Evidence-based Applications of Proton Therapy for Brain Tumors

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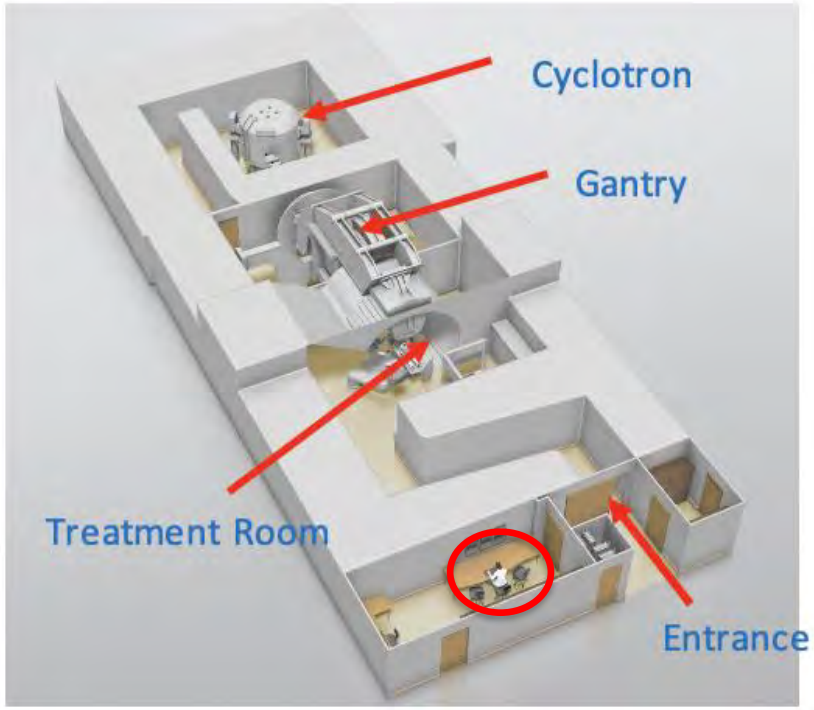
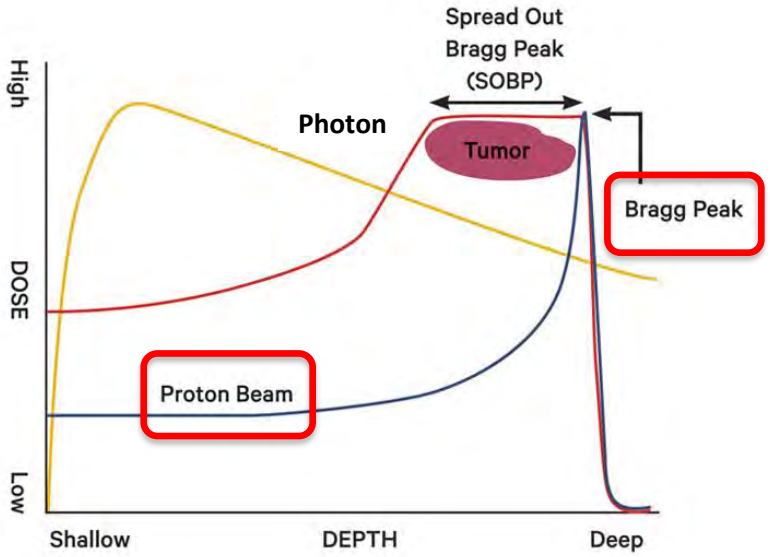
Outline

- Introduction to proton therapy
- Trials/studies on:
  - Pediatric brain tumors
  - Adult brain tumors
    - GBM
    - Leptomeningeal metastasis
    - LGG
    - Meningioma
- Conclusions

Introduction

Up to early 2023, there were **42 proton therapy centers** in the United States, and a total of 89 worldwide.



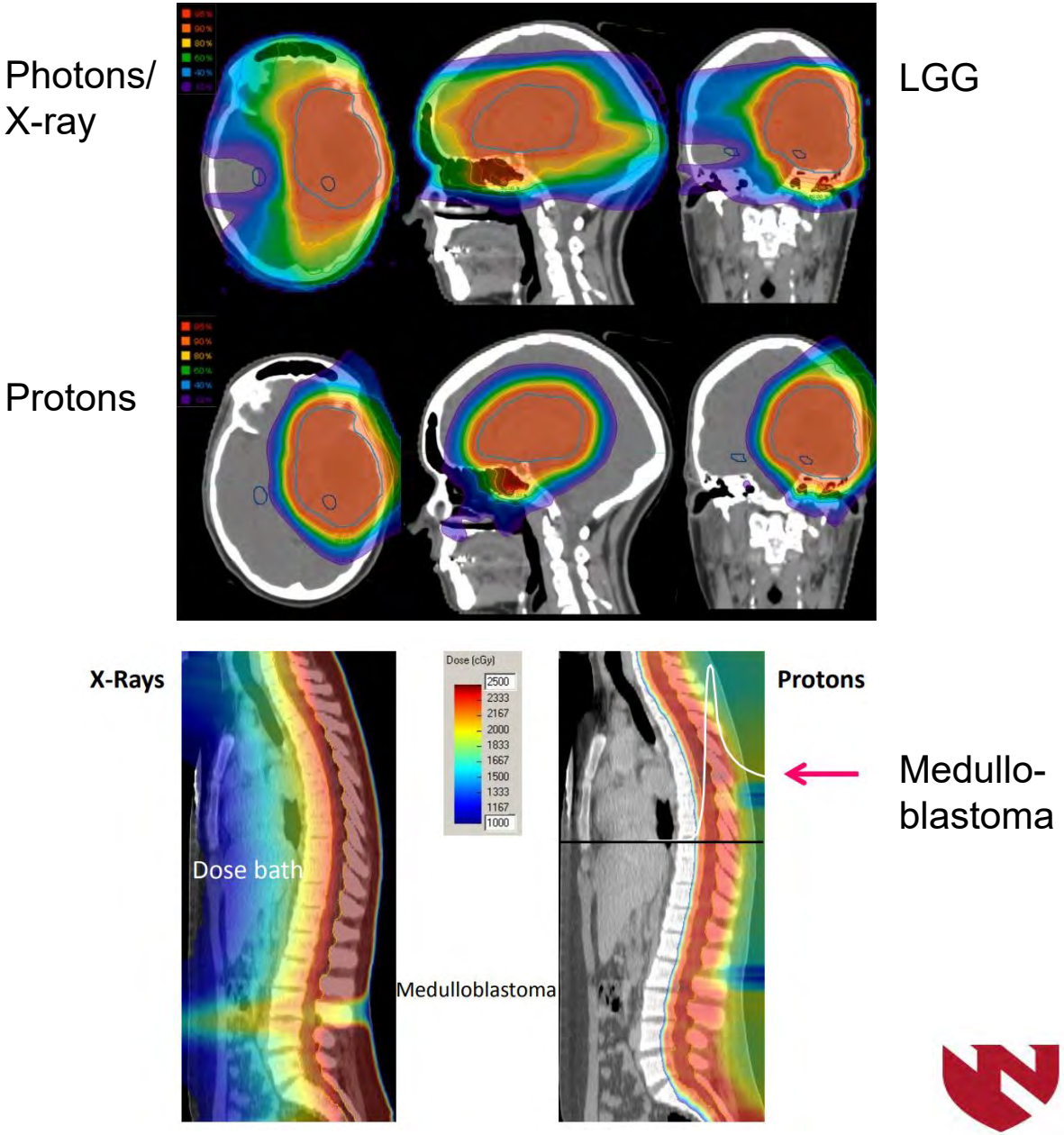


www.proton-therapy.org/map/

Introduction

- Due to protons remarkable physical properties, delivering their radiation to a very precise brain volume with no exit dose, protons are particularly appropriate for these tumors.
- The decrease of the brain integral dose may translate with a reduction of neuro-cognitive toxicity and increase of quality of life, particularly so in children.

Byskov et al., 2021;
Weber et al., 2020



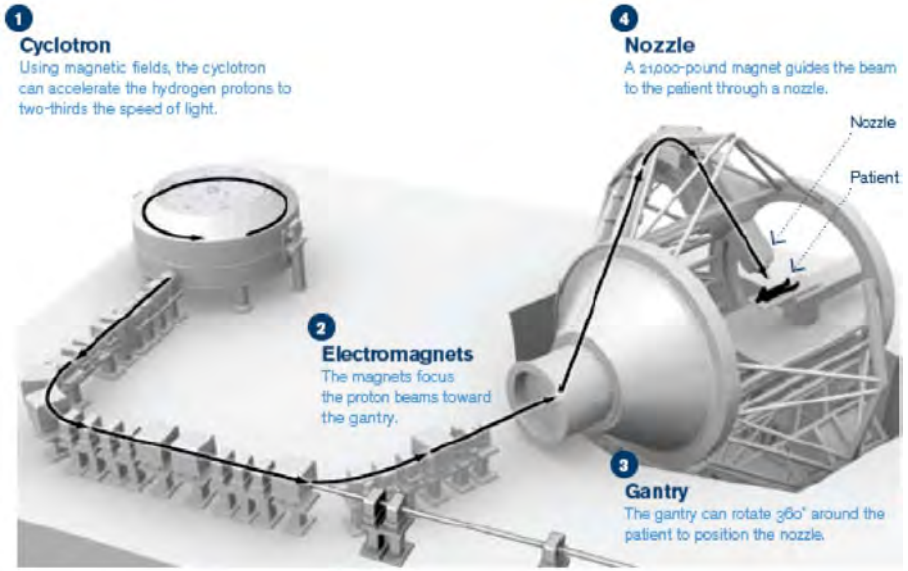
Introduction
-Proton therapy (PT) for brain tumors

- PT comes however with a large additional cost factor!

- Approximately 150’000 patients have been treated with PT. **However, no level I evidence has been demonstrated for this treatment.** High- quality data and new prospective trials to compare photons to protons in a randomized design are essential.

- Consequentially, radiation- induced toxicities and tumor recurrences, which are cost-intensive, may decrease with PT resulting in an optimized photon/ proton financial ratio in the end.

Cost: 30 up to 110 million US dollars including construction!!!
PT: cost factor of ~2.5 compared with modern photon techniques.



Goitein M, Jermann M 2003

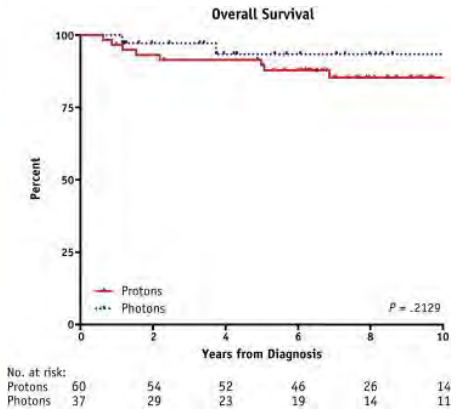
Proton therapy in pediatric brain tumors

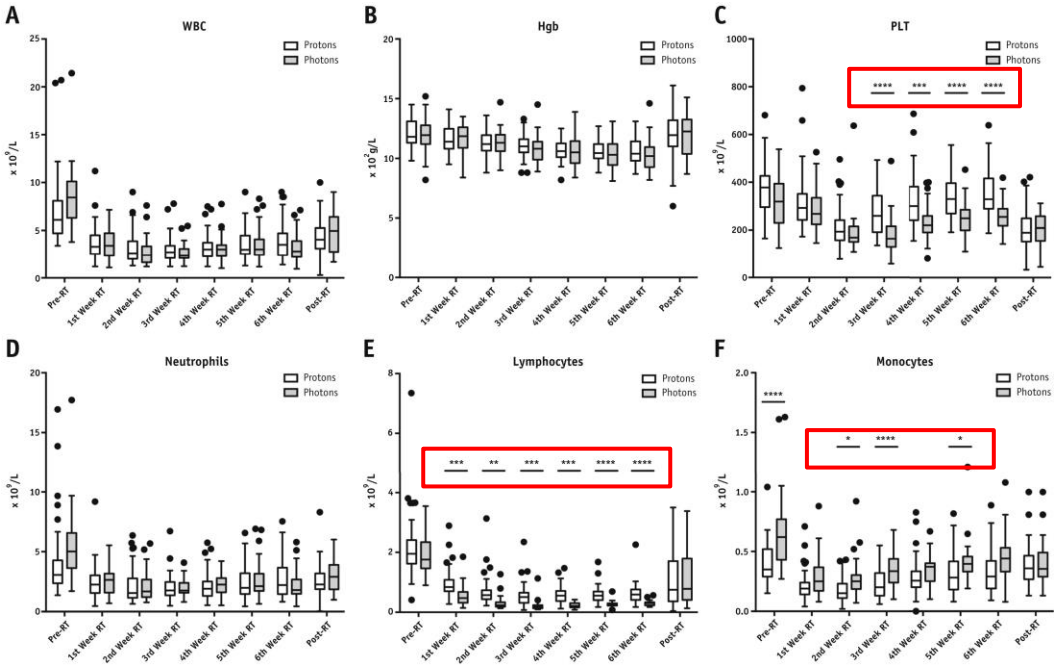
- The most common pediatric tumors are leukemia (30%) followed by brain/CNS tumors (26%), many are long-term survivors.
- Treatment- related toxicity brings a significant morbidity burden on childhood cancer survivors, most of all for patients with primary brain cancers.
- Children have increased sensitivity to RT due to
  - ongoing tissue growth and neuro- cognitive development,
  - smaller anatomic dimensions bringing critical organs closer to treatment areas and
  - a longer lifespan left to develop side- effects.
- The most significant toxicities associated with brain tumor irradiation are
  - vascular complications such as radiation necrosis (RN) and Moya-Moya syndrome,
  - impairment of neurocognitive development, including loss of IQ scores,
  - visual, hearing or endocrine deficits,
  - skin changes such as alopecia,
  - decrease of adult height, and
  - Secondary malignancies

Author [ref]	year	Tumor type	# pts	Median Age [years]	Median Dose [GyRBE] (range)	Median FU [months] (range)	Outcome	Late Toxicity
Mc Govern et al.	2014	AT/RT	31	1.6	50.4 (9–54); 14 pts CSI (23.4–36)	24 (3-53)	Median OS 34.3mo, PFS 20.8mo	five pts imaging changes interpreted as RN
Weber et al.	2015	AT/RT	15	1.4	54 all patients, no CSI	33.4 (9.7–69.2)	LF 20%, DBF 27%, SF 2%. 2y OS 64.6%, 2y PFS 66%	2y tox free survival 90%. No decrease of QoL after PT
Bishop et al.	**2014**	**Craniopharyn-gioma**	**52 (21 PT)**	**8.9**	**50.4 (50.4–54)**	**59.6 (PT 33mo)**	**3y OS 96%, nodular FFS 96%, cystic FFS 76%. Same outcome for PT and IMRT**	**Endocrine G2 77%. No difference between PT and IMRT**
MacDonald et al.	2013	Ependymoma	70	3.2	55.8 (50.4–60)	46 (12–140.4)	3y LC 83%, PFS 76%, OS 95% 5y LC 77%, DC 83%	one pt hypothyroidism, two pts GH deficit, two pts hearing loss, two pts cavernoma. No drop in MI and OAS scores
Mizumoto et al.	2015	Ependymoma	6	5	56.7 (50.4–61.2)	24.5 (13-44)	OS 100%, PFS 80%	one pt one-time seizure, one pt alopecia, no difficulty in daily life
Ares et al.	2016	Ependymoma	50	2.6	59.4 (54–60)	43.4 (8.5–113.7)	5y LC 78%, OS 84%	38% G1/2, two pts G3 deafness, one pt G5 brainstem necrosis
Sato et al.	**2017**	**Ependymoma**	**79 (41 PT)**	**3.7**	**55.8 (50.4–59.4)**	**PT 31.2 (7.2–86.4) IMRT 58.8 (13.2–140.4)**	**3y OS 81% IMRT *vs* 97% PT (p = .08), PFS 60% IMRT *vs* 82% PT (p = .0307), Recurrence 55% IMRT *vs* 17% PT (p = .005)**	**Vascular disorder G2 + 10% (6 RN, one stroke, one cavernoma)**
MacDonald et al.	2011	Germ cell tumors	22	11	Total 44 (30.6–57.6) 1pt IF only 7 pts WVRT 19.5–23.4 1pt WBRT 25.5 13 pts CSI 18.3–27	28 (13-97)	LC 100%, PFS 95%, OS 100%	two pts hypothyroidism, 2pts GH deficit. No new NC or auditory deficit
Hug et al.	2002	Low grade glioma	27	8.7	55.2 (50.4–63)	39.6 (7.2–81.6)	LF 22%, OS 85%	Moya-Moya one pt
Greenberger et al.	2014	Low grade glioma	32 (9 mix PT and photons)	11	52.2 (48.6–54)	91.2 (38.4–218.4)	6y PFS 89.7%, 8y PFS 82.8%, 8y OS 100%	Endocrine G2 > 80% at 10y (>40 GFy to pituitary and hypothalamus is RF), two pts G3 vasculopathy (Moya-Moya), age > 7y and hippocampus dose RF for NC decline, VA/VF decline four events, other visual tox nine events
Jimenez et al.	2013	Medulloblastoma / supratentorial PNET	15	2.9	Total 54 (39.6–54) CSI 21.6 (18–30.6)	39 (3-102)	3y LF 7.7%, OS 85.6%	Ototoxicity nine pts (2 G3), Endocrine G2 three pts, significant height loss, NS if GH deficiency pts excluded, no loss from baseline IQ
Eaton et al.	**2016**	**Medulloblastoma**	**88 (45 PT)**	**6**	**Total 54–55.8 CSI 23.4 (18–27)**	**74.4 PT pts 84 photon pts**	**6y RFS 78.8% PT *vs* 76.5% photon (p = .948). 6y OS 82% PT *vs* 87.6% photon (p = .285)**	**NR**
Yock et al. (phase 2, one arm)	2016	Medulloblastoma	59	6.6	Total 54 CSI 23.4 (23.4–36)	84 (62.4–98.4)	3y PFS 83% 5y PFS 80%, OS 83% 7y PFS 75%, OS 81%	Ototoxicity G3 + 12% at 3y and 16% at 5y and 7y, FSIQ decline by 1.5 point/y, Endocrine deficit 27%, 55 and 63% at 3, 5 and 7y, Cataract two pts, BS injury one pt, Stroke two pt

Proton therapy in pediatric brain tumors -Toxicities

- Pediatric medulloblastoma (mostly standard risk):
  - Multi-institutional retrospective study (Liu et al., 2020)
  - Median total dose to IF or PF was 54.0 Gy/Gy relative biological effectiveness (RBE) and median CSI dose was 23.4 Gy/Gy(RBE) for both cohorts.
  - Proton and photon CSI have similar OS but proton CSI resulted in significantly decreased hematologic toxicity.





CTCAE grade of toxicity	Proton cohort, n (%)	Photon cohort, n (%)	*P* value
Leukopenia	60	37	.044*
0	2 (3.3)	0 (0.0)	
1	10 (16.7)	3 (8.1)	
2	26 (43.3)	14 (37.8)	
3	22 (36.7)	19 (51.4)	
4	0 (0.0)	1 (2.7)	
Neutropenia	59	35	.762
0	11 (18.6)	6 (17.1)	
1	4 (6.8)	8 (22.9)	
2	29 (49.2)	10 (28.6)	
3	13 (22.0)	10 (28.6)	
4	2 (3.4)	1 (2.9)	
Lymphopenia	59	34	<.0001*
0	0 (0.0)	0 (0.0)	
1	0 (0.0)	0 (0.0)	
2	14 (23.7)	0 (0.0)	
3	35 (59.3)	11 (32.4)	
4	10 (16.9)	23 (67.6)	
Anemia	60	37	.011*
0	4 (6.7)	0 (0.0)	
1	35 (58.3)	16 (43.2)	
2	21 (35.0)	18 (48.6)	
3	0 (0.0)	3 (8.1)	
4	0 (0.0)	0 (0.0)	
Thrombocytopenia	60	37	.066
0	43 (71.7)	20 (54.1)	
1	17 (28.3)	16 (43.2)	
2	0 (0.0)	1 (2.7)	
3	0 (0.0)	0 (0.0)	
4	0 (0.0)	0 (0.0)	

Liu et al., 2020

Cost-effectiveness for proton *vs* photon therapy of brain tumors

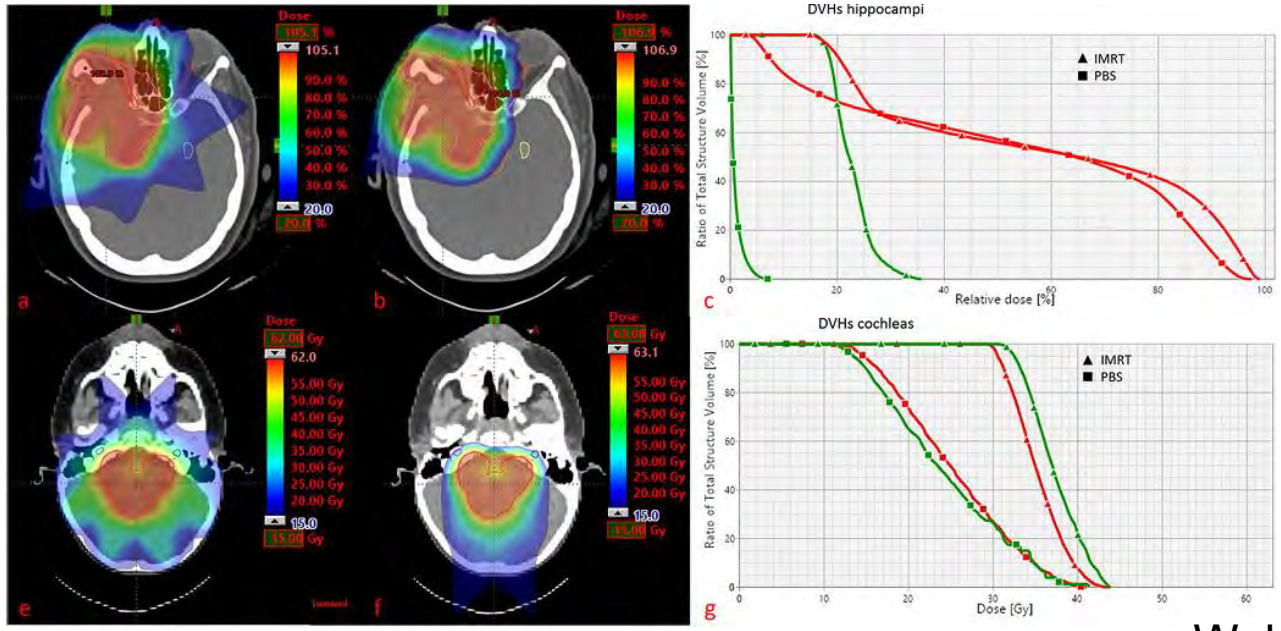
Author [ref]	year	Tumor type	Study design	Statistical Model Method	Included Parameters	Results
Lundkvist et al.[110]	2005	Pediatric medulloblastoma	Comparison PBT *vs* IMRT	Markov cohort simulation model	Risk of hearing loss, IQ loss, GHD, hypothyroidism, osteoporosis, cardiac disease, fatal and nonfatal SMN	Gain of QUALY of 0.68 per patient; Estimated cost difference (protons *vs* photons) per patient –23,646.5 EUR ICER of –34,622 EUR/QUALY →Cost effective →Cost saving
Mailhot Vega et al.[111]	2013	Pediatric medulloblastoma	Comparison of PBT *vs* photon RT	Monte Carlo simulation	Risk of GHD, hearing loss, hypothyroidism, congestive heart failure coronary artery disease, ACTH deficiency, gonadotropin deficiency, SMN, death	Gain of QUALY of 3.46; Total difference in costs (protons *vs* photons): - 32,579.1 Dollar ICER of –9,416 Dollar/QUALY →Cost effective →Cost saving
Hirano et al.[112]	2014	Pediatric medulloblastoma	Comparison of PBT *vs* IMRT	Markov cohort simulation model	Risk of hearing loss due to cochlear dose for three different QoL measures (EQ-5D, HUI3, SF-6D)	Gain of QUALY between 0.98 and 1.82 and ICER of 11,773 and 21,716 Dollar/QUALY dependent on QoL measure used →Cost effective
Mailhot Vega et al.[113]	2015	Pediatric CNS tumors	Comparison of PBT *vs* photon RT in hypothalamic dose sparing	Markov cohort simulation model	Risk of GHD	Hypothalamic proton doses between 5 and 25 Gy can be cost-effective, between 5 and 20 Gy even cost saving in some scenarios

High quality clinical evidence in adult brain tumors?

- No phase III randomized trial ever conducted comparing proton therapy *vs* photon therapy !!!
- The ethical issues of RCTs for proton therapy have been long debated.
- Dosimetric advantages are not enough!!! (less likelihood of secondary malignancy, short duration of life expectancy, higher percentage of high grade tumors with poor prognosis, etc.)

Meningioma

Infratentorial Ependymoma



Green IDLs: contralateral side of hippocampus
left: proton, right: photon IMRT

Green IDLs: contralateral side of cochlea
left: proton, right: photon

Weber et al., 2020

REALLY high quality clinical evidence!
-Glioblastoma (GBM) (WHO grade 4)

Neuro-Oncology

23(8), 1337–1347, 2021 | doi:10.1093/neuonc/noab040 | Advance Access date 27 February 2021

A prospective phase II randomized trial of proton radiotherapy vs intensity-modulated radiotherapy for patients with newly diagnosed glioblastoma

Paul D. Brown,[†] Caroline Chung,[†] Diane D. Liu, Sarah McAvoy, David Grosshans, Karine Al Feghali, Anita Mahajan, Jing Li, Susan L. McGovern, Mary-Fran McAleer, Amol J. Ghia, Erik P. Sulman, Marta Penas-Prado, John F. de Groot, Amy B. Heimberger, Jihong Wang, Terri S. Armstrong, Mark R. Gilbert, Nandita Guha-Thakurta, and Jeffrey S. Wefel[†]

GBM: IMRT *vs* PT (Majority IMPT) -Eligibility

- Adult patients (18 years of age or older) with newly diagnosed GBM or gliosarcoma (WHO grade IV) but no prior brain RT or other resected brain tumors
- Karnofsky Performance Status (KPS) score 70 or greater
- RPA class III, IV, or V were eligible for this trial
- MMSE score of 21 or greater (21-26 vs 27-30)
- Able to adequately read, write, and speak to participate in the cognitive and patient-reported outcome (PRO) assessments.

Brown et al., 2021

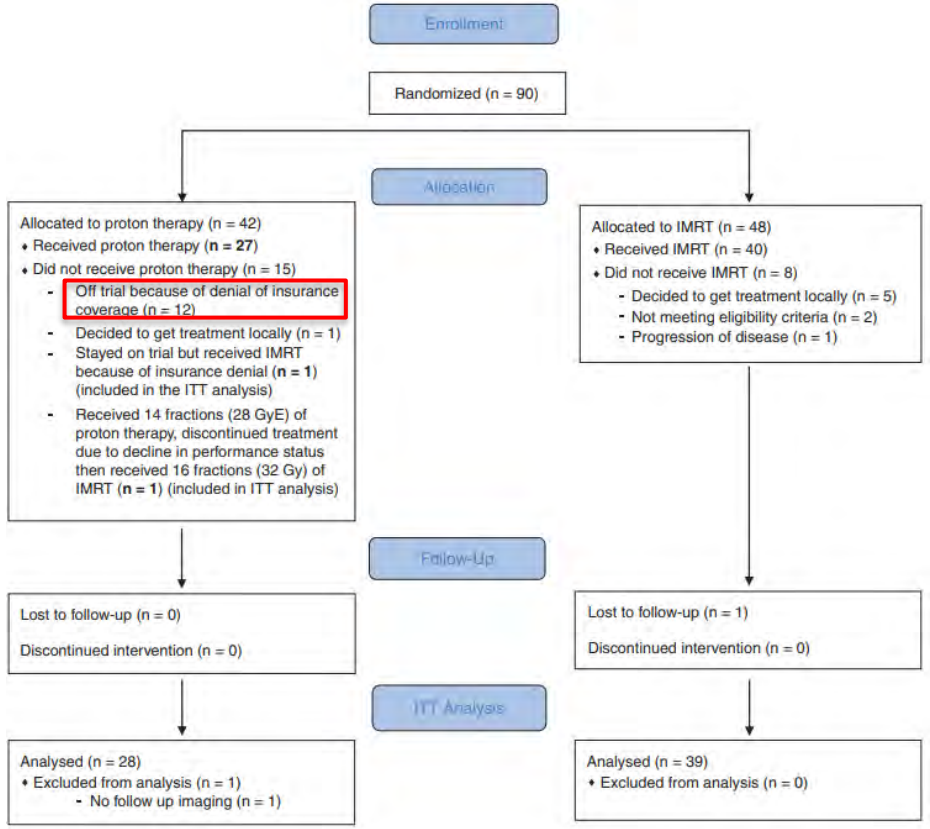
GBM: IMRT *vs* PT (Majority IMPT) -Trial Design

- Randomization:
  - Intensity Modulated Radiotherapy (IMRT)
    vs.
  - Intensity Modulated Proton Radiotherapy (IMPT)
    (RBE: 1.1, 250MeV proton beam)
    (7 out of 27 with passive scatter due to delay of start)

  •once daily fractions, 60Gy (GyE) in 30 fractions

  •Concurrent and adjuvant temozolomide

- Outcome Measure
  - Primary endpoint: time to cognitive failure
  - Second endpoints:
    - Local control (RANO criteria)
    - OS, PFS, PROs/toxicities



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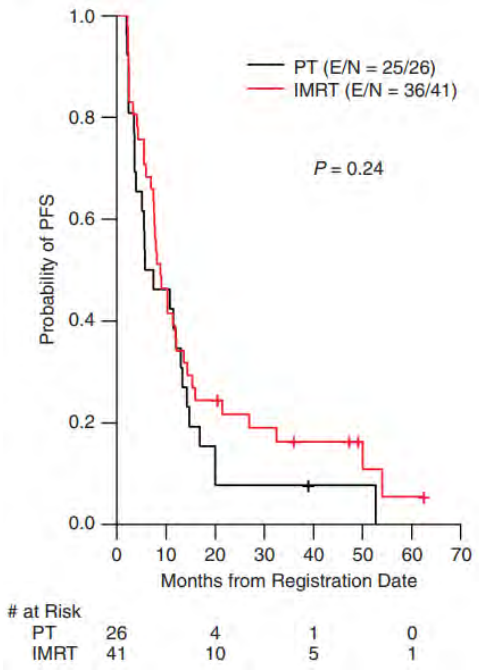
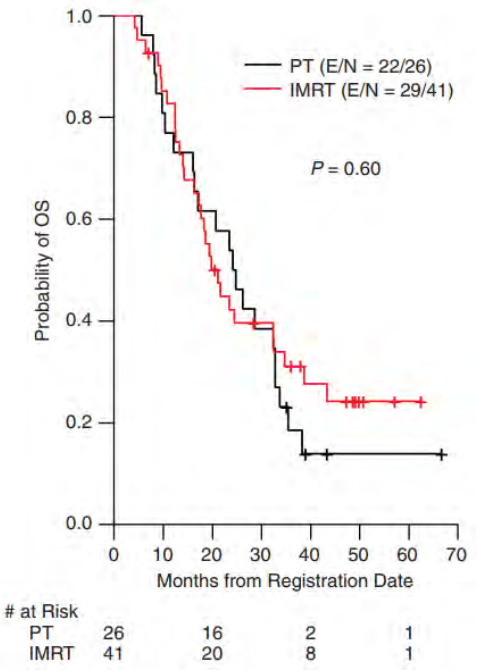
GBM: IMRT *vs* PT (Majority IMPT) -Results

		IMRT	PT	*P* Value
Overall	N	41 (61.2%)	26 (38.8%)	
Age at diagnosis	Mean ± Std	52.1 ± 13.9	55.2 ± 11	.46
	Median (Min, Max)	53 (26, 82)	54.5 (33, 72)	
Ethnicity	White	33 (80.5%)	24 (92.3%)	.72
	Hispanic	5 (12.2%)	1 (3.8%)	
	African American	2 (4.9%)	1 (3.8%)	
	Asian	1 (2.4%)	0 (0%)	
Gender	Male	21 (51.2%)	15 (57.7%)	.60
	Female	20 (48.8%)	11 (42.3%)	
Mini-mental status score	Mean ± Std (N)	27.7 ± 2 (41)	28.2 ± 1.7 (26)	.30
	Median (Min, Max)	28 (21, 30)	28.5 (23, 30)	
Extent of resection	Gross total	20 (48.8%)	19 (73.1%)	.14
	Subtotal	17 (41.5%)	5 (19.2%)	
	Biopsy	4 (9.8%)	2 (7.7%)	
RPA	III	12 (29.3%)	5 (19.2%)	.25
	IV	15 (36.6%)	15 (57.7%)	
	V	14 (34.1%)	6 (23.1%)	
Tumor hemisphere	Left	14 (34.1%)	13 (50%)	.36
	Right	26 (63.4%)	12 (46.2%)	
	Bilateral	1 (2.4%)	1 (3.8%)	
Tumor lobe	Frontal	14 (34.1%)	9 (34.6%)	.71
	Temporal	12 (29.3%)	8 (30.8%)	
	Parietal	9 (22%)	8 (30.8%)	
	Occipital	3 (7.3%)	1 (3.8%)	
	Central/midbrain	3 (7.3%)	0 (0%)	
MGMT	Unmethylated	3 (50%)	3 (75%)	.57
	Methylated	3 (50%)	1 (25%)	
	Not tested	35	22	
IDH-1	Normal	19 (82.6%)	18 (90%)	.67
	Mutated	4 (17.4%)	2 (10%)	
	Not tested	18	6	
GTV volume (cc)	Mean ± Std	48.5 ± 33.9	42.4 ± 30.6	.63
	Median (Min, Max)	40.3 (7.9, 143.9)	40.1 (3.9, 133.8)	
CTV volume (cc)	Mean ± Std	235.6 ± 85.5	206.5 ± 84	.24
	Median (Min, Max)	232.9 (86, 471.2)	215.6 (31.4, 404.4)	
HVLT-R Total Recall	Median	−0.9	−0.9	.49
HVLT-R Delayed Recall	Median	−1	−1	.96
HVLT-R Recognition	Median	−0.2	−0.6	.98
TMT Part A	Median	−0.4	0.4	.12
TMT Part B	Median	−1.9	−0.7	.12
COWA	Median	−0.9	−1	.90
CTB Composite	Median	−1.1	−0.6	.24

- Median follow-up 48.7 months (7.2 – 66.7 months)





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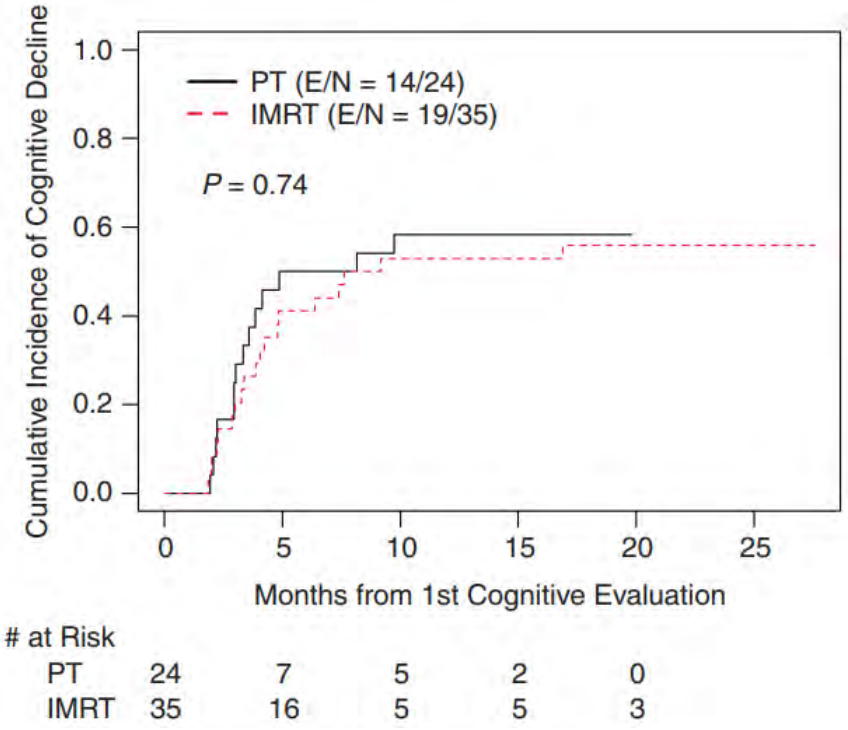
GBM: IMRT *vs* PT (Majority IMPT) -Results

- Cumulative incidence rate of cognitive decline



- Definition of Cognitive failure/decline
  - A decline that meets or exceeds the reliable change index (RCI) for any of the six cognitive test variables (HVLT-R Total Recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition, TMT Part A or Part B, COWA).

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GBM: IMRT *vs* PT (Majority IMPT) -Results

- Deterioration of Cognitive Function, QOL, and Symptoms at 6 Months
  - There were no statistically significant differences in the rates of deterioration between the two treatment arms at 6 months, except a **lower rate of worsening fatigue (PT)** (24% vs 58%, P = .05)

    (Note: no difference at 2 months)
  - Despite of significant dosimetric superiority of PT to normal tissues (whole brain, hippocampus, cochlea, pituitary gland)

Test/Measure and Component	IMRT		PT		PValue
	N	%	N	%	
Cognitive function					
HVLT-R					
Total Recall	5	21	2	12	.68
Delayed Recall	0	0	0	0	1.00
Recognition	3	13	2	12	1.00
TMT					
Part A	2	8	1	6	1.00
Part B	4	17	4	24	.70
COWA	2	8	2	12	1.00
CTB Composite	19	79	11	65	.48
EORTC QOL C30					
Scale					
Global HS/QOL	2	9	4	25	.21
Physical	5	21	2	12	.68
Role	3	13	2	12	1.00
Emotional	1	4	1	6	1.00
Cognitive	9	39	3	19	.29
Symptom items					
Social	0	0	1	6	.41
Fatigue	14	58	4	24	.05
Nausea/vomiting	2	8	1	6	1.00
Pain	1	4	3	18	.29
Dyspnea	0	0	2	12	.17
Insomnia	5	21	2	12	.68
Appetite loss	5	21	1	6	.37
Constipation	3	13	4	24	.42
Diarrhea	3	13	2	13	1.00
Financial	2	9	2	13	1.00
BN20					
Scale					
Future uncertainty	4	17	2	12	1.00
Visual disorder	3	13	2	12	1.00
Motor dysfunction	7	29	1	6	.11
Comm deficit	4	17	4	24	.70
Symptom items					
Headaches	3	13	1	6	.62
Seizures	1	4	1	6	1.00
Drowsiness	5	21	6	35	.48
Hair loss	7	29	2	12	.26
Itchy skin	4	17	3	18	1.00
Weak legs	3	13	1	6	.63
Bladder	3	13	1	6	.64
MDASI-BT					
Subscales					
Core	4	17	1	6	.38
Brain tumor	3	13	1	6	.63

Brown et al., 2021

GBM: IMRT *vs* PT (Majority IMPT) -Conclusion

- PT was not associated with a delay in time to cognitive failure but did significantly reduce dose to normal structures and fatigue.
- PT did not differ in PFS/OS from IMRT.
- Off-trial use of protons to decrease the risk of cognitive decline does not appear justified for patients with GBM.
- Larger randomized trials are also needed to determine the potential of dose escalation with PT on GBM tumor control and survival.

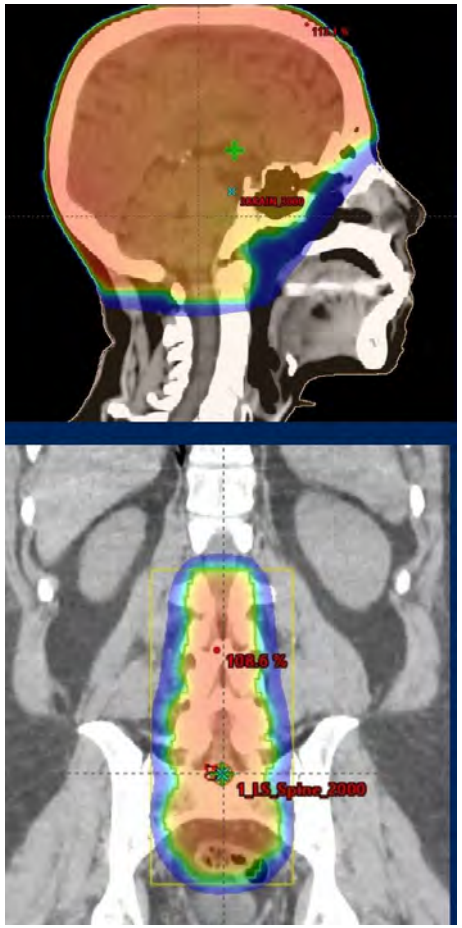
Brown et al., 2021

REALLY high quality clinical evidence!

-Leptomeningeal Metastasis from Solid Tumors

- Leptomeningeal Metastasis (LM) involves seeding of the cerebrospinal fluid (CSF)-filled leptomeningeal space surrounding the brain and spinal cord.
    - Can lead to death within 4-6 weeks without treatment or
    - 4-6 months with standard therapies

- Standard-of-care/most common practice is photon involved-field radiotherapy (IFRT), such as whole brain radiotherapy or focal spine radiotherapy, is effective for relieving symptoms but does not halt progression of disease along the leptomeningeal space
    - Supported by NCCN guidelines
    - Does not seem to improve survival

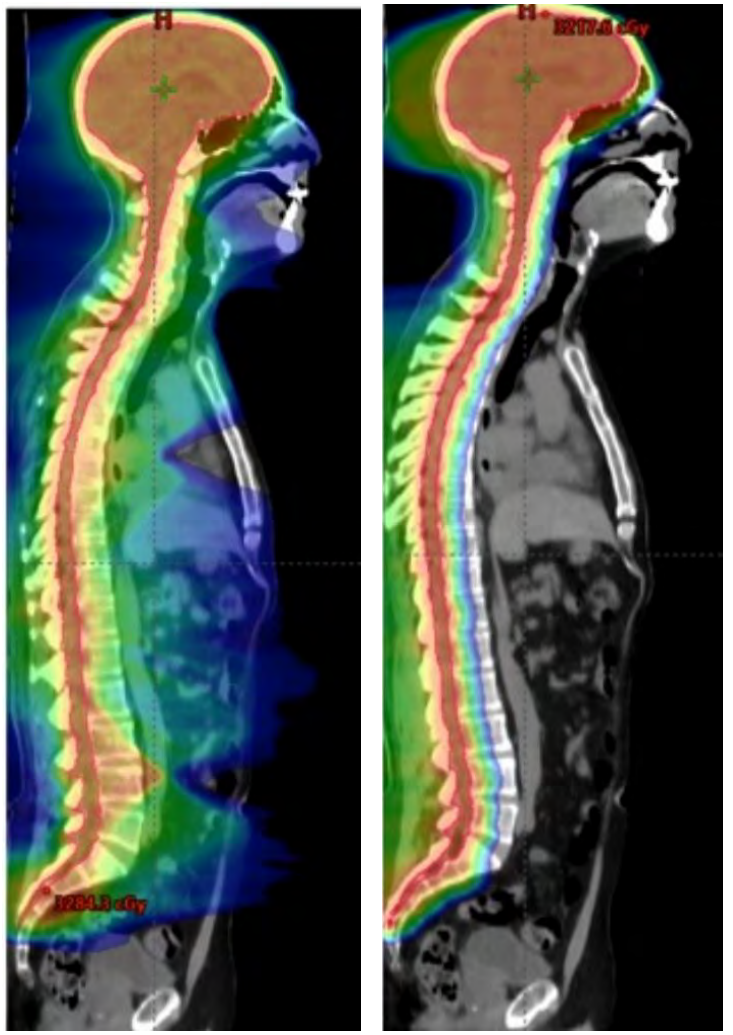


Leptomeningeal Metastasis from Solid Tumors

- Craniospinal irradiation (CSI) may potentially be beneficial in disease control as the entire leptomeningeal space is targeted.

- Proton CSI (pCSI) significantly less toxic compared to x-ray-based photon CSI evaluated prospectively in patients with Medulloblastoma

>5% weight loss:	64% photon	vs. 16% proton
Grade 2+ n/v:	71%	vs. 26%
Grade 3+ esophagitis:	57%	vs. 5%



Phase II Randomized Study Comparing Proton Craniospinal Irradiation (pCSI) with Photon Involved Field Radiotherapy (IFRT) for Patients with Solid Tumor Leptomeningeal Metastasis

Jonathan T. Yang, N. Ari Wijetunga, Elena Pentsova, Suzanne Wolden, Robert Young, Denise Correa, Zhigang Zhang, Junting Zheng, Allison Betof Warner, Helena Yu, Mark Kris, Andrew Seidman, Rachna Malani, Andrew Lin, Lisa DeAngelis, Nancy Lee, Simon Powell, Adrienne Boire

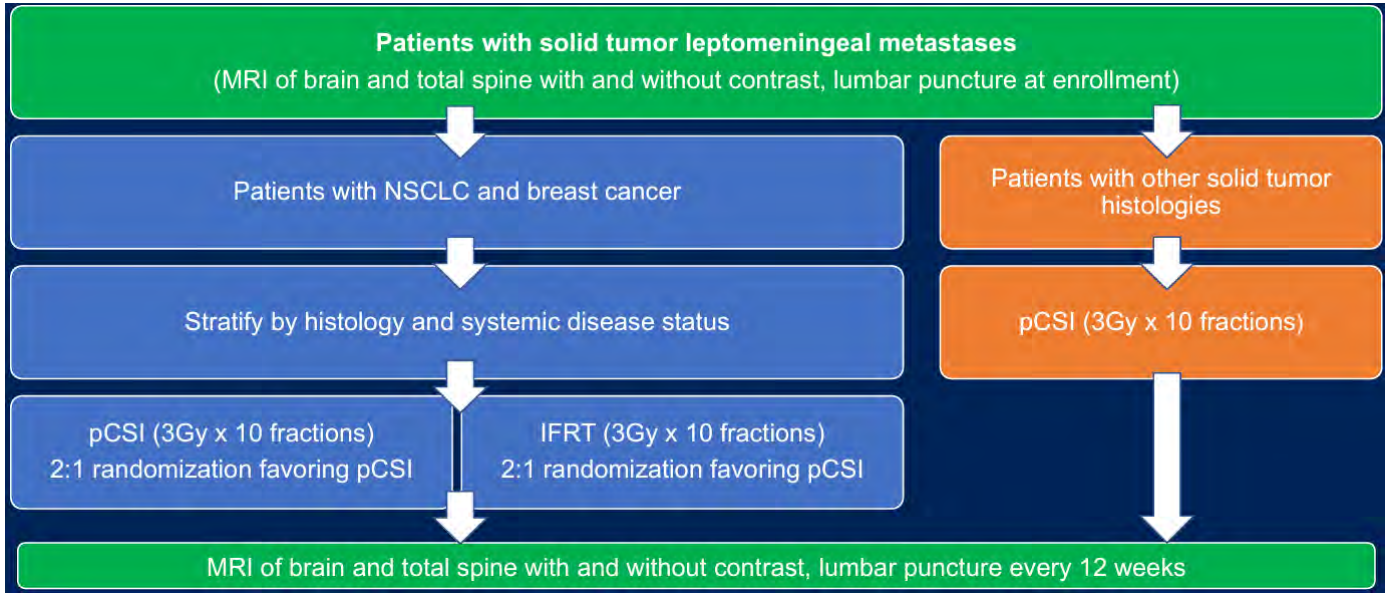
Memorial Sloan Kettering Cancer Center

Randomized Phase II Trial

Proton craniospinal irradiation **(pCSI)** *vs* photon involved field RT (**IFRT)** in patients with non–small-cell lung cancer and breast cancers with LM. Patients were assigned (2:1) to pCSI or IFRT. 30Gy in 10 fx.

Patients with other solid tumors to an exploratory pCSI group.

The primary end point was CNS PFS. Secondary end points included overall survival (OS) and treatment-related adverse events (TAEs).



Patient Selection Criteria

- Inclusion Criteria:
  - LM established radiographically and/or with CSF cytology
  - KPS ≥ 60

- Exclusion Criteria:
  - Multiple, serious major neurologic deficits including encephalopathy
  - Extensive systemic disease without reasonable systemic treatment options

- Progression of disease in the CNS defined as 1 or more below:
  - Clinical: new neurologic deficit
  - Radiographic: progressive disease
  - Cytologic: new positive cytology in patients with previously negative cytology

Interim Analysis
-Patient Characteristics

Characteristic	pCSI (N=42)	Photon IFRT (N=21)
Age (median, range)	56 (49-55)	61 (54-65)
Sex		
Female	34 (81%)	18 (86%)
Male	8 (19%)	3 (14%)
Primary Disease		
NSCLC	24 (57%)	12 (57%)
EGFR+	12 (29%)	7 (33%)
Breast	18 (43%)	9 (43%)
HER2+	6 (14%)	4 (19%)
Systemic Disease Status		
Active	22 (52%)	11 (52%)
Stable/None	20 (48%)	10 (48%)

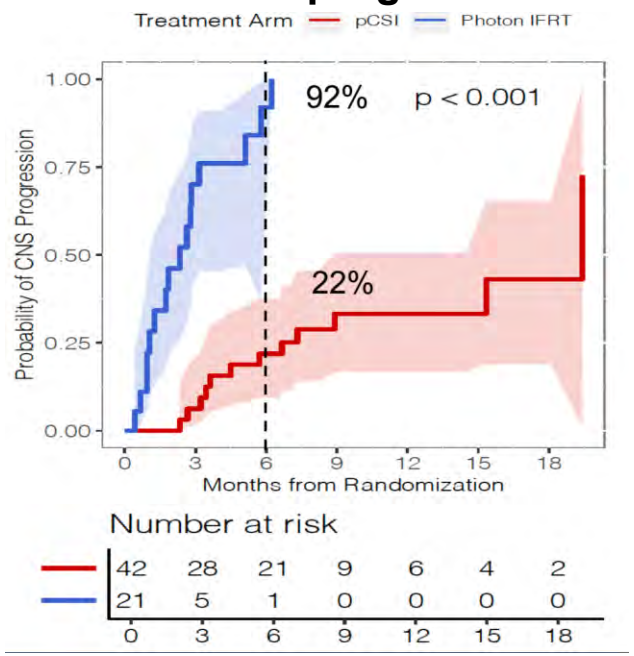
Characteristic	pCSI (N=42)	Photon IFRT (N=21)
KPS (median, range)	80 (60-90)	80 (60-90)
At Enrollment		
Positive MRI	38 (91%)	21 (100%)
Positive Cytology	28 (67%)	11 (52%)
Positive CSF CTC	36 (86%)	17 (81%)
Brain Metastases		
Yes	28 (67%)	15 (71%)
No	14 (33%)	6 (29%)
Median Lines of Prior Systemic Therapy	2 (0-8)	2 (0-8)
IFRT Fields		
WBRT		9 (43%)
Spinal RT		1 (5%)
Both		8 (38%)

CNS Progression after pCSI vs IFRT

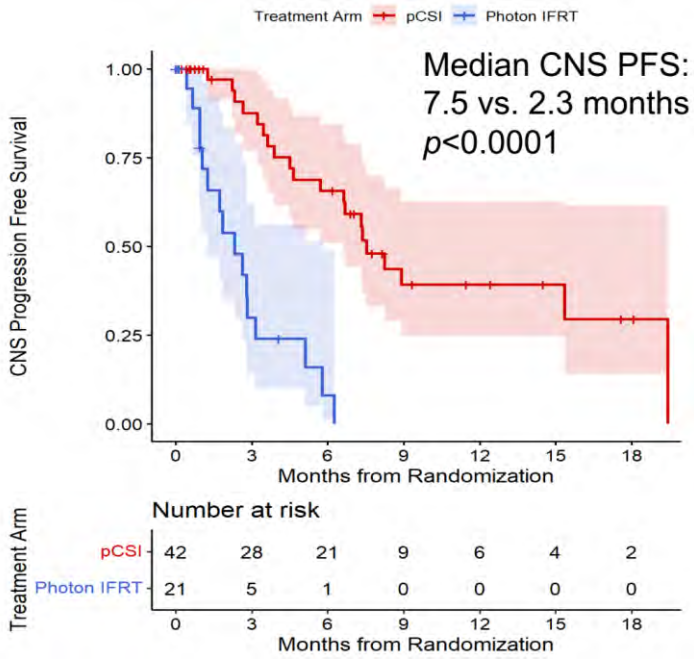
Interim analysis:

Median follow-up time: 9.3 months (95% CI 7.8-17.6 months)

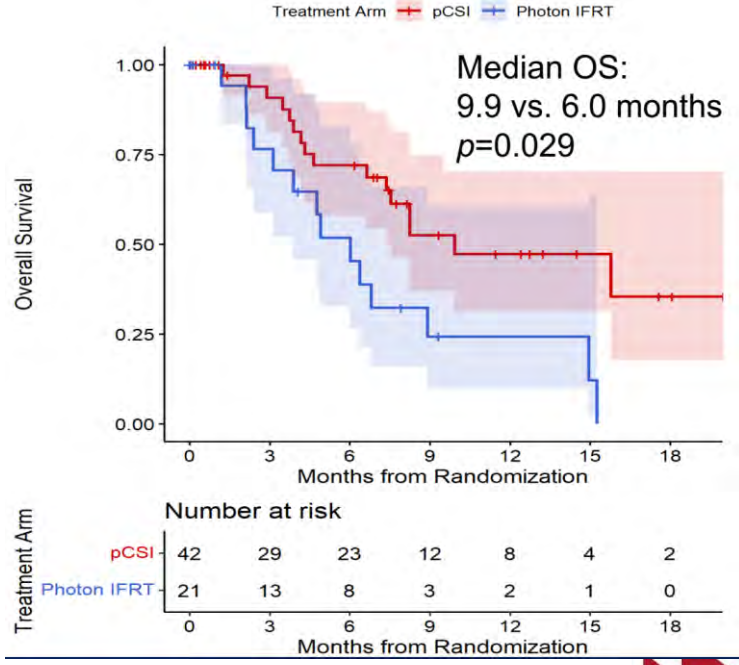
CNS progression



PFS



OS



Proton therapy for adult lower grade gliomas (WHO grade 2 or 3)

A substantial number of Lower Grade Glioma (LGG) (particularly grade 2) patients are long-term survivors.

The negative impact of photon radiation therapy on cognition has been demonstrated. Up to ~50% of long-term survivors of LGG patients who had RT developed cognitive disabilities deficits compared with 27% patients who were radiotherapy naïve (Douw et al., 2009).

Reported results however regarding long- term toxicities from clinical proton studies show encouraging results, although the patient numbers are small.

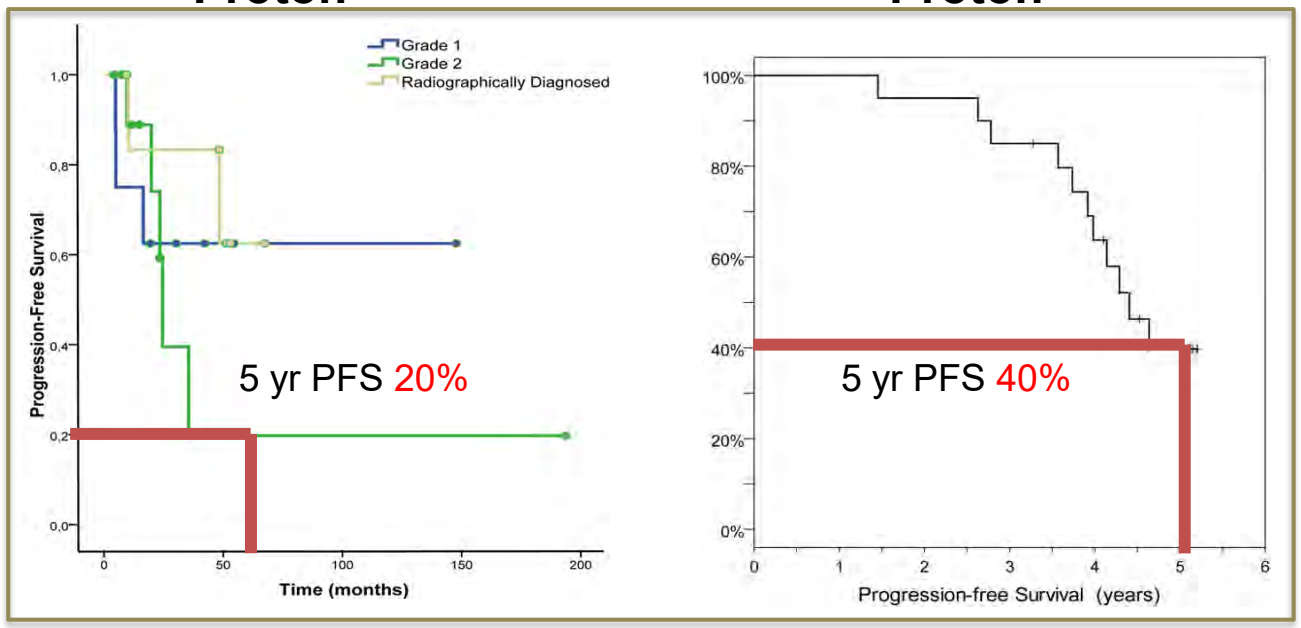
Currently, there are no published data of randomized trials comparing protons with photons for these tumors

More elucidation on the real benefit of PT in treating LGGs can be expected from the results from the ongoing randomized trial.

Douw et al., 2009

Proton *vs* Photon therapy for LGG

Proton

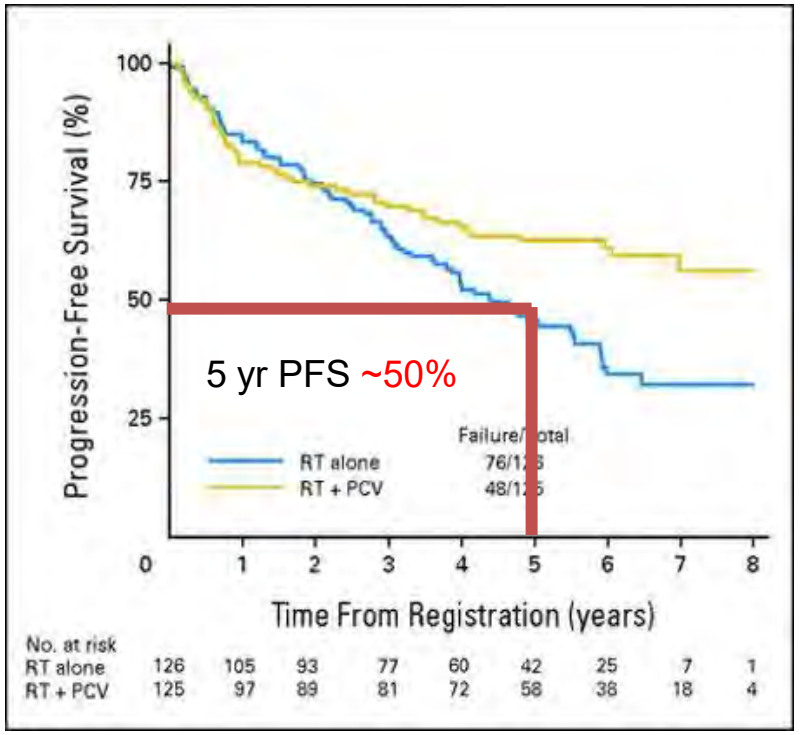


Badiyan et al., 2017
Pencil beam scanning proton therapy
28 patients (1997-2014)
(12 grade 2, 9 grade 1)
(20 younger than 18)
39% received chemo

Proton

Shih et al., 2015
20 adult patients (2007 to 2010)
(8 newly diagnosed, 12 at progression).
All WHO grade 2 glioma.

Photon



Shaw et al. 2012
Phase III, RTOG 9802
125 adult patients (each arm) (1998-2002)
All WHO grade 2 glioma

Acute toxicities of Proton vs Photon therapy in LGG

Proton (Shih et al., 2015) (20 pts, Prospective single arm)

CTCAE Event	No. of Events		
	Grade 1	Grade 2	Grade 3
Fatigue	8	10	2
Erythema	13	3	1
Headache	10	4	1
Seizure	NA	5	0
Taste/smell alteration	1	2	NA
Anorexia	1	1	0
Alopecia	17	0	NA
Cognitive deficit	1	0	0
Nausea/vomiting	4	0	0
Paresthesia	2	0	0
Dizziness	2	0	0
Anxiety	2	0	0
Insomnia	2	0	0
Motor dysfunction	2	0	0
Photophobia	1	0	0
Itching	1	0	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable.

28 events in 20 pts)

Photon (Buckner et al., 2016) (125 pts, RTOG 9802)

Event	Radiation Therapy Alone (N = 126)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
					no. of patient
Constitutional symptoms	43	20	4	1	0
Fatigue	42	20	3	1	0
Weight loss	8	0	1	0	0
Blood or bone marrow disorder	2	2	1	0	0
Hemoglobin decreased	2	0	0	0	0
Packed red-cell transfusion required	0	0	0	0	0
Platelet count decreased	1	1	0	0	0
Platelet transfusion	0	0	0	0	0
Neutropenia	0	0	1	0	0
Febrile neutropenia	0	0	0	0	0
Infection	0	1	0	0	0
Lymphopenia	0	1	0	0	0
Gastrointestinal disorder	32	6	2	0	0
Anorexia	8	1	0	0	0
Constipation	3	0	0	0	0
Nausea	20	4	2	0	0
Vomiting	3	2	2	0	0
Hepatic disorder	2	0	0	0	0

75 events in 125 pts)

Author [ref]	year	Tumor type	# patients	Median Dose (GyRBE) (Range)	Median FU (months) (range)	Proton Therapy only	PBS only	Outcome	Toxicity
Halasz et al.[39]	2011	Menigioma WHO Grade 1–2	*n* = 50 Grade 1: *n* = 12 (24%) Grade 2: *n* = 6 (12%) Grade not known: *n* = 32 (64%)	13 (10–15.5) in one fraction	32 (6–133)	yes	Scattering (stereotactic)	**3y-LC:** 94%	**Acute** Transient facial pain 4% **Late** Seizures associated with cerebral edema 12% Panhypopituitarism 2%
Weber et al.[40]	2012	Menigioma WHO Grade 1–3	*n* = 39 (three re-irradiation)	Grade 1–2: 52.2–56 Grade 3: 60.8 (±5.3)	54.8 (6.2–146.8)	yes	yes	**5y-LC:** Grad1: 100% Grade 2–3: 49.1%	**Acute: (**CTCAE) Grade 2: 12.5% Grade 3: 0% **Late:** Grade ≥ 3: 12.8%
Slater et al.[41]	2012	Meningioma Grade 1–2	Entire cohort *n* = 72 Grade 1: *n* = 47 (65%) Grade 2: *n* = 4 (6%) Grade not known: 21 (29%)	Grade 1: 50.4–66.6 Grade 2: 54–70.2	74 (3–183)	yes	Scattering	**5y-LC** Overall: 96% Grade 1: 99% Grade 2: 50% **5y-OS** 99% (disease-specific)	optic neurologic symptoms: 4.2% brain edema: 2.8% Transient diplopia 1.4% Panhypopituitarism 4.2%
Combs et al.[42]	2013	Meningioma WHO Grade 1–3	Entire cohort *n* = 107 WHO Grade 1: 71 (66%) WHO Grad 2/3: *n* = 36 (34%)	Grade 1: 57.6 Grade 2/3: N.R.	12 (2–39)	Grade 1: PT only Grade2/3: photons/carbon ion boost	Grade 1. Yes Grade 2/3: combination of photon/carbon	**2y-LC:** Grade 1: 100% Grade 2/3: 33%	N.R.
McDonald et al.[38]	2015	Meningioma WHO Grade 2	*n* = 22	63 (54–68.4)	39 (7–104)	yes	N.R.	**5y-LC:** 71.1%	**Acute** ≥Grade III: 0% **Late** ≥Grade III: one pt.
Vlachogiannis et al.[43]	2017	Meningioma WHO Grade 1	*n* = 170	21.9 (14–46) 2–6 Gy/fx	84 (range N.R)	yes	Scattering (stereotactic)	**5y-PFS:** 93% **10y-PFS:** 85%	Pituitary insuffiency: 3.5% Radiation necrosis: 2.9% Visual impairment: 2.9% Expansive tumour cyst: 0.5%
Murray et al.[44]	2018	Menigioma WHO Grad 1–3	Entire cohort: *n* = 96 Grade 1: *n* = 61 (63%) Grade 2: *n* = 33 (34.1%) Grade 3: 2 (2.1%)	Grade I: 54 (50.4–64) Grade II and II: 62 (54-68)	56.9 (range, 12–207)	Yes	Yes	**5y-LC:** Entire cohort: 86,4% Grade 1: 95.7% Grade 2/3: 68% **5y-OS:** entire cohort: 88.2% Grade 1: 92.1% Grad 2/3: 80.7%	**Acute (**CTCAE) ≥Grade III: 0.96% **Late** ≥Grade III overall: 10% optic toxicity: 6.7% brain edema: 0.96% brain necrosis: 1.9%
El Shafie et al.[45]	2018	Meningioma WHO Grade 1–3	Entire cohort: *n* = 110 Grade 1: 60 Grade 2: 7 Grade 3: 1 not known:42	Protons: 54 (50-60); 1.8–2.0/fx Carbon ion: 18; 3.0/fx	46.8 (95%CI: 39,9–53.7)	Proton: *n* = 104 Photons/Carbon ion: *n* = 6	Yes Grade 2/3: combination of photon/carbon	**5y-PFS:** Entire cohort: 96.6% Low risk: 96.6% High risk: 75%, **5y-OS**: 96.2 %	**Acute (**CTCAE)**:** Grade III: 1.8% (mucositis, nausea) **Late:** Grade III:3.6% (hypopituitarism, radionecrosis)

Modified based on Weber et al., 2020

Summary

The dose deposition advantage of PT for the treatment of brain tumors are instantly apparent when planning comparisons of proton vs photon are made.

Delivering protons to children with brain tumors may increase the therapeutic ratio and likely cost-effective.

Evidence for PT in adult benign and low- grade tumors is however limited on retrospective analyses.

For adult brain tumors, it is unlikely that PT for high-grade brain tumors might translate into a substantial clinical benefit for CNS-tumor patients (phase II study). Protons could however be administered to low-grade (i.e. glioma) or benign (i.e. meningioma) brain tumors, as these patients experience substantial long survival times, in order to possibly decrease long term toxicity.

In the era of EBM, high-quality data needs to be generated to justify the higher cost factor of proton therapy which can have substantial financial toxicity to the patients and their families.

Tumor type	NCT number	Allocation	Activation [year]	# of patients	Age limit	Hypothesis	Primary endpoint	Total dose (dose per fx) [GyRBE]	status
Europe (lead)									
All brain tumors (*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* Prot ons)	2019	80	≥18 years	Less impairment °f 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 or 59,4 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*	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 (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
Recurrent Ependymoma *St Judes Children*	02125786	Non-Randomized 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 OS @ 3 years	NR	Accruing
IDH mutant Glioma (GII/III) *NRG BN005*	03180502	Randomized Phase II	2017	120	≥18 years	PT will preserve cognition compared with IMRT	Change in cognition (CTB COMP scoreb) up to 10 years	NR	Accruing
Medulloblastoma *St Judes Children*	01878617	Phase II	2013	625	3–39 years	Assess clinical and molecular risk directed therapy	PFS @ 2 years, neurocognition @ baseline and 12 weeks	NR	Accruing

Thank you!