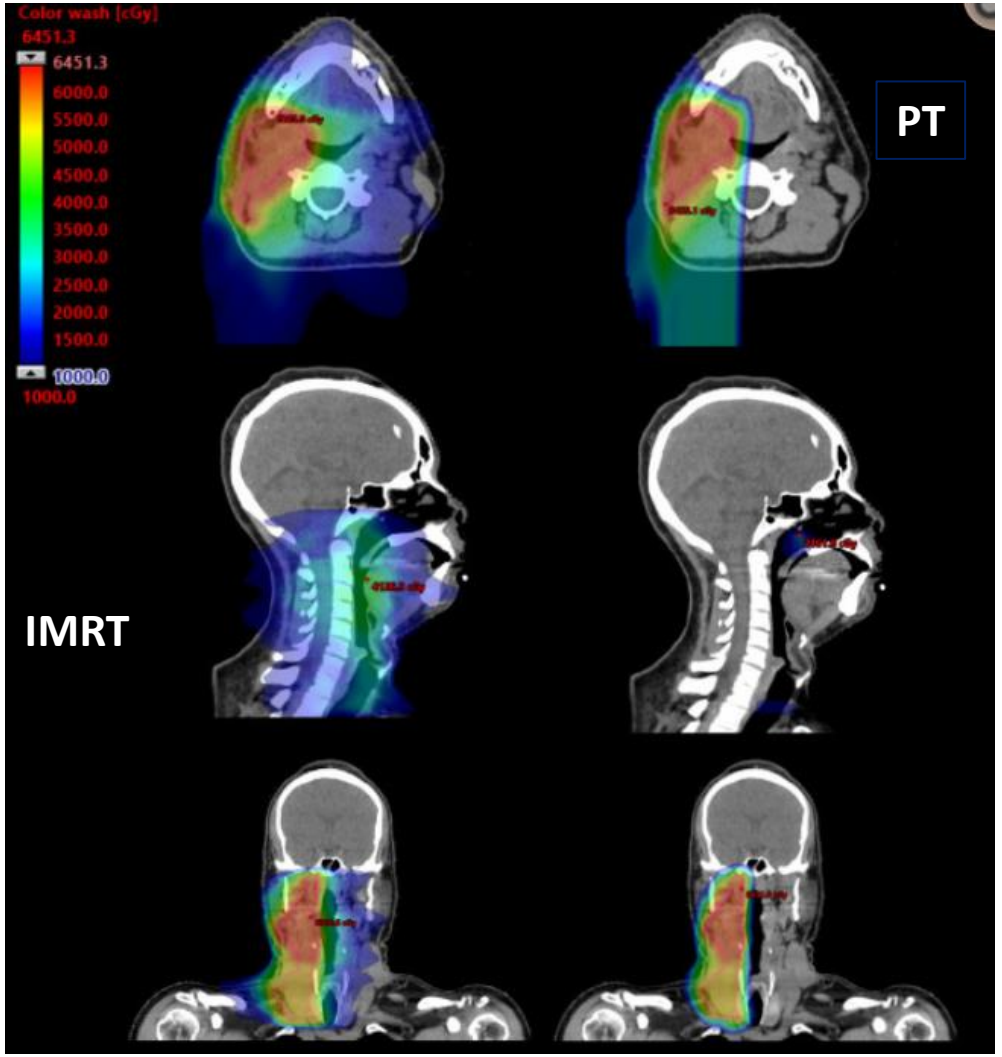
UNILATERAL HEAD AND NECK IRRADIATION

- Reduction of 10 times of higher to critical medline (oropharyngeal mucosa) and contralateral OARS.

Table 1. Summary of dosimetric studies for ipsilateral head and neck irradiation.

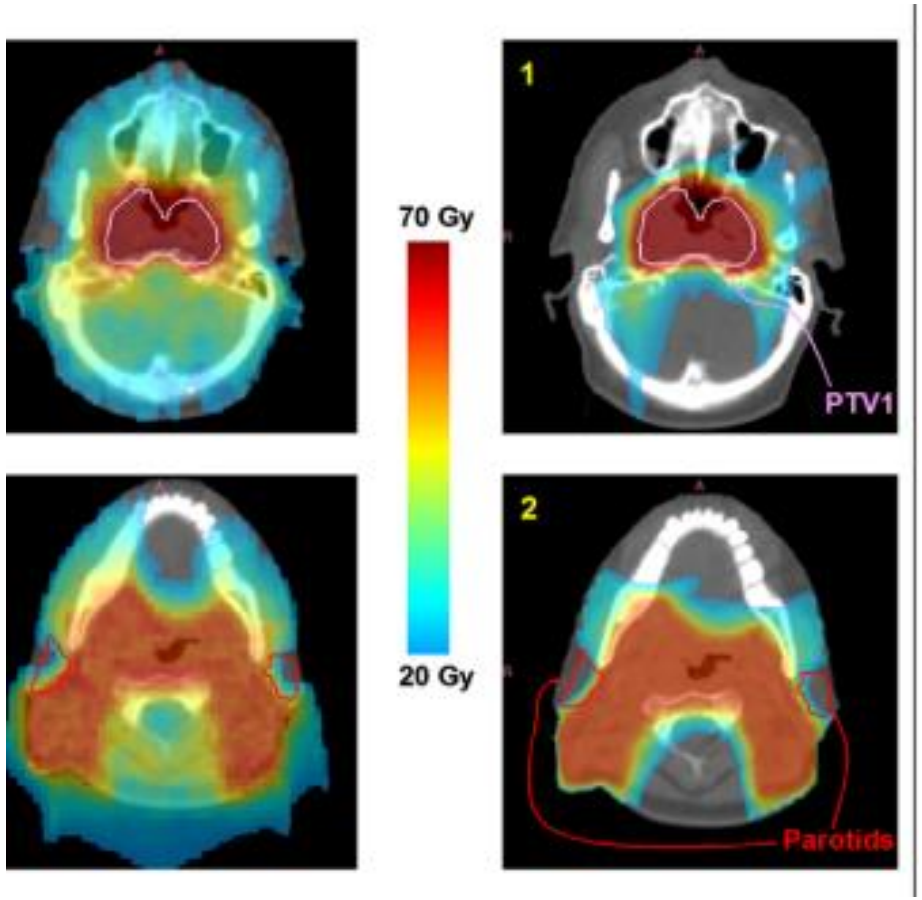
	Kandula et al [4]	Swisher-McClure et al [5]	Romesser et al [7]	Dagan et al [10]	Grant et al [11]
Radiation Modality	PBS vs IMRT	PBS vs IMRT	USPT vs IMRT	PSPT	PSPT/PBS vs EBT/IMRT
Oral cavity (mean)					
Photon	1760	1348	2060	NR	2070
Proton	458	58	94	750	460
Contralateral parotid gland (mean)					
Photon	533	464	140	NR	460
Proton	49	0	0	10	0
Contralateral submandibular gland (mean)					
Photon	639	534	410	NR	1350
Proton	4	2	0	180	0
Ipsilateral submandibular (mean)					
Photon	NR	3894	NR	NR	NR
Proton	NR	1659	NR	NR	NR
Larynx (mean)					
Photon	NR	NR	2140	NR	4430
Proton	NR	NR	1030	720	1130
Spinal cord (maximum)					
Photon	3692	NR	3630	NR	3940
Proton	2014	NR	190	NR	81
Brainstem (maximum)					
Photon	3412	3091	2970	NR	NR
Proton	1388	710	62	NR	NR

Abbreviations: PBS, pencil beam scanning; IMRT, intensity-modulated radiation therapy; USPT, uniform scanning proton therapy; PSPT, passive scattered proton therapy; EBT, electron beam therapy; NR, not reported.



Press et al. 2021, Kandula S 2013, Stromberger C 2016

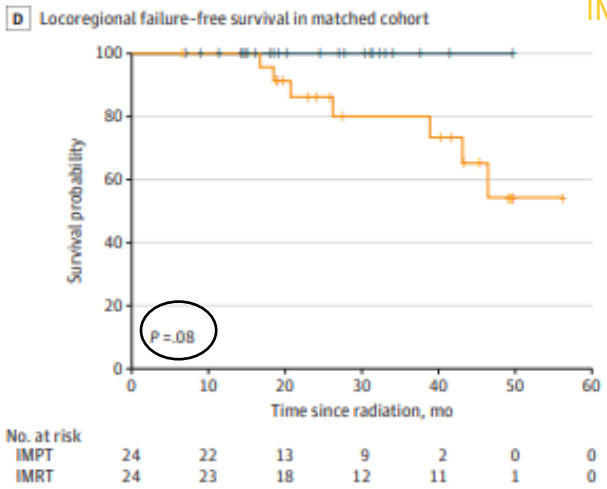
PROTON THERAPY FOR NASOPHARYNX



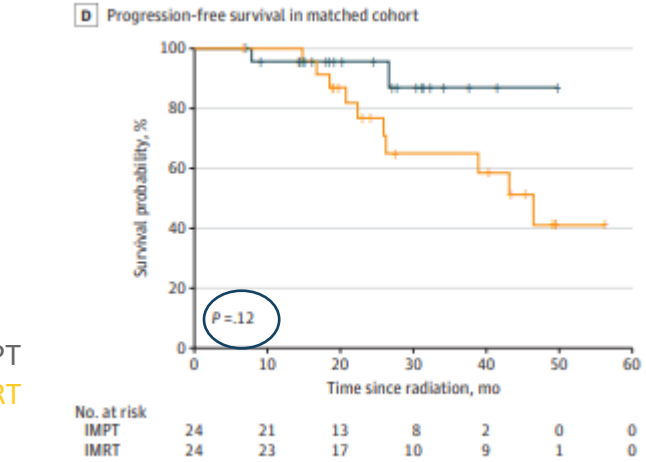
- Rare, unique epidemiological and histological features
- RT is the milestone of the treatment, with or without chemotherapy (CHT) in different settings (concurrent and or adjuvant and or neoadjuvant) according to disease stage and EBV-plasma load
- IMRT represents the current standard RT technique
- However, toxicity rate are still relevant, especially for advanced clinical stages, with substantial effects on quality of life
- Lower doses to multiple OARs, including major salivary glands, spinal cord, brainstem and optic chiasm; reduction of the averaged mean dose to OARs by a factor of 2–3; reduction of low-to medium dose volumes.
- PT could be an alternative to VMAT, reducing radiation-induced side-effects to OARs while guaranteeing highly conformal coverage of the target.

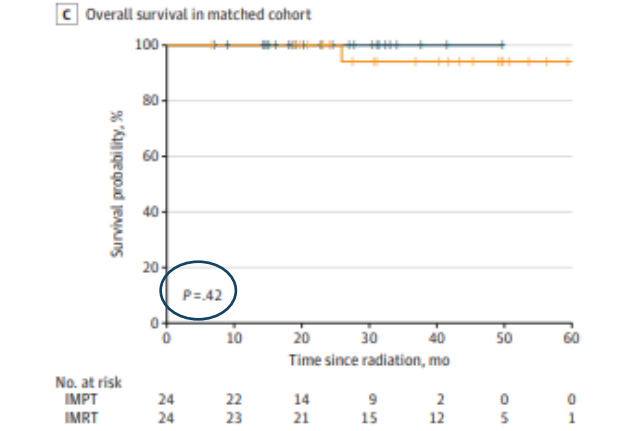
PTCOG Consensus Guidelines on Particle Therapy for the Management of Head and Neck Tumors, Lin et al. (2021)
(Widesott L, 2008) (Liu SW, 2010; Lewis GD 2016)

Intensity-modulated proton therapy (IMPT) may significantly improve the toxicity profile for NPC



IMPT
IMRT





eTable 2. Comparison of Specific Acute Adverse Events for Patients Treated w IMPT vs IMRT

Toxicities		Acute Adverse Events[a] (%)				P value[b]
		None	Grade 1	Grade 2	Grade 3	
Oral Pain	IMPT	14.3	75.0	10.7	0	.66
	IMRT	12.2	69.4	18.4	0	
Dysphagia	IMPT	21.4	60.7	14.3	3.6	**.05**
	IMRT	10.2	42.9	42.9	4.1	
Fatigue	IMPT	25.0	64.3	10.7	0	**.02**
	IMRT	4.1	73.5	22.4	0	
Xerostomia	IMPT	50.0	42.9	7.1	0	**.002**
	IMRT	14.3	63.3	22.4	0	
Dysgeusia	IMPT	39.3	53.6	7.1	0	**.004**
	IMRT	12.2	57.1	30.6	0	
Dermatitis	IMPT	7.1	64.3	25.0	3.6	.45
	IMRT	10.2	46.9	40.8	2.0	
Mucositis	IMPT	10.7	64.3	21.4	3.6	**.03**
	IMRT	8.2	32.7	49.0	10.2	
Weight Loss	IMPT	39.3	25.0	35.7	0	**<.001**
	IMRT	4.1	36.7	49.0	10.2	
Hoarseness	IMPT	92.9	7.1	0	0	**.007**
	IMRT	63.3	32.7	4.1	0	
Nausea	IMPT	50.0	28.6	7.1	14.3	**.03**
	IMRT	30.6	55.1	12.2	2.0	

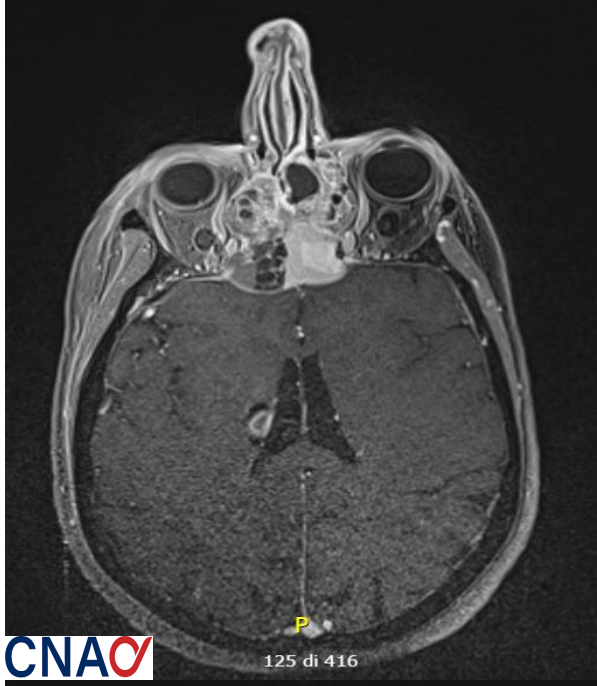
Li X, Jama Network Open 2021

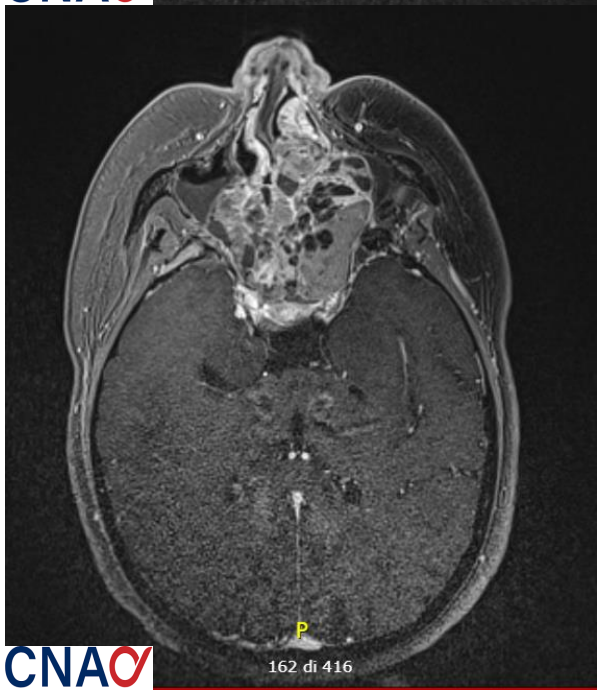
SINONASAL MALIGNANCIES

- Primary tumors of the nasal cavity and paranasal sinuses are uncommon
- Molteplicity of histological types (SCC, ADK, SNUC, ESBN, MMM, ACC..)
- In the majority of cases of LA-SNCs, the therapeutic strategy relies on the combination of surgery, radiotherapy (RT) and chemotherapy. For unresectable disease or inoperable patients, definitive RT is proposed, often with concurrent chemotherapy.
- Intensity-modulated radiotherapy (IMRT-VMAT) is the standard RT technique.
- Data on the efficacy of Protons (PT) and carbon ions (CIRT) is recentlessly growing.

NCCN 2023

Either IMRT or proton therapy is recommended for maxillary sinus or paranasal/ethmoid sinus tumors to minimize dose to critical structures.





PARANASAL SINUSES CANCERS: can particle therapy improve LC and survival?

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

	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)	0·0003	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

TOXICITY

	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

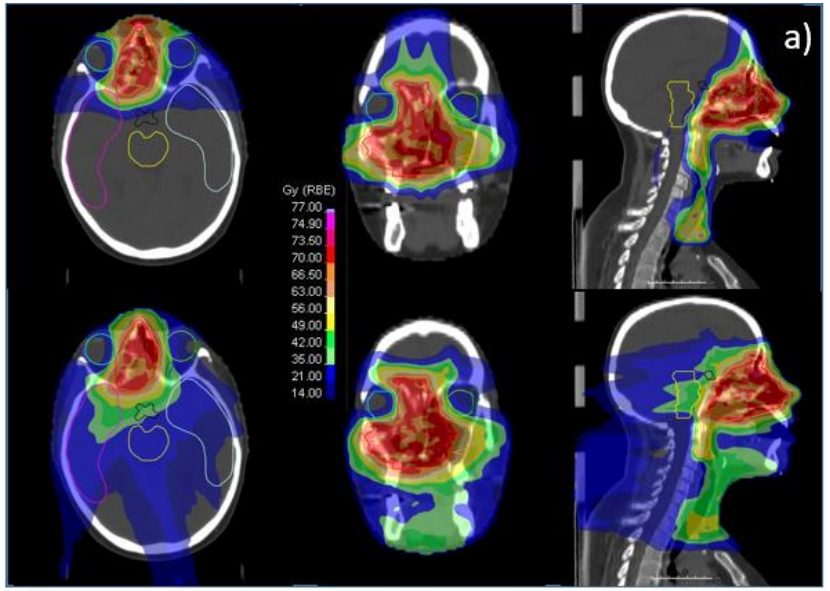
- PT studies more detailed on toxicity vs photon (92% *vs* 57%; p=0·03).
- Challenging cases sent to PT instead of photons
- Higher biological and phyiscal doses delivered in PT studies compared to photon

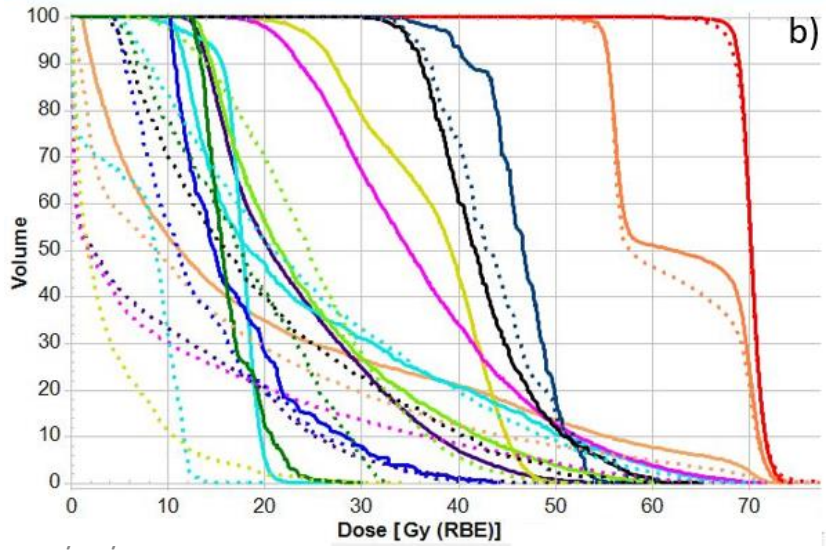
Need for international PT register for comparison or randomized trials with independent and prospective enrolment and rigorous collection of prognostic variables.

Lancet Oncol 2014; 15: 1027–38

Which patients for protons?

In silico comparative study , 22 LA or unresectable SNUC





cancers

CNAO

MDPI

Article

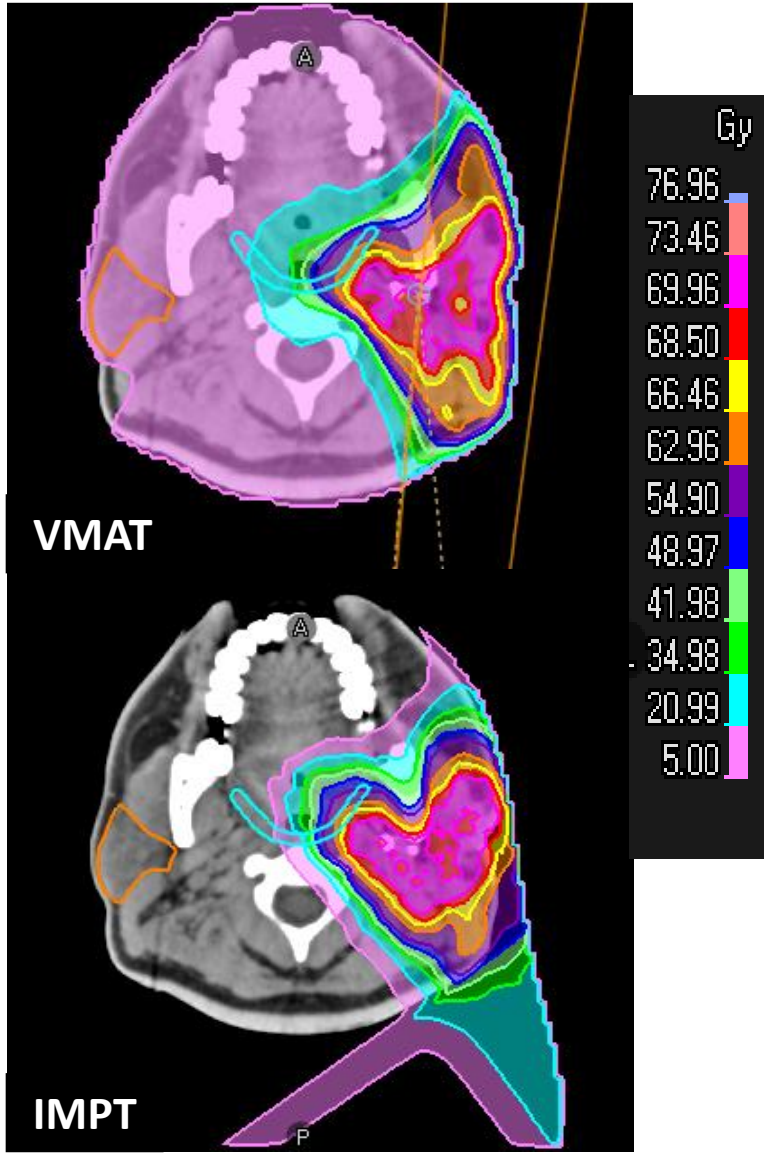
A Patient Selection Approach Based on NTCP Models and DVH Parameters for Definitive Proton Therapy in Locally Advanced Sinonasal Cancer Patients

Alfredo Mirandola [1,*,†], Stefania Russo [1,†], Maria Bonora [2], Barbara Vischioni [2], Anna Maria Camarda [2], Rossana Ingargiola [2], Silvia Molinelli [1], Sara Ronchi [2], Eleonora Rossi [1], Alessandro Vai [1], Nicola Alessandro Iacovelli [3], Juliette Thariat [4], Mario Ciocca [1] and Ester Orlandi [2]

Toxicity Endpoint (Scoring)	Author	NTCP Model	OAR
Blindnessn Late (Severe)	Burman et al.	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} exp\left(\frac{-u^2}{2}\right)du, \quad t = \frac{gEUD - TD_{50}}{m * TD_{50}}$	Optic Chiasm, Left/Right Optical Nerve
Brain Necrosis Late (Severe)	Bender et al.	$NTCP = \left(1 + \left(\frac{D_{50}}{EQD_2}\right)^{4\gamma}\right)^{-1}$	Brainstem, Brain outside CTV
Overall Ocular Toxicities Acute (Intermediate)	Batth et al.	$NTCP = \left(1 + e^{-\beta_0 - \beta_1 * D_{max}}\right)^{-1}$	Left/Right Lacrimal Gland
Temporal Lobe Necrosis Late (Severe)	Kong et al.	$NTCP = \left(1 + e^{-\beta_0 - \beta_1 * D_{max}}\right)^{-1}$	Left/Right/Frontal Lobe
Tinnitus Late (Intermediate)	Lee et al.	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} exp\left(\frac{-u^2}{2}\right)du, \quad t = \frac{gEUD - TD_{50}}{m * TD_{50}}$	Left/Right Cochlea
Cataract Requiring Intervention Late (Intermediate)	Burman et al.	$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} exp\left(\frac{-u^2}{2}\right)du, \quad t = \frac{gEUD - TD_{50}}{m * TD_{50}}$	Left/Right Lens
Dry Eye Syndrome Late (Severe)	Jeganathan et al.	$NTCP = \frac{e^{\left(4\gamma\left(\frac{D}{D_{50}}-1\right)\right)}}{1 + e^{\left(4\gamma\left(\frac{D}{D_{50}}-1\right)\right)}}$	Left/Right Lacrimnal Gland
G2 Brain necrosis Late (Intermediate)	Niyazi et al.	$NTCP = \left(1 + \frac{39.5^{\ 10}}{gEUD}\right)^{-1}$	Brain oustide CTV

Over 22 patients, 17 would benefit from PT (77,3%)

SALIVARY GLAND CANCER

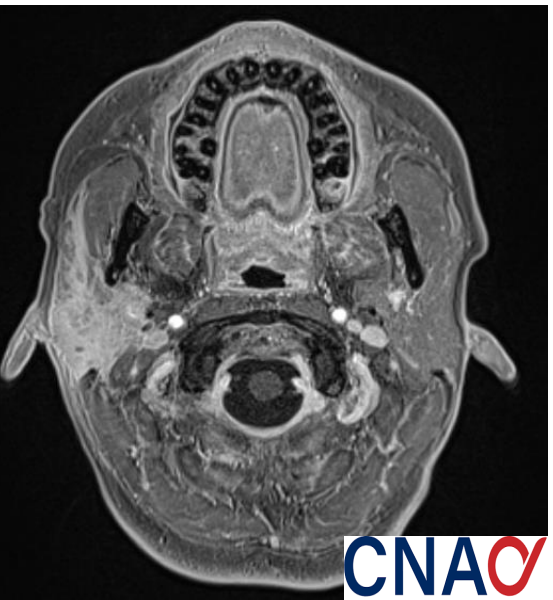


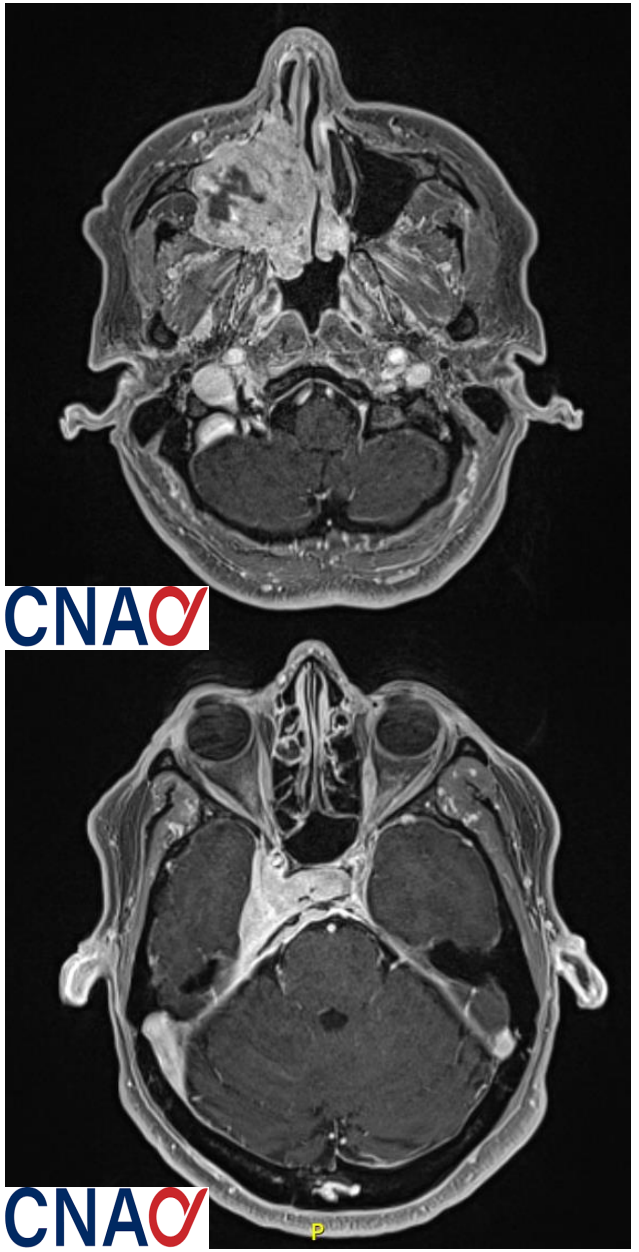
- 2-6 % of all H&N cancers
- Wide variability in histology (>20 subtypes) and natural history
- Challeging scenario for RO community for their historically known radioresistance.
- Requires a high radiation dose to be controlled.
- RT primarily applied in post-operative setting.
- Advances in radiation techniques, IMRT, PT and CIRT have led to more strategic planning and delivery with higher RT doses potentially minimizing toxicity.
- Despite the lack of randomized evidence, PT or CIRT should be taken into account, when available, as first option for inoperable, macroscopically residual or recurrent SGCs.

ACC Adenoid cistic carcinoma

- 1% of malignant H&N tumors
- Unpredicatable, slow and indolent course
- Radioresistance with frequent LRR and DM → **CIRT**
- Standard treatment consists of surgical resection with adiuvant RT (T sixe, N, Rclose/R1, VI, PNI, high grade).

Typical perineural invasion to cranial nerves

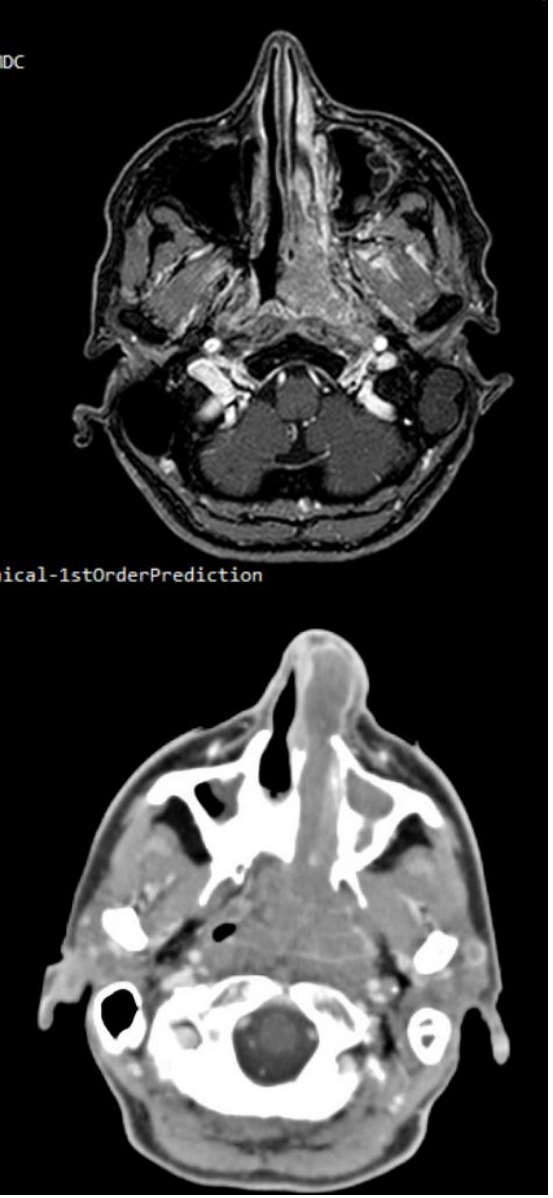




Salivary Gland. Photon beam and particle radiotherapy: Present and future Ester Orlandi et al. 2016 Oral Oncology

ADENOID CYSTIC CARCINOMA: comparing experiences

Institutions	No of patients	Treatment	Local Control (%)	Overall Survival (%)
Iowa, 2009	54 10	Surgery alone Photon alone	72 (5y) 27 (5y)	85 (5y) 25 (5y)
Florida, 2004	101	Photon alone	27 (5y)	25 (5y)
MGH, 2006	23	Proton +/- surgery	93 (5y)	77 (5y)
GSI, 2005	34 29	Photon alone Photon + carbon boost	25 (4y) 78 (4y)	78 (4y) 76 (4y)
NIRS, 2011	151 32 119	Carbon alone (all pats) Carbon alone (T1-T3) Carbon alone (T4 or recurrence)	74 (5y) 96 (5y) 71 (5y)	72 (5y) 92 (5y) 69 (5y)
HIT, 2015	58 37	Photon + carbon boost Photon (IMRT)	59.6 (5y) 39,9 (5y)	76.5 (5y) 58,7 (5y)
Japan (4 centers), 2018	289	Carbon alone	74 (5y)	68 (5y)
CNAO (unpublished confidential data)	184	Carbon alone	75 (3y) 53 (5y)	85 (3y) 65 (5y)



MUCOSAL MELANOMA OF HEAD AND NECK

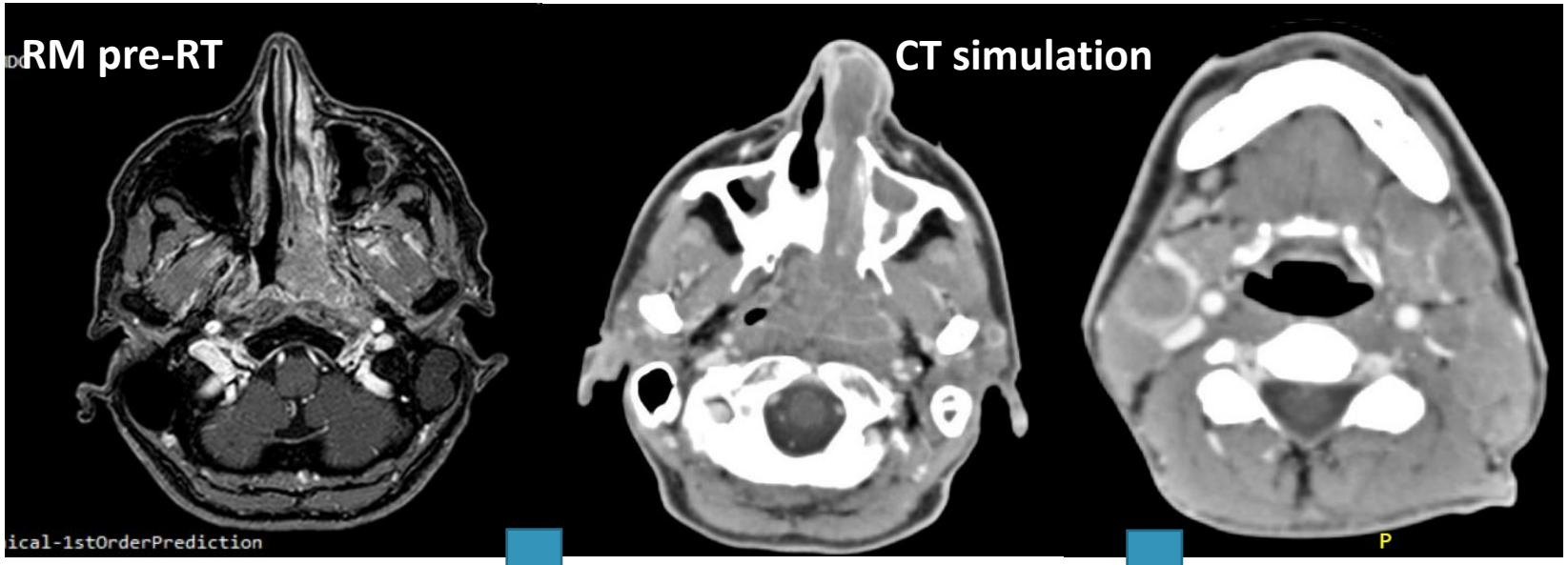
- less than 1.3% of all melanomas, worst and unpredictable prognosis
- Half arise in the H&N, typically in the nose, paranasal sinuses, oral cavity, pharynx, and/or larynx
- Notable epidemiologic variation exists between races
- Surgery is the mainstay of treatment, though it traditionally yields >50% recurrence
- Focused particle radiation improves therapeutic ratio with a goal to overcome radioresistance, while high-LET irradiation has been theorized to further offer improved immunogenicity, leading to enhanced systemic response

CIRT

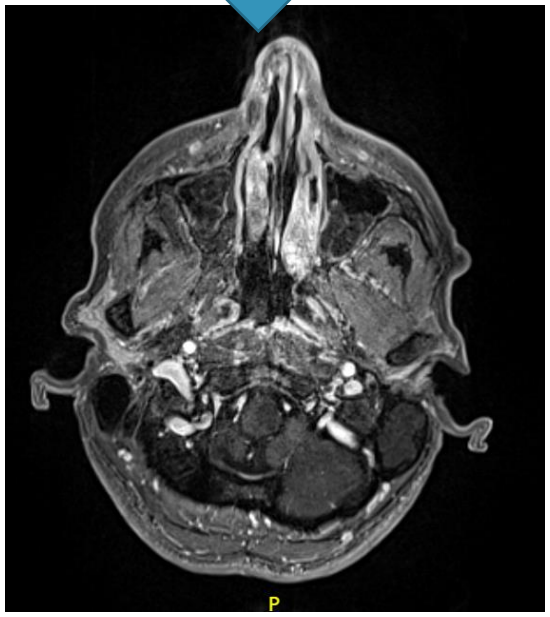
MALIGNANT MUCOSAL MELANOMA: : comparing experiences

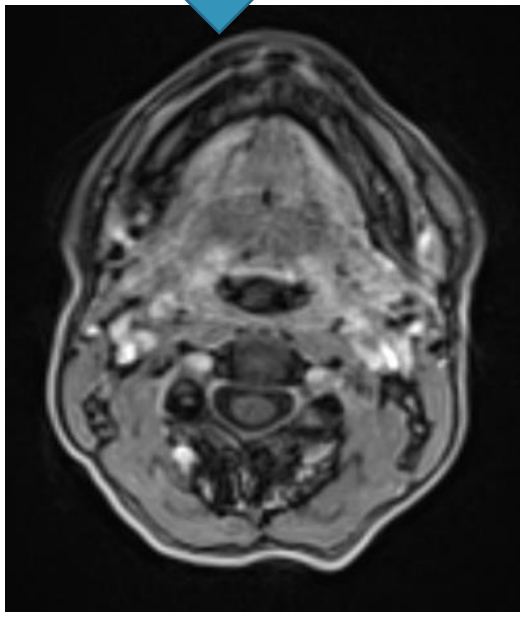
Author, year of publication	No of patients	Treatment	Local Control (%)	Overall Survival (%)
Gilligan et al. 1991	28	Photon	70 (1y)	18 (5y)
Wada et al. 2004	31	Photon alone (n=21) Surgery and photon (n=10 R2)	61 (1y all pts) 39 (2y all pts)	73 (1y all pts) 33 (3y all pts)
Krengli et al. 2006	74	Surgery alone (n=17) Surgery and photon (n=42) Photon alone (n=11)	57 (3y) 71 (3y) n.d.	41 (3y) 14 (10y) n.d.
Yanagi et al. 2009	72	Carbon alone	84 (3y) 84 (5y)	46 (3y) 27 (5y
Zenda et al. 2016	32	Proton alone	75.8 (1y)	55.9 (2y)
Koto et al. 2016	260	Carbon alone	83.9 (2y) 72.3 (5y)	69.4 (2y) 44.6 (5y)
Takayasu et al. 2019	21	Carbon alone	92.3 (2y) 92.3 (3y)	56.2 (2y) 49.2 (3y)
CNAO confidential unpublished data	40	Surgery and carbon (n=28) Carbon alone (n=10) ''Sandwich modality'' (n=2)	84.5 (2y all pts) 84.5 (3y all pts)	58.6 (2y all pts) 53.3 (3y all pts)

CLINICAL CASE: LOCALLY ADVANCED MUCOSAL MELANOMA



CR after 3 months from CIRT





Review Oral Oncol. 2020 Nov;110:104879.

Past, present and future of proton therapy for head and neck cancer

Xingzhe Li[a], Anna Lee[a], Marc A. Cohen[b], Eric J. Sherman[c], Nancy Y. Lee[a,*]

[a] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, United States
[b] Department of Surgery, Memorial Sloan Kettering Cancer Center, United States
[c] Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, United States

Table 1
Ongoing clinical trials investigating proton therapy in head and neck cancer.

	Institution	Trial name	Inclusion	Treatment	Primary Endpoints	Study Start
NCT03829033	Lund University Hospital	Photon Therapy Versus Proton Therapy in Early Tonsil Cancer	Early stage SCC of the tonsil, unimodal and unilateral treatment	Randomized to PBT vs conventional RT	Acute and late side effects	January 2019
NCT03539198	Mayo Clinic	Study of Proton SBRT and Immunotherapy for Recurrent/ Progressive Locoregional or Metastatic Head and Neck Cancer	Recurrent locoregional or recurrent metastatic HNC	Proton SBRT + Nivolumab	Objective response rate	July 2018
NCT03274414	MSKCC	A Clinical Trial of Endoscopic Surgery Followed by Chemotherapy and Proton Radiation for the Treatment of Tumors in the Sinus and Nasal Passages	Cancer of the nasal cavity and / or paranasal sinuses	Endoscopic surgical resection and PBT	Local control at 1 year	September 2017
NCT03217188	MSKCC	A phase II study of proton re-irradiation for recurrent head and neck cancer	Recurrent or second primary HNC, previous head and neck radiation	PBT	Locoregional control at 1 year	July 2017
NCT03164460	MDACC	Stereotactic Body Radiation Therapy or Intensity Modulated Radiation/Proton Therapy in Treating Patients with Recurrent Head and Neck Cancer	Recurrent or second primary HNC, previous head and neck radiation (at least 30 Gy)	Randomized to SBRT vs IMPT/IMRT	Incidence of grade 3 + toxicity within 2 years post RT	May 2017
NCT02923570	MSKCC, Mayo Clinic, Mount Sinai Hospital	A phase II randomized study of proton beam versus photon beam radiotherapy in the treatment of unilateral head and neck cancer	Unilateral head and neck targets (salivary, skin tumors)	Randomized to PBT vs IMRT	Acute toxicity	October 2016
NCT02736786	Mayo Clinic	A Study of Mucosal Sparing Proton Beam Therapy (PBT) in Resected Oropharyngeal Tumors	Resected oropharyngeal tumors	Mucosal sparing PBT	Local control at 2 years	March 2016
NCT02663583	MDACC	Intensity-Modulated Proton Therapy (IMPT) or TransOral Robotic Surgery (TORS) for the Treatment of Low-Risk Oropharynx Squamous Cell	Stage I-III* previously untreated oropharyngeal squamous cell carcinoma	IMPT vs transoral surgery	Functional outcome measured with patient reported outcome and longitudinal digital wristband activity monitoring of study participants	January 2016
NCT01973179	Technische Universität Dresden	Re-irradiation of Recurrent Head and Neck Cancer	Previously irradiated head and neck cancer	PBT	Late toxicity within 24 months post RT	July 2015
NCT01893307	MDACC, MGH, NCI, NIDCR	Phase II/III Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck	Stage III-IV * SCC of the oropharynx	Randomized to IMRT vs IMPT	Rates of severe late toxicity 90 days to 2 years post RT	August 2013
NCT01586767	MGH, NIH, NCI	A Phase II Study of Intensity-Modulated or Proton Radiation Therapy for Locally Advanced Sinonasal Malignancy	Locally advanced sinonasal tumors	PBT or IMRT	Local control at 2 years	July 2011
NCT01228448	MGH, NCI	In-Room PET in Proton Radiation Therapy	Brain, head and neck, and skull base tumors	PBT	Effectiveness of PBT quality assurance using in-room PET	October 2010
NCT03513042	Leiden University Medical Center	Early Response Evaluation of Proton Therapy by PET-imaging in Squamous Cell Carcinoma Located in the Head and Neck	Primary unresected HNSCC	IMPT	3-year local recurrence-free survival	Planned for June 2020
NCT03981068	Danish Head and Neck Cancer Group	A Phase II Study of Intensity Modulated Proton Therapy (IMPT) for Re-irradiation With Curative Intent for Recurrent or New Primary Head and Neck Cancer	Recurrent or second primary HNC, previous head and neck radiation	PBT	Any new grade > =3 toxicity within 3 years post RT	Planned for September 2019
NCT03450967	Samsung Medical Center	Durvalumab Plus Tremelimumab Combined with Proton Therapy for HNSCC	Recurrent or metastatic HNSCC	PBT + Durvalumab plus Tremelimumab	Response rate	Planned for March 2018
..	UK National Health Service Proton Service	A Phase III Trial of Intensity-modulated Proton Beam Therapy Versus Intensity-modulated Radiotherapy for Multi-toxicity Reduction in Oropharyngeal Cancer	locally advanced OPSCC	Randomized to IMPT vs IMRT	Patient reported outcomes and feeding tube dependence or severe weight loss 12 months post RT	Planned for January 2020

PBT = Proton Beam Therapy. RT = Radiation Therapy. MSKCC = Memorial Sloan Kettering Cancer Center. SBRT = Stereotactic Body Radiation Therapy. HNC = Head and Neck Cancer. MDACC = MD Anderson Cancer Center. MGH = Massachusetts General Hospital. NCI = National Cancer Institute. NIDCR = National Institute of Dental and Craniofacial Research. NIH = National Institutes of Health. PET = Positron Emission Tomography. HNSCC = Head and Neck Squamous Cell Carcinoma. OPSCC = Oropharyngeal Squamous Cell Carcinoma.
* AJCC 7th edition.

INDICATIONS for sarcoma

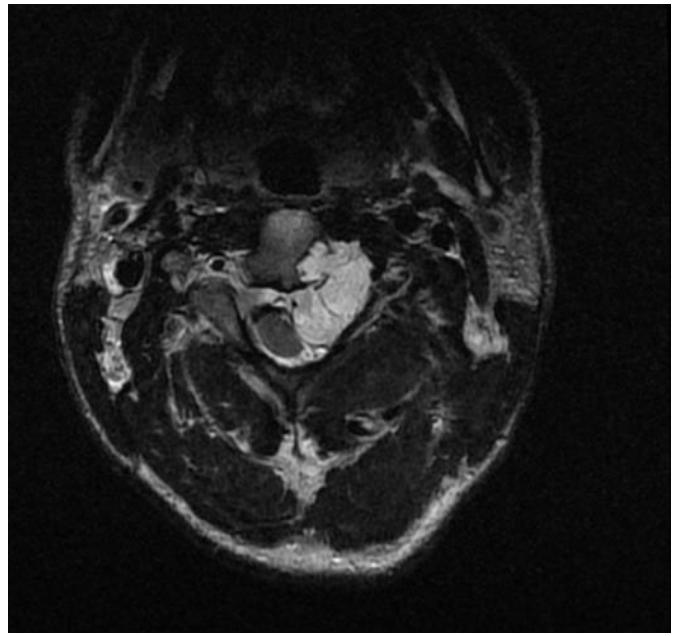
- Tumors of mobile spine
- chordomas of spine and sacrum
- Soft tissue sarcomas

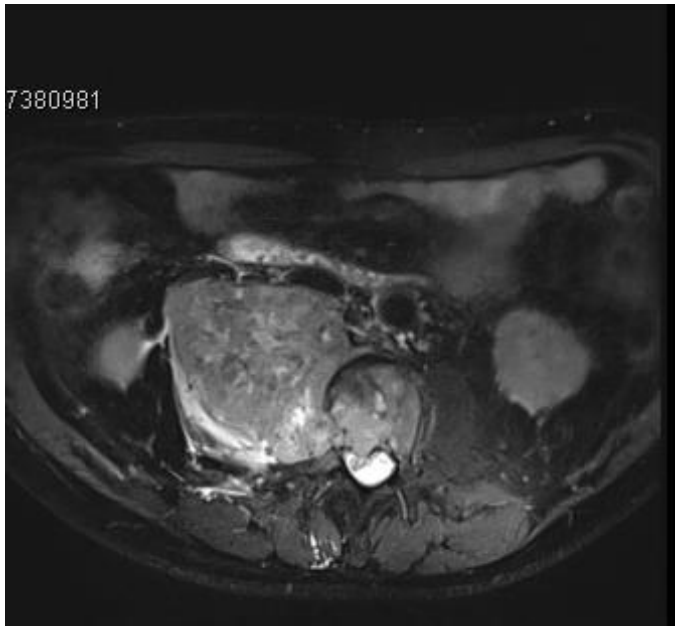
PRIMARY SPINE TUMORS

Chordoma, CS, sarcoma..

are uncommon tumors characterized by

- Locally aggressive growth pattern
- High local recurrence rates
- Most frequent sites after skull base is spine and sacrum
- Most frequent histologies: chordoma, chondorsarcoma
- Less frequent: osteosarcoma , Ewing sarcoma et al.
- **Peculiar aspect is the proximity to structures deputed to relevant functions**

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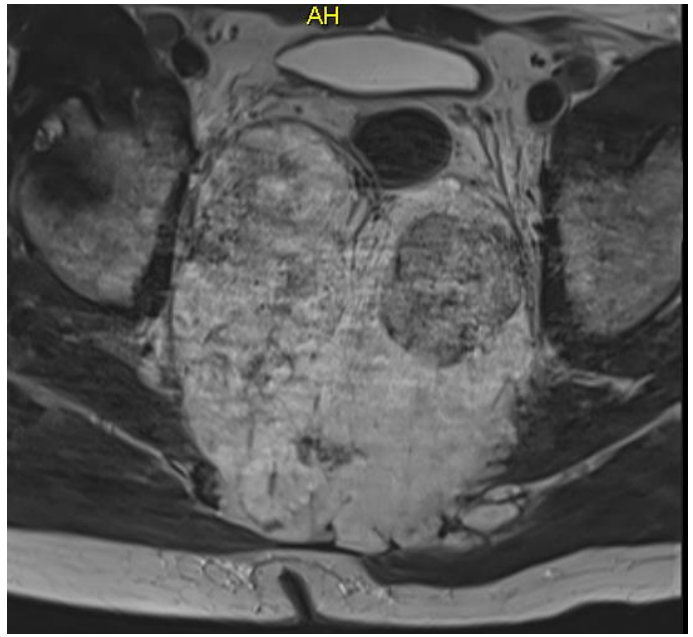
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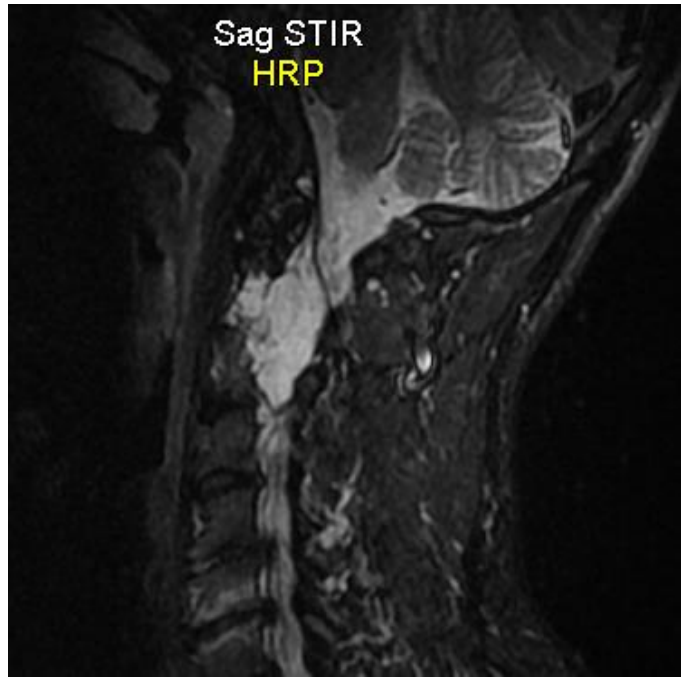
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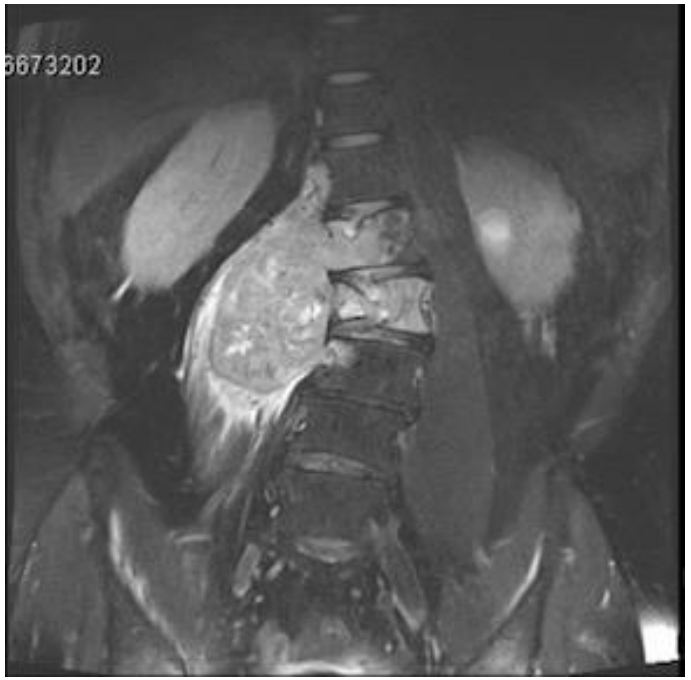
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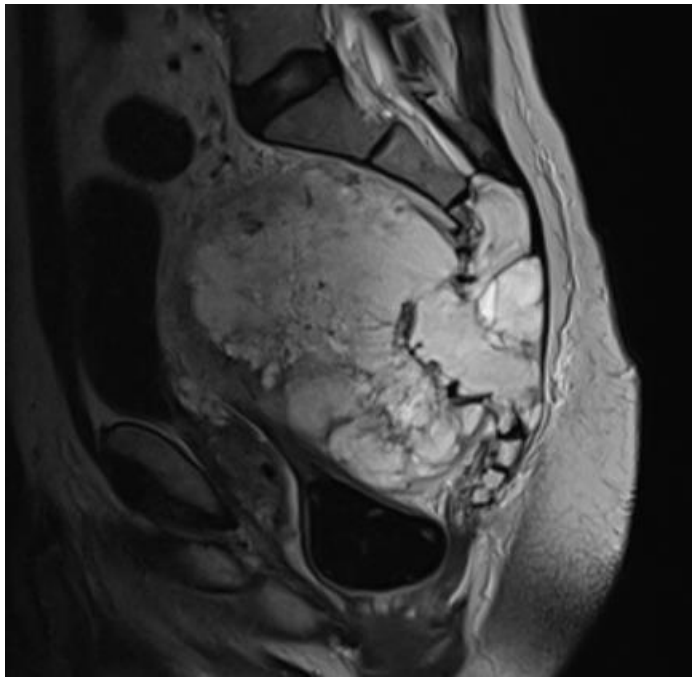
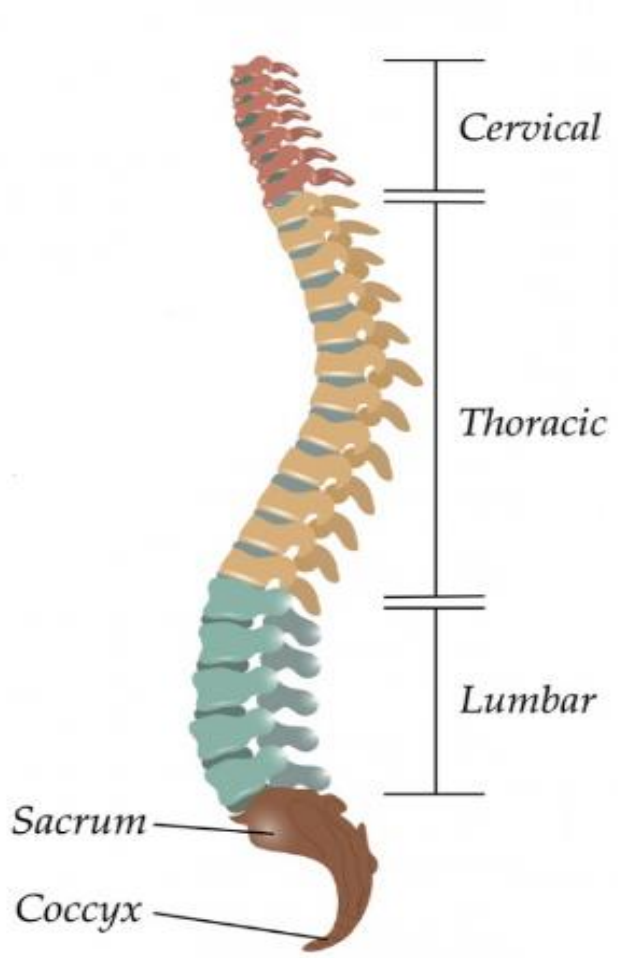
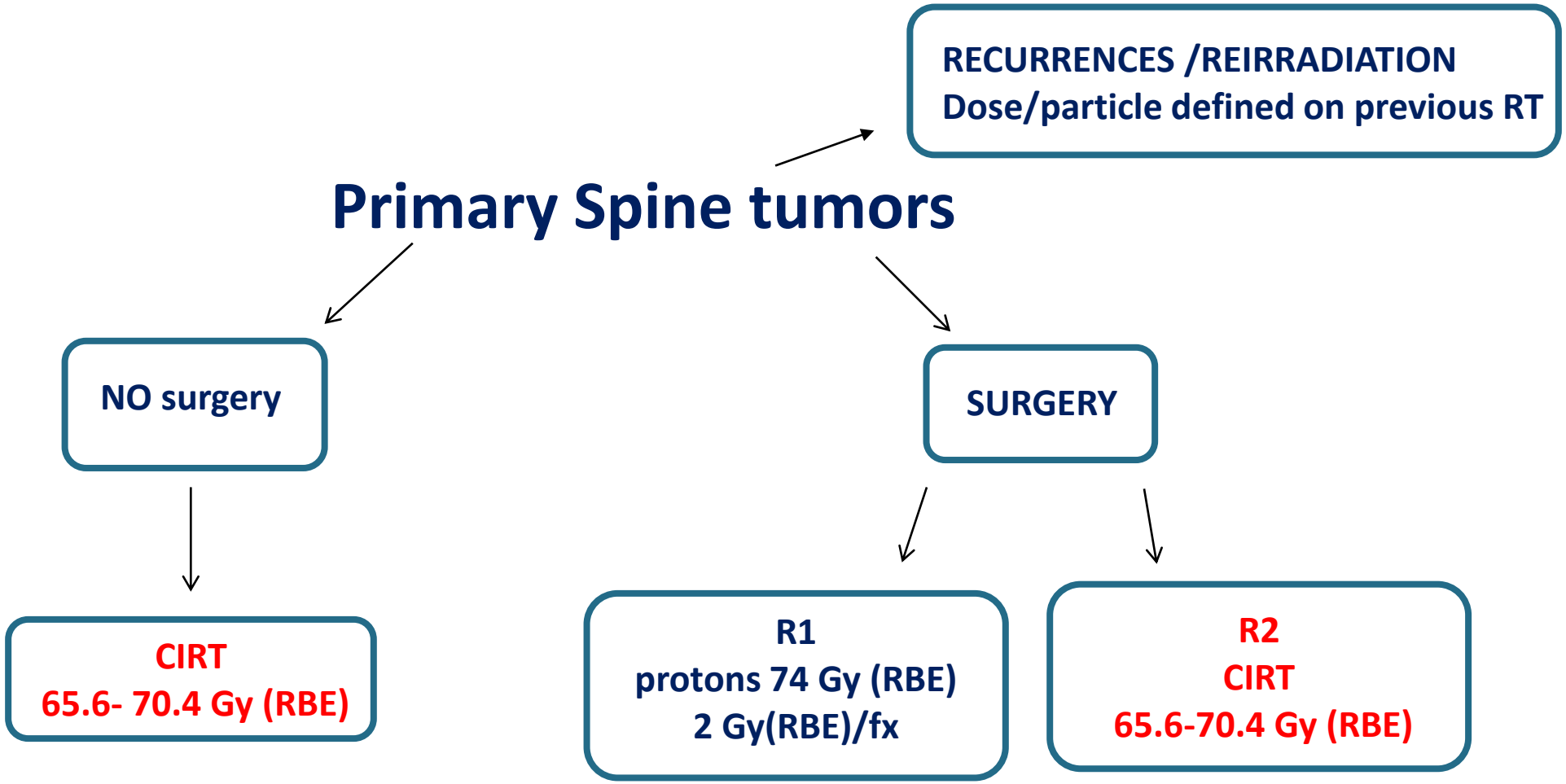


SPINE TUMORS

- **En bloc resection appeared to improve both local recurrence and disease free survival in chordoma and chondrosarcoma patients.**
- **Radiation therapy as an adjuvant treatment for chordoma and chondrosarcoma of the spine, when there had been incomplete resection or an intralesional margin (recommended with dose >60 Gy)**
- Dose < 60 Gy with photon radiation therapy have hystorically led to poor outcome: recurrence rate >70%
- Particle therapy has been employed to overcome dose-limiting structures



Boriani 2006
Delaney 2018

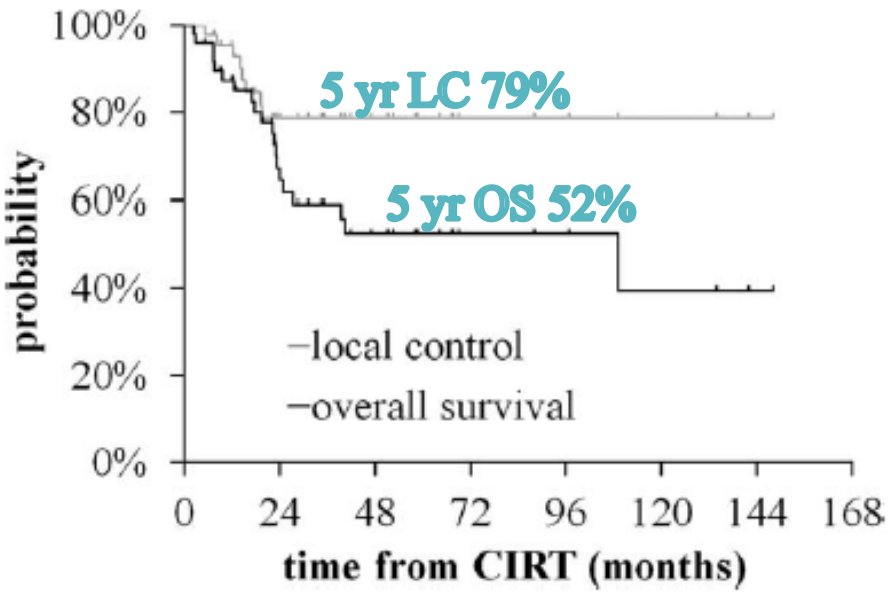

RECURRENCES /REIRRADIATION
Dose/particle defined on previous RT
Primary Spine tumors
NO surgery
SURGERY
CIRT
65.6- 70.4 Gy (RBE)
R1
protons 74 Gy (RBE)
2 Gy(RBE)/fx
R2
CIRT
65.6-70.4 Gy (RBE)

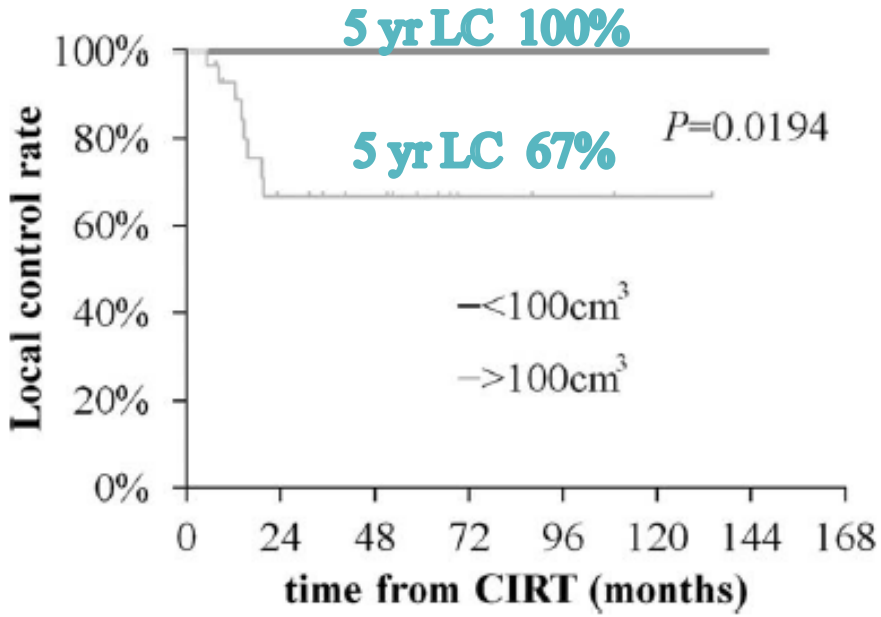
Impact of Carbon Ion Radiotherapy for Primary Spinal Sarcoma

Keiji Matsumoto, MD[1]; Reiko Imai, MD, PhD[1]; Tadashi Kamada, MD, PhD[1]; Katsuya Maruyama, MD[1]; Hiroshi Tsuji, MD, PhD[1]; Hirohiko Tsujii, MD, PhD[1]; Yoshiyuki Shioyama, MD, PhD[2]; Hiroshi Honda, MD, PhD[2]; and Kazuo Isu, MD, PhD[3]; the Working Group for Bone and Soft Tissue Sarcomas

47 pts sarcoma..
35 pts primary tumor
12 pts recurrence after surgery
CIRT median dose 64 GyE (52.8 GyE-70.4GyE)/16 frx

F-UP mediano 25 mo

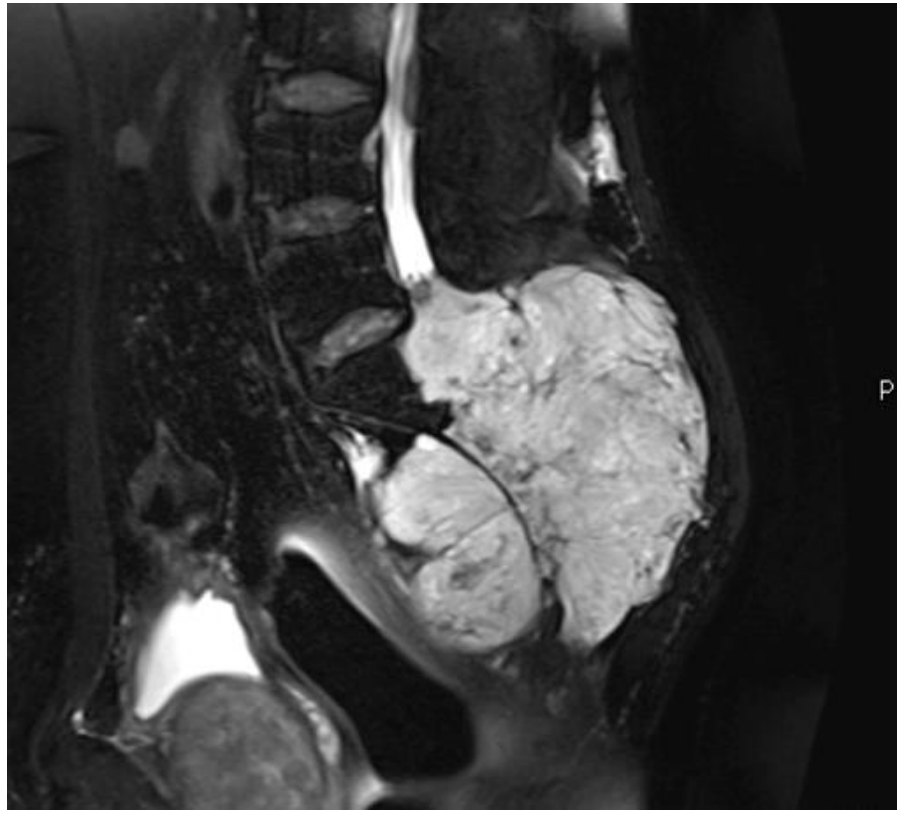


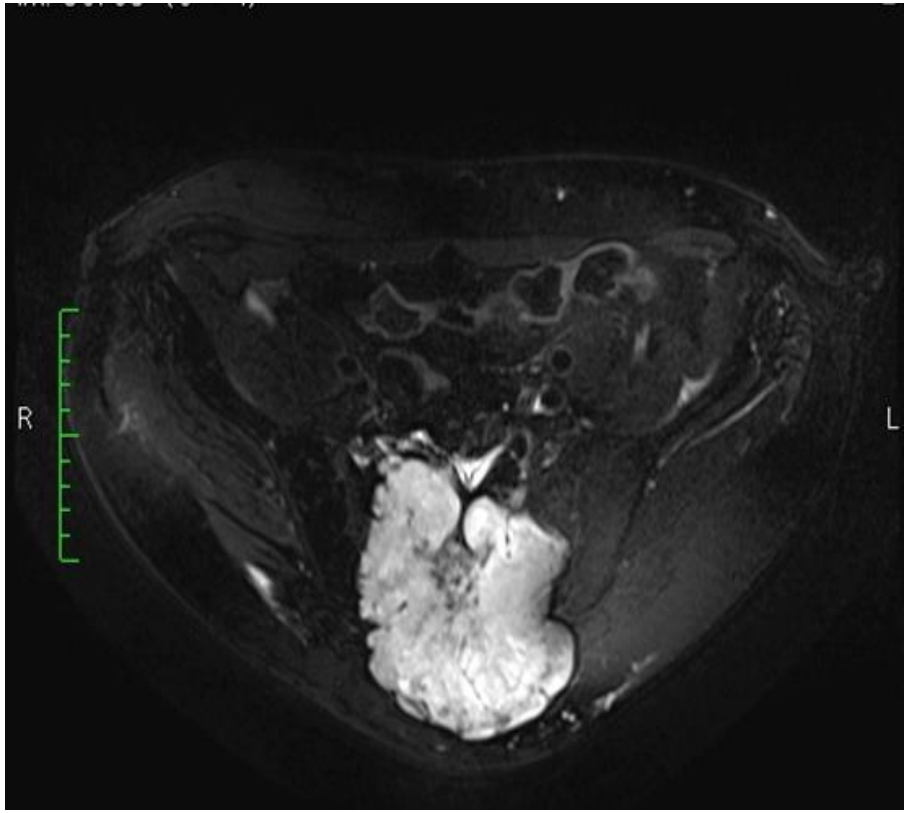


Cancer October 1, 2013

Sacral chordoma

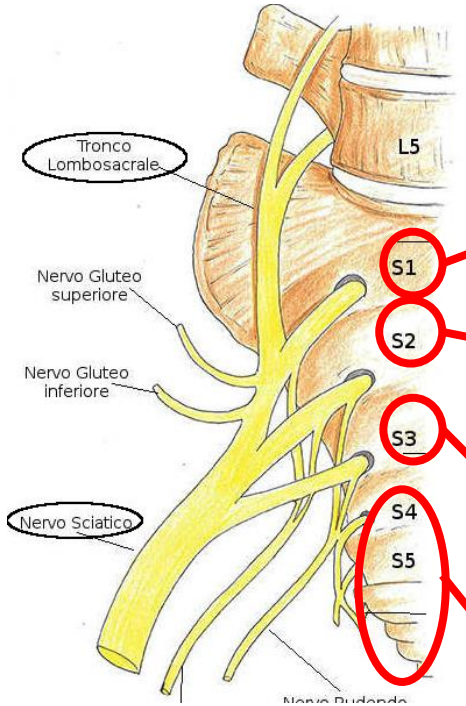
Higher local control associated with wide surgical margin





Wide margin surgery it is not always possible

S1-S2 extension → RT as an alternative to be considerated because of invalidating sequelae



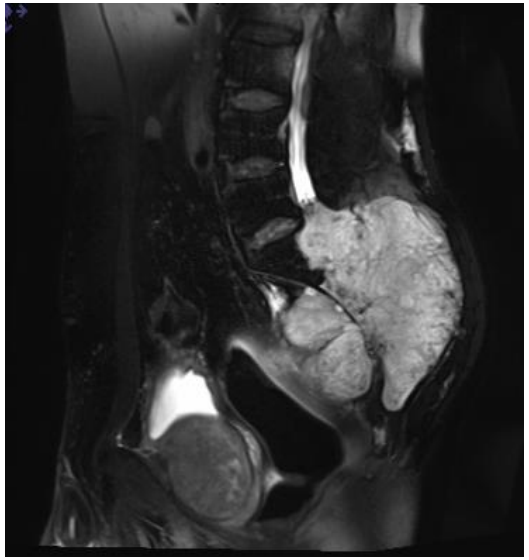
Permanent urinary/rectal disfunction → RT

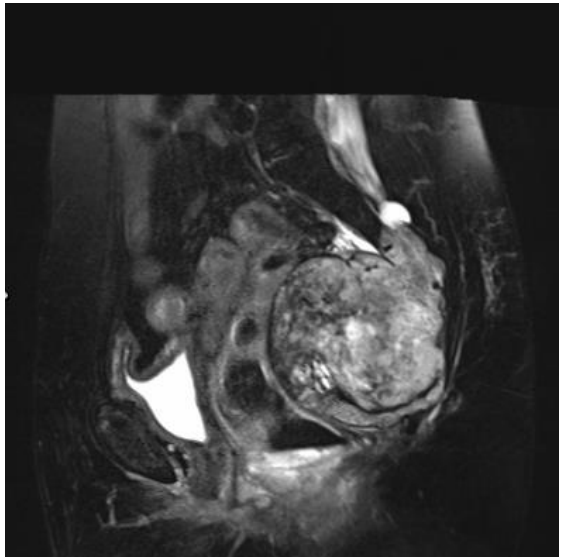
High risk of severe sequelae → patients preference based on expected QoL

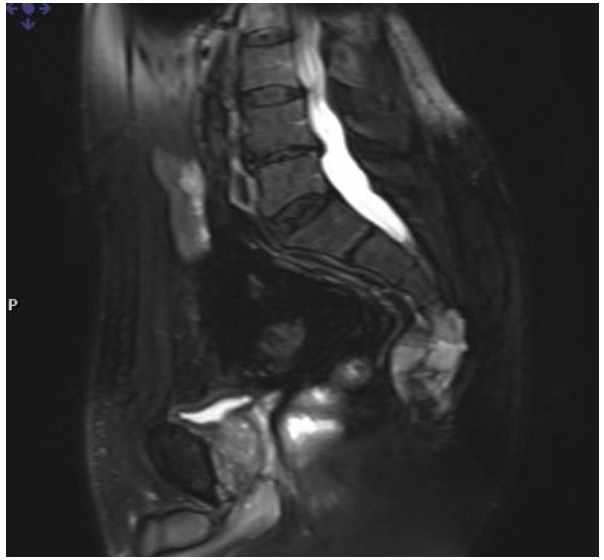
Low risk of severe sequelae,
40% of recovering possibility
Depending on S2 nerve roots
Involved → surgery

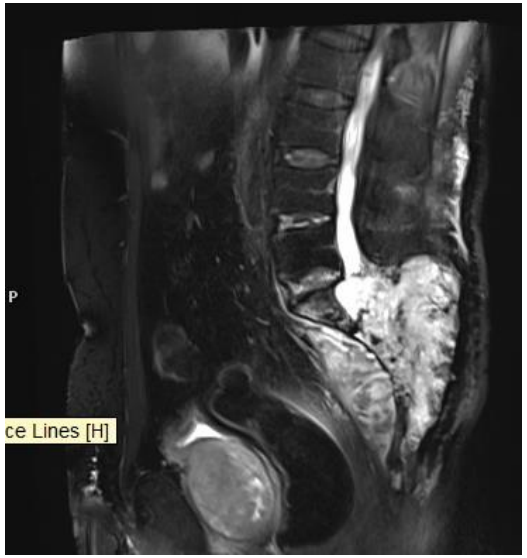
Not expected severe sequelae → surgery

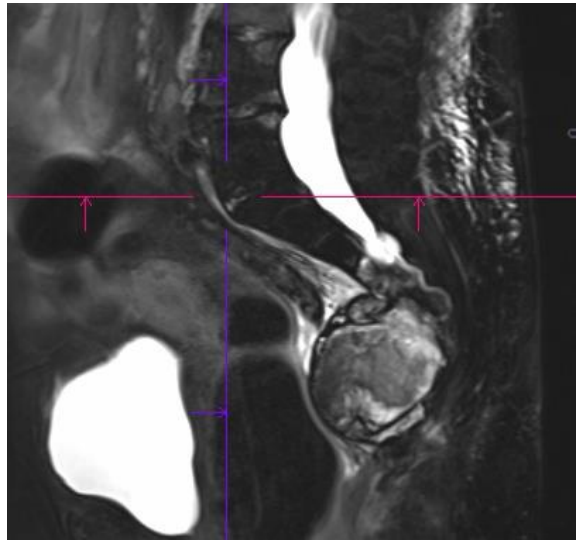
CNAO experience after 1 year

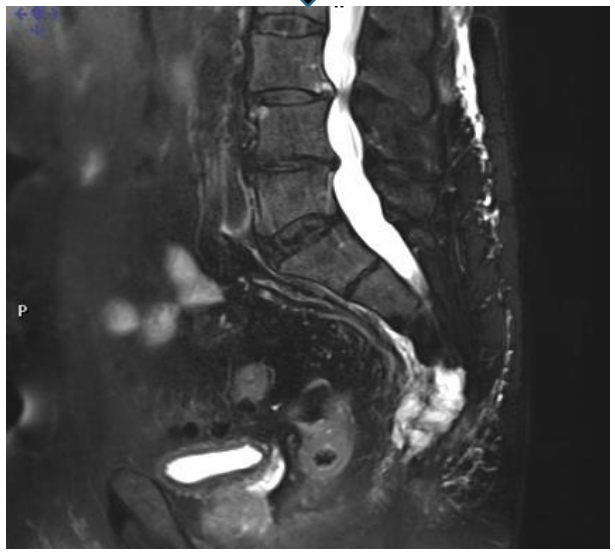




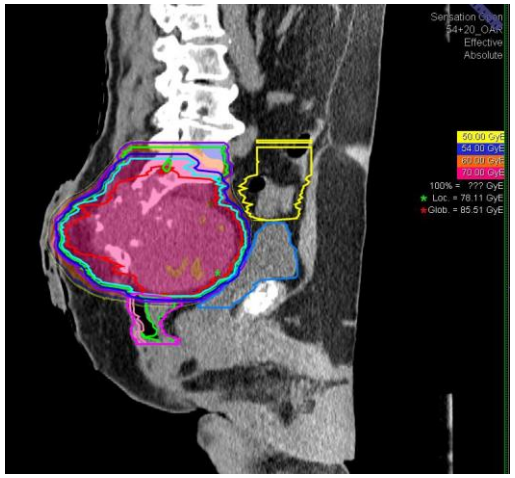








Spine- Sacrum Chordomas and Chondrosarcomas

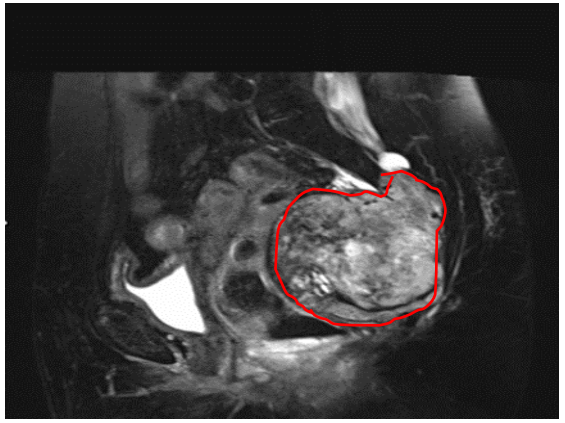


CNAO experience

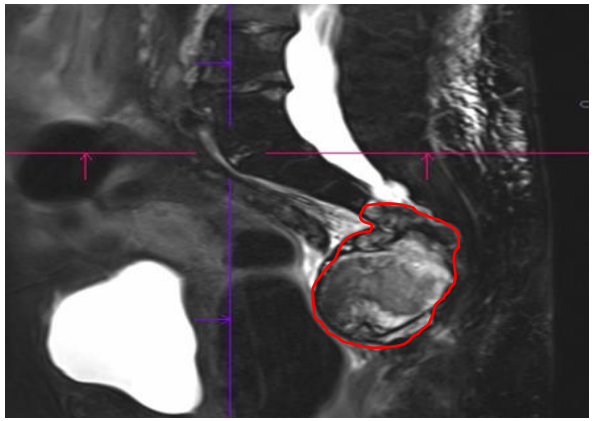
Unresectable

Carbon ions: 70.4 – 73.6 Gy(RBE) 4.4 – 4.6 Gy(RBE)/fx/16 fx

Response rate 86%



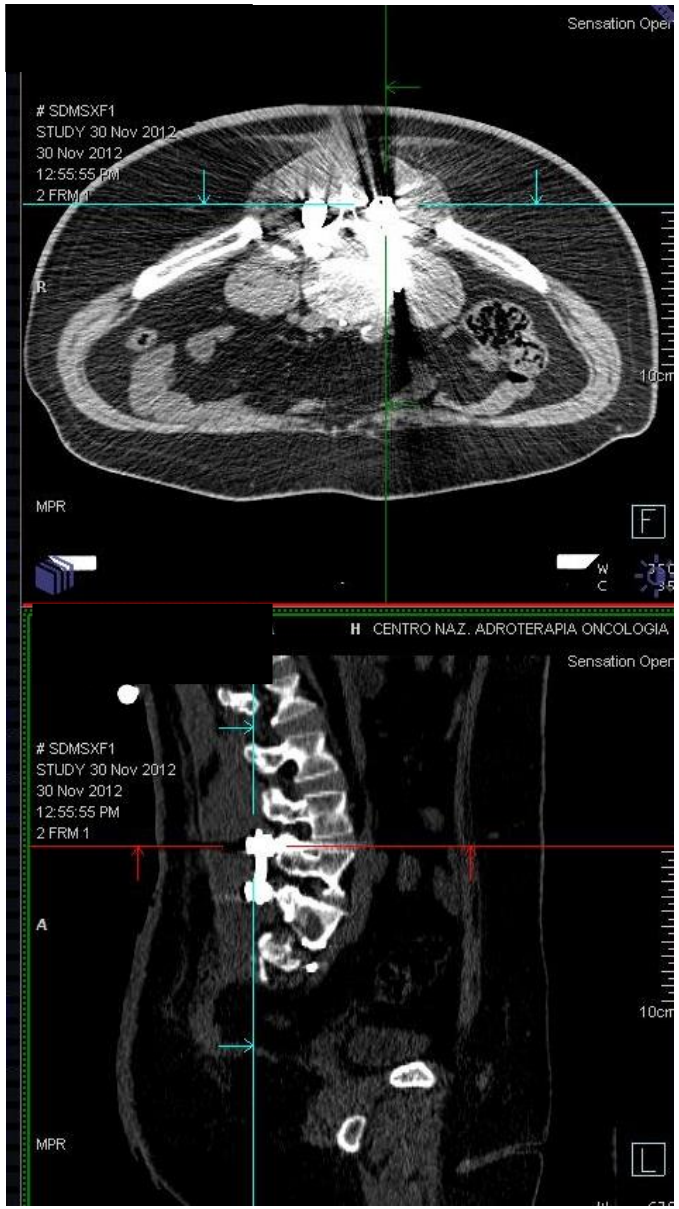
1 anno

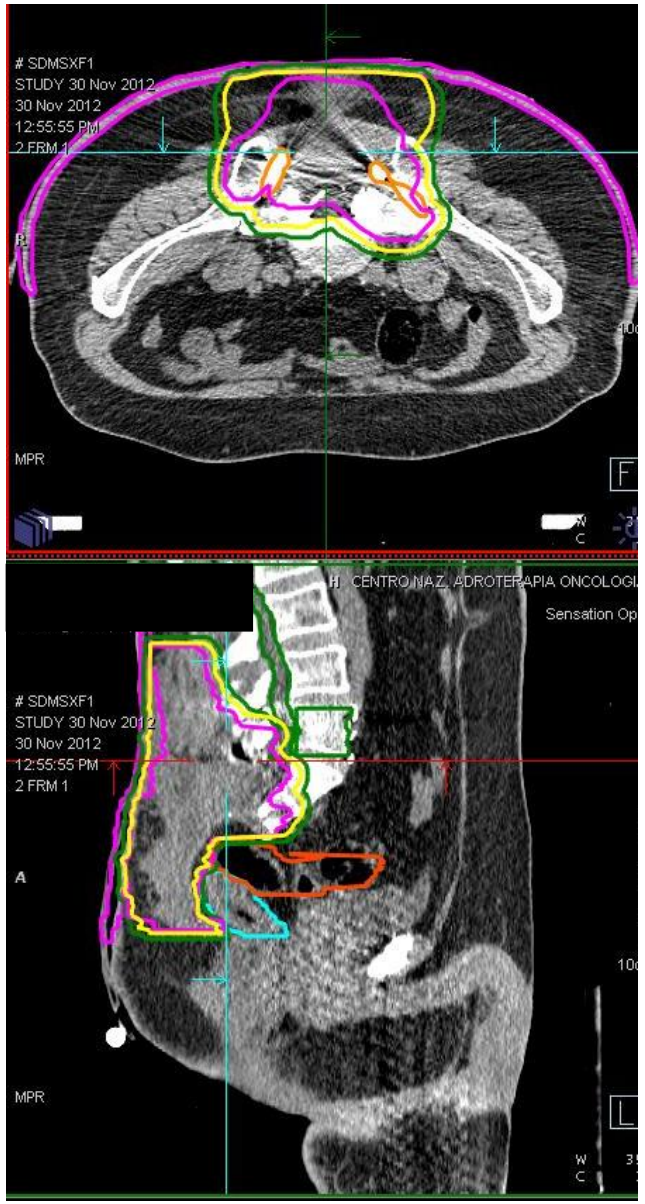


Italian Sarcoma Group

SAcral Chordoma (SACRO): studio randomizzato e osservazionale sulla chirurgia in confronto alla radioterapia nella malattia primitiva localizzata **INTISG**

Titanium implants





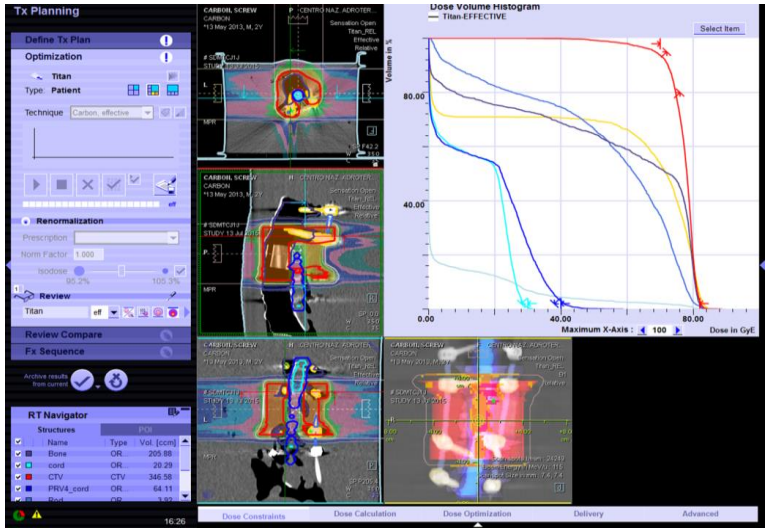
Dosimetric characterization of carbon fiber stabilization devices for post-operative particle therapy

E. Mastella[a,*], S. Molinelli[a], G. Magro[a], A. Mirandola[a], S. Russo[a], A. Vai[a], A. Mairani[a,b], K. Choi[a,c], M.R. Fiore[a], P. Fossati[a,d], F. Cuzzocrea[e], A. Gasbarrini[f], F. Benazzo[e], S. Boriani[f], F. Valvo[a], R. Orecchia[a,d], M. Ciocca[a]

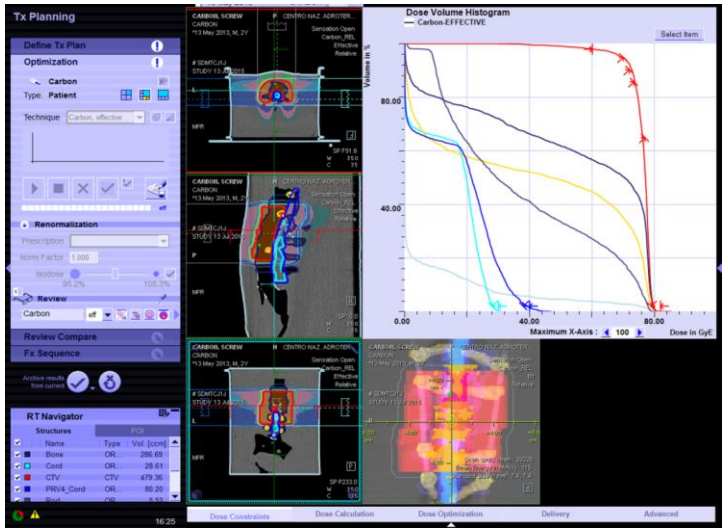
- Carbon fiber stabilization devices lead to less image alteration and consequently reduced contouring uncertainties together with a **significantly higher dosimetric treatment planning accuracy.**

- **Carbon fiber resulted dosimetrically more suitable than titanium implants**

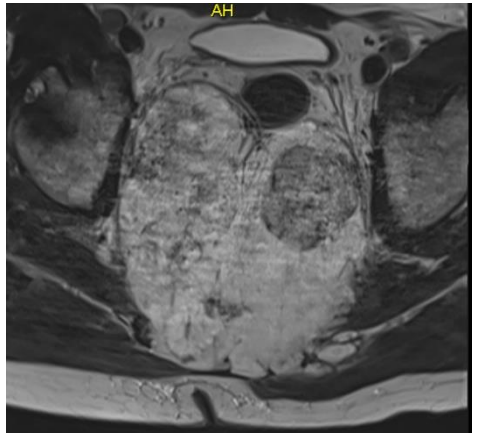
Titanium

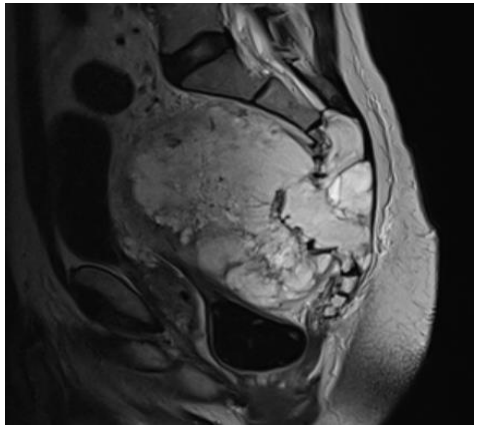


Carbons fiber

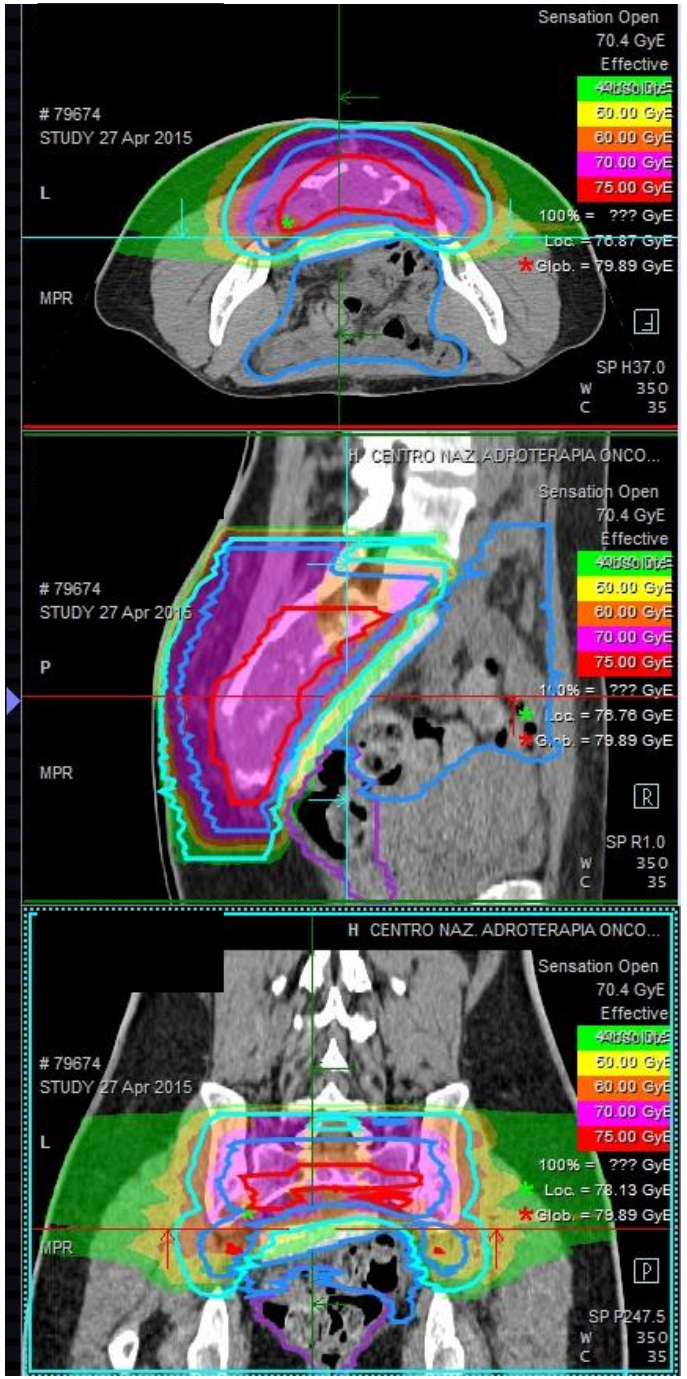


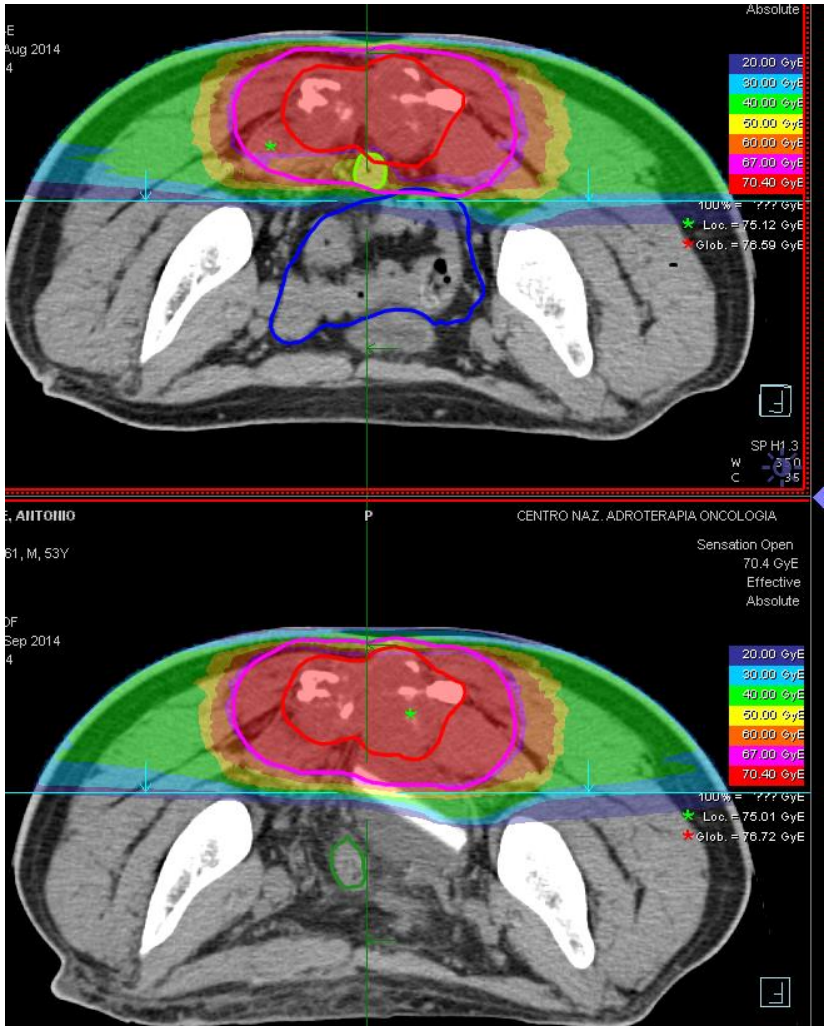
Physica Medica 44 (2017)





Underdosage OAR
Surgical bowel displacement





Soft tissue sarcomas

Literature studies of particle therapy for bone and soft tissue sarcomas (indicates 3-years rates).*

Author	Patients (n)	Anatomical Site	Histology	Particle	5-yr LC	5-yr OS
Serizawa *et al*. (2009)	24	Retroperitoneum	Various	Carbon ions	69%	50%
Ciernik *et al*. (2011)	55	Various	Osteosarcoma	Protons ± Photons	82%*	67%*
Staab *et al*. (2011)	40	Spine	Chordoma	Protons ± Photons	62%	80%
Sugahara *et al*. (2012)	17	Extremities	Various	Carbon ions	76%*	68%*
Matsunobu *et al*. (2012)	78	Various	Osteosarcoma	Carbon ions	62%	33%
Matsumoto *et al*. (2013)	47	Spine	Various	Carbon ions	79%	52%
DeLaney *et al*. (2014)	50	Spine	Various	Protons ± Photons	81%	84%
Mima *et al*. (2014)	23	Sacrum	Chordoma	Carbon ions/Protons	94%*	83%*
Uhl *et al*. (2015)	56	Sacrum	Chordoma	Carbon ions ± Photons	79%	52%
Imai *et al*. (2016)	188	Sacrum	Chordoma	Carbon ions	77%	81%
Demizu *et al*. (2016)	91	Pelvis	Various	Carbon ions	92%*	83%*
Imai *et al*. (2018)	128	Axis	Various	Carbon ions	65%	46%
CNAO (2020)	54	Axis	Various	Carbon ions	67%*	64%*

Cuccia F (CNA), Outcome and Toxicity of Carbon Ion Radiotherapy for Axial Bone and **Soft Tissue** Sarcomas, Anticancer Res. 2020 May;40(5):2853-2859

Delaney et al, Advances in Radiation Oncology (2017) 2, 85-93

Phase 1 trial of preoperative image guided intensity modulated proton radiation therapy with simultaneously integrated boost to the high risk margin for retroperitoneal sarcomas

IMPT and SIB, 28 fractions

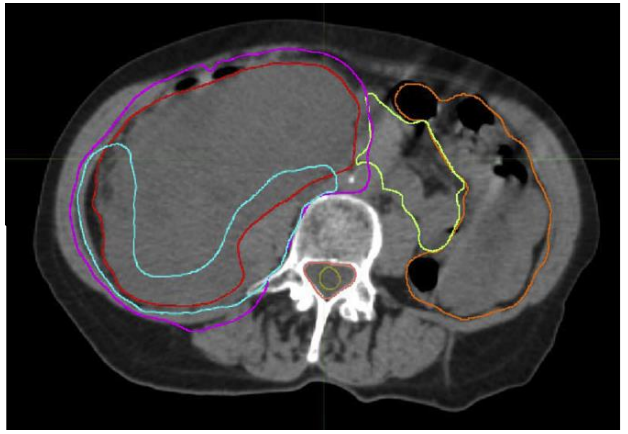
CTV1: GTV + adjacent tissues at risk of subclinical disease
50.4 GyRBE , 1,8 G

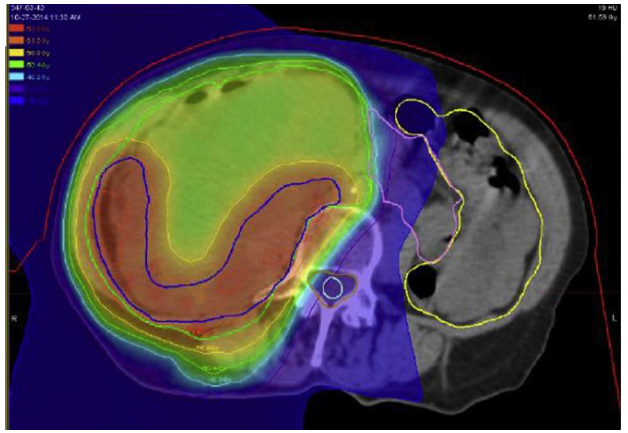
NCT01659203 trial -phase II

Still recruiting patients

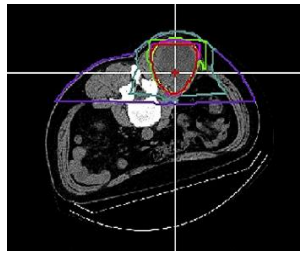
Foreseen conclusion 08.2025

CTV2: high risk are
60.2 GyRBE, 2.15
61.6 GyRBE 2.20 GyRBE/fr
63.0 GyRBE 2.25 GyRBE/fr → maximum tolerate dose



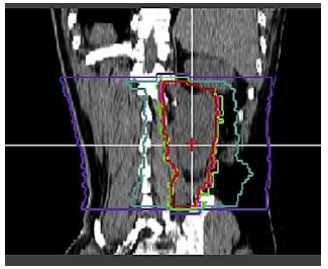


IMPT dose escalation feasible



CARBON ION RADIOTHERAPY FOR UNRESECTABLE RETROPERITONEAL SARCOMAS

Serizawa et al 2009 Int. J. Rad Oncol Biol. Phys., 75, 4



24 pts: 16 primitive/8 r
median follow-up 36 m

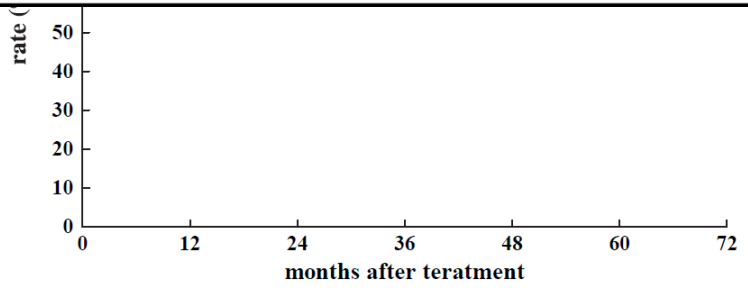
70.4 -73.6 Gy RBE; 16 fr

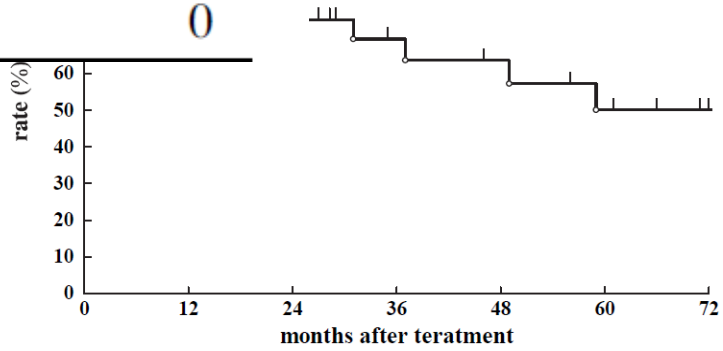
Table 2. Toxicity in study patients

Acute reaction	G1 *n*	G2 *n*	G3 *n*	G4 *n*
Skin	20	4	0	0
Gastrointestinal	0	0	0	0
Late reaction	**G1 n**	**G2 n**	**G3 n**	**G4 n**
Skin	22	1	0	0
Gastrointestinal	0	0	0	0
Neurologic	0	5	0	0

Histologic subtype	n
MFH	6
Liposarcoma	3
MPNST	3
Ewing/PNET	2
Other	10
Histological grade	
G3 (high grade)	15
G2–3 (high grade) 2	2
G2 (intermediate grade) 3	3
G1 (low grade) 0	0
Unknown 4	4
Total	24

2 yrs OS 75%
5 yrs OS 50%





Axial and pelvic bone and soft tissue sarcoma

CNAO experience

50 patients

- January 2013 to September 2018
- Median follow-up: 24 (range = 4-61)
- 76% first diagnosis
- Most common tumor site: pelvis

OUTCOME:

3y LC rate: 67.4%:

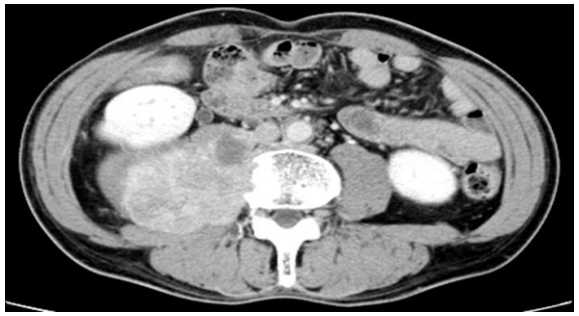
3y OS rate 64%

4% late G3 Neuropathy

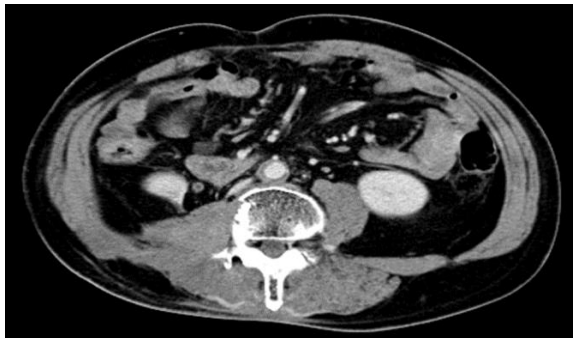
ANTICANCER RESEARCH *40*: 2853-2859 (2020)
doi:10.21873/anticanres.14260

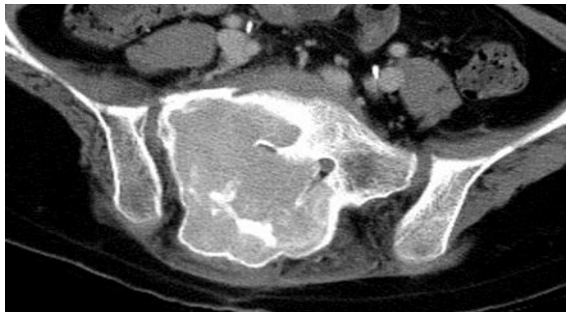
Outcome and Toxicity of Carbon Ion Radiotherapy for Axial Bone and Soft Tissue Sarcomas

FRANCESCO CUCCIA[1,2], MARIA ROSARIA FIORE[1], AMELIA BARCELLINI[1], ALBERTO IANNALFI[1], BARBARA VISCHIONI[1], SARA RONCHI[1], MARIA BONORA[1], GIULIA RIVA[1], ALESSANDRO VAI[1], ANGELICA FACOETTI[1], LORENZO PREDA[1,3], FRANCESCA VALVO[1] and VIVIANA VITOLO[1]

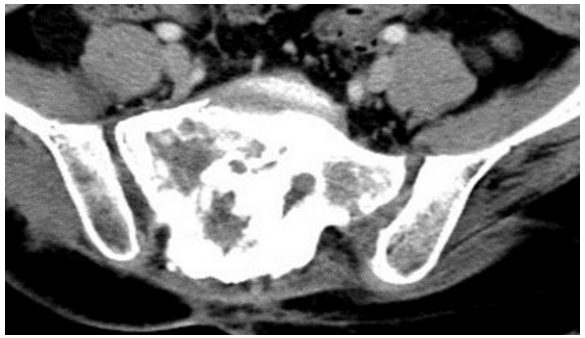


Retroperitoneal rhabdomyosarcoma after 5 years

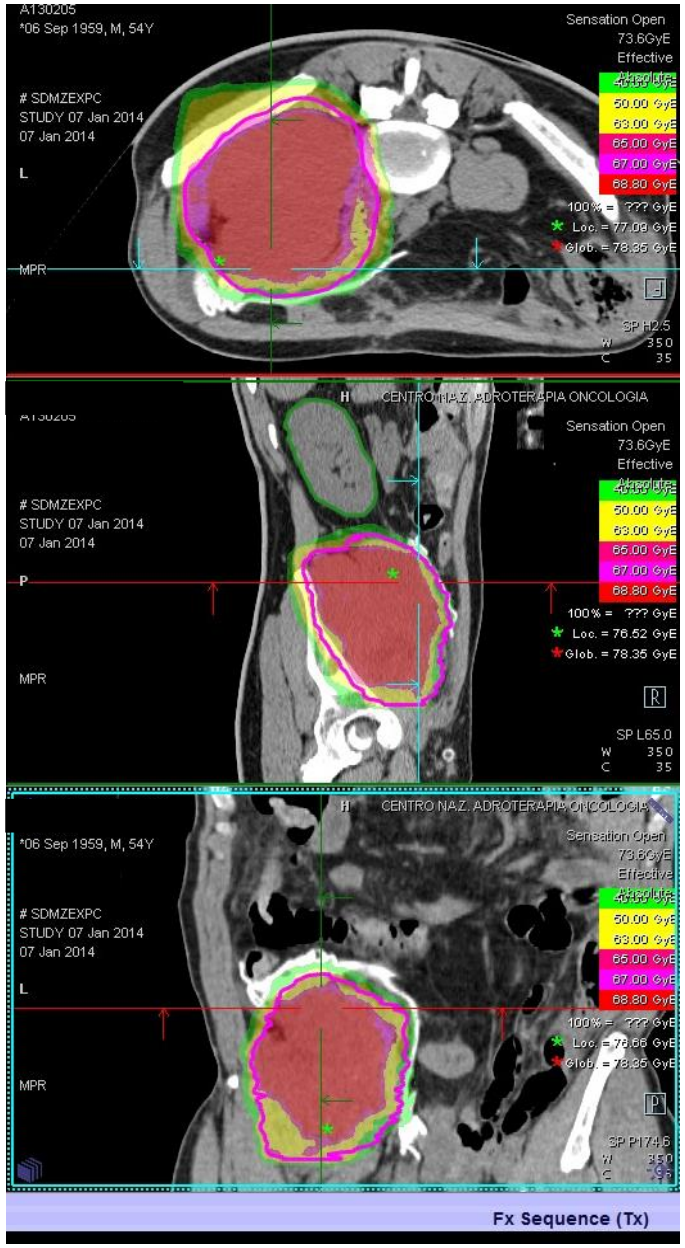




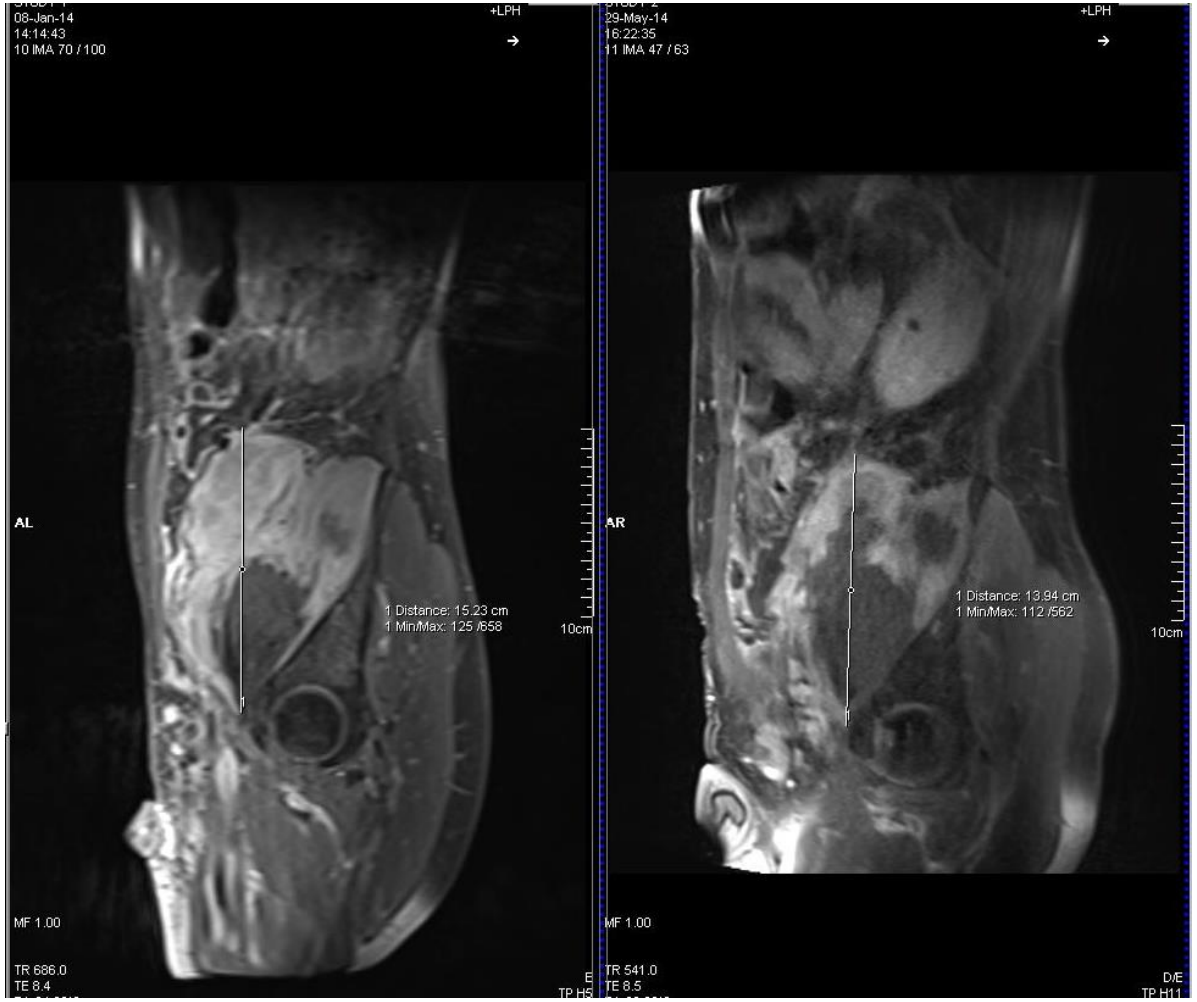
Sacral osteosarcoma after 5 years



Clinical case: DDLS

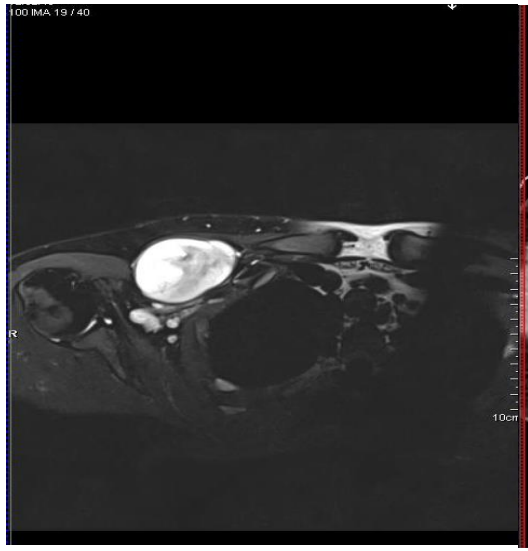


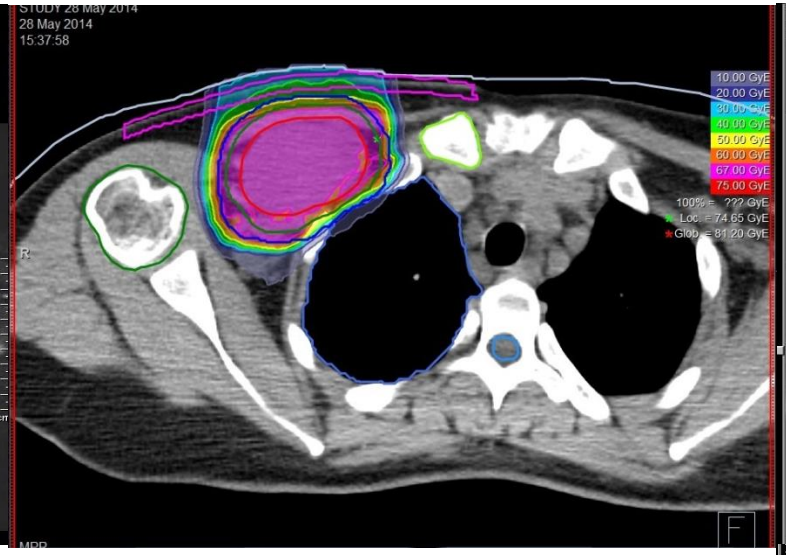
6 months later



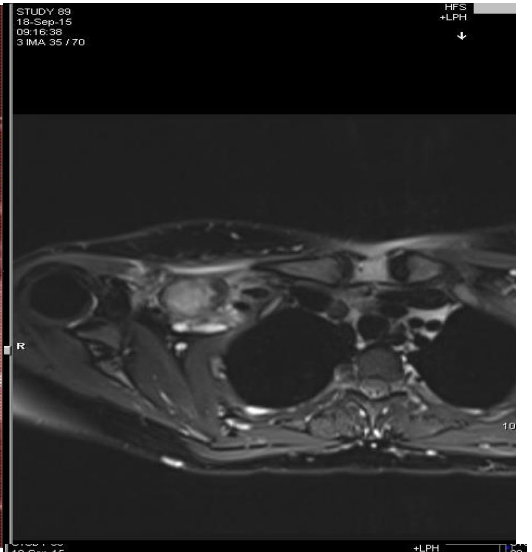
Clinical case: MPNST

Pre-CIRT

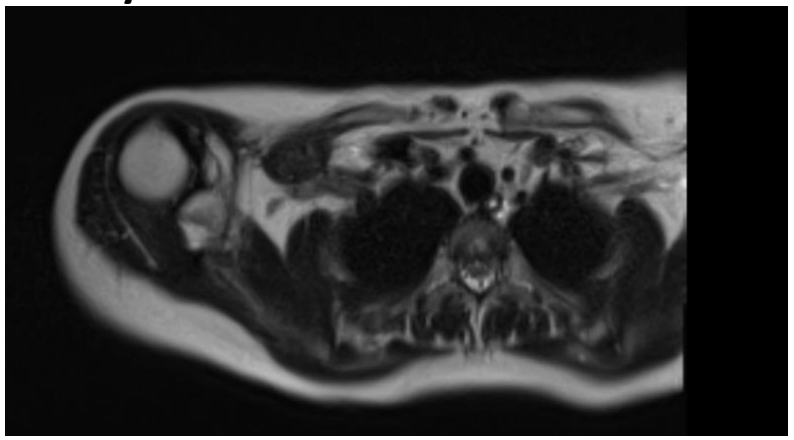


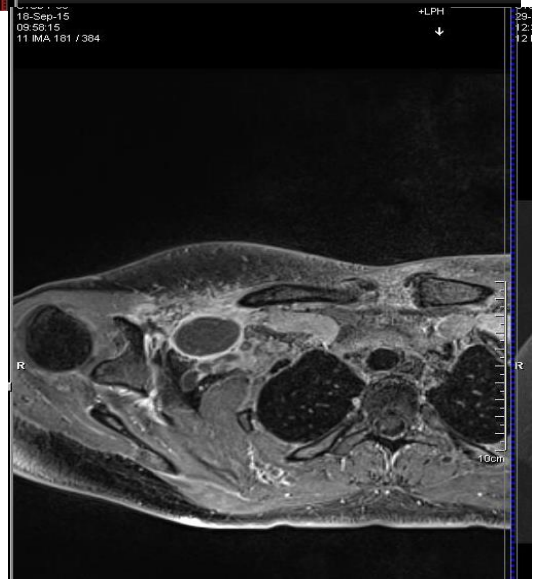


15 month later



8 years





Any role of particle therapy for gastrointestinal malignancies?

Consensus Report From the Miami Liver Proton Therapy Conference

Michael D. Chuong[1], Adeel Kaiser[2], Fazal Khan[1], Parag Parikh[3], Edgar Ben-Josef[4], Christopher Crane[5], Thomas Brunner[6], Toshiyuki Okumura[7], Niek Schreuder[8], Søren M. Bentzen[2], Alonso Gutierrez[1], Alejandra Mendez Romero[9,10], Sang Min Yoon[11], Navesh Sharma[12], Tae Hyun Kim[13], Kazushi Kishi[14], Fred Moeslein[15], Sarah Hoffe[16], Tracey Schefter[17], Steven Hanish[2], Marta Scorsetti[18] and Smith Apisarnthanarax[19]*

Rationale for PBT is sparing uninvolved liver
PBT should be considered if dose liver constraints cannot be achieved with XRT

PBT strongly recommended for

- At least CP-B cirrhosis
- High tumor-to-liver ratio
- Larger tumor size
- Smaller uninvolved liver volume
- Higher number of tumors
- Prior RT to the liver

Clinical decision making

-treatment planning comparisons PBT vs XRT
- NTCP models?

Consensus that PBT is expected to dramatically improve clinical outcomes **for some, but not all** liver cancer patients compared to XRT.

Future studies should focus on **identifying which patient subgroups** achieve the greatest clinical advantage from PBT to guide treatment decision making.

Front. Oncol. 2019

- **For primary hepatocellular carcinoma (HCC), cholangiocarcinoma, and isolated hepatic metastases**, the normal tissue sparing with proton therapy allows escalation of dose. Such escalation shows great promise, especially for large tumors that are a huge challenge to treat with photons without **severe radiation-induced liver disease**.

- An HCC randomized trial “Radiation Therapy with Protons or Photons in Treating Patients with Liver Cancer” (NCT03186898) is being conducted within the auspices of NRG

WHAT ABOUT ESOPHAGEAL CANCERS?

PROton Versus Photon Therapy for Esophageal Cancer - a Trimodality Strategy (PROTECT)

ClinicalTrials.gov Identifier: NCT05055648

Arms and Interventions Go to

Arm	Intervention/treatment
Active Comparator: Photon Arm Standard arm with neoadjuvant chemoradiotherapy (nCXT) with photons	Radiation: Photon Radiotherapy nCXT consists of weekly carboplatin and paclitaxel for 5 weeks, following the CROSS trial. The radiation dose will be either 41.4 Gy in 23 fractions or 50.4 Gy in 28 fractions
Experimental: Proton Arm Experimental arm with neoadjuvant chemoradiotherapy (nCPT) with protons	Radiation: Proton Radiotherapy nCPT consists of weekly carboplatin and paclitaxel for 5 weeks, following the CROSS trial. The radiation dose will be either 41.4 Gy in 23 fractions or 50.4 Gy in 28 fractions Other Name: Proton Therapy

Outcome Measures Go to

Primary Outcome Measures :

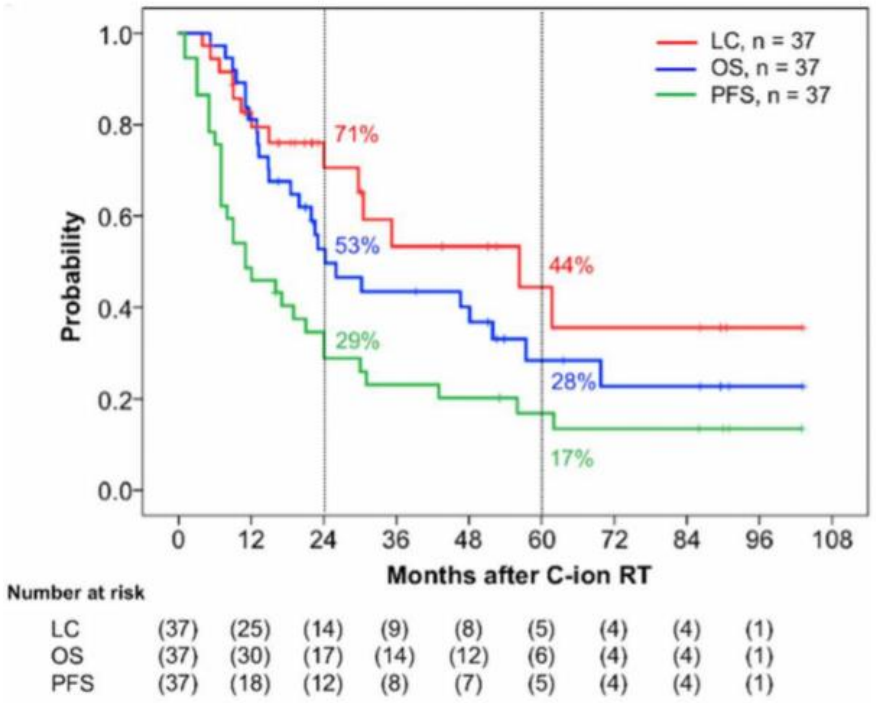
1. Pulmonary complications [Time Frame: from randomization until 90 days after surgery]

   Incidence of pulmonary complications during and following nCPT or nCXT and surgery

Any role of particle therapy for gynecological malignancies?

Literature data: Mucosal Malignant Melanomas

Gynecological Mucosal Malignant Melanoma and CIRT



- Retrospective analysis of 37 patients
- Median follow-up periods: 23 months (range: 5–103 months) for all patients and 53 months (range: 16–103 months) for survivors
- Within 6 months **: 19 CR, 14 PR and 4 SD**

Acute Toxicity	CTCAE v.4 Scoring				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4–5
Dermatitis/mucositis	2	18	14	3	0
Genitourinary toxicity	28	9	0	0	0
Lower gastrointestinal toxicity	17	14	6	0	0
Late toxicity	**RTOG/EORTC Scoring**				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4–5
Dermatitis/mucositis	28	9	0	0	0
Genitourinary toxicity	30	3	4	0	0
Lower gastrointestinal toxicity	29	5	3	0	0

Murata et al Cancers (Basel). 2019

CYCLE

Carbon ion radiation therapy in the treatment of mucosal melanomas of the female lower genital tract

Study Design	Monocentric, prospective phase II study
Statistical Considerations	Fleming one stage design
Treatment	The low-dose CTV (clinical target volume) will receive a total dose of 43 GyRBE in 10 fractions, 4 fractions per week. The high-dose CTV will receive a total dose of 68.8 GyRBE in 16 fractions, 4 fractions per week.
Endpoints	**The primary endpoint** of the study is to estimate **2-year PFS** in patients diagnosed with mucosal melanoma of the lower genital tract, treated with carbon ion radiation therapy. **Secondary endpoints:** •Overall survival (OS) •Toxicity according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0) •Objective response rate (ORR) according to RECIST •Evaluation of the association between the clinical-radiological response at 6 weeks and the late response (> 6 months) •Quality of life.

INDICATIONS reirradiation

- Re-irradiation of large-complex recurrent meningiomas
- Re-irradiation salivary gland cancer
- Re-irradiation of rectal recurrences
- Re-irradiation of gynecological recurrences

RE-IRRADIATION OF SKULL BASE MENINGIOMA WITH PARTICLE RT

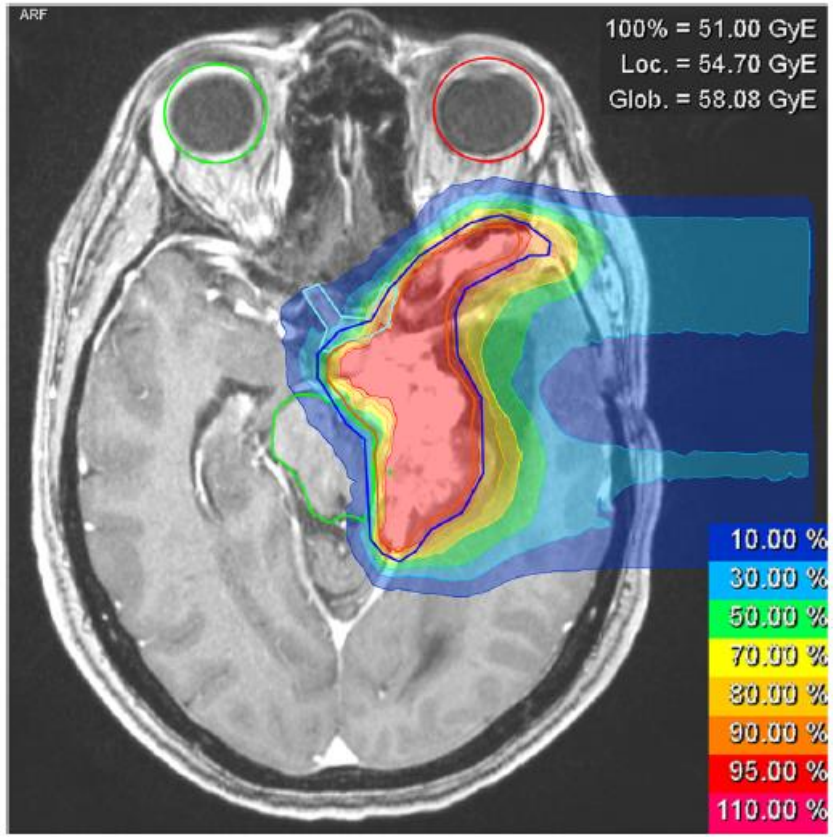


Fig. 7 Exemplary treatment plan for re-irradiation of a large recurrent meningioma of the skull base. A re-irradiation dose of 17 × 3 Gy(RBE) carbon ions was applied and a dose of 11 × 3,8 Gy photons had been applied one year earlier in a FSRT-setting. Dose to the directly adjoining optic chiasm could be reduced to 11,0 Gy(RBE) mean (33,3 Gy(RBE) max) and dose to the brain stem to 6,5 Gy(RBE) mean (36,3 Gy(RBE) max). CTV is delineated in red and PTV in blue

Large/Very Large and complex shaped recurrent tumors: very difficult situation to treat effectively in reirradiation setting

Carbon ions RT to be considered in order to overcome radioresistance

	median (ml)	Q1-Q3	mean (ml)
GTV	18,1	6,7–82,6	51,3
CTV	48,9	22,5–93,9	82,3
PTV	75,1	37,1–126,2	102,9

El Shafie et al (2018) particle RT series from Department of Radiation Oncology, University Hospital of Heidelberg :
available all advanced photon techniques further than particle RT.

Reirradiation of salivary gland tumors

CNAO experience

- November-2013-September2016
- 51 pts
- Median CIRT dose 60 Gy[RBE]/ 3Gy[RBE] FS
- Median follow-up: 18 months

PFS 1y/2y: 71.7% e 52.2%

OS 1y/2y: 90.2% e 64%

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

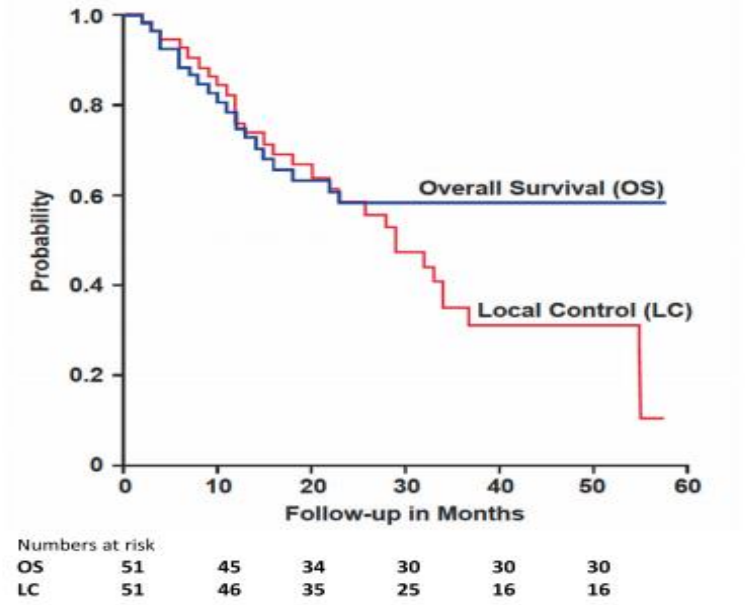


Fig. 2. Local control (LC) and overall survival (OS) following reirradiation with CIRT in a series of inoperable recurrent salivary gland tumors treated at CNAO.

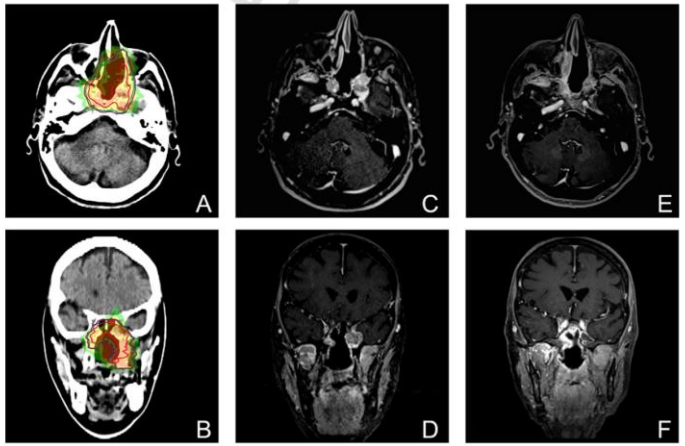


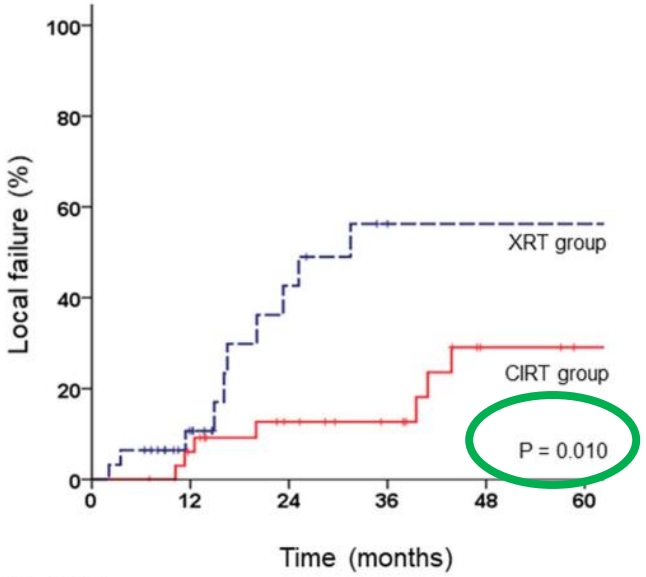
Table 4
Acute and late toxicity at last follow up.

	ACUTE TOXICITY *N* (%)	LATE TOXICITY *N* (%)
G0	11 (21.5)	14 (27.5)
G1	19 (37.3)	9 (18)
G2	19 (37.3)	19 (37)
G3	2 (3.9)	9 (17.5)

Re-irradiation of rectal recurrences: literature data

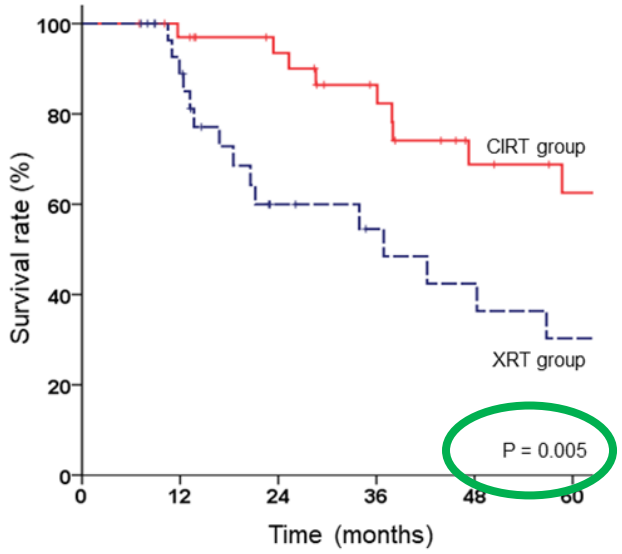
Comparison of clinical outcomes between carbon ion radiotherapy and X-ray radiotherapy for reirradiation in locoregional recurrence of rectal cancer

35 pts treated with CIRT (70.4GyE/16 fx) **vs** 31 treated with XRT (median dose 50 Gy/25fx)



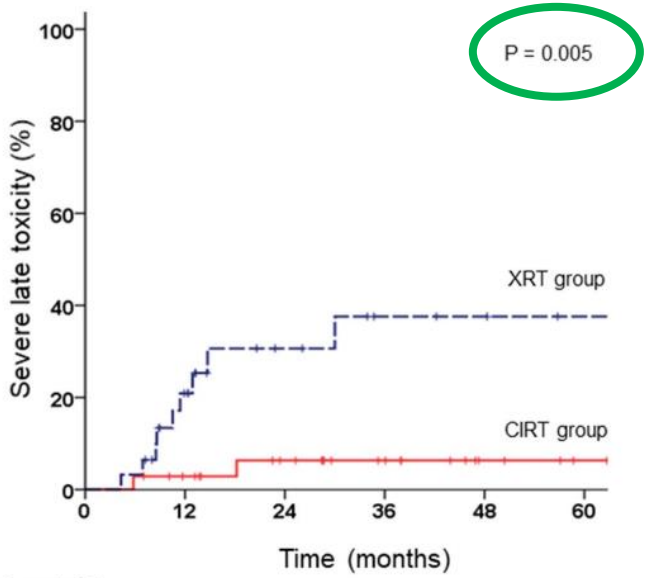
Number at risk

CIRT	35	30	23	19	10	8
XRT	31	20	9	4	4	4



Number at risk

CIRT	35	32	27	21	13	10
XRT	31	24	12	9	7	5



Number at risk

CIRT	35	31	25	19	12	9
XRT	31	20	11	7	6	4

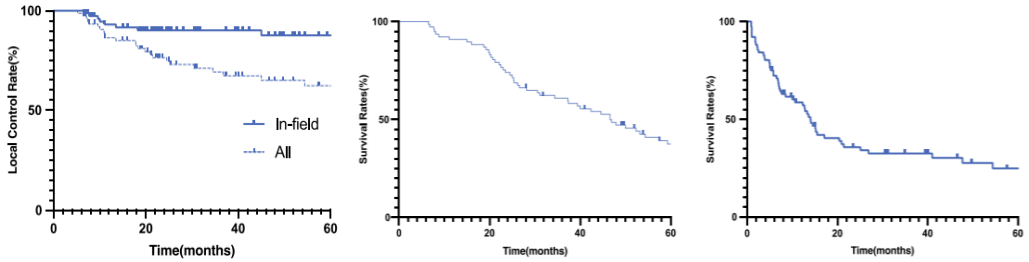
CIRT showed better control, better overall survival and lower severe late toxicity rate

Chung, Seung Yeun et al., Scientific reports vol. 12,1 1845 (2022)

Re-irradiation of rectal recurrences: literature data vs CNAO experience

Yamada, Annals of surgical oncology 2022

77 pts treated with **CIRT (70.4GyE/16 fx)** after a prior XRT on the pelvis (median dose of 50.4Gy (range 20–74 Gy)

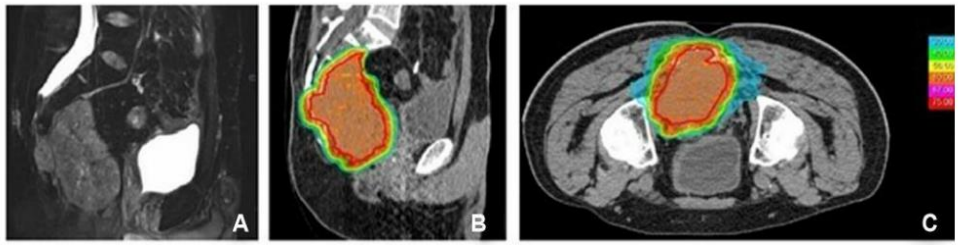


3-y LC (all): 69 % (95 % CI 56–79 %) 5-y LC (all):62% (95 % CI 51–73 %)	3-y OS: 61 % (95 % CI 49–71 %) 5-y OS:38% (95 % CI 26 –49 %)	3-y PFS: 33 % (95 % CI 22–44 %) 5-y PFS: 33 % (95 % CI 22–44 %)

Acute grade 3 toxicities (10 %) and late grade 3 toxicities (21 %)

Re-irradiation with CIRT could be an evaluable option,
Prognostic factors for the outcome needed to be elucidate

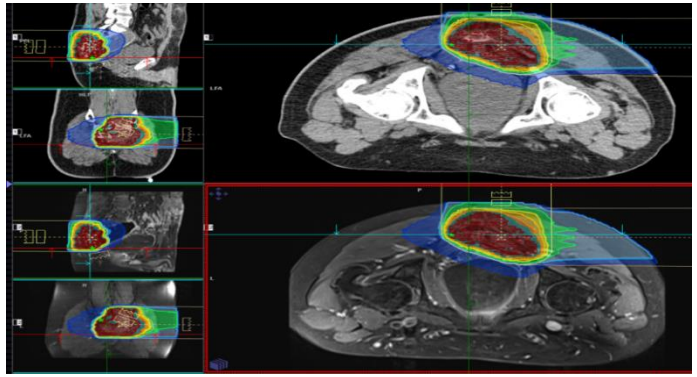
CNAO



14 pts treated with **CIRT (35-76.8 GyE/ 15-20 fx)** after a prior XRT on the pelvis (median dose:58.5 Gy)Gy)

- Median follow-up : 18 months
- **Overall Survival**: 1-year OS 100%; 2-year OS 76.2%
- **Local Control**: 1-year LC 78%; 2-year LC 52%

No G≥3, no pelvic infection → pre-CIRT surgery with **spacer implantation** by open surgery in 4 cases



Barcellini, In vivo 2020

Literature data: local recurrence

CIRT as re-irradiation for gynecological recurrences

Case	Primary site, Stage	Histology	Initial treatment	Dose of prior RT	Duration of prior RT to C-ion RT (months)	Tumor size (mm)	Dose of C-ion RT	Recurrence
1	Cervical cancer, T2bN1M0	Squamous cell carcinoma	CCRT	50 Gy/25 fr.	26	33	48 Gy (RBE)/12 fr.	NER
2	Cervical cancer, T2aN0M0	Squamous cell carcinoma	RT alone	50 Gy/25 fr.	25	28	48 Gy (RBE)/12 fr.	NER
3	Endometrial cancer, T1N0M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	68	25	48 Gy (RBE)/12 fr.	NER
4	Cervical cancer, T4N0M0	Squamous cell carcinoma	CCRT	50 Gy/25 fr.	26	14	48 Gy (RBE)/12 fr.	LN metastasis
5	Cervical cancer, T1b1N0M0	Squamous cell carcinoma	Surgery	66 Gy/33 fr.	11	33	52.8 Gy (RBE)/12 fr.	NER
6	Endometrial cancer, T3aN0M0	Carcinosarcoma	Surgery	60 Gy/30 fr.	12	20	57.6 Gy (RBE)/12 fr.	LN metastasis
7	Cervical cancer, T3bN1M0	Squamous cell carcinoma	Surgery	50 Gy/25 fr.	17	15	52.8 Gy (RBE)/12 fr.	Local recurrence, LN and Lung metastases
8	Cervical cancer, T2bN1M0	Squamous cell carcinoma	CCRT	50.6 Gy/27 fr.	33	24	57.6 Gy (RBE)/12 fr.	LN metastasis
9	Endometrial cancer, T3bN1M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	20	80	57.6 Gy (RBE)/16 fr.	Local recurrence
10	Cervical cancer, T2aN0M0	Squamous cell carcinoma	CCRT	46 Gy/23 fr.	77	30	52.8 Gy (RBE)/12 fr.	NER
11	Ovarian cancer, T1bN0M0	Serous adenocarcinoma	Surgery	56 Gy/28 fr.	40	18	52.8 Gy (RBE)/12 fr.	Lung metastasis
12	Endometrial cancer, T3aN0M0	Endometrioid adenocarcinoma	Surgery	50 Gy/25 fr.	130	22	52.8 Gy (RBE)/12 fr.	NER
13	Endometrial cancer, T1bN0M0	Small cell carcinoma	Surgery	54 Gy/27 fr.	17	75	52.8 Gy (RBE)/12 fr.	Lung metastasis
14	Cervical cancer, T1bN0M0	Mucinous adenocarcinoma	Surgery	50.4 Gy/28 fr.	21	38	57.6 Gy (RBE)/12 fr.	NER
15	Endometrial cancer, T1bN0M0	Endometrioid adenocarcinoma	Surgery	58.6 Gy/32 fr.	29	42	52.8 Gy (RBE)/12 fr.	Liver metastasis
16	Cervical cancer, T1bN1M0	Squamous cell carcinoma	Surgery	50 Gy/25 fr.	64	20	52.8 Gy (RBE)/12 fr.	NER

CCRT, Concurrent chemoradiotherapy; C-ion RT, carbon-ion radiotherapy; fr., fractions; LN, lymph node; NER, no evidence of recurrence; RT, radiotherapy.

- Retrospective series of **16 cases**
- **Unresectable** recurrence at the edge of the previously irradiated field
- Median age 57 years (range=35-79 years)
- Median **tumor size was 27 mm** (range=14-80 mm)
- Total dose range: **48-57.6 GyE**

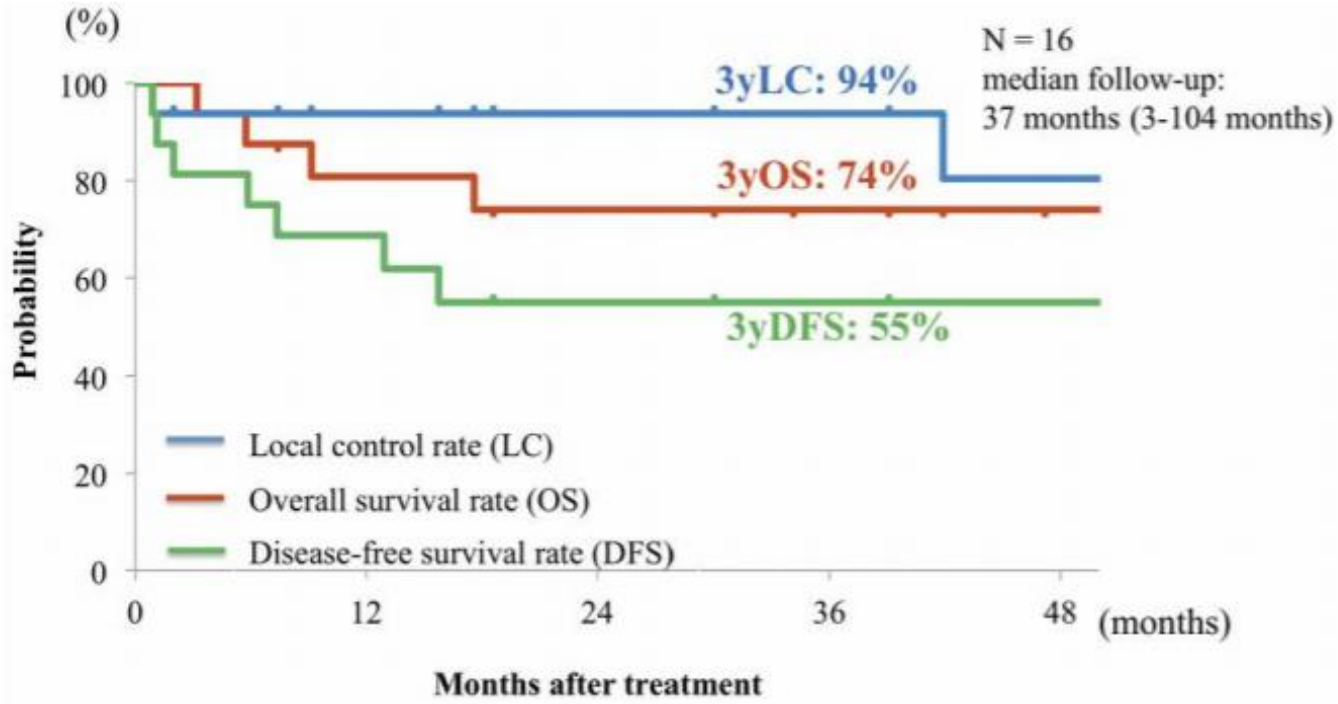
Organs involved	G0	G1	G2	G3	G4
Gastrointestinal tract	14	2	0	0	0
Urinary tract	15	1	0	0	0
Leg edema	15	0	1	0	0
Lower extremity nerve	14	2	0	0	0

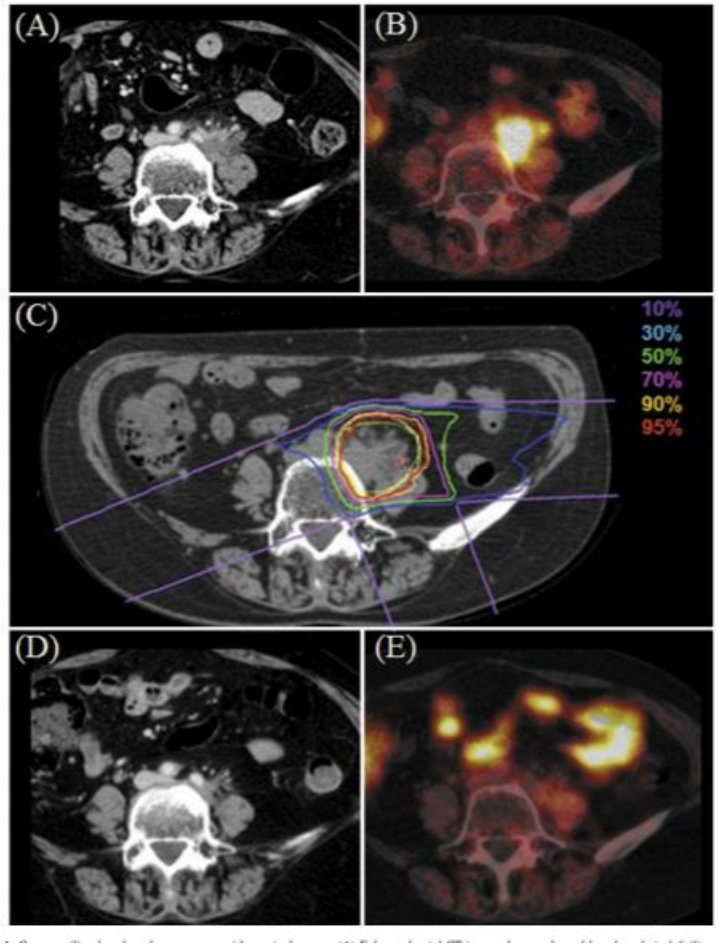
RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

Shiba et al., Anticancer Res. 2017

Literature data: local recurrence

CIRT as re-irradiation for gynecological recurrences





Two patients had local recurrence, and 7 patients had distant metastases

Shiba et al., Anticancer Res. 2017

CNAO

CYCLOPS

Study Design	Monocentric, prospective phase II study
Study Population	Patients affected by pelvic recurrence of gynecological neoplasia, already undergone to radiotherapy on pelvis, will be enrolled in the study.
Treatment	PTV will receive a total dose of 48-52.8 GyRBE in 12 fractions, 4 fractions per week. Treatment expected duration is 3 weeks, 4 fractions per week.
Statistical Considerations	Fleming one stage design
Aims	Primary endpoint: 1-year local control (LC) Secondary endpoints: • Overall survival (OS) • Toxicity according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0) • Symptoms control, evaluating pain reduction (screened by NRS scale) and variation in the use of analgesic drugs (decrease or increase) • Subgroup success rate analysis with stratification according to: Histology (adenocarcinoma vs squamo-cellular)
Sample size	55 subjects

Dilemma: how to select patients to particle therapy?

HOW TO SELECT PATIENTS TO CIRT?

✓ ***Biological factors***

- High LET radiation should be selectively used for radiobiological reasons in tumors that are hypoxic, slowly proliferating; that have a high capacity for damage repair, genetic/biological, microenvironmental features that promote radioresistance.

- High LET radiation should be used in those histologies which have been shown to be highly resistant to conventional photon-based RT (recurrent disease, very extensive disease).

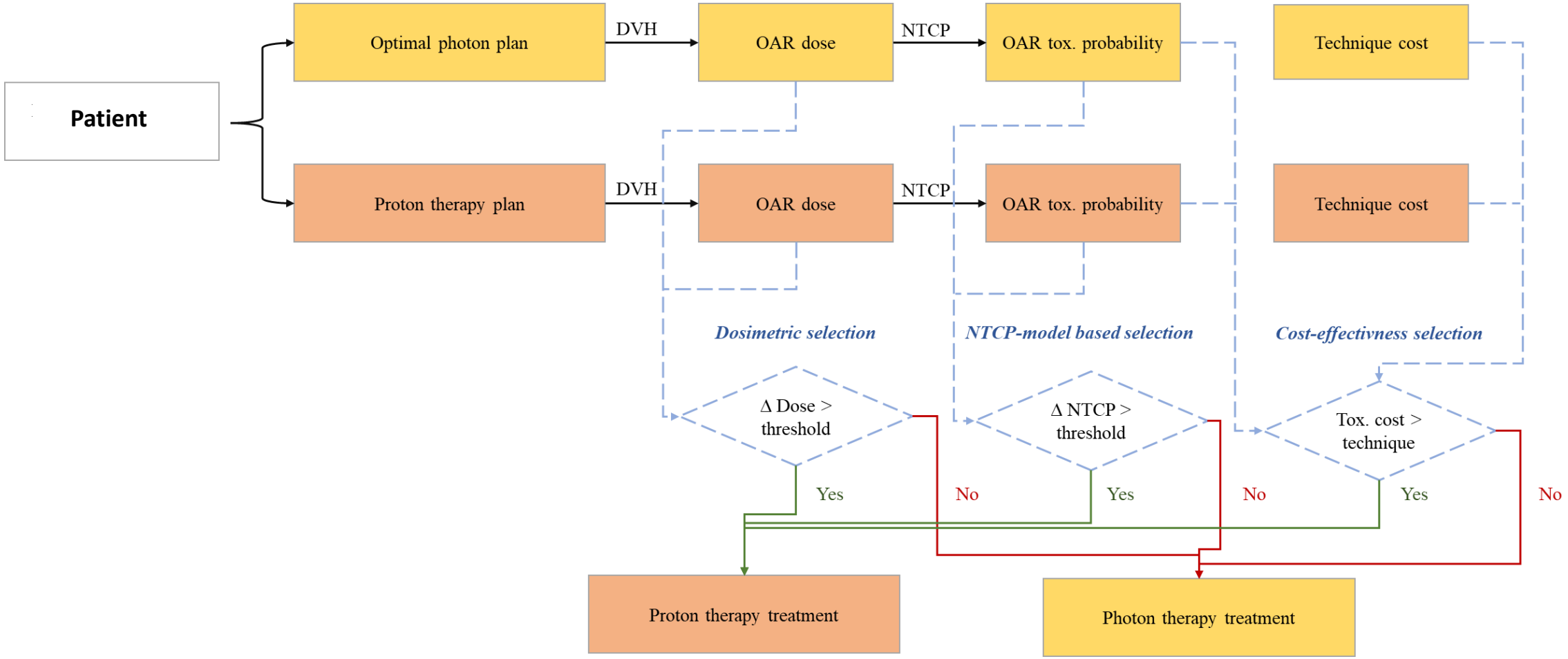
✓ ***Anatomical constraints:***

- Difficult location:
  inability to irradiate with a curative dose without overdosing the organs at risk;
  inability to resect the tumor with negative margins or with the impair of important structures.
  (radioresistant, unresectable disease)

Fokas 2009, Schlaff 2014, Durante 2012, Tinganelli 2020, Griffin 1988, Debus 1999

HOW TO SELECT PATIENTS TO PROTON THERAPY?

- National treatment capacity
- Cancer epidemiology



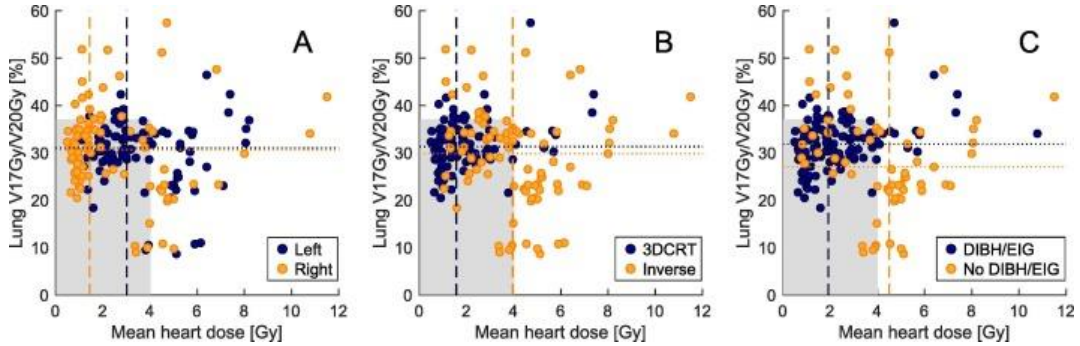
Example of dosimetric selection : Denmark (Aarhus Hospital)

Based on **national treatment capacity**

- Capacity to treat **100 breast cancer patients with proton each year**
- **= 11% of all breast cancers with adjuvant locoregional irradiation indication**

Based on dosimetric evaluation of treated patients, proton therapy is indicated in Denmark when :

- **Mean heart dose (MHD) ≥4 Gy** with optimal photon RT plans → *not the case for PBI*
- **Ipsilateral lung V17Gy/V20Gy ≥ 37%** with optimal photon RT plans



Stick et al., ctro, 2021

HOW TO SELECT PATIENTS TO PROTON THERAPY?

ELSEVIER

Seminars in RADIATION ONCOLOGY

Clinical Trial Strategies to Compare Protons With Photons

Johannes A. Langendijk, MD, PhD,[*,‖] Liesbeth J. Boersma, MD, PhD,[†,‖] Coen R.N. Rasch, MD, PhD,[†,‖] Marco van Vulpen, MD, PhD,[‡,‖] Johannes B. Reitsma, MD, PhD,[§,‖] Arjen van der Schaaf, PhD,[*,‖] and Ewoud Schuit, PhD[§,‖]

2018

First experience with model-based selection of head and neck cancer patients for proton therapy

Makbule Tambas [a,*], Roel J.H.M. Steenbakkers [a], Hans P. van der Laan [a], Atje M. Wolters [a], Roel G.J. Kierkels [a,b], Dan Scandurra [a], Erik W. Korevaar [a], Edwin Oldehinkel [a], Tineke W.H. van Zon-Meijer Stefan Both [a], Johanna G.M. van den Hoek [a], Johannes A. Langendijk [a]

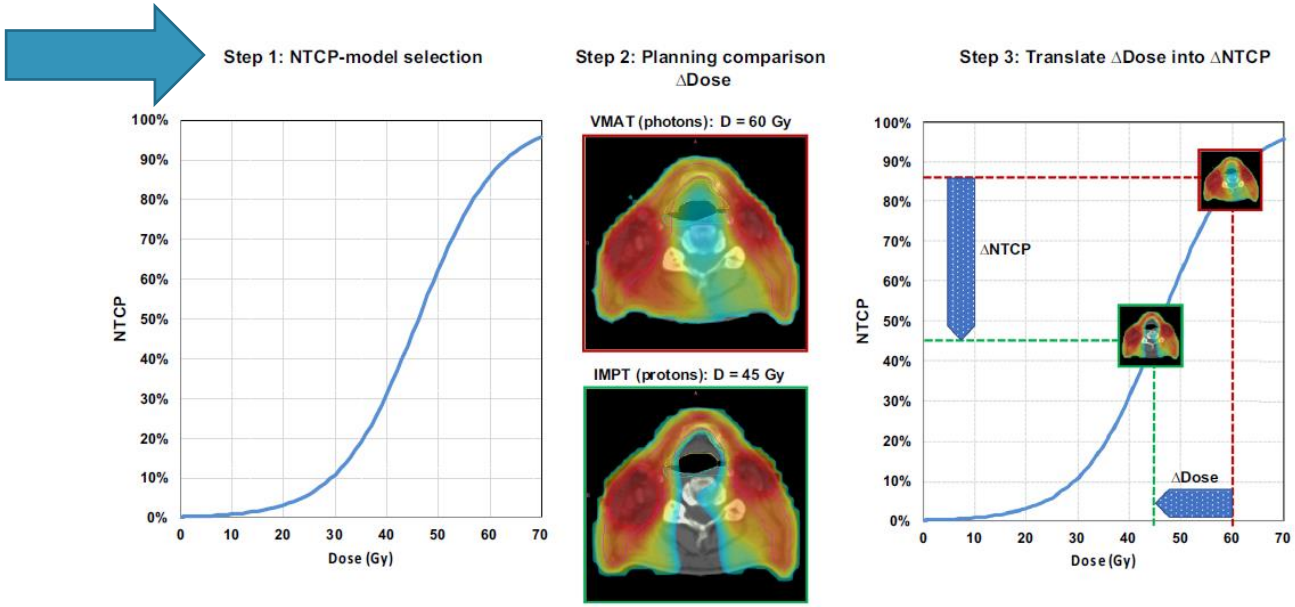
[a] *University of Groningen, University Medical Center Groningen, Department of Radiation Oncology; and* [b] *Radiotherapiegroep, Department of Radiation Oncology, Deventer, the Netherlands*

2020

1. **Model-based approach (NTCP):** to estimate the potential clinical benefit for protons over photons in terms of reduction in normal tissue complication probability (NTCP) for each individual patient and assign the patient to PBT only if the reduction in toxicity is above a specified threshold (precision medicine).

2. **Evidence based medicine:** Randomized controlled trials (RCTs) randomization of the study population into photon and proton treatment. RCTs run the risk of being ethically compromised.

3. **Prospective institutional national and international registries.**



Ramaekers, 2012
Blanchard 2017
Lagendijk 2013

Radiotherapy and Oncology 151 (2020) 206–213

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Radiotherapy and Oncology

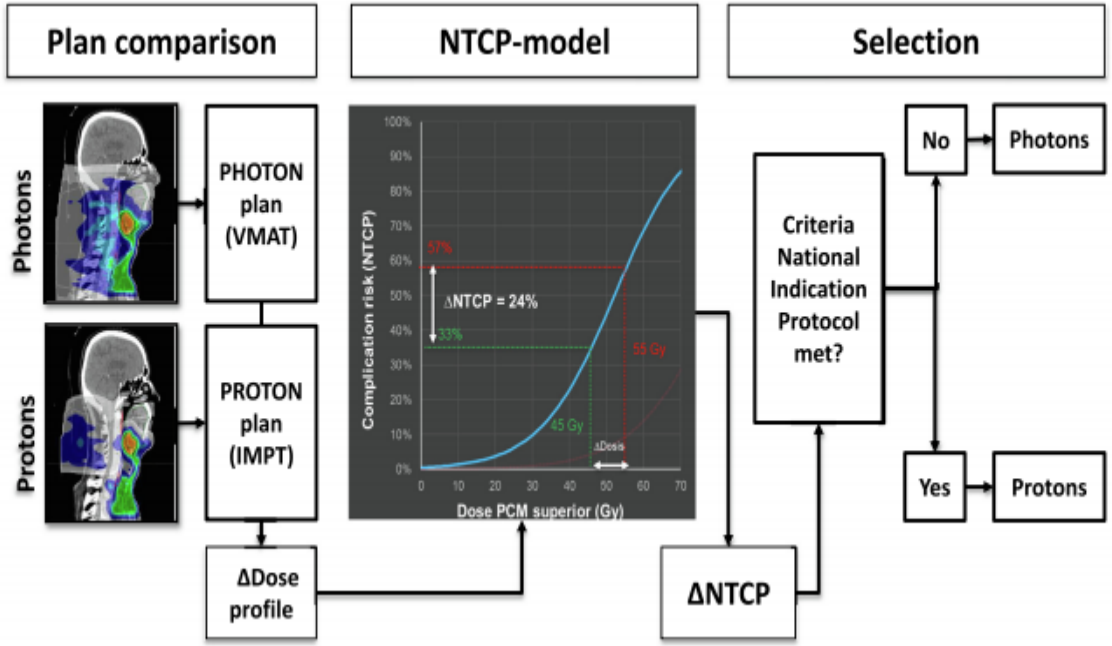
journal homepage: www.thegreenjournal.com

Original Article

2020

First experience with model-based selection of head and neck cancer patients for proton therapy

Makbule Tambas [a,*], Roel J.H.M. Steenbakkers [a], Hans P. van der Laan [a], Atje M. Wolters [a],



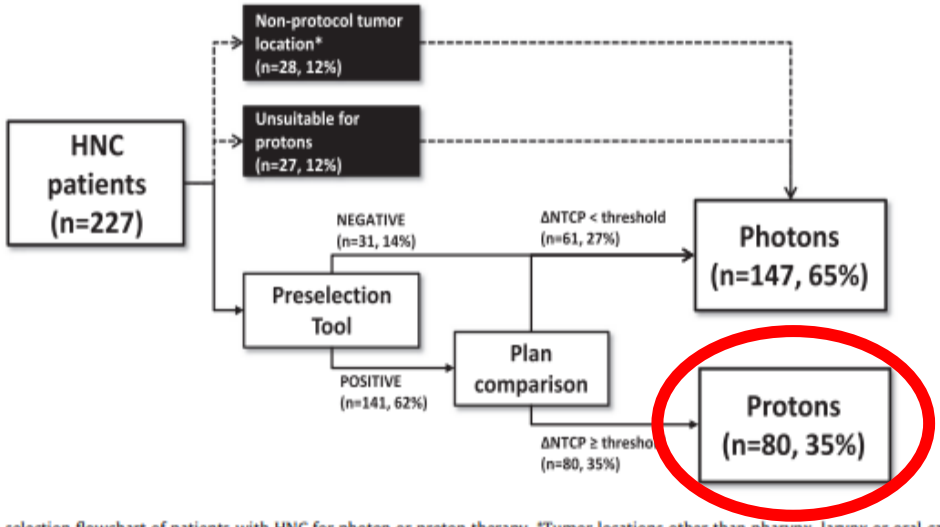


Fig. 2. A selection flowchart of patients with HNC for photon or proton therapy. *Tumor locations other than pharynx, larynx or oral cavity.

Original Article

Identification of patient benefit from proton beam therapy in brain tumour patients based on dosimetric and NTCP analyses

NTCP differences (ΔNTCP) were calculated for 11 models predicting: brain necrosis, delayed recall, temporal lobe injury, hearing loss, tinnitus, blindness, ocular toxicity, cataract, endocrine dysfunction, alopecia, and erythema.

Results:

PBT substantially reduced the dose in almost all investigated OARs, especially in the low and intermediate dose ranges and for contralateral organs.

Considering ΔNTCP of all models, 80 patients (87.0%) would have been selected for PBT in this in-silico study, mainly due to predictions of a model on delayed recall (51 patients).

Dutz et al, Radiotherapy and Oncology , 2021

Advanced Drug Delivery Reviews 109 (2017) 26–44

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Proton therapy – Present and future☆

Radhe Mohan [a,*], David Grosshans [b]

[a] Department of Radiation Physics, MD Anderson Cancer Center, Houston, TX 77030, United States
[b] Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX 77030, United States

- **Lung cancer challenging disease sites**. Conflicting results A multi-institutional randomized phase III study "Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer" (NCT01993810) is underway through NRG and is nearing completion. Another phase II randomized trial "Image-Guided, Intensity-Modulated Photon or Proton Beam Radiation Therapy in Treating Patients with Stage II-IIIB Non-small Cell Lung Cancer" (NCT01629498) is also being conducted.

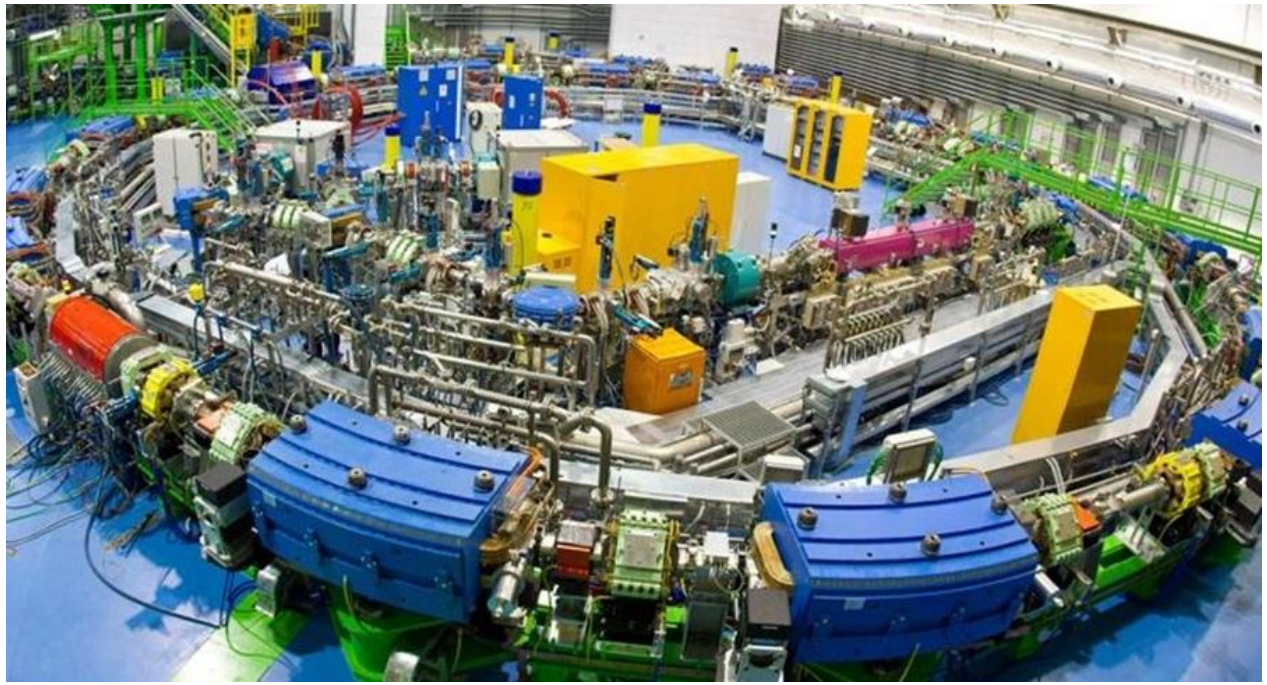
- **Breast**….. For breast cancer, one of the malignancies most commonly treated with radiation therapy, there are relatively few reports involving proton therapy. However, increasingly there is interest in utilizing proton therapy both for patients having undergone lumpectomy as well as those requiring adjuvant radiation following mastectomy

Lymphoma	Supradiaphragmatic localisation (mediastinal, HNC, axillary, precardiac)
	Gender (female)
	Cardiovascular risk factors
Lung cancer	Non-small cell lung cancer
	Maximal tumour motion <2 cm
Breast cancer	Cardiovascular risk factors
	Left-sided tumours
	Internal mammary chain RT
	Accelerated partial breast RT
Prostate cancer	Difficult anatomic situations (such as bowel loops)
	Comorbidities (such as colitis ulcerosa)
	Patient preference

- Prostate..
- Lymphoma….
- Re-irradiation…

CONCLUSIONS

- Despite the high potential of proton therapy, the clinical evidence supporting the broad use of protons is mixed.
- It is generally acknowledged that proton therapy is safe, effective and recommended for many types of cancers (pediatric, ocular melanomas, chordomas and chondrosarcomas).
- Although promising results have been and continue to be reported for many other types of cancers, they are based on small studies.
- General consensus is that there is a need to conduct randomized trials and/or collect outcomes data in multi-institutional registries to unequivocally demonstrate the advantage of protons.



THANKS FOR YOUR ATTENTION