Proton Beam Therapy in Pediatric Malignancies

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PROTONS

Positively charged within the atomic nucleus (nucleon)

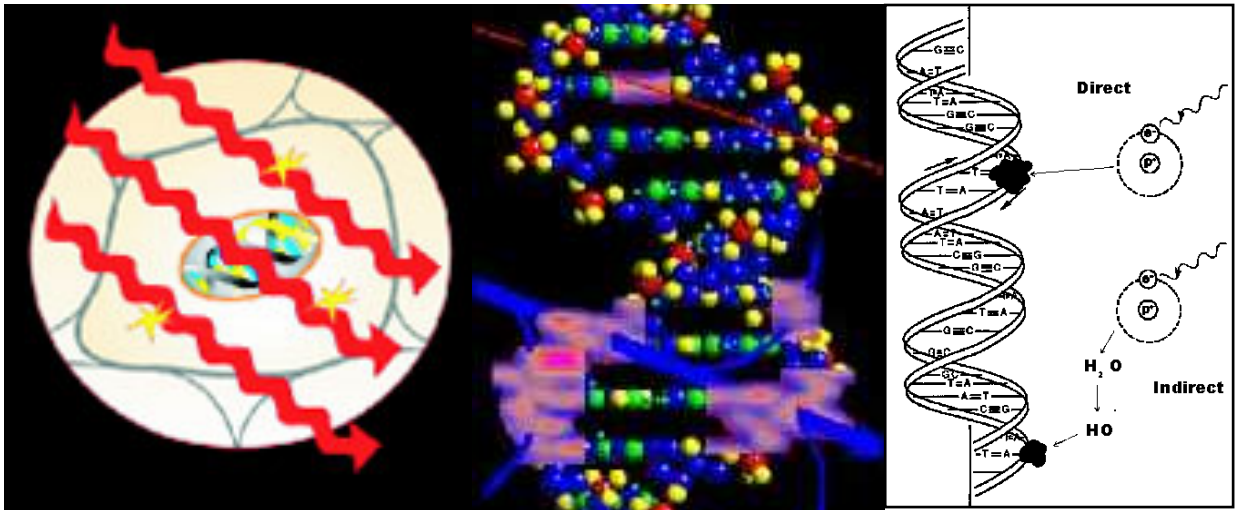
Proton charge +1 (1.602×10^{-19} Coulombs)

Mass approximately 1,836 times of e-

Diameter: 1.65×10^{-15} m

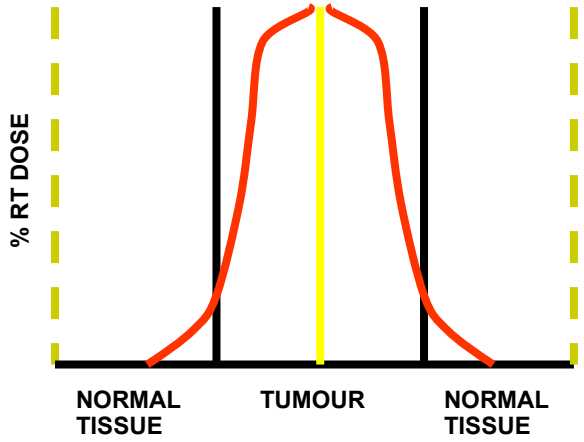
Proton is comprised of Quarks held together by Gluons

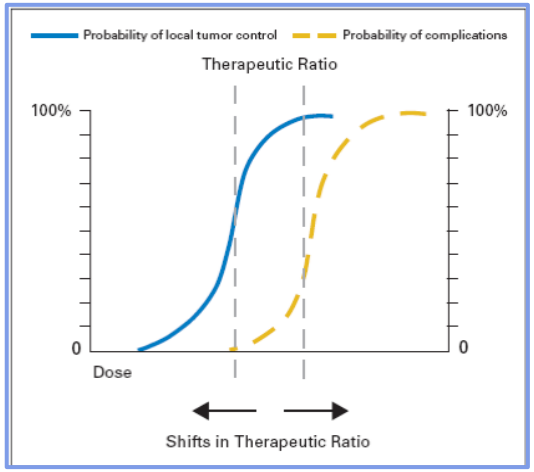
GOAL OF RADIATION THERAPY



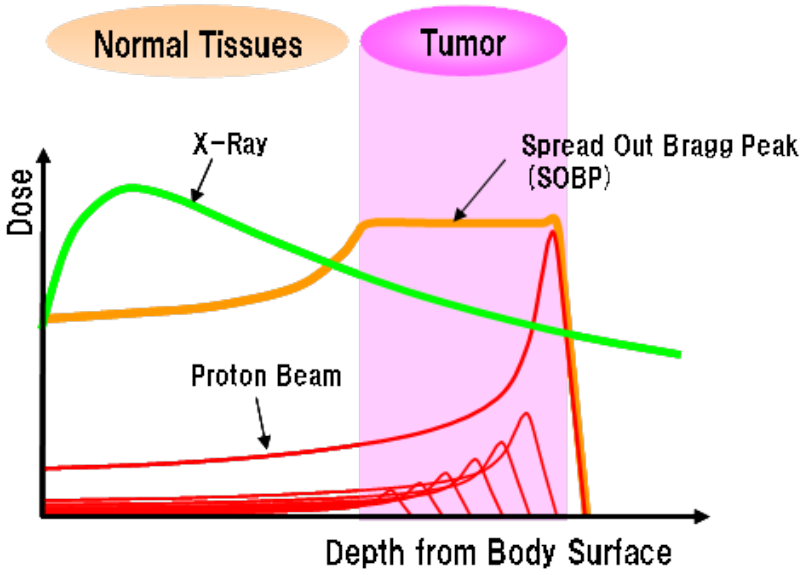
← Heavy Ions

← X Rays/ Protons

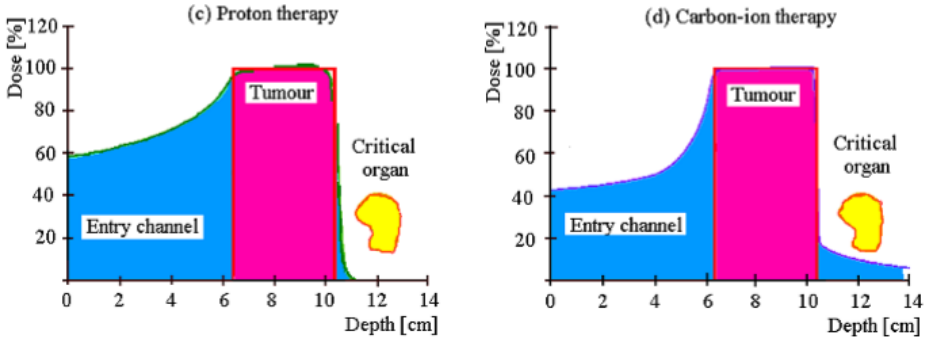




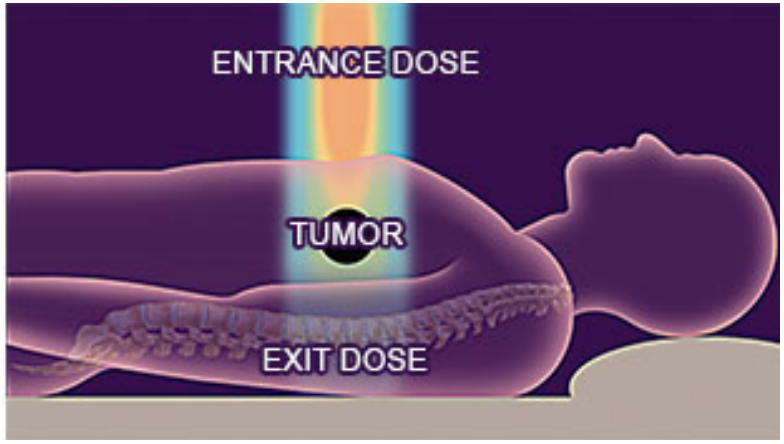
PHYSICAL & BIOLOGICAL ADVANTAGES OF PROTONS/ HEAVY IONS



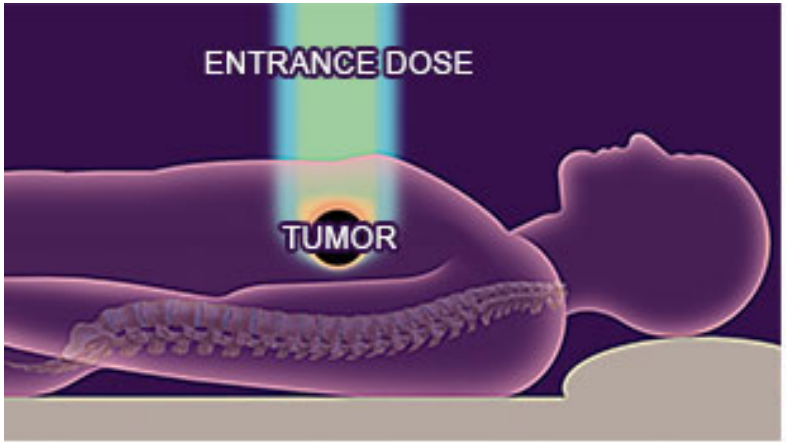
- Relatively Low Entrance Dose (Plateau)
- Maximum Dose at Depth (Bragg peak)
- Rapid Distal Dose Fall-off (No Exit Dose)
- Energy Modulation (Spread-out Bragg Peak)
- Relative Biological Effectiveness (Higher)



X RAYS

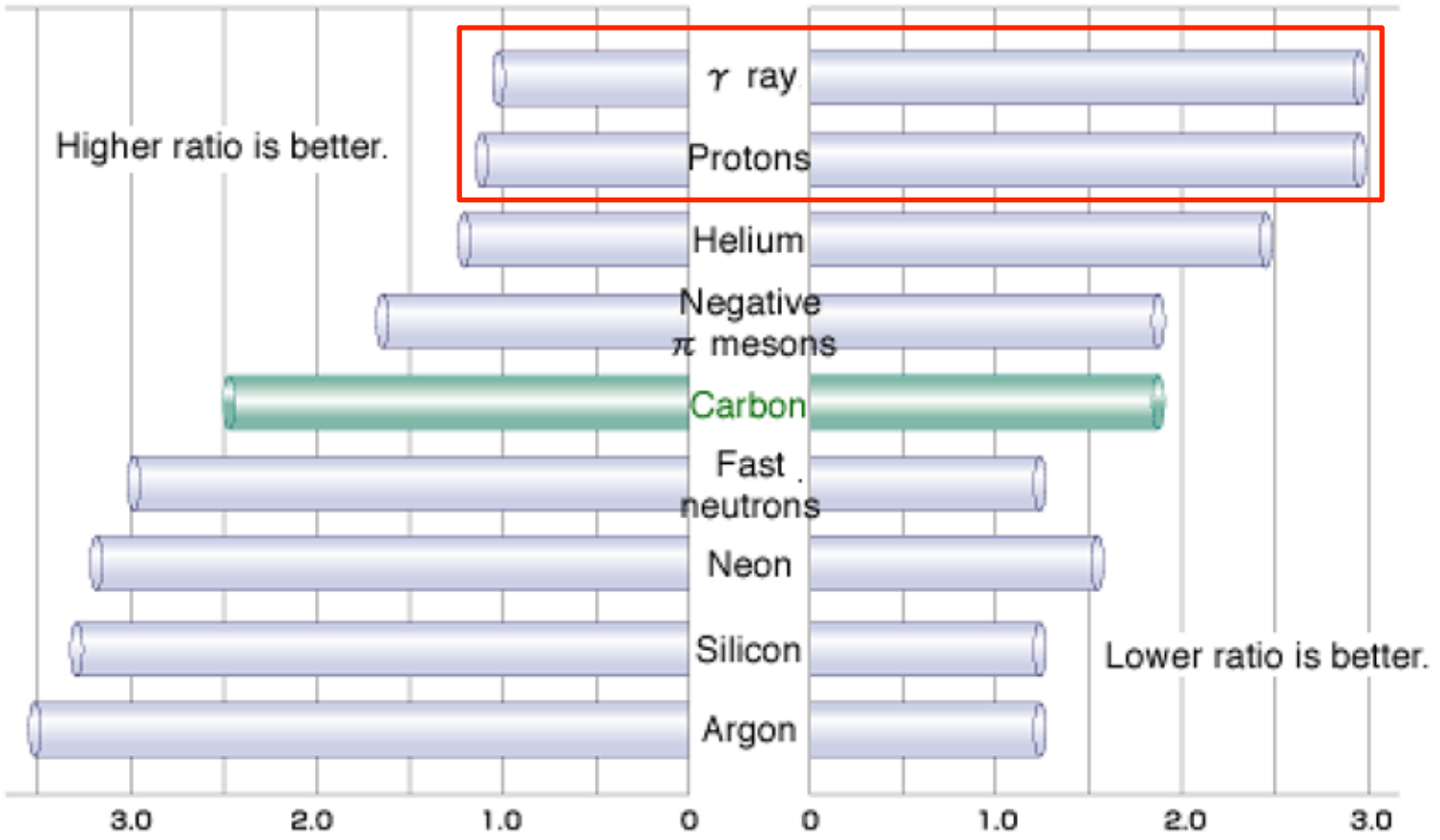


HEAVY IONS



RADIOBIOLOGICAL ASPECTS

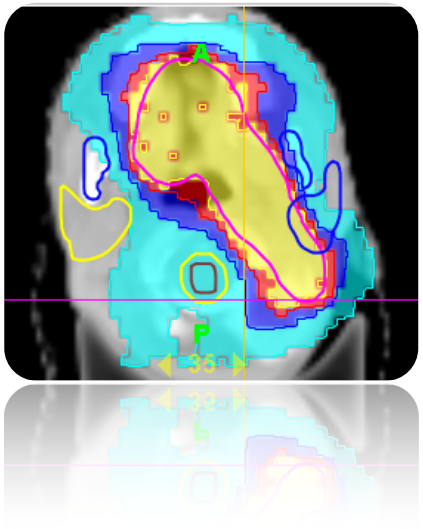
Relative biological effectiveness (RBE) and
oxygen enhancement ratio (OER) of various radiation types



RBE represents the biological effectiveness of radiation in the living body.
The larger the RBE, the greater the therapeutic effect on the cancer lesion.

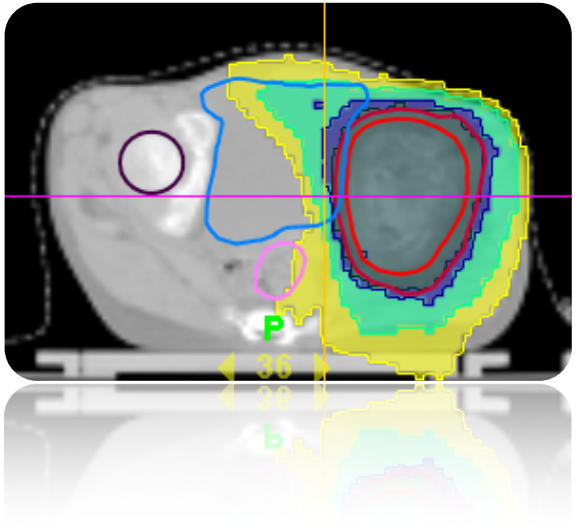
OER represents the degree of sensitivity of hypoxic cancer cells to radiation.
The smaller the OER, the more effective the therapy for intractablecancer cells with low oxygen concentration.

CLINICAL IMPLICATIONS



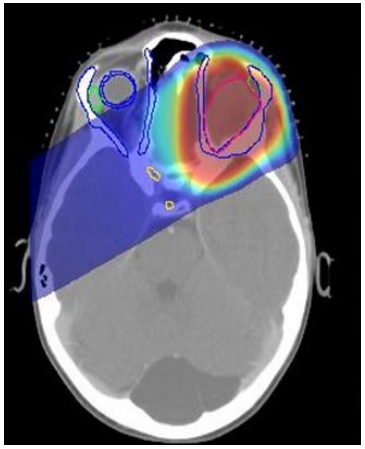
IMPROVED CONFORMITY

Reduced Non Target Dose
Reduced Acute/ Late Toxicity
RT Dose Escalation
Conc use with CTh/ Surg
Hypofractionation
Re-Irradiation
Better Disease Control
Improved Therapeutic Ratio



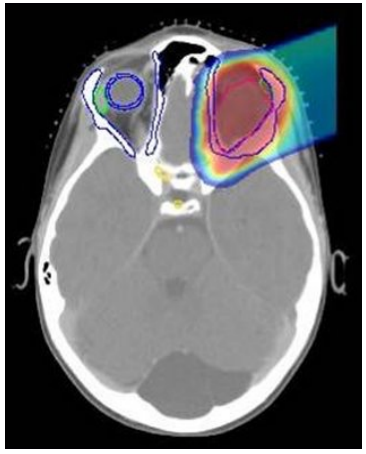
REDUCED NON TARGET LOW DOSE VOLUME

Acute/ Late Toxicity
Integral Dose
2nd Cancer Risk

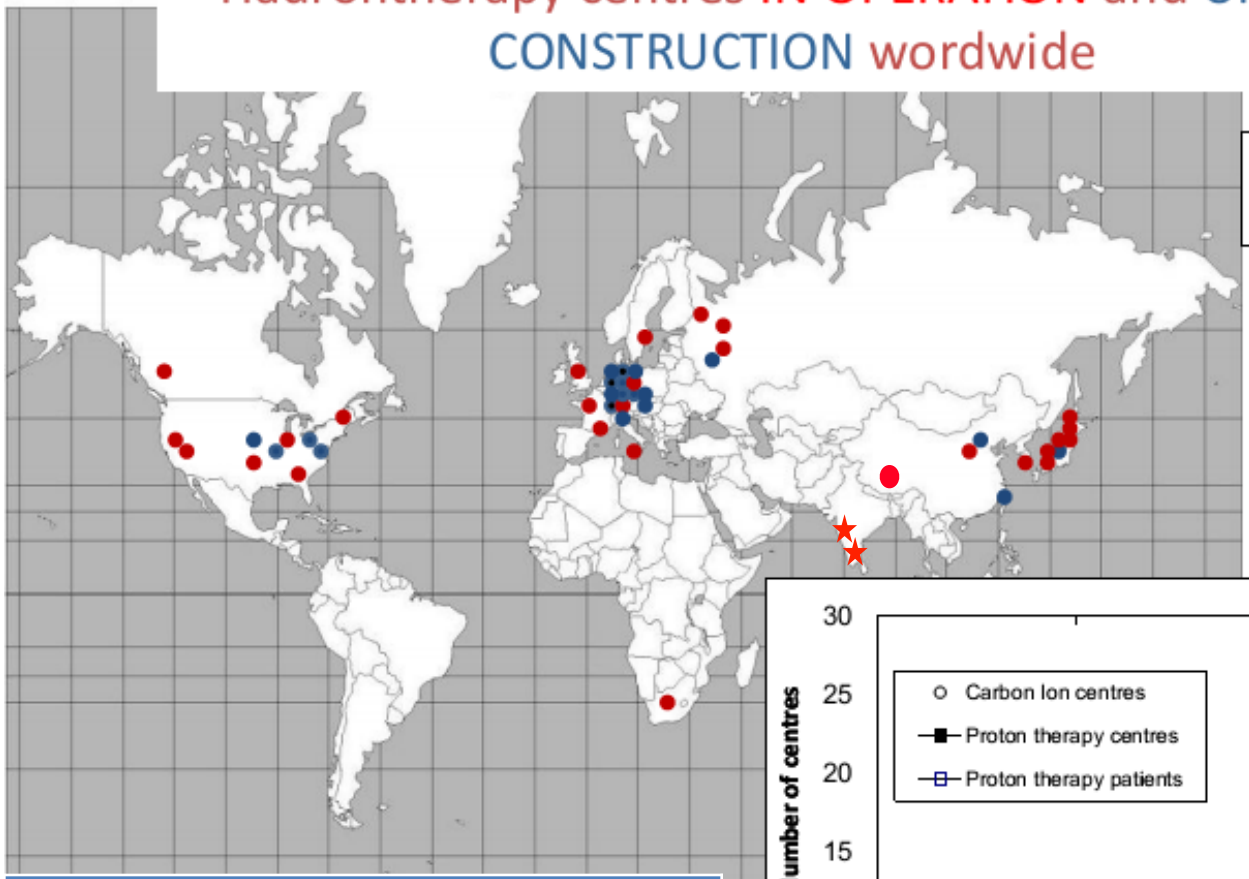


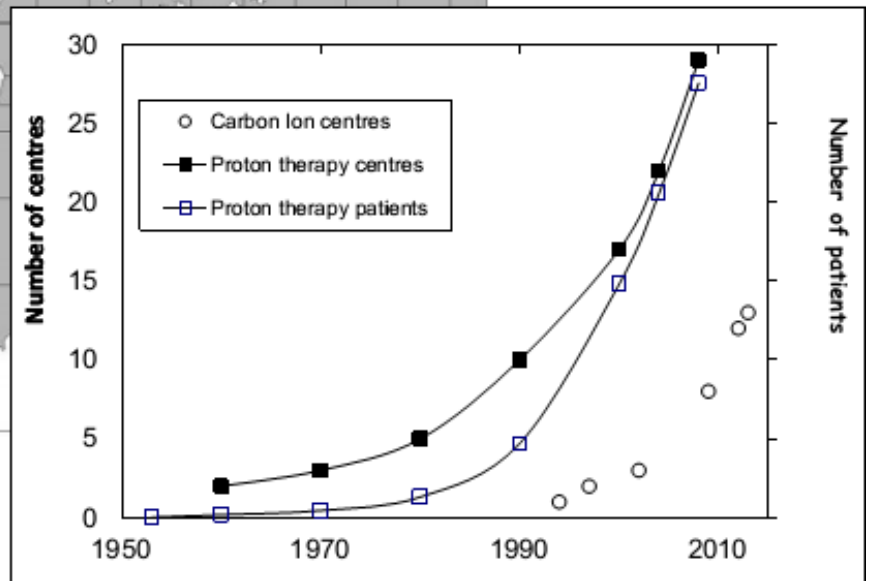
HIGHER BIOLOGICAL EFFICACY

Cell Kill
Immune Modulation



Hadrontherapy centres IN OPERATION and UNDER CONSTRUCTION wordwide





PTCOG Database Updated Jan 2019		
	Proton	Carbon
Functional	77	12
Under Construction	44	5
Under Planning	19	1
Pts Treated Till Date	1,18,195	15,736

Functional Facilities:

Proton: 77 (Japan – 8, China – 1, S Korea – 1, India - 1)

Carbon: 12 (Japan – 4, China – 1)

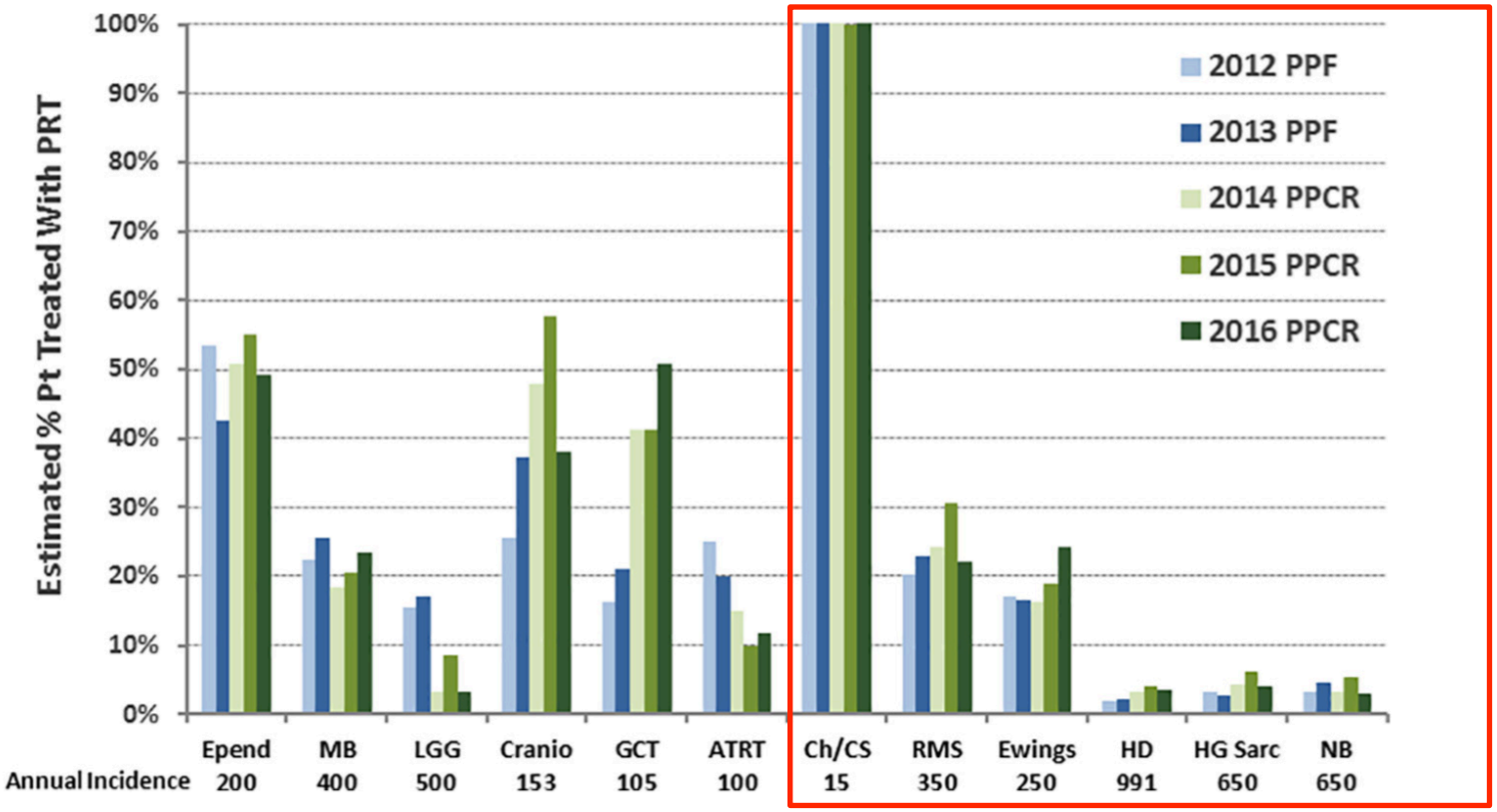
Facilities Under Construction:

Proton: 44 (Japan – 4, China – 1, S Arabia – 1, S Korea – 1, Taiwan – 1, **India - 1**)

Carbon: 5 (Japan – 1, China – 2)

Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN

Damien C. Weber [a,*], Jean Louis Habrand [b], Bradford S. Hoppe [c], Christine Hill Kayser [d], Nadia N. Laack [e], Johanes A. Langendijk [f], Shannon M. MacDonald [g], Susan L. McGovern [h], Luke Pater [i], John P. Perentesis [j], Juliette Thariat [b], Beate Timmerman [k], Torunn I. Yock [g], Anita Mahajan [e]



Pediatric Proton Foundation (PPF): 2012 - 2013
Pediatric Proton Consortium Registry (PPCR): 2014 - 2016

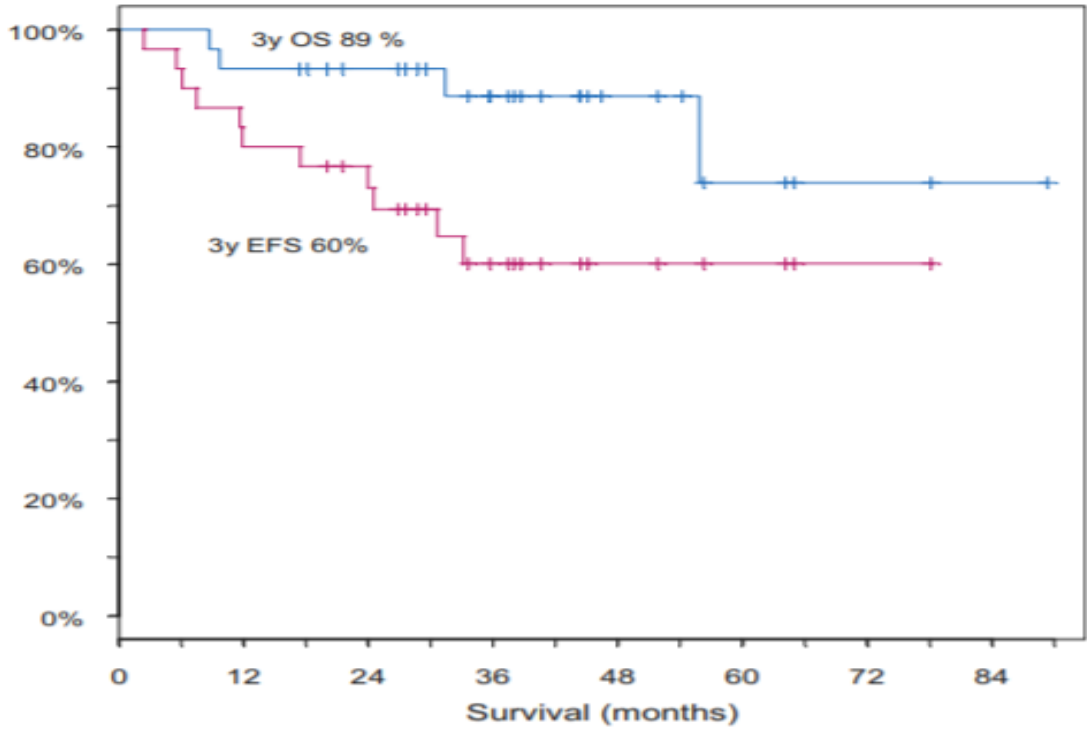
Radiother & Oncol 2018

PROTON RADIOTHERAPY FOR PEDIATRIC EWING'S SARCOMA: INITIAL CLINICAL OUTCOMES

BARBARA ROMBI, M.D.,* THOMAS F. DELANEY, M.D.,† SHANNON M. MACDONALD, M.D.,† MARY S. HUANG, M.D.,‡ DAVID H. EBB, M.D.,‡ NORBERT J. LIEBSCH, M.D., PH.D.,† KEVIN A. RASKIN, M.D.,§ BEOW Y. YEAP, M.D.,‖ KAREN J. MARCUS, M.D.,¶ NANCY J. TARBELL, M.D.,† AND TORUNN I. YOCK, M.D., M.C.H.†

*ATreP (Provincial Agency for Proton Therapy), Trento, Italy; Departments of †Radiation Oncology, ‡Pediatric Hematology and Oncology, §Orthopaedic Surgery, and ‖Medicine, Massachusetts General Hospital–Harvard Medical School, Boston, MA; and ¶Division of Radiation Oncology, Children's Hospital Boston, MA

April 2003 to April 2009
n=30
Unresectable Ewings Sarcoma
Radical Proton Beam Radiation Therapy
Median dose: 54 Gy (RBE)
Median age: 10 years
Median FU: 38.5 months



3 year local control :88%
Secondary malignancies: 3 AML, 1 MDS
No severe late toxicity

IJROBP 2013

Pencil beam scanned protons for the treatment of patients with Ewing sarcoma

Damien C. Weber[1,2,3] | Fritz R. Murray[1] | Dora Correia[1,2] | Alessandra Bolsi[1] | Martina Frei-Welte[4] | Alessia Pica[1] | Antony J. Lomax[1,5] | Ralf Schneider[1] | Barbara Bachtiary[1]

Data from PSI Switzerland

2005 to 2016, n=38
Sites: Axial Skeleton/ Pelvis - 71%
Median Age: 11.3 Yrs
Tumor Size: 1.7 - 24cm
CTh + Radical Proton Beam Radiation Therapy
Dose: 54.9Gy RBE
Median FU: 49.6 months
5 Yr LC: 81.5%
5 Yr EFS: 76.4%
5 Yr OS: 83%

Poor Prognostic Factors

Age > 10 Yrs
Tumor Volume: > 200cc
Metastatic Disease at Presentation

Toxicities

Late Grade III: 03/38 (7.8%)

COMPARATIVE DATA: PROTON VS. IMRT (EWINGS SARCOMA)

Study/ Year	Type of RT	Number of patients	Local control at years	Remarks/ Toxicity
Weber (Def+ Post Op)	Proton Dose: (45-60 cGyE)	38 Median Fu: 49 months	5y LC: 82% 3y OS: 83%	The 5y toxicity-free survival was 90.9%, only 2 grade 3 toxicities were observed in this series
Rombi (Def+ Post Op)	Proton Dose: 43-59 cGyE)	30 Median Fu:39 months	3y LC: 86% 3y OS: 89%	8 % of these patients presented grade 3 toxicities
EICESS 92	Photons	347 Median Fu:8.5 Years	3-year EFS rates were 73% and 74% in the SR-VACA and SR-VAIA arms, respectively 3 Year OS:88%	Severe Haematological Toxicity:70% Severe Non Haematological toxicity: 15%

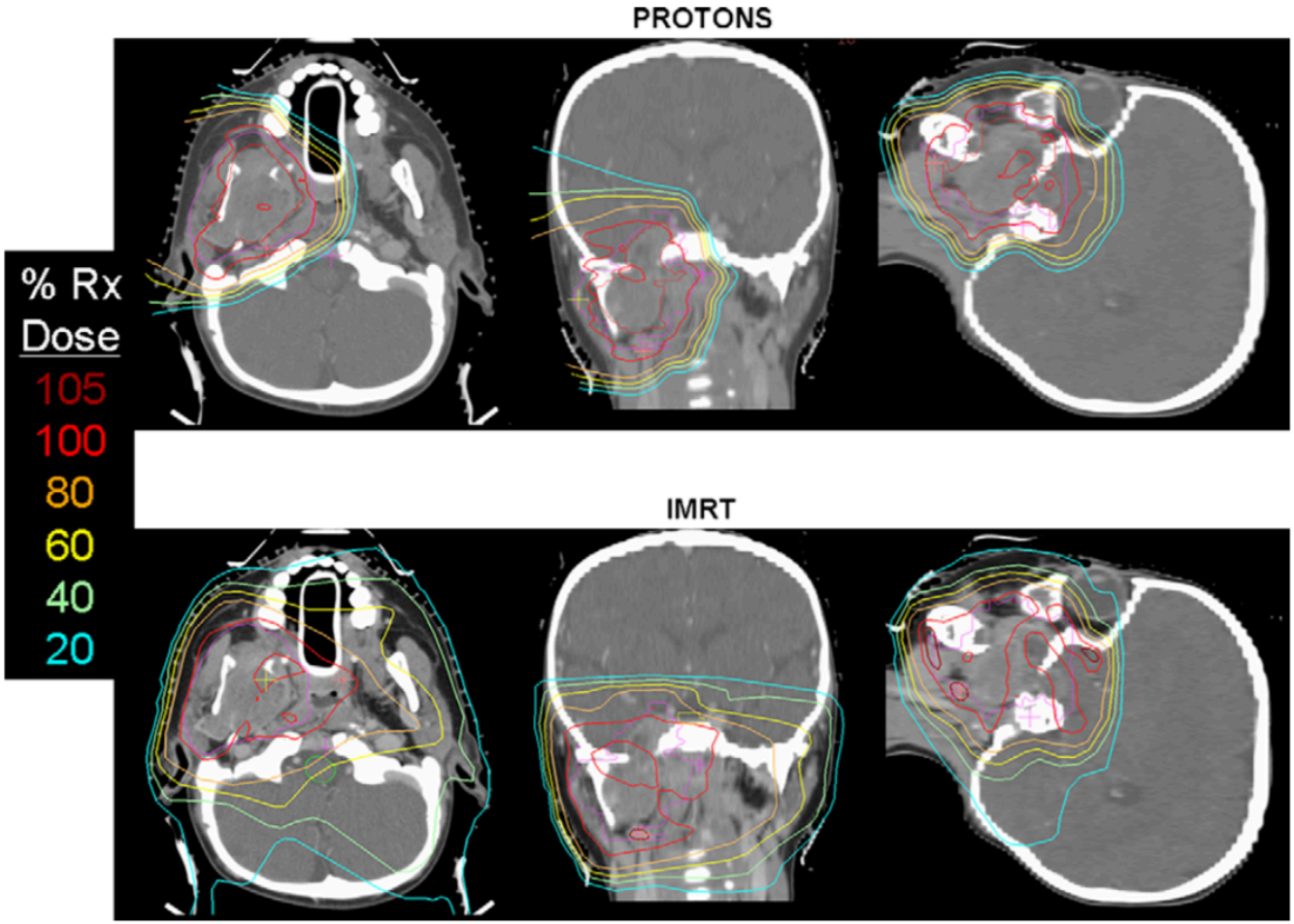
Disease control: Marginally superior with Protons

Toxicity: Lesser with Proton (Marrow Sparing)

A DOSIMETRIC COMPARISON OF PROTON AND INTENSITY-MODULATED PHOTON RADIOTHERAPY FOR PEDIATRIC PARAMENINGEAL RHABDOMYOSARCOMAS

KEVIN R. KOZAK, M.D., PH.D., JUDITH ADAMS, C.M.D., STEPHANIE J. KREJCAREK, M.D., NANCY J. TARBELL, M.D., AND TORUNN I. YOCK, M.D.

Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA



COMPARATIVE OAR DOSE: PROTON VS. IMRT (Dose: 50.4Gy/ 28#)

	Proton beam therapy		IMRT		
Anatomic site	Mean ± SE	Median (range)	Mean ± SE	Median (range)	*p*
Contralateral globe	310 ± 130	30 (0–1100)	1330 ± 190	1190 (630–2540)	<0.01
Ipsilateral globe	850 ± 230	730 (0–2690)	1640 ± 230	1570 (540–2860)	<0.01
Contralateral lens	90 ± 80	0 (0–810)	580 ± 70	610 (240–950)	<0.01
Ipsilateral lens	170 ± 100	50 (0–1000)	680 ± 80	730 (240–1000)	<0.01
Contralateral retina	460 ± 190	80 (0–1470)	1800 ± 280	1400 (800–3320)	<0.01
Ipsilateral retina	1360 ± 300	1360 (0–3560)	2080 ± 300	1850 (720–3930)	<0.01
Contralateral optic nerve	1390 ± 460	1120 (0–4200)	3060 ± 330	2960 (1750–4740)	<0.01
Ipsilateral optic nerve	3020 ± 450	3070 (0–5110)	3730 ± 320	3990 (1990–5060)	0.01
Optic chiasm	1770 ± 470	1230 (0–4570)	3330 ± 380	3690 (1130–4990)	<0.01
Whole brain	330 ± 60	270 (110–720)	810 ± 130	740 (310–1610)	<0.01
Brainstem	690 ± 150	810 (0–1170)	2640 ± 280	2990 (1050–3730)	<0.01
Contralateral temporal lobe	200 ± 90	30 (0–740)	1560 ± 150	1400 (1000–2280)	<0.01
Ipsilateral temporal lobe	1320 ± 250	1400 (30–2700)	2250 ± 260	2260 (1230–3800)	0.01
Pituitary	2890 ± 580	3270 (10–5350)	4340 ± 240	4320 (3020–5360)	<0.01
Hypothalamus	1200 ± 450	380 (0–3720)	2240 ± 470	2480 (170–4170)	0.01
Contralateral parotid	230 ± 130	80 (0–1310)	2430 ± 320	2790 (30–3300)	<0.01
Ipsilateral parotid	3090 ± 740	4390 (0–5460)	3750 ± 600	4780 (30–5440)	0.05
Contralateral lacrimal	130 ± 80	0 (0–820)	1250 ± 260	1000 (450–2690)	<0.01
Ipsilateral lacrimal	630 ± 210	380 (0–1690)	1650 ± 310	1570 (580–3320)	0.01
Contralateral cochlea	430 ± 270	20 (0–2630)	2920 ± 340	3160 (190–3860)	<0.01
Ipsilateral cochlea	3680 ± 620	4990 (0–5200)	4060 ± 520	4710 (210–5710)	NS
Contralateral mastoid	110 ± 100	0 (0–1000)	1930 ± 240	2120 (20–2670)	<0.01
Ipsilateral mastoid	2920 ± 710	4210 (0–5170)	3460 ± 550	4450 (20–5100)	NS

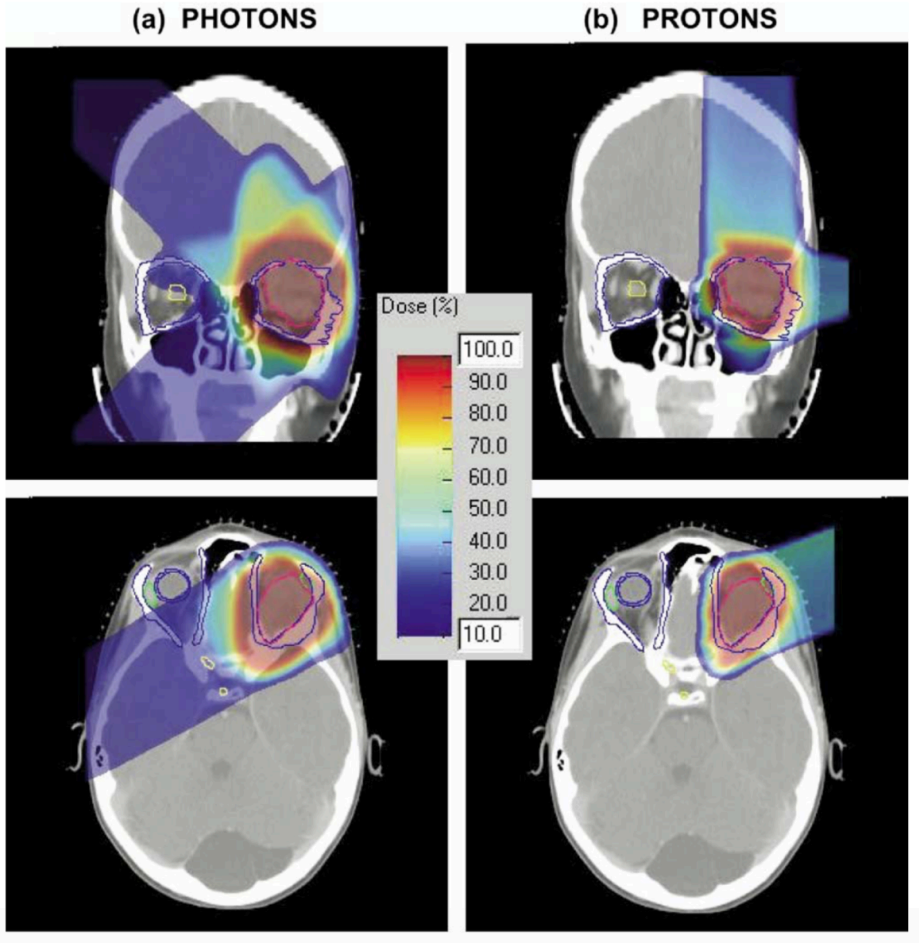
CONCLUSION: Proton beam therapy for PRMS reduces radiation doses to several critical structures. Based on historical dose–response relationships, proton beam therapy may reduce the risk of cataracts, hearing loss, neurocognitive decline, xerostomia/ poor dentition, growth delay, and endocrinopathies compared with IMRT. However, proton use may increase the risk of late facial asymmetry.

IJROBP 2009

PROTON RADIOTHERAPY FOR ORBITAL RHABDOMYOSARCOMA: CLINICAL OUTCOME AND A DOSIMETRIC COMPARISON WITH PHOTONS

TORUNN YOCK, M.D., M.C.H., ROBERT SCHNEIDER, C.M.D., ALISON FRIEDMANN, M.D., JUDITH ADAMS, C.M.D., BARBARA FULLERTON, PH.D., AND NANCY TARBELL, M.D.

Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA



COMPARATIVE OAR DOSE & CLINICAL OUTCOME

Ipsilateral orbital structures	X-ray dose average (%)*	Proton dose average (%)*	Difference (%)	Percent savings†
Retina	73.8	53.4	20.4	27.6
Optic nerve	86.1	62.9	23.1	26.9
Orbital bone	83.0	53.9	29.1	35.0
Lens	61.5	21.4	40.1	65.1
Lacrimal gland	94.3	69.8	24.5	26.0

ID	Gender	Date treated	Dose (CGE)	Age (yrs)	Histology	Tumor volume (cc)	Follow-up time (yrs)	Disease status and eye function	Pituitary function
1	F	6/13/2001	46.6	8.3	Embryonal	12.6	3.5	NED, 20/20 OD, 20/25 OS, 3 mm-enophthalmos OS, no cataract, normal fundus	Normal
2	M	1/17/1996	55.0	8.4	RMS (NOS)	1.2	6.4	NED, Moderate bony hypoplasia of R orbit, vision intact OU, no cataract	Normal
3	M	7/9/1997	40.0	6.6	Embryonal	6.4	7.0	NED, Vision is excellent, no abnormalities except mild enophthalmous (2 mm), no cataract	Normal
4	F	1/1/1995	50.0	7.6	Embryonal	2.4	9.7	NED, Vision excellent, enophthalmous, no cataract	Normal
5	M	5/13/1998	46.8	4.1	Alveolar	8.7	6.3	NED, 20/20 OU vision, no cataracts, lacrimal gland surgically removed at diagnosis, mild orbital hypoplasia, requires occasional eye lubrication	Normal
6	M	12/21/1999	45.0	0.46	Embryonal	7.1	4.7	LF, s/p enucleation and SRS salvage, currently NED	Normal
7	M	6/28/2000	41.4	8.1	Embryonal	11	4.3	NED, mild enophthalmous, mild ptosis, lubricant required at night (occasional use during the day), two surgeries required to correct double vision present before RT, vision otherwise intact	Normal

Patterns of failure following proton beam therapy for head and neck rhabdomyosarcoma

Ethan B. Ludmir [a], David R. Grosshans [a], Mary Frances McAleer [a], Susan L. McGovern [a], Douglas J. Harrison [b], M. Fatih Okcu [c], Murali M. Chintagumpala [c], Anita Mahajan [d], Arnold C. Paulino [a,*]

[a] Division of Radiation Oncology; [b] Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston; [c] Department of Pediatrics, Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston; and [d] Department of Radiation Oncology, Mayo Clinic, Rochester, United States

2006 to 2015, n=46
Location: Parameningeal - 54%, I/C Extension - 24%
Primary Tumor > 5cm: 28%
Radical Proton Beam Radiation Therapy
Dose: 50.4Gy RBE
Median Cyclophosphamide Dose: 13.2g/m^2
Median FU: 3.9 Yrs
5 Yr LC: 84% (Compared to IMRT series- COG ARST0531 - JCO 2018 LF rate: 22.4%)
5 Yr PFS: 57%
5 Yr OS: 76%

Poor Prognostic Factors
Intracranial Extension (ICE)
Tumor Size > 5cm
Delay in RT > 4wks of CTh in Pts with ICE
Suggest RT Dose escalation to 59.4Gy - for tumors > 5cm (COG ARST1431)

Significant Observations
No Marginal Failures
Acute Grade III Toxicity: 9%
Late Grade III Non Cataract Toxicity: 11% (Compared to IMRT series - 47%, PBC 2016)

Radiother & Oncol 2019

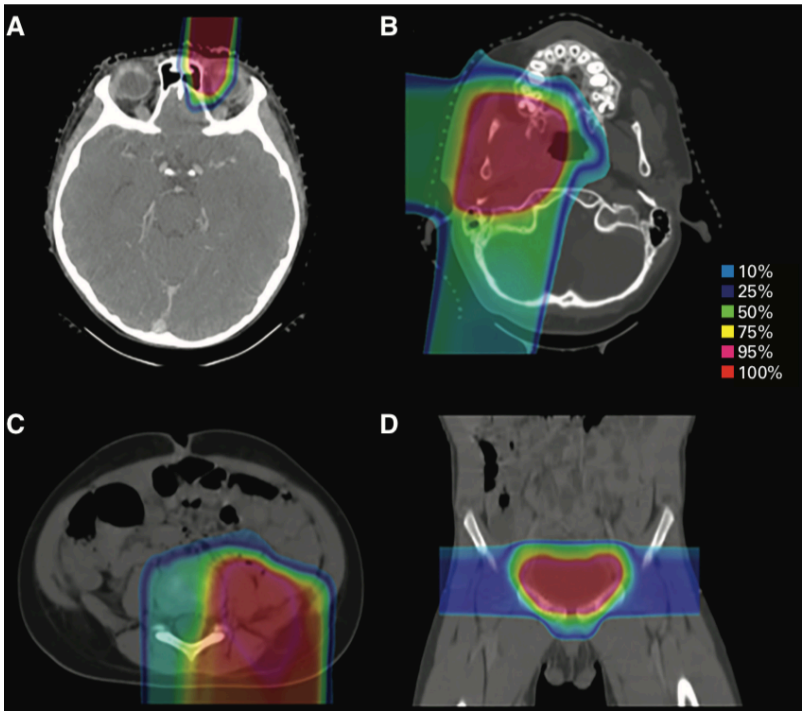
Preliminary Results of a Phase II Trial of Proton Radiotherapy for Pediatric Rhabdomyosarcoma

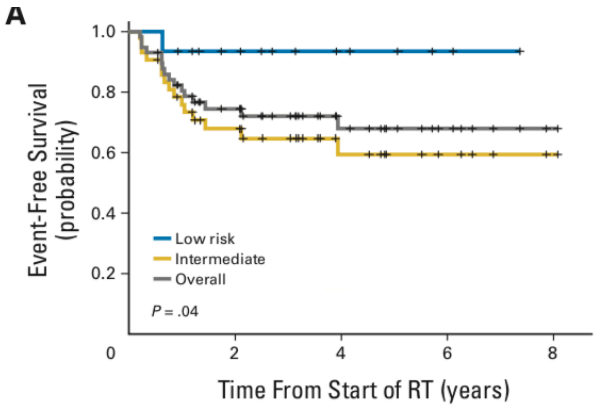
Matthew M. Ladra, Jackie D. Szymonifka, Anita Mahajan, Alison M. Friedmann, Beow Yong Yeap, Claire P. Goebel, Shannon M. MacDonald, David R. Grosshans, Carlos Rodriguez-Galindo, Karen J. Marcus, Nancy J. Tarbell, and Torunn I. Yock

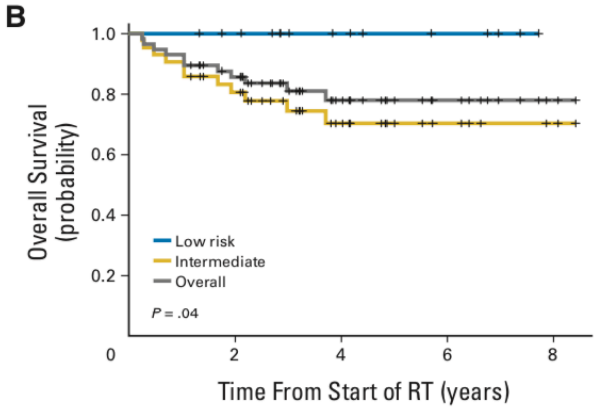
Combined COG & EPSSG Protocols
2005 to 2012, n=57
Sites: H&N, Thorax, Extremeties, Pelvis (All Sites)
Age: < 21 Yrs
Radical Proton Beam Radiation Therapy
Dose: 50.4Gy RBE
Median FU: 47 months
5 Yr LC: 69% (Low Risk - 93%, Int Risk - 77%)
5 Yr EFS: 78%
5 Yr OS: 81%

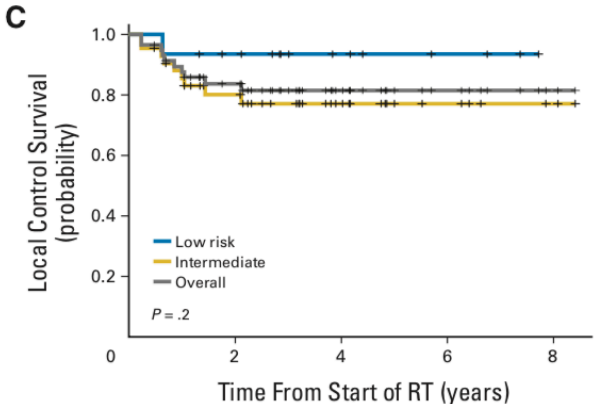
Toxicities
Acute Grade III: 13/57 (22.8%)
Late Grade III: 03/57 (5.2%)

JCO 2014


A
B
C
D
10%
25%
50%
75%
95%
100%


A
Event-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
Low risk
Intermediate
Overall
P = .04
Time From Start of RT (years)


B
Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
Low risk
Intermediate
Overall
P = .04
Time From Start of RT (years)


C
Local Control Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
Low risk
Intermediate
Overall
P = .2
Time From Start of RT (years)

COMPARATIVE DATA: PROTON VS. IMRT (RMS)

Study/ Year	Type of RT	Number of patients	Local control at years	Remarks/ Toxicity
Ladra, 2014 JCO	Proton, Definitive+ Post op RT (Median 50.4 cGYE) Median Fu:47 months	52	3y LC: 81% 5y LC: 81% 3y OS: 81% 5y OS: 78%	20 incidents of late grade 2 toxicity in 12 patients (28%).
Leiser (Radiotherapy and Oncology, 2016)	Proton Median Dose: 54 cGYE	83	5y LC: 78.5% 5y OS: 80.6%	14% Grade 3 toxicity Hameatological :80%
IRS IV, 2001 JCO	Photons (40- 50 Gy) Post Op RT for all Median FU: 5 years	883	Overall 3-year FFS and survival were 77% and 86%, respectively.	> 90% severe myelosuppression, 55% infection

Disease Control: Similar

Toxicity: Lesser with Proton (Marrow Sparing)

RADIOTHERAPY FOR LOCAL CONTROL OF OSTEOSARCOMA

THOMAS F. DELANEY, M.D.,* LILY PARK, B.A.,* SAVELI I. GOLDBERG, PH.D.,* EUGEN B. HUG, M.D.,† NORBERT J. LIEBSCH, M.D., PH.D.,* JOHN E. MUNZENRIDER, M.D.,* AND HERMAN D. SUIT, M.D., D.PHIL*

*Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA; †Department of Radiation Oncology, Dartmouth Hitchcock Medical Center, Lebanon, NH

Massachusetts General Hospital

1980 to 2002, n=41

Inoperable/ +ve Resection Margins

Gross Total Resection: 65.8%, Subtotal Resection: 21.9%, Biopsy: 12.2%

Median RT Dose: 66 Gy

Proton + XRT: 56% pts

Median FU: months

5 Yr LC: 68.3% Overall

GTR - 78.4% +/- 8.6%

STR - 77.8% +/- 13.9%

Biopsy - 40% +/- 21.9%

Grade III Late Toxicity: 24%

IJROBP 2005

COMPARATIVE DATA: PROTON VS. IMRT (OGS)

Study/ Year	Type of RT	Number of patients	Local control at years	Remarks/ Toxicity
Ciernik,Cancer 2011 (MGH)	Proton or mixed photon proton Dose: (68.4 cGyE)	55 Median Fu: 49 months Only unresectable or Partially resectable OGS	5y LC: 82% 3y LC: 72% 5 Year OS:67%	Grade 3 to 4 late toxicity was seen in 30.1 % of patients. One patient died from treatment-associated acute lymphocytic leukemia, and 1 from secondary carcinoma of the maxilla.
DeLaney, 2011, IJROBP	Photons Median Dose:66 Gy	41 Median Fu: 40 months Only unresectable or Partially resectable OGS	5 year LC: 68% 5 year OS:72%	Ten patients (24%) experienced significant late complications related to RT that required hospitalization or surgery

Disease control: Marginally superior with Protons

Toxicity: Lesser with Proton

Spot-Scanning Proton Radiation Therapy for Pediatric Chordoma and Chondrosarcoma: Clinical Outcome of 26 Patients Treated at Paul Scherrer Institute

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June 2000 to June 2010, n=26

Unresectable Chordoma (19), Chondrosarcoma (7)

Base Shull (17), Axial Skeleton (9)

Radical Proton Beam Radiation Therapy

Dose: Chordoma - 74 Gy RBE, Chondrosarcoma - 66 Gy RBE

Median age: 13.2 years

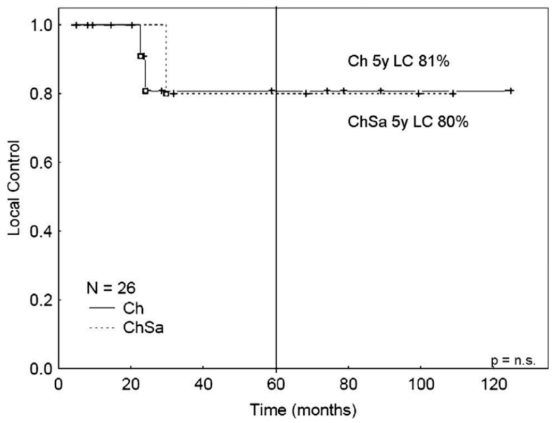
Median FU: 46 months

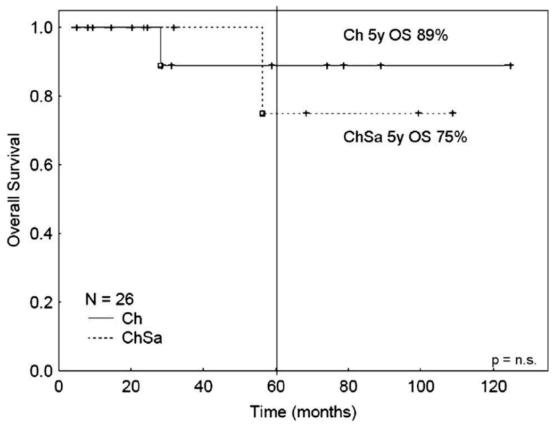
5 Yr LC: Chordoma - 81%, Chondrosarcoma - 80%

5 Yr OS: Chordoma - 89%, Chondrosarcoma - 75%

No Avute Grade III Toxicity

Late Grade II Toxicity: 19%, No Grade III





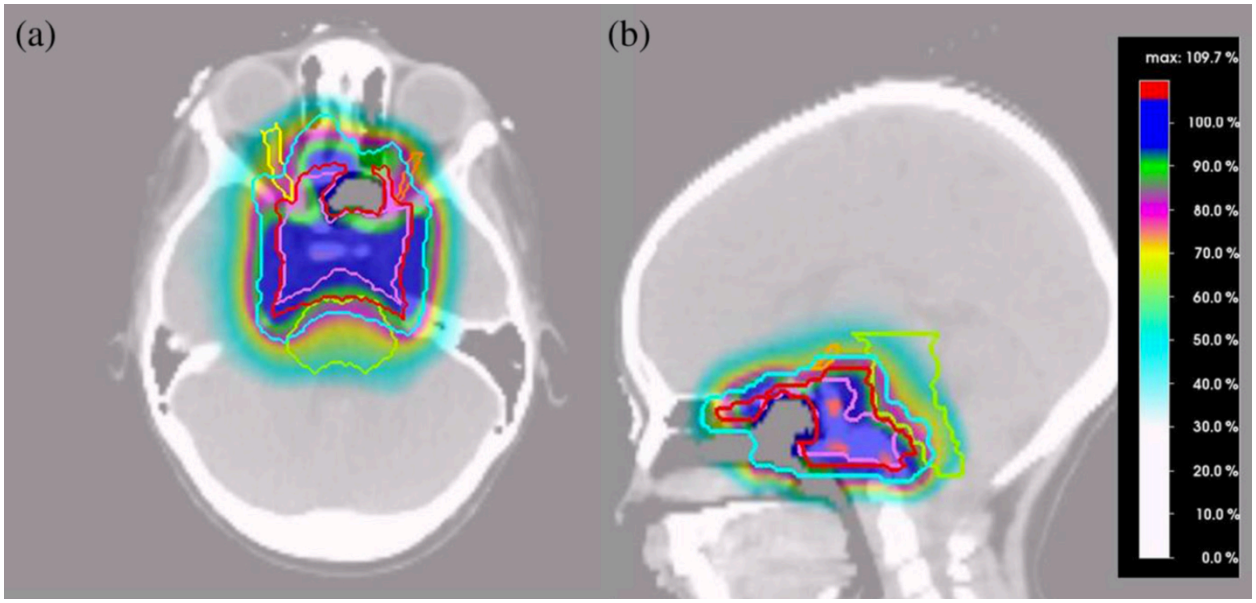


Table 3 Summary of studies using PT in pediatric chordomas and chondrosarcomas

Author	†	Tumor site (no. of patients)	Histology	RT type (no. of patients)	Dose in Gy (RBE)	% of 5-y LC	% of 5-y OS	Follow-up in mo (range)
MGH Benk [1995]	18	SB (15) C-spine (3)	All CH	P + Ph (18)	Median, 69.0	63%	68%*	Median, 72 (19-120)
LLUMC Hug [2002]	13	SB (13)	10 CH 3 CS	P (6) P + Ph (4) P + Ph (3)	Median, 73.7 Median, 70.0	60% (CH)† 100% (CS)†	60% (CH)‡ 100% (CS)	Mean, 37 (13-86)
PSI Rutz [2008]	10	SB (6) Axial Skeleton (4)	6 CH 4 CS	P	Median, 74.0 Median, 66.0	100% †	100% †	Median, 36 (8-77)
CPO Habrand [2008]	30	SB (16) C-spine (1) Both (13)	27 CH 3 CS	P + Ph (29) P (1)	Mean, 69.1 Mean, 65.3	77% (CH) 100% (CS)	81% (CH) 100% (CS)	Mean, 26.5 (5-102)
PSI Current Study	26	SB (17) Axial Skeleton (9)	19 CH 7 CS	P	Mean, 74.0 Mean, 66.0	81% (CH) 80% (CS)	89% (CH) 75% (CS)	Mean, 46 (5-126)

Proton Radiation Therapy for the Treatment of Retinoblastoma

Kent W. Mouw, MD, PhD,[*,†] Roshan V. Sethi, MD,[†] Beow Y. Yeap, ScD,[†] Shannon M. MacDonald, MD,[†] Yen-Lin E. Chen, MD,[†] Nancy J. Tarbell, MD,[†] Torunn I. Yock, MD, MCH,[†] John E. Munzenrider, MD,[†] Judith Adams, CMD,[†] Eric Grabowski, MD, ScD,[‡] Shizuo Mukai, MD,[§] and Helen A. Shih, MD[†]

**Harvard Radiation Oncology Program, Boston, Massachusetts; Departments of [†]Radiation Oncology and [‡]Pediatrics, Massachusetts General Hospital, Boston, Massachusetts; and [§]Retina Service, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts*

Massachusetts General Hospital

1986 to 2012, n=49

60 Eyes (49 pts)

Bilateral Retinoblastoma: 85%

Median RT Dose: 45 Gy RBE

Median FU: 8 Years

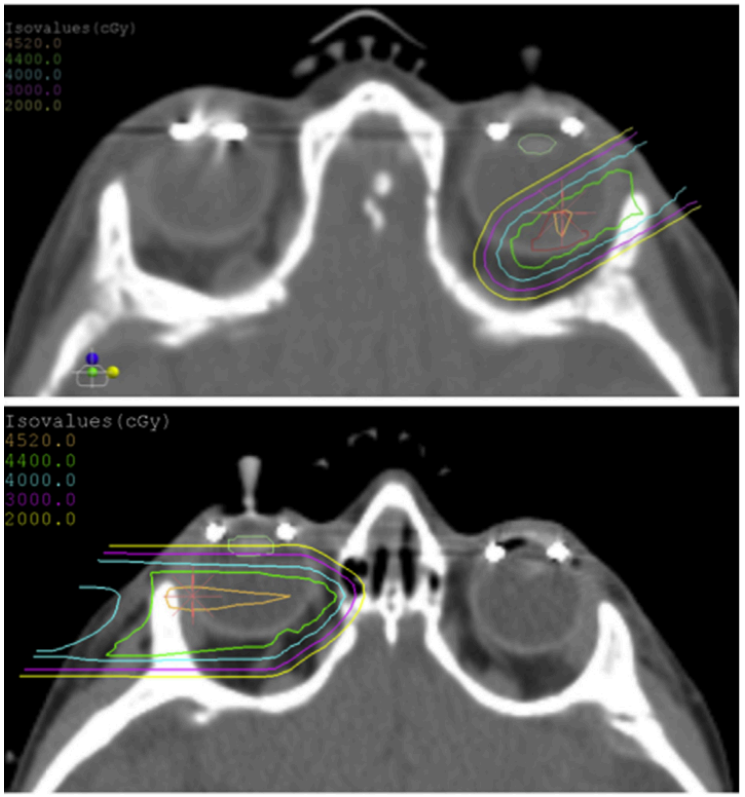
No death due to Retinoblastoma, No Mets

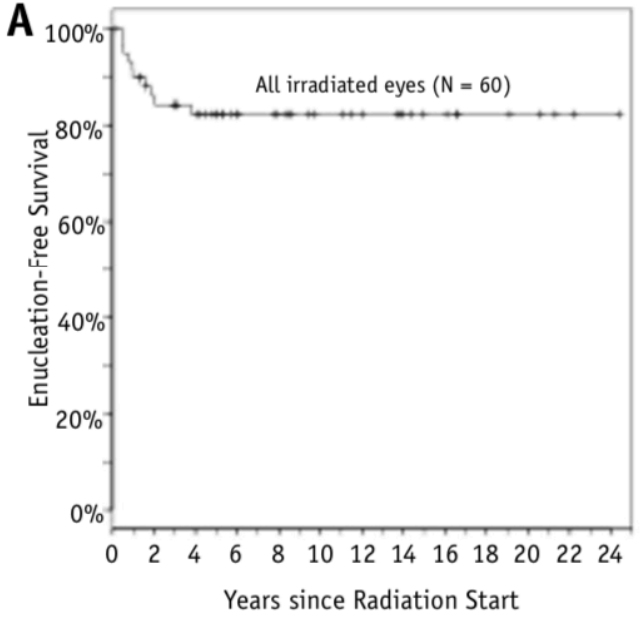
Data on Vision Status available: 30/49 (61%)

14/30 (47%): Vision 20/40 - Good Vision

07/30 (23%): Vision 20/40 - 20/600 - Moderate Vision

09/30 (30%): No Vision





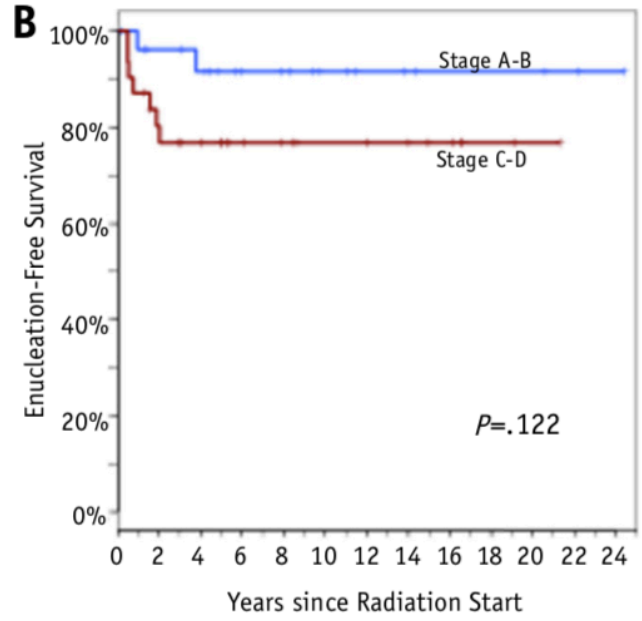


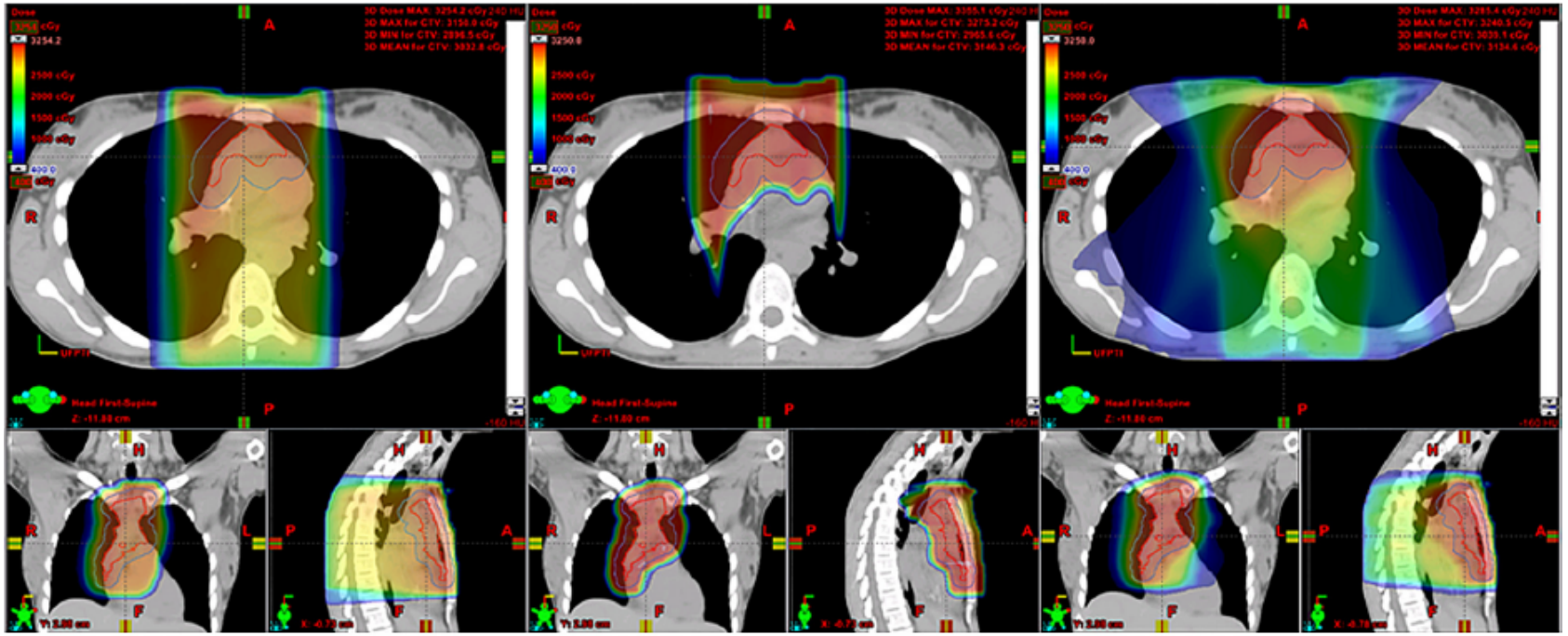
Table 2 Follow-up details

Median length of follow-up (range)	8 y (1-24 y)
Median age at last follow-up (range)	9 y (2-24 y)
No. of irradiated eyes enucleated	11/60 (18)
Stage A-B	3/11
Stage C-D	7/11
Stage unknown	1/11
Enucleation location	
Our institution	6 (55)
Outside institution	5 (45)
Median time between PRT and enucleation for all patients (range)	10 mo (5-44 mo)
Median time between PRT and enucleation at our institution	20 mo
Median time between PRT and enucleation at outside institution	7 mo
Indication for enucleation	
Progressive disease	8/11
Ocular complication(s)	2/11
Unknown	1/11
Nonenucleative ocular complication requiring procedure	
Cataracts	4
Radiation retinopathy	3
Glaucoma	1
Neovascularization/hemorrhage	1
Other	2
Multiple	1
No. of patients with metastatic disease	0
No. of patients with second malignancy	1
No. of patients with in-field second malignancy	0

COMPARATIVE DATA: PROTON VS. XRT (RETINOBLASTOMA)

Study/ Year	Type of RT	Number of patients	Local control at years	Remarks/ Toxicity
Mouw, IJROPBP, 2015	Proton Median Dose:44 Gy(RBE)	49 60 eyes Median Fu:9 years 85% had b/l disease	Post RT enucleation rate 18% (11 vs 23% for group A_B vs Advanced group) Enucleation mostly due to progression	14/30 eyes (47%) had 20/40 visual acuity or better, 7/30 (23%) had moderate visual acuity (20/40 - 20/600), and 9/30 (30%) had little or no useful vision (worse than 20/600). Twelve of 60 treated eyes (20%) experienced a post-PRT event requiring intervention, with cataracts the most common (4 eyes). No patients developed an in-field second malignancy Average Useful Vision:70%
Pradhan, IJROBP,1997	Photons Dose:45 Gy	120 192 Eyes	2 Year LC (Overall for all groups: 71%)	Useful vision: Stage 1 to 5: 7 of 7, 6 of 6, 4 of 8, 10 of 15, and 7 of 28 eyes Average Useful Vision:50%)

Involved-Node Proton Therapy in Combined Modality Therapy for Hodgkin Lymphoma: Results of a Phase 2 Study☆



Structure	3DCRT Mean	3DCRT ±SD	IMRT Mean	IMRT ±SD	PT Mean	PT ±SD
Integral dose (joules)	122.9	62.3	103.8	48.6	53.6	32.0
Heart (Gy)	16.5	7.6	12.3	6.2	8.9	5.1
Lung (Gy)	11.6	3.7	9.8	2.8	7.1	2.5
Breast (Gy)	6.3	3.5	6.0	3.4	4.3	3.0
Thyroid (Gy)	19.3	10.1	17.7	9.3	15.8	9.7
Esophagus (Gy)	20.3	4.8	16.4	3.9	13.4	5.6

Conclusions

INPT reduced the dose to the OARs and total-body dose compared with 3DCRT or IMRT. Clinical disease control outcomes 3 years after completing treatment are similar to those of 3DCRT to an involved field RT field. Proton therapy is an important new strategy for RT, offering patients seeking the most effective and safe treatment available for HL.

B Hoppe, IJROBP 2014

PROTONS FOR RETINOBLASTOMA / LYMPHOMA/ NEUROBLASTOMA: CLINICAL OUTCOME

Author [ref]	Method	Med FU (mo) [range]	N	Med Dose Gy(RBE) [range]	PS/PBS	Chemo Y/N	Outcome
Retinoblastoma							
Agarwal [102]	R	3	16	36 [36–45]	PS	Y	ENS: 63% No in-field SMN
Mouw [101]	R	8	60	44 [40–46.8]	PS	Y	ENS:80% No in-field SMN
Lymphoma							
Hoppe [107]	R	32	138 (mix)	21 ped 30.6 adult	PS/US	Y	3y PFS: 96% adults 3y PFS: 87% peds No G3 toxicity
Nanda [110]	R	24	59 (mix)	30.6 CGE	PS/US	Y	No G 2/3 pneumonitis
Wray [109]	R	36	22 (peds)	21 CGE	PS/US	Y	3 yr PFS: 86%; No G3 toxicity
Neuroblastoma							
Fuji [124]	R	NR	5	36 [21.6–41.4]	PS	Y	NR
Hattangadi [125]	R	38 [11–70]	9 [7–1 site, 2–2 sites]	22 [10.8–36]*	PS	Y	LC: 100% 5/9 NED 7/9 alive
Hill-Kayser [126]	P	16 [5–27]	13pt [8–1 site, 5 – ≥2 sites]	21.6 [21.6–36.0]	PS	Y	LC: 100% 11/13 alive
Oshiro [127]	R	21 [5–348]	14 [9–1 site, 5 – ≥2 sites]	30.6 [19.8–45.5]	PS	Y	LC:100% 8/14 alive

COMPARATIVE DATA: PROTON VS. IMRT (NEUROBLASTOMA)

Study/ Year	Type of RT	Number of patients	Local control at years	Remarks/ Toxicity
Hill-Kayser 2019, IJROBP High RIsk	Proton Median Dose:21.6cGyE	45 Median Fu: 49 months	5y LC: 97% 3y LC: 97% 5 Year OS:80% 3 year OS:88%	No patient has experienced World Health Organization grade 3 or 4 long-term renal or hepatic toxicity.
Casey, 2016, IJROBP High Risk	Photons Dose:21 Gy	213 Median Fu: 6.4 years (Surviving patients)	2 Year LC:92.9% 5 year LC:90.2%	5% severe haematological toxicity 2 severe renal and hepatic dysfunction

Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

Christine S. Chung, MD, MPH,* Torunn I. Yock, MD, MCh,† Kerrie Nelson, PhD,‡ Yang Xu, MS,§ Nancy L. Keating, MD, MPH,§,¶ and Nancy J. Tarbell, MD†,||

**Department of Radiation Oncology, Alta Bates Summit Medical Center, Berkeley, California; †Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; ‡Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts; §Department of Health Care Policy and ||Office of the Executive Dean, Harvard Medical School, Boston, Massachusetts; and ¶Department of General Internal Medicine, Brigham and Women's Hospital, Boston, Massachusetts*

Massachusetts General Hospital

1973 to 2001, n=558 Treated with Protons

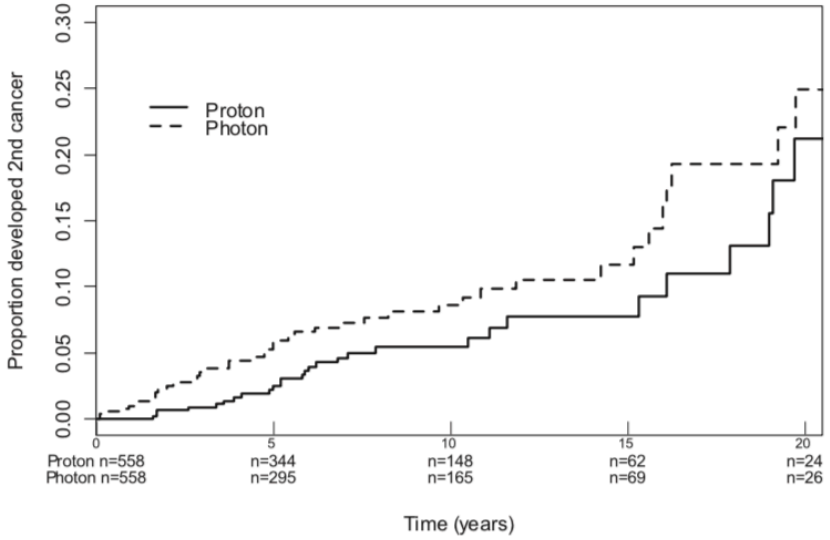
Matched Pair (n=558) - SEER Database. Treated with X Rays

Median FU: 6.7 Years

Median Age at Treatment: 59 Years

2nd Malignancy: With Protons - 29/558 (5.2%)

With X Rays - 42/558 (7.5%)



IJROBP 2013

Long-term follow-up after proton beam therapy for pediatric tumors: a Japanese national survey

Masashi Mizumoto,[1] Shigeyuki Murayama,[2] Tetsuo Akimoto,[3] Yusuke Demizu,[4] Takashi Fukushima,[5] Yuji Ishida,[6] Yoshiko Oshiro,[1] Haruko Numajiri,[1] Hiroshi Fuji,[7] Toshiyuki Okumura,[1] Hiroki Shirato[8] and Hideyuki Sakurai[1]

Aim: Evaluate the long- term benefits of PBT in cancer survivors

n=343

> 5 Yrs follow up - 62/343 (18%)

1983 to 2014, treated at 4 Japanese Institutions

Median Age: 10.8 Years (0 - 19 Years)

Proton Dose: 10.8 - 81.2 Gy RBE (Median - 50.4 Gy RBE)

Median FU: 8.1 Years

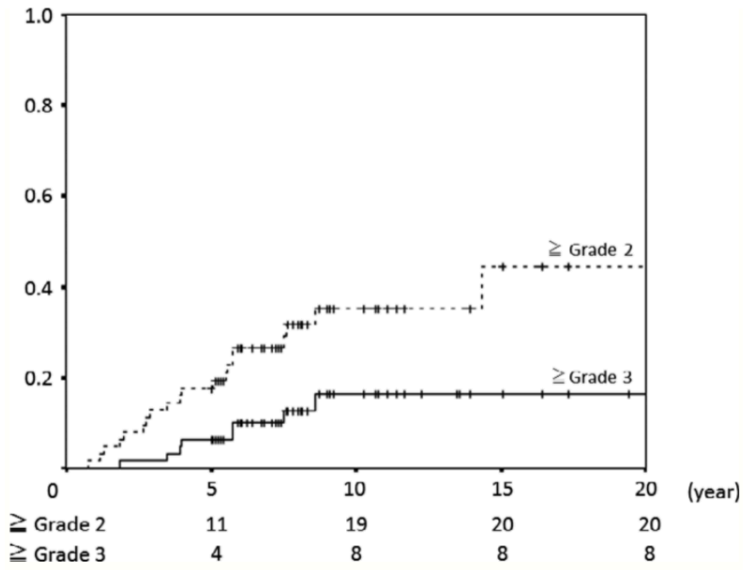


Fig. 1. Incidence of late adverse events in all patients.

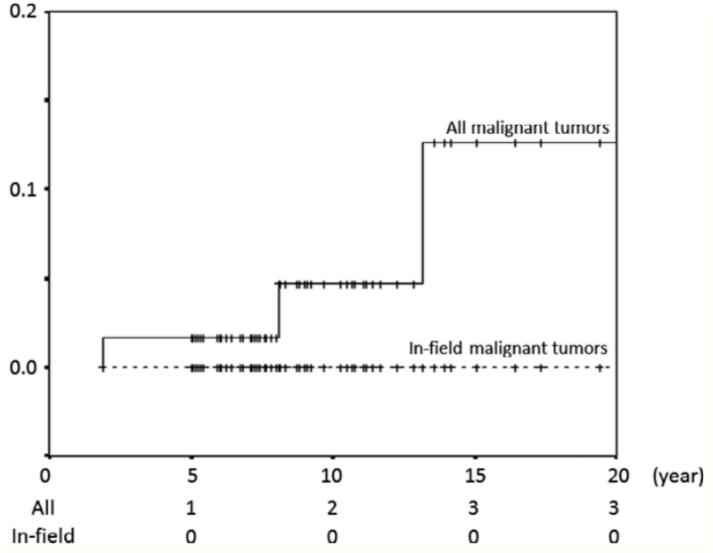


Fig. 4. Incidences of all malignant secondary cancers and in-field malignant secondary cancers.

Cancer Sci 2017

Consensus Report From the Stockholm Pediatric Proton Therapy Conference

Daniel J. Indelicato, MD,* Thomas Merchant, DO, PhD,†
Normand Laperriere, MD, FRCPC,‡ Yasmin Lassen, MD, PhD,§
Sabina Vennarini, MD,‖ Suzanne Wolden, MD, FACR,¶
William Hartsell, MD,# Mark Pankuch, PhD,# Petter Brandal, MD, PhD,**
Chi-Ching K. Law, MD,†† Roger Taylor, MD,‡‡ Siddhartha Laskar, MD,§§
Mehmet Fatih Okcu, MD, MPH,‖‖ Eric Bouffet, MD,¶¶
Henry Mandeville, MBChB, MRCP, FRCR, MD,##
Thomas Björk-Eriksson, MD, PhD,*** Kristina Nilsson, MD, PhD,***
Hakan Nyström, PhD,*** Louis Sandy Constine, MD,†††
Michael Story, PhD,‡‡‡ Beate Timmermann, MD,§§§
Kenneth Roberts, MD,‖‖‖ and Rolf-Dieter Kortmann, MD¶¶¶

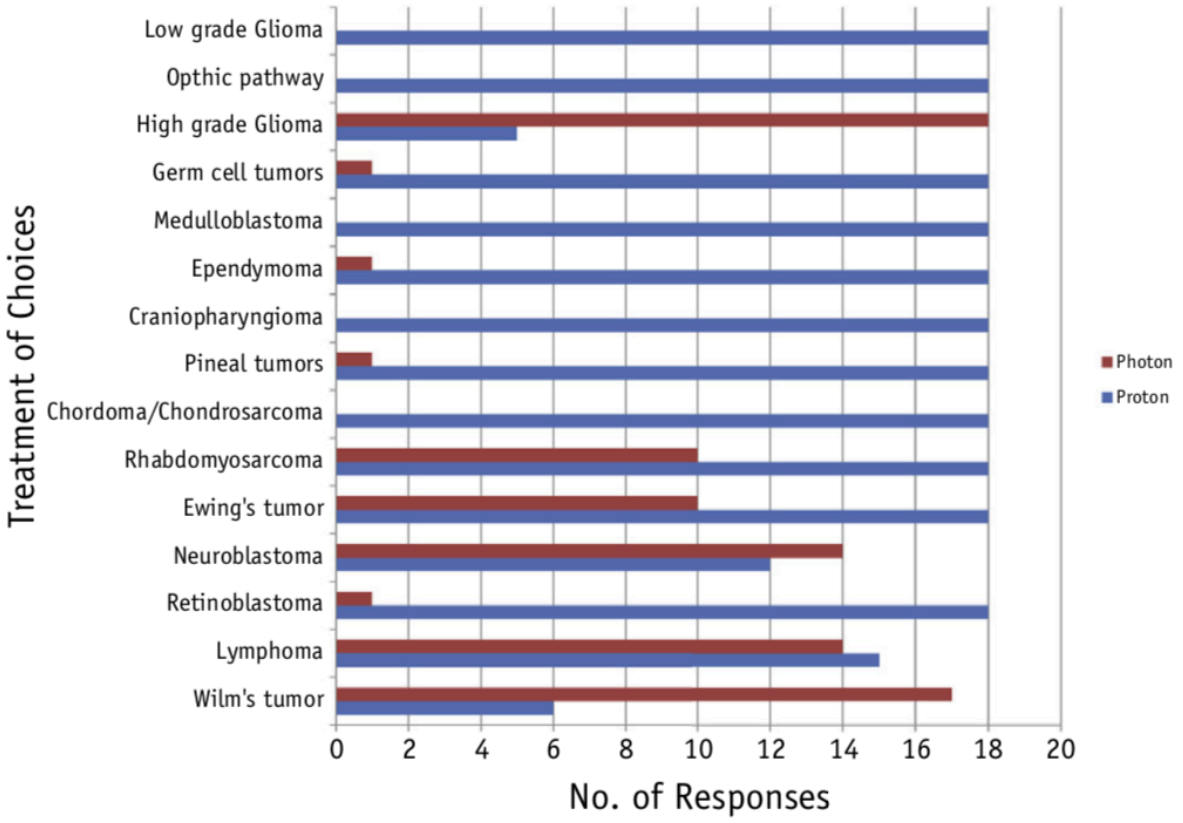


Fig. 1. Participants' responses to the question: "What is the treatment of choice for the following pediatric tumors?" Participants could answer "proton therapy," "photon therapy," or "both, depending on circumstances." Eighteen of 24 conference attendees participated in the survey.

IJROBP 2016

SUMMARY

- Proton beam therapy results in similar / improved disease control
- Potentially result in reduced dose to surrounding structures/ tissues (reduced toxicity)
- Robust level III data still not available to support or refute the use
- Paucity of comparative data on QOL/ Functional Outcome
- Dosimetric robustness (e.g: end of range RBE)
- Neutron contamination
- Expensive treatment
- Significant role in management of Pediatric Malignancies