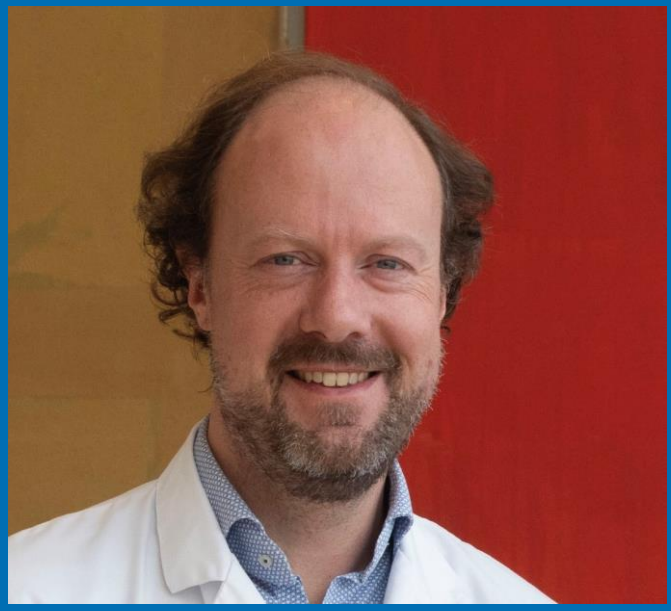
Publieksdag
Hersentumoren

Behandelingen zonder 'snijden'

Joost Verhoeff MD PhD

Radiotherapeut-oncoloog

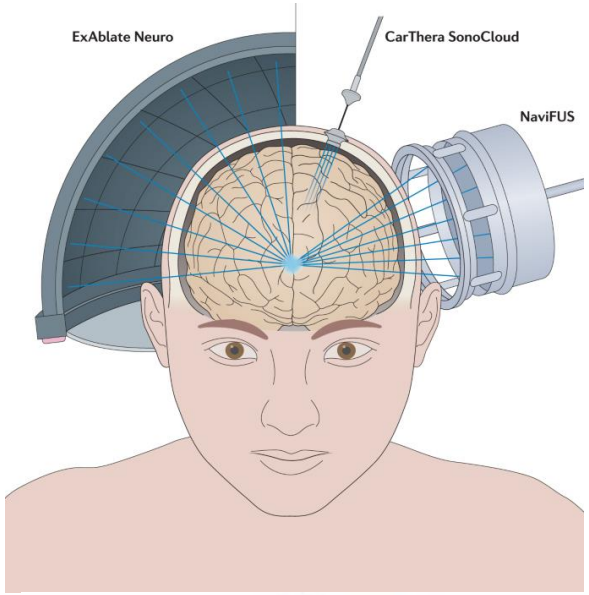
Zaterdag 26-11-2022

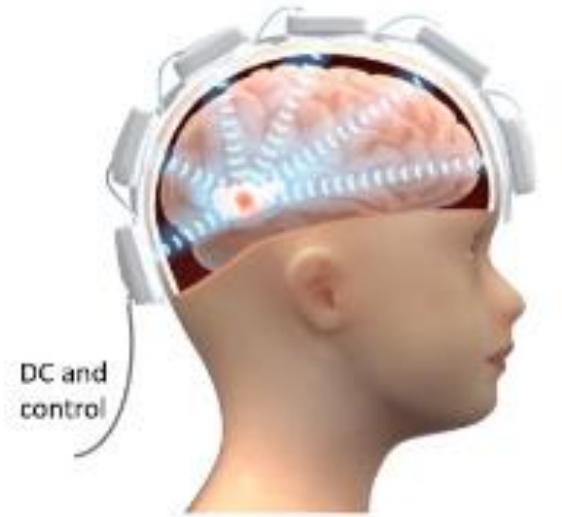


In samenwerking met:

Plaatselijke behandelingen zonder 'snijden'

- Radiotherapie
  - Fotonen
  - Protonen
  - FLASH
- HIFU en FUS
- Hyperthermie

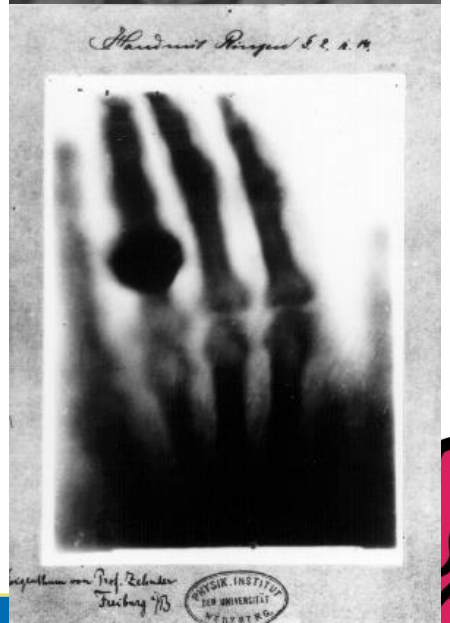




Straling, de hype van de vorige eeuwwisseling

- Henri Becquerel (1852-1908)
  - 1 maart 1896: natuurlijke radioactiviteit ontdekt

- 1901 eerste Nobelprijs voor de Natuurkunde:
  - Wilhelm Röntgen (1845-1923)
  - Vacuüm buis waarin elektronen door een zeer groot elektrische spanningsverschil werden versneld.



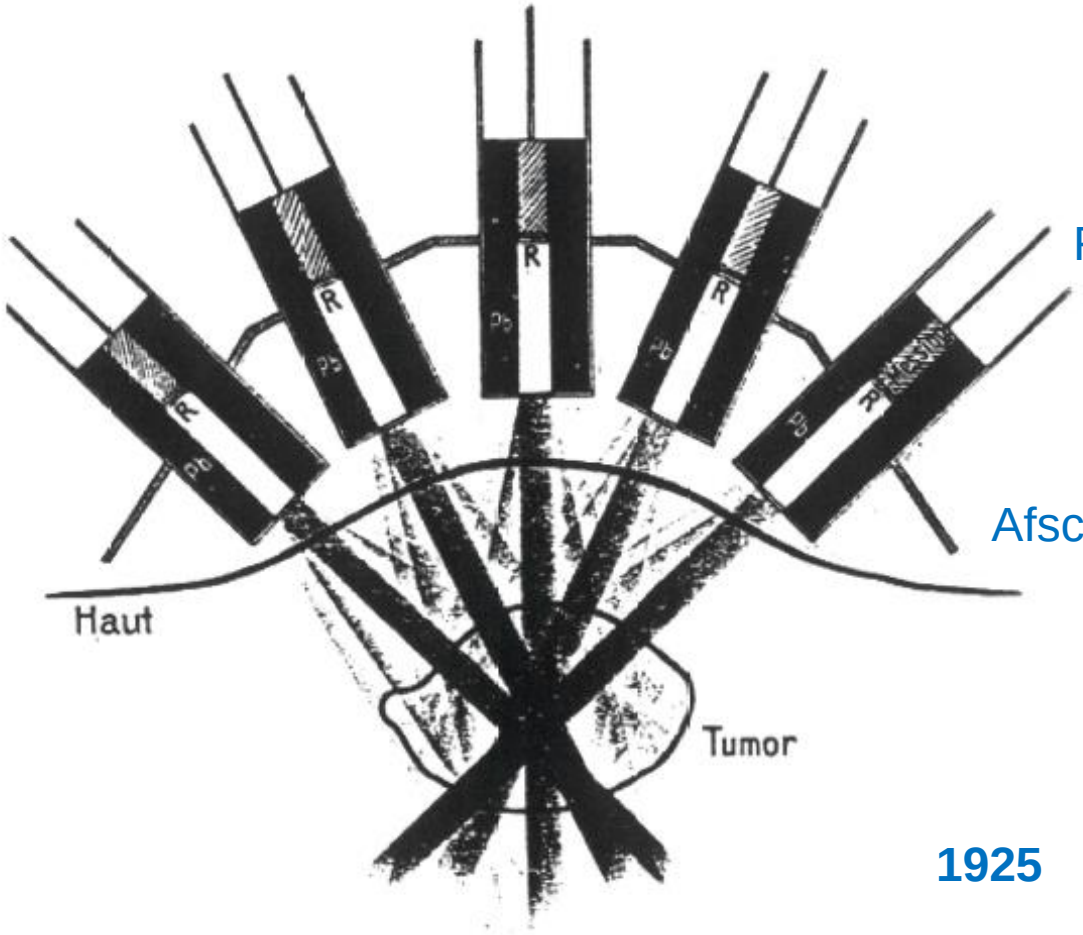
Marie Skłodowska-Curie

- Ontdekking van Polonium en Radium
  - 1903 Nobelprijs voor de Natuurkunde (met Becquerel en Pierre)
  - 1911 Nobelprijs voor de Scheikunde

Lorentz, Warburg, Curie, Planck, Rutherford, Kamerlingh Onnes, Einstein

100 jaar geleden bedacht hoe het optimaal moet

Meerdere richtingen



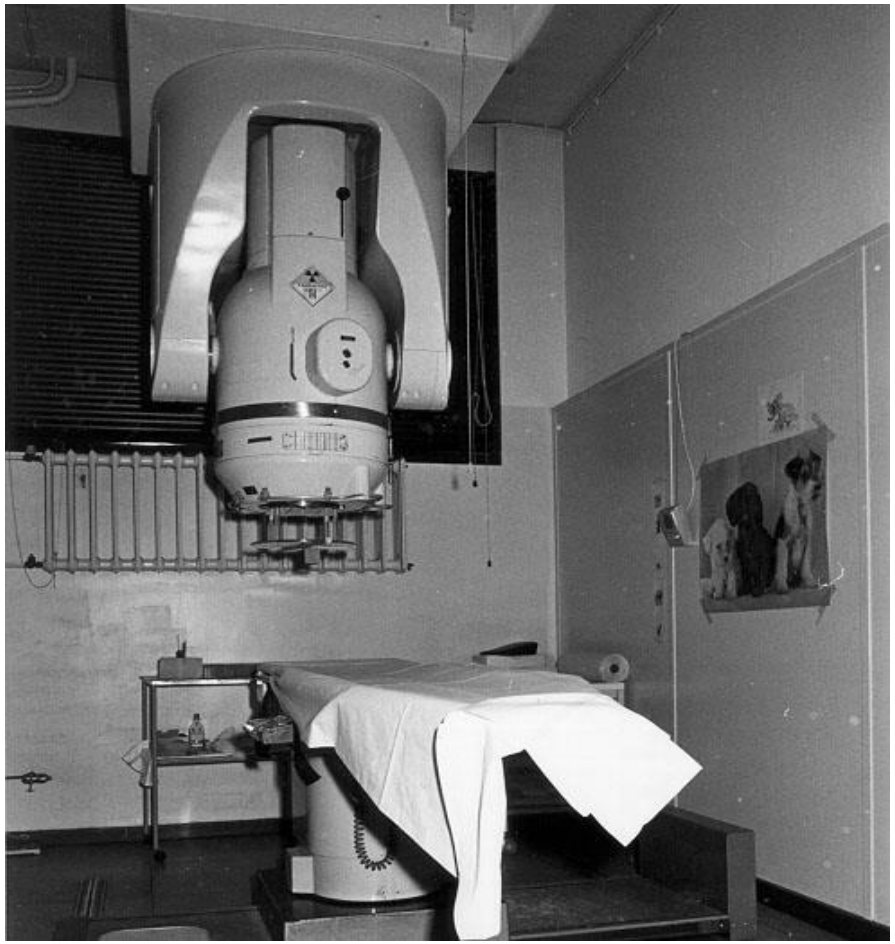
Radium bronnen

Afscherming

1925

Uitdagingen en verbeteringen

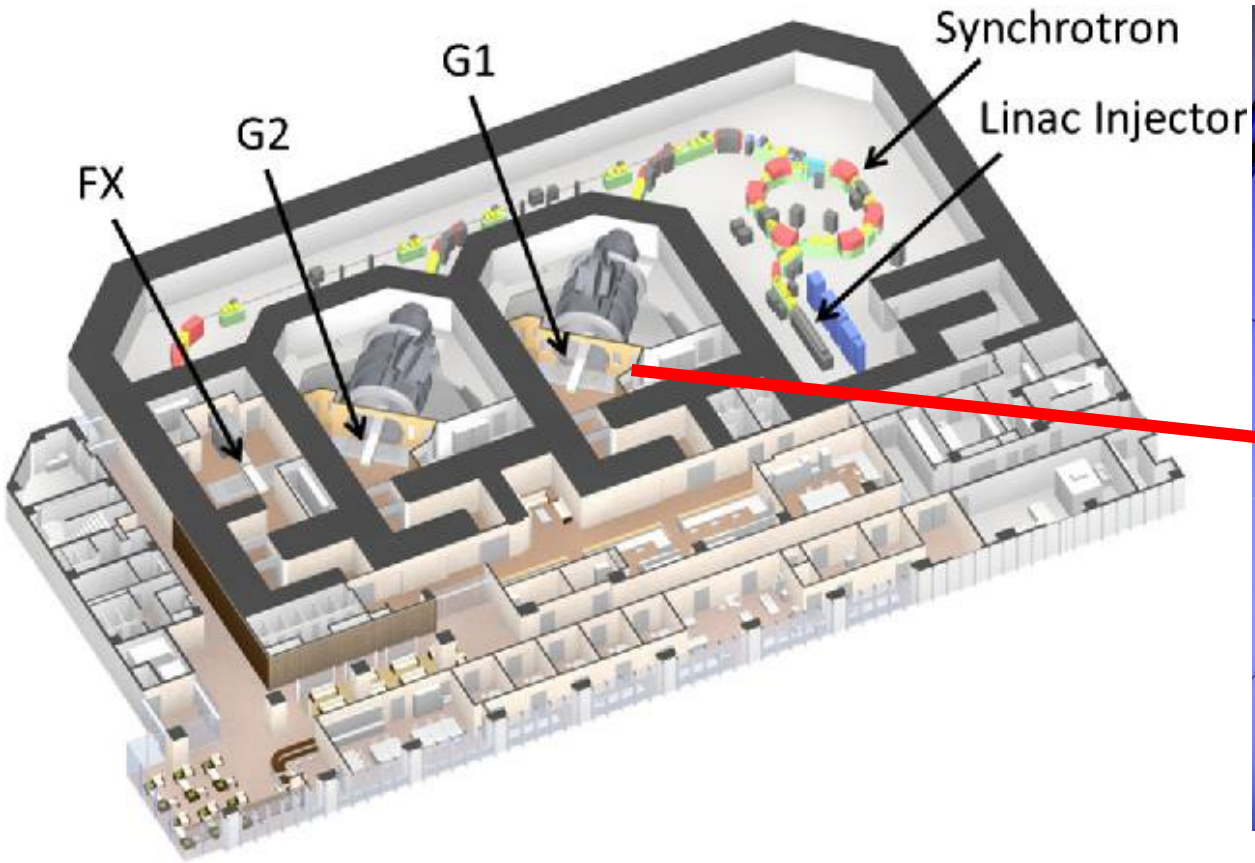
- Juiste dosis op de juiste plek
  - Fotonen VMAT boogbestralingen
  - Protonen
  - MRI-linac
- Minder vaak bestralen
  - Stereotactische technieken
- Snel bestralen
  - FLASH



Uitdagingen en verbeteringen

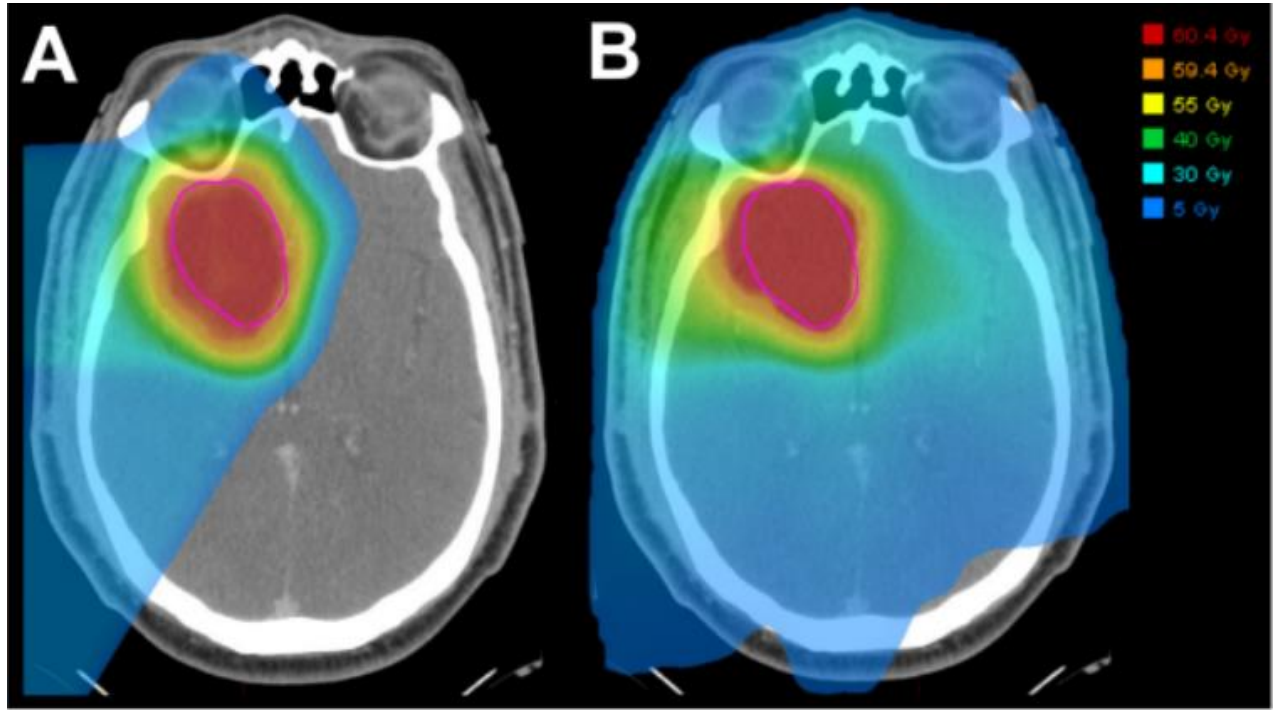
- Juiste dosis op de juiste plek
  - Fotonen VMAT boogbestralingen
  - Protonen
  - MRI-linac
- Minder vaak bestralen
  - Stereotactische technieken
- Snel bestralen
  - FLASH

Protonen bestraling



Protonen bestraling

- Is het doelgebied goed bekend?
- Minder dosis buiten doelgebied
- Dosis RBE: 10% omrekenen
- Nieuwe effecten
- Radiation-induced contrast enhancement (RICE)
- Radiation-induced leukoencephalopathy (RIL)
- Radiation-induced Brain Lesions (**RIBL**)



RADT-23 - Modality-specific CNS injury following proton vs photon beam radiotherapy in glioma

Friday, November 18, 2022 7:30 PM – 9:30 PM ET Location: West/Central Hall

EANO September 2022

- RIBL bij 15% van de patienten
- Na een jaar

JOURNAL ARTICLE

JS09.6.A Low incidence of radiation-induced brain lesions and stable QoL following proton irradiation for CNS and Skull Base tumors- results from the prospective MedAustron register REGI-MA-002015

FREE

C Lütgendorf-Caucig, B Flechl, L Konrath, M Pelak, A Fraller, U Mock, P Fossati, M Stock, P Georg, E Hug

Neuro-Oncology, Volume 24, Issue Supplement_2, September 2022, Page ii9,
https://doi.org/10.1093/neuonc/noac174.028
Published: 05 September 2022

Poster Session

RADT-23 - Modality-specific CNS injury following proton vs photon beam radiotherapy in glioma

Friday, November 18, 2022 7:30 PM – 9:30 PM ET Location: West/Central Hall

NON CME

Poster Session

RADT-41 - Iatrogenic influence on prognosis of radiation-induced contrast enhancements in patients with glioma WHO 1-3 following photon and proton radiotherapy

Poster Presenter(s

Seba

Divisi
Cente
Harva
Bosto

Friday, November 18, 2022 7:30 PM – 9:30 PM Poster Session

NON CME

Poster Presenter(s)

Tanja Eichkorn, MD (she/her/hers)

Department of Radiation Oncology, Universit
Hospital Heidelberg, and Heidelberg Institute
Radiation Oncology (HIRO)
Heidelberg, Germany

RADT-40 - Radiation-induced contrast enhancement following proton radiotherapy for low-grade glioma depends on tumor characteristics and is rarer in children than adults

Friday, November 18, 2022 7:30 PM – 9:30 PM ET Location: West/Central Hall

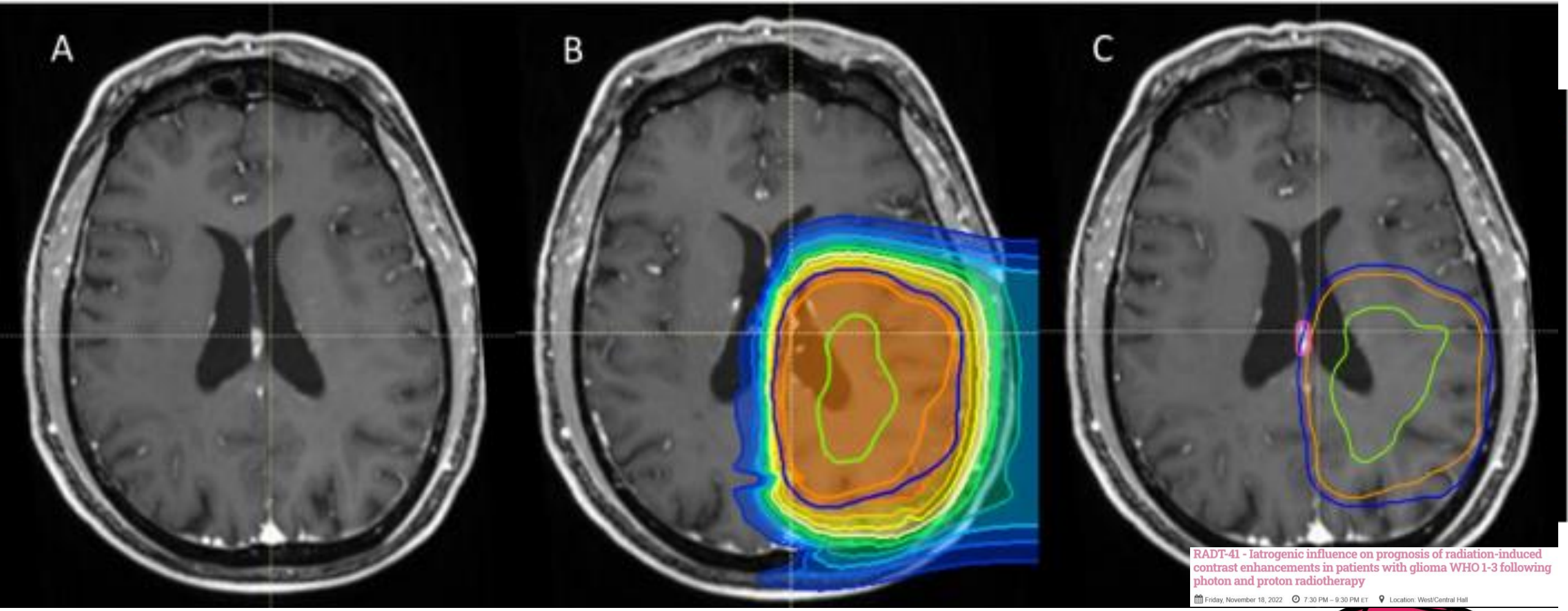
NON CME

Poster Presenter(s)

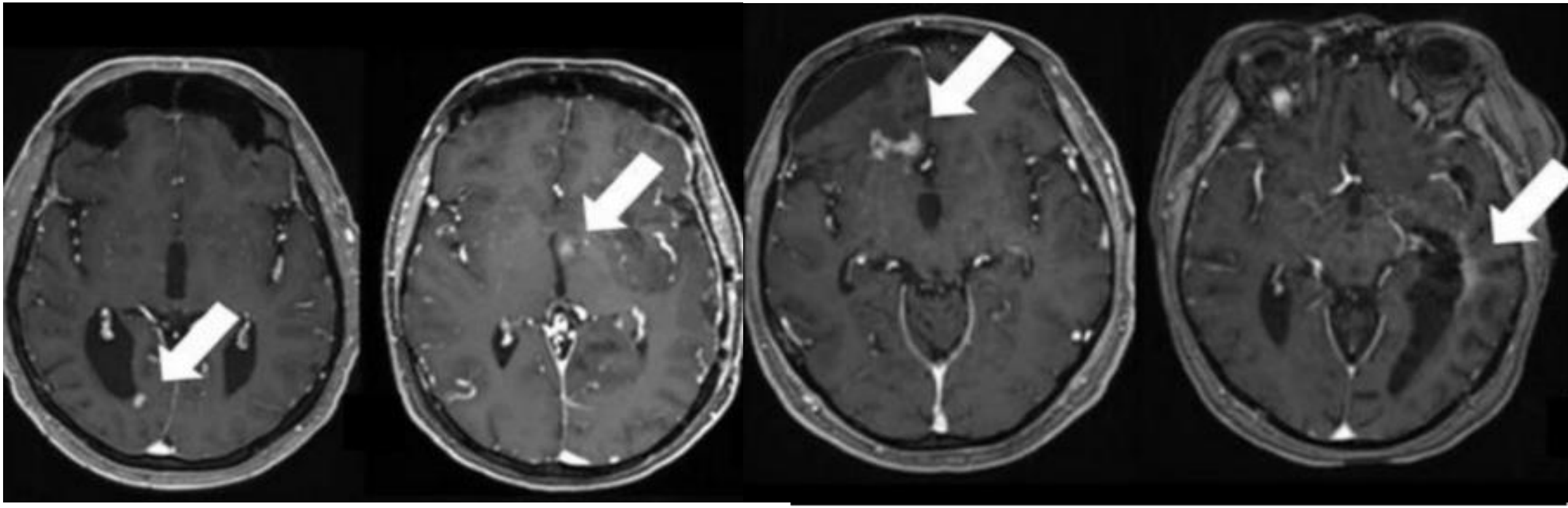
Tanja Eichkorn, MD (she/her/hers)

Department of Radiation Oncology, University Hospital Heidelberg, and Heidelberg Institute for Radiation Oncology (HIRO)
Heidelberg, Germany

Protonen therapie: RIBL



Protonen therapie: RIBL



RADT-40 - Radiation-induced contrast enhancement following proton radiotherapy for low-grade glioma depends on tumor characteristics and is rarer in children than adults

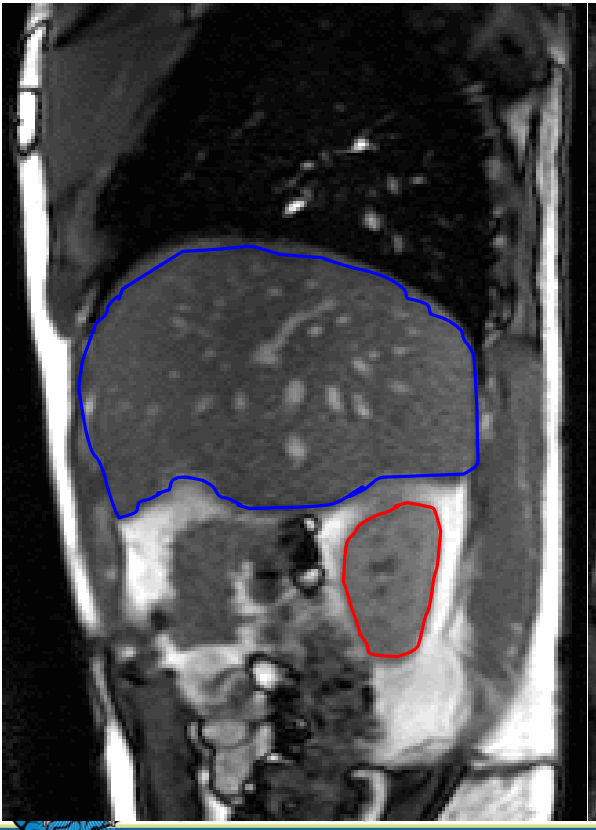
Friday, November 18, 2022 7:30 PM – 9:30 PM ET Location: West/Central Hall

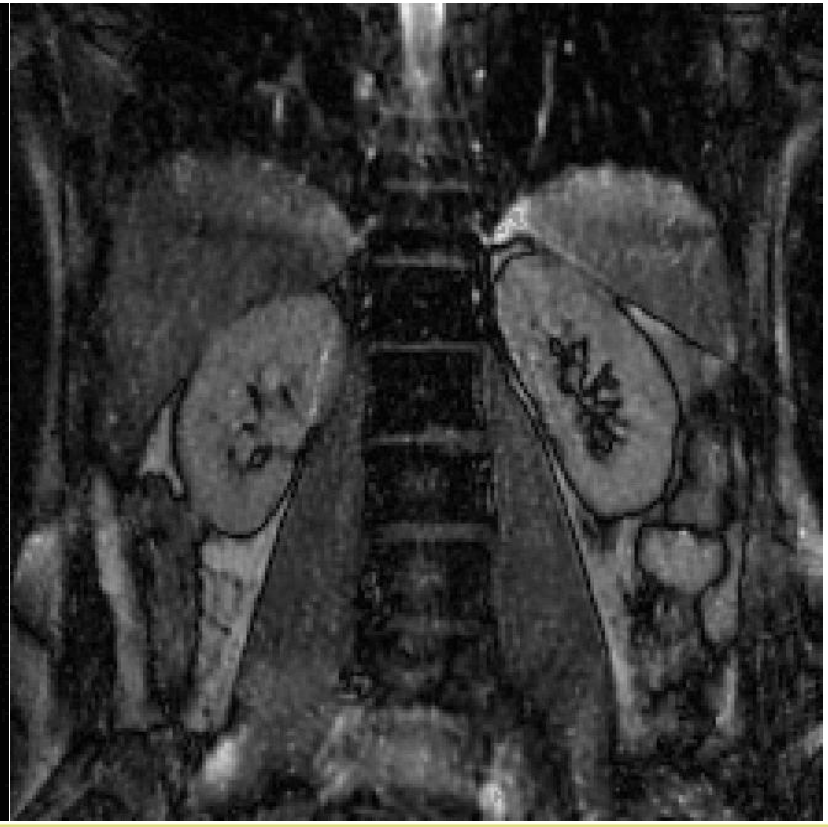
Uitdagingen en verbeteringen

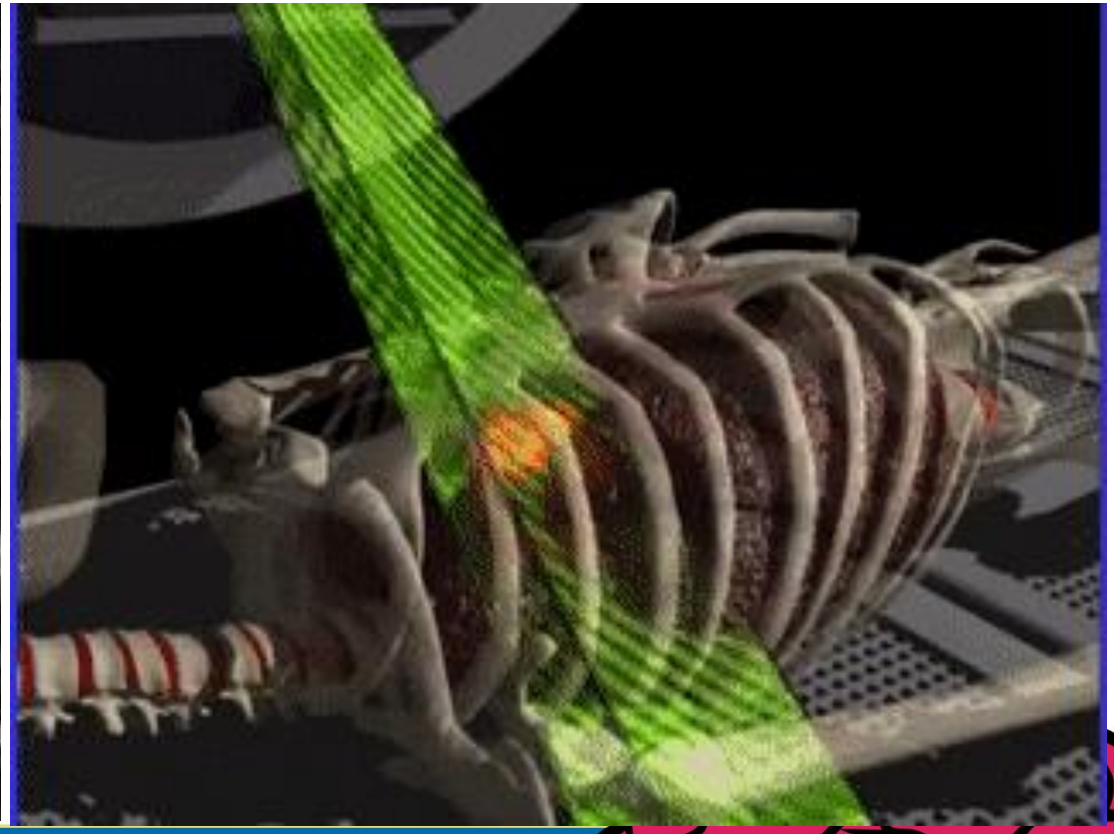
- Juiste dosis op de juiste plek
  - Fotonen VMAT boogbestralingen
  - Protonen
  - MRI-linac
- Minder vaak bestralen
  - Stereotactische technieken
- Snel bestralen
  - FLASH

MRI – linac: zien waar je schiet

- Real-time imaging met MRI
- Ideaal voor bewegende doelgebieden (prostaat, long, buik)





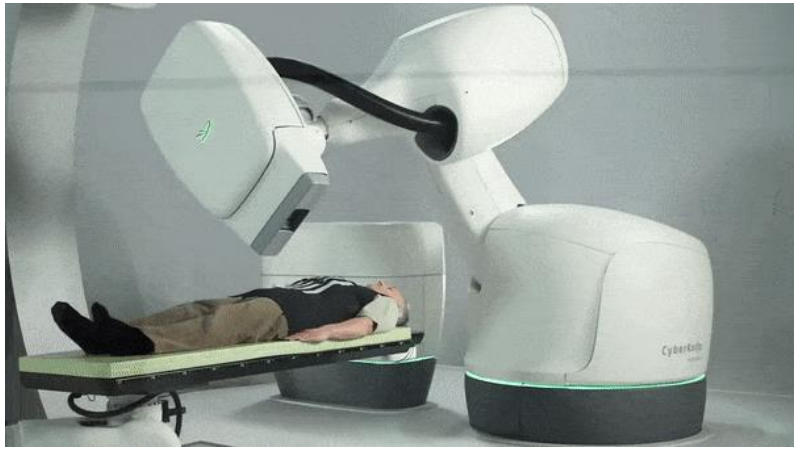


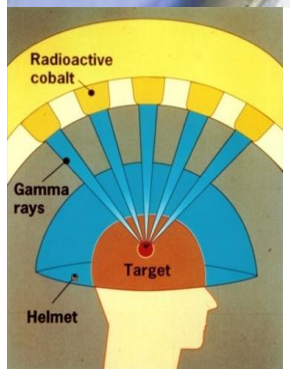
Uitdagingen en verbeteringen

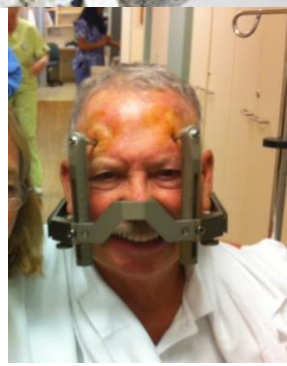
- Juiste dosis op de juiste plek
  - Fotonen VMAT boogbestralingen
  - Protonen
  - MRI-linac
- Minder vaak bestralen
  - Stereotactische technieken
- Snel bestralen
  - FLASH

Stereotactische technieken

- Gamma knife (1968)
- Cyber knife (1991)
- VMAT CT-linac (2010)







Stereotactische technieken

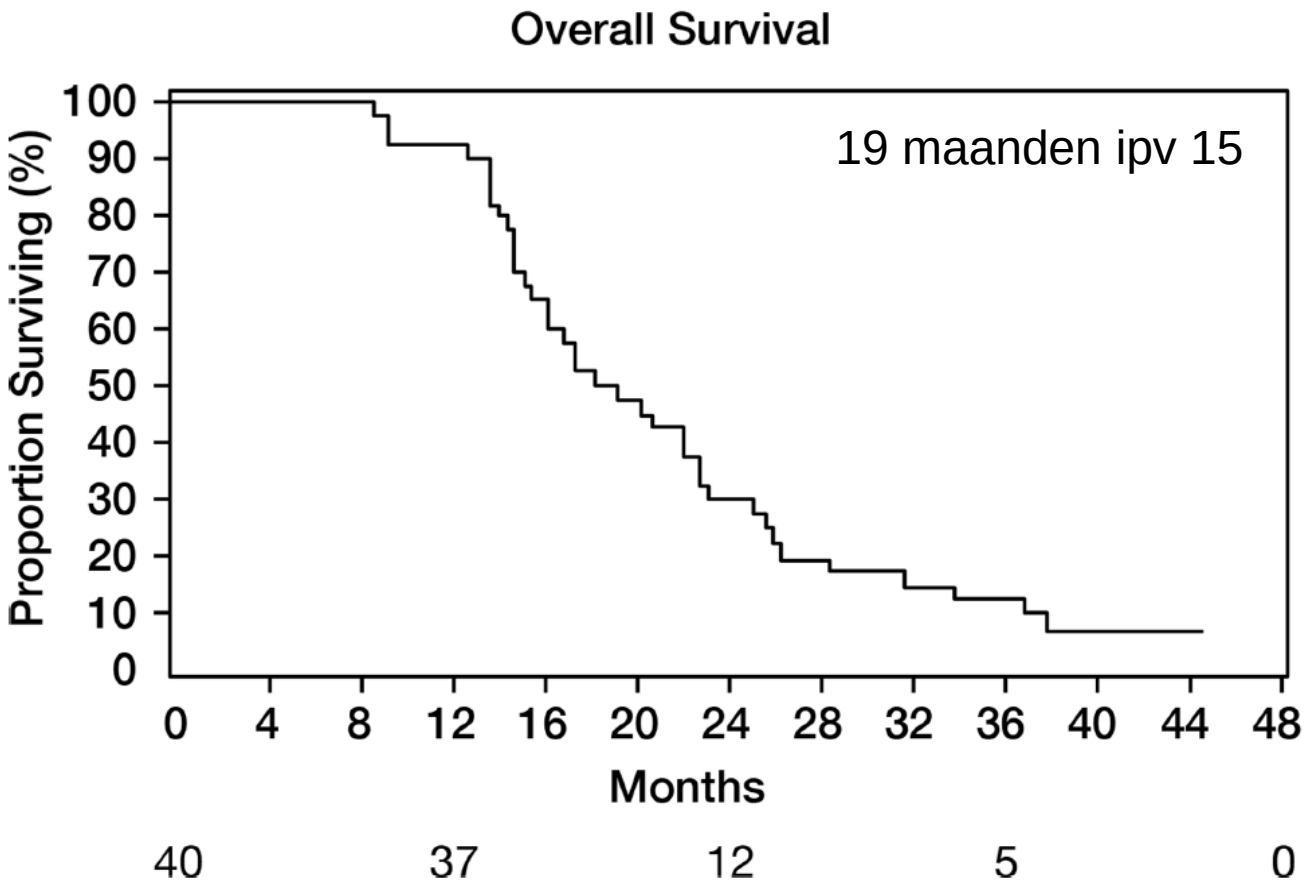
Gewoon gedoseerd

Stereotactisch gedoseerd

Tweet by @DrewMoghanaki Nov 24

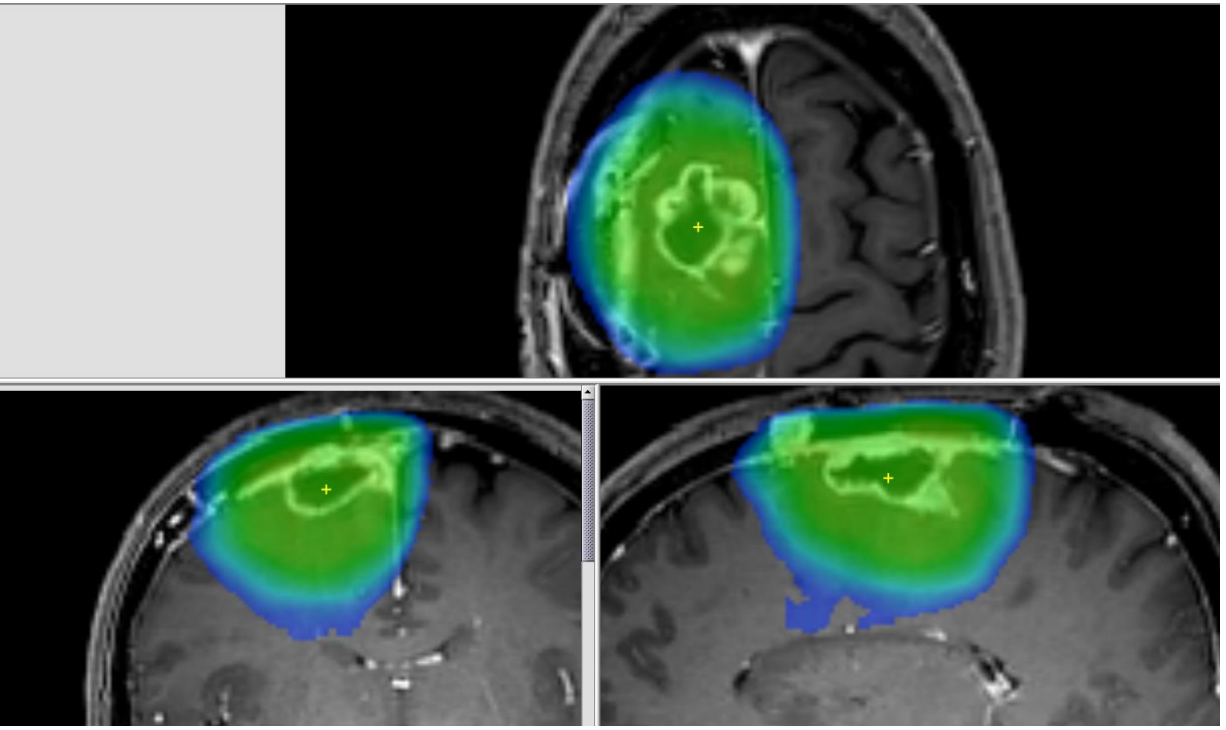
Stereotactische technieken bij gliomen

- Dr Omuro, New York 2014
- 40 patienten
- 6x6Gy + temozolomide

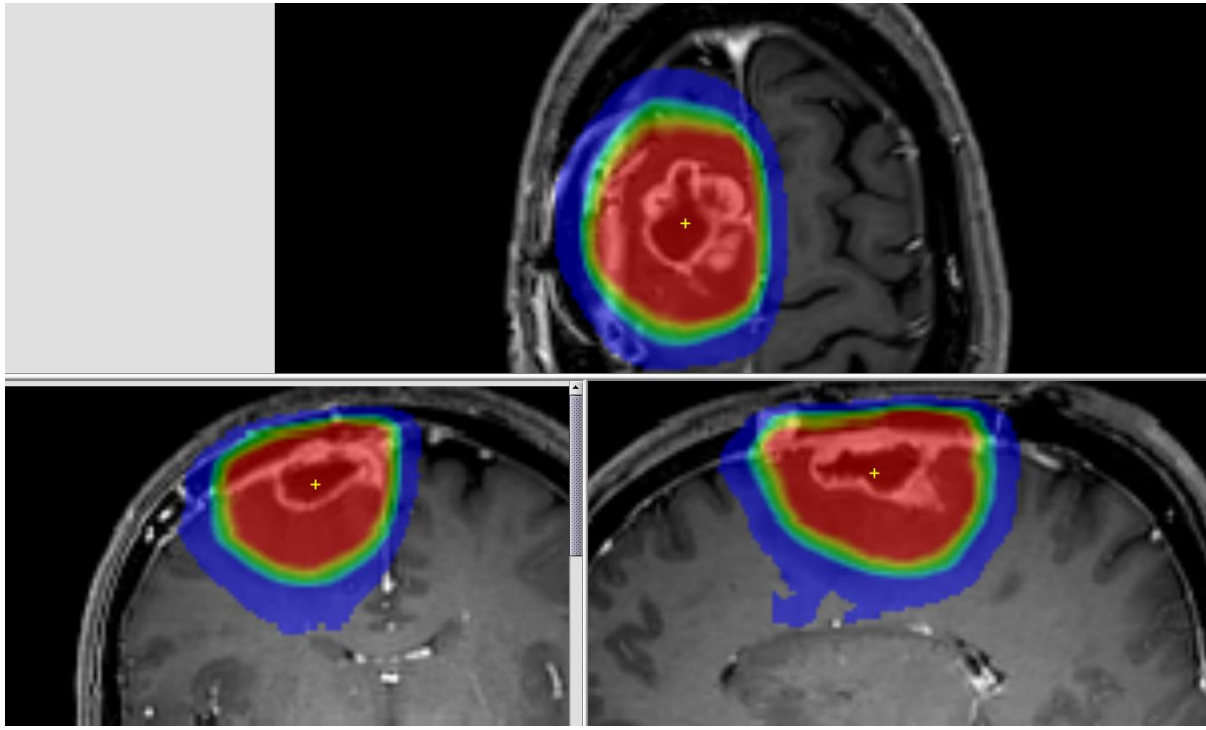


Stereotactische technieken bij gliomen

- In studieverband: 30x2Gy of 6x6Gy (Nederlandse GOLD studie)



Groen = 60Gy



Blauw = >40Gy, Rood = >72Gy

Uitdagingen en verbeteringen

- Juiste dosis op de juiste plek
  - Fotonen VMAT boogbestralingen
  - Protonen
  - MRI-linac
- Minder vaak bestralen
  - Stereotactische technieken
- Snel bestralen
  - FLASH

FLASH radiotherapie

- *Nog lang niet* in de kliniek
- 2014 eerste preklinische proeven
- 1 minuut stralen
  - 2Gy
  - 3600Gy
- 2Gy in 0.03 seconden
- Immuunsysteem gespaard
- Normale cellen gespaard

Volume 19 Issue 12, December 2022

COVER: Delivering FLASH radiotherapy

Cover design: Simon Bradbrook.

FLASH radiotherapie

- *Nog lang niet* in de kliniek voor neurologie
- Eerste patienten bestraald met FLASH

New Online | Views 10,671 | Citations 1 | Altmetric 588

Download PDF | More | Cite This | Permissions

Original Investigation | ONLINE FIRST | FREE

October 23, 2022

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases

The FAST-01 Nonrandomized Trial

Anthony E. Mascia, PhD[1,2]; Emily C. Daugherty, MD[1,2]; Yongbin Zhang, MS[1,2]; et al

Author Affiliations

JAMA Oncol. Published online October 23, 2022. doi:10.1001/jamaoncol.2022.5843

Tumor Microenvironment

Poster Session

TMIC-68 - Evaluating FLASH and conventional dose-rate radiation and immune response with single-cell sequencing in Diffuse Midline Glioma (DMG)

Friday, November 18, 2022 7:30 PM – 9:30 PM ET

Poster Presenter(s)

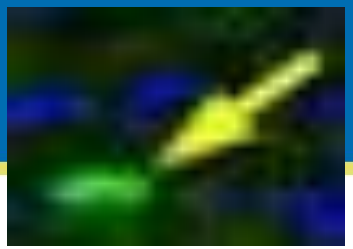
Hanna E. Minns

Research Technician

Columbia University Irving Medical Center

New York, United States

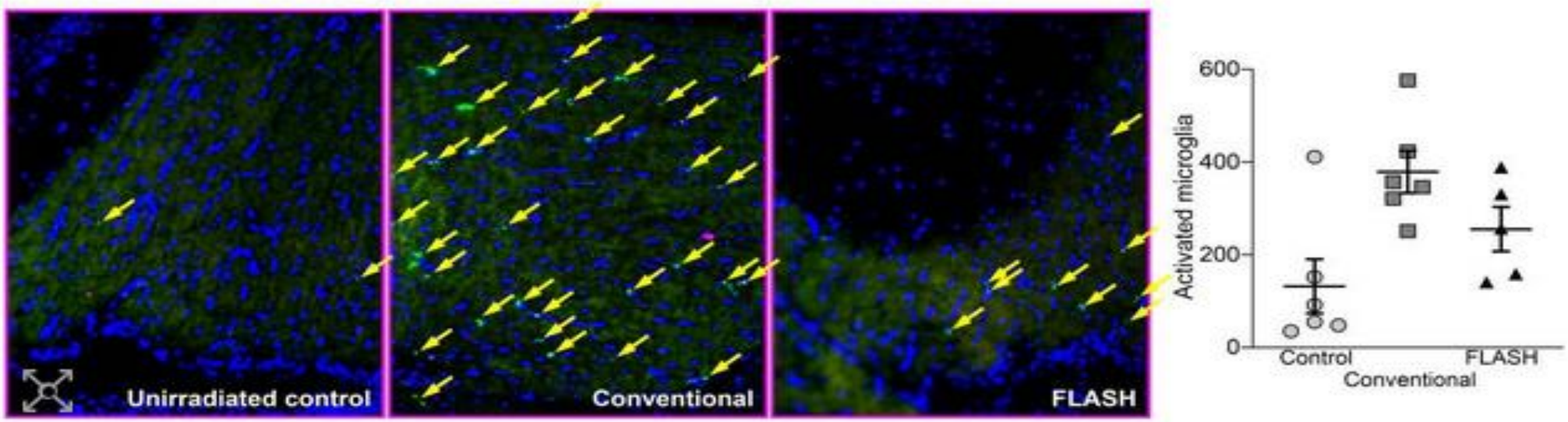
FLASH radiotherapie en hersentumoren



RADIOTHERAPY | RESEARCH UPDATE

Instantaneous brain irradiation limits cognitive impairment

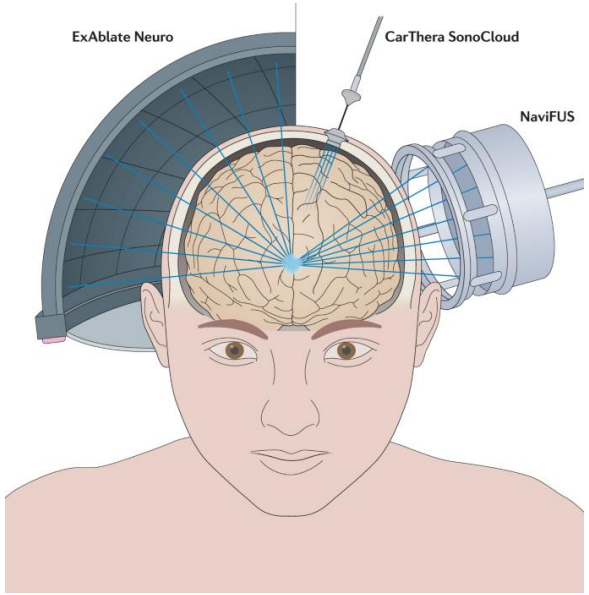
05 Aug 2019



Representative sections of mouse hippocampus with fluorescent staining of activated microglia (bright green cells), which are mediators of neuroinflammation. FLASH induced less activation of microglia than conventional irradiation, leading to preserved neurocognitive function. (Courtesy: Billy W Loo Jr)

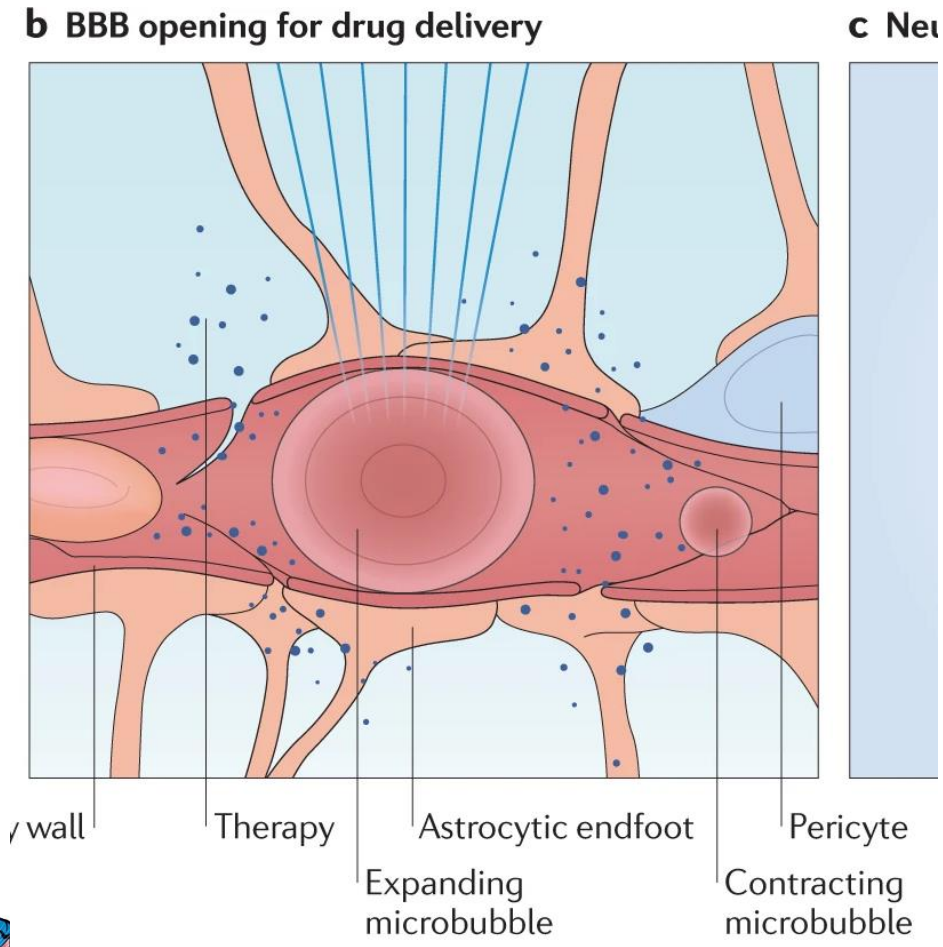
Plaatselijke behandelingen zonder 'snijden'

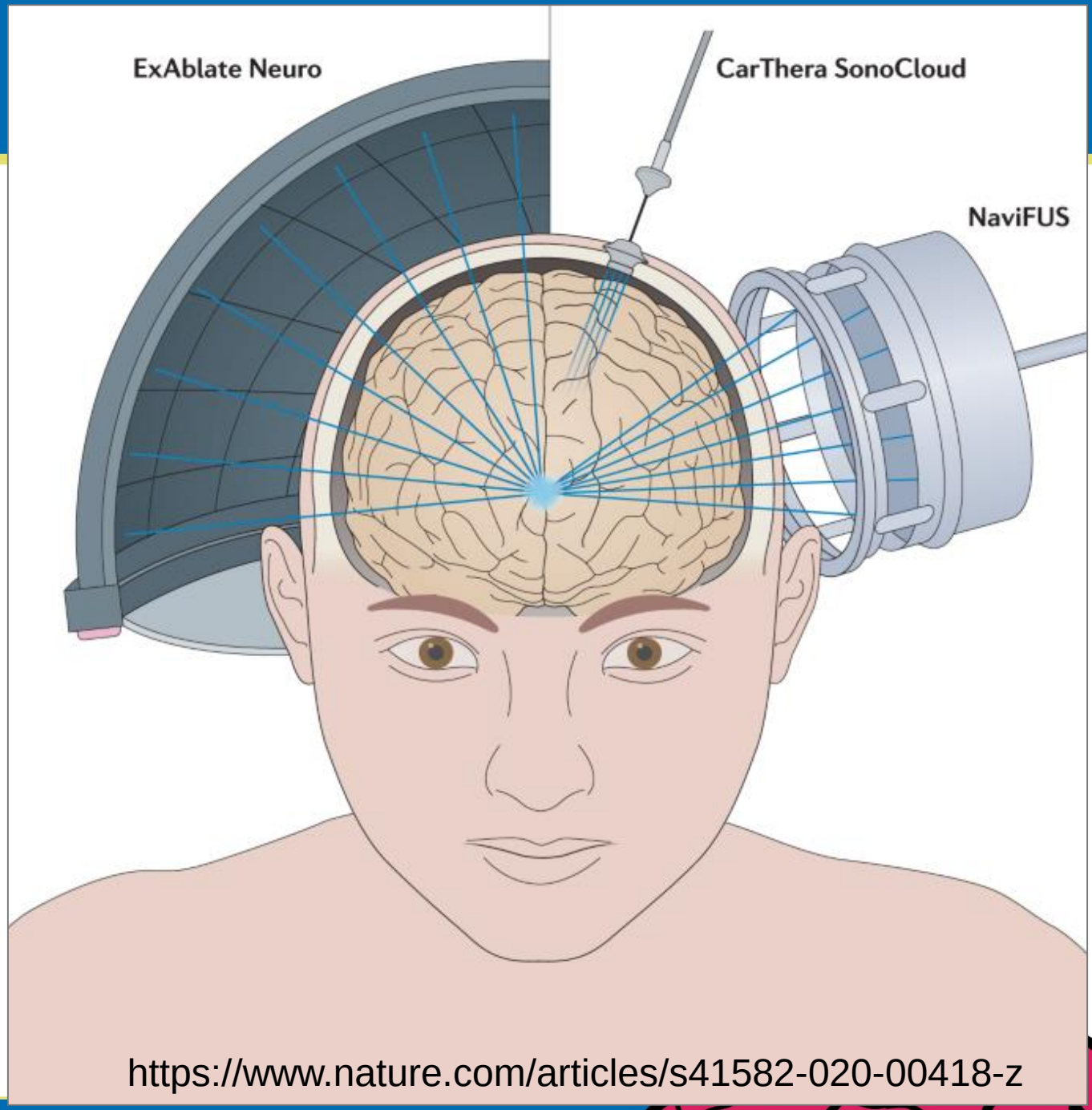
- Radiotherapie
  - Fotonen
  - Protonen
  - FLASH
- HIFU en FUS
- Hyperthermie



HIFU / FUS

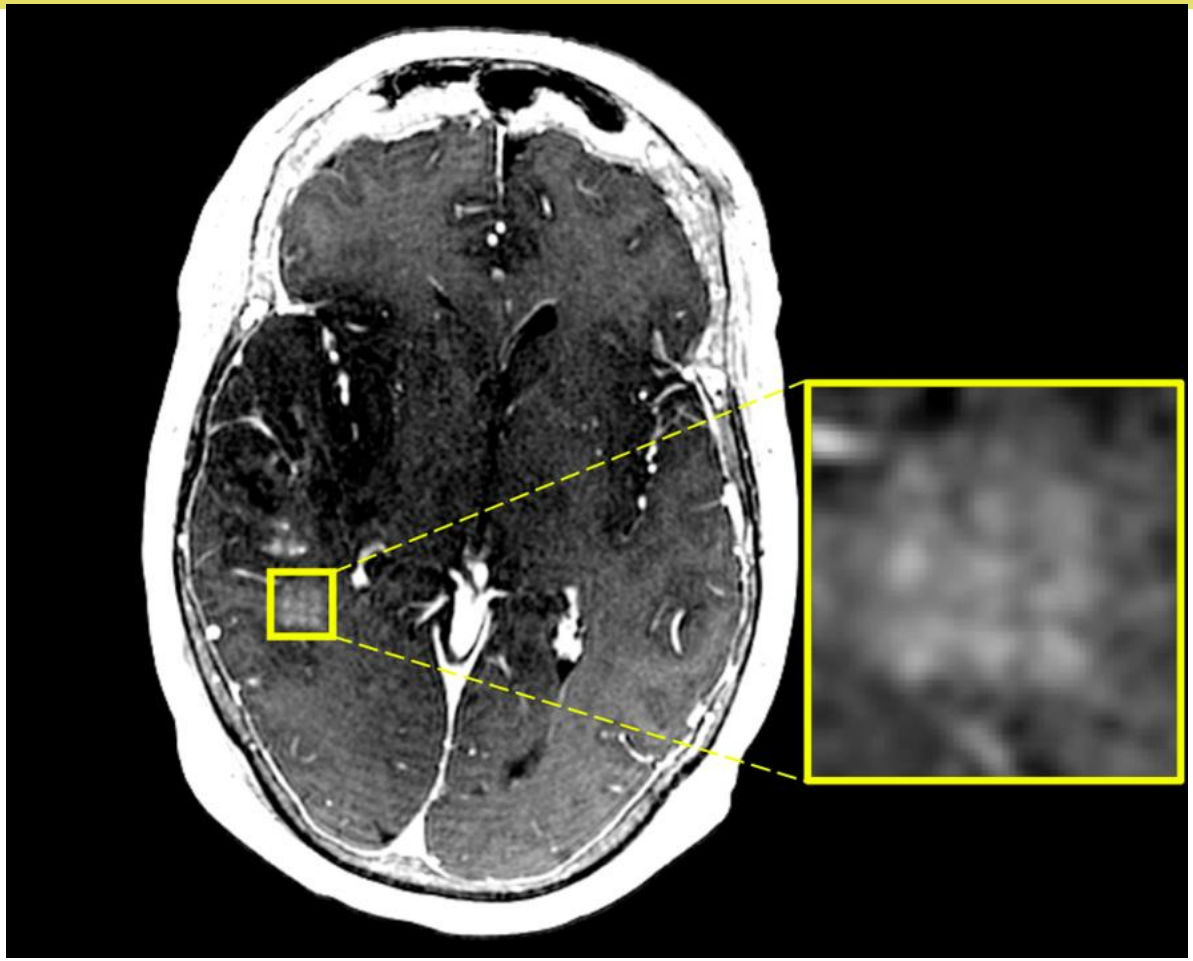
- Bloed hersen barriere openen





https://www.nature.com/articles/s41582-020-00418-z

Focused Ultra Sound



Focused Ultra Sound

Focused Ultra Sound sinds 2015 in studies

Sunnybrook
HEALTH SCIENCES CENTRE

Contact Us | News | Events | DONATE NOW

Search

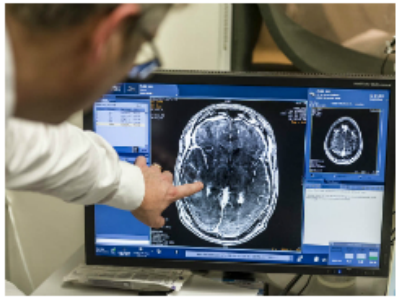
HOSPITAL | FOUNDATION | RESEARCH | EDUCATION

WELCOME | PATIENTS & VISITORS | CARE PROGRAMS | DEPARTMENTS | CAREERS | VOLUNTEERS

Hospital > News & Media > News

Share:

World first: blood-brain barrier opened non-invasively to deliver chemotherapy



View more photos and learn more about this world-first in our Q&A / backgrounder

Related news stories

Sound over scalpel »

Sunday, November 08, 2015 View full media release »

Sunnybrook scientists made history this week as they used focused ultrasound to non-invasively breach the blood-brain barrier and more effectively deliver chemotherapy into the brain tumour of a patient.

Each person has a protective barrier that normally restricts the passage of substances from the bloodstream into the brain protecting it from toxic chemicals.

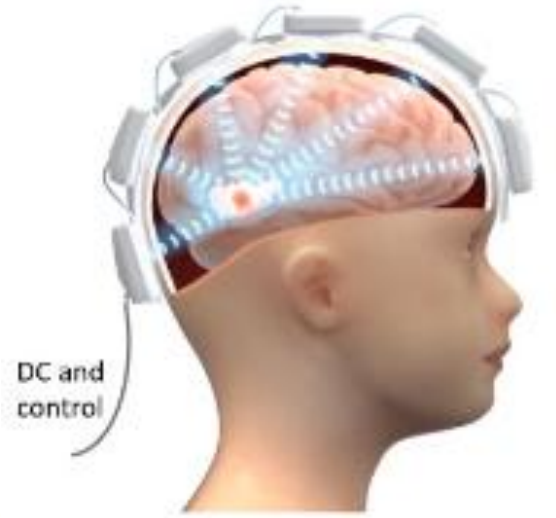
"The blood-brain barrier (BBB) has been a persistent obstacle to delivering valuable therapies to treat disease such as tumours," says Dr. Todd Mainprize, principal investigator of the study and Neurosurgeon in the Hurvitz Brain Sciences Program at Sunnybrook Health Sciences Centre.

"We are encouraged that we were able to temporarily open this barrier in a patient to deliver chemotherapy directly to the brain tumour."

The research team infused a chemotherapy drug, then tiny, microscopic bubbles, into the

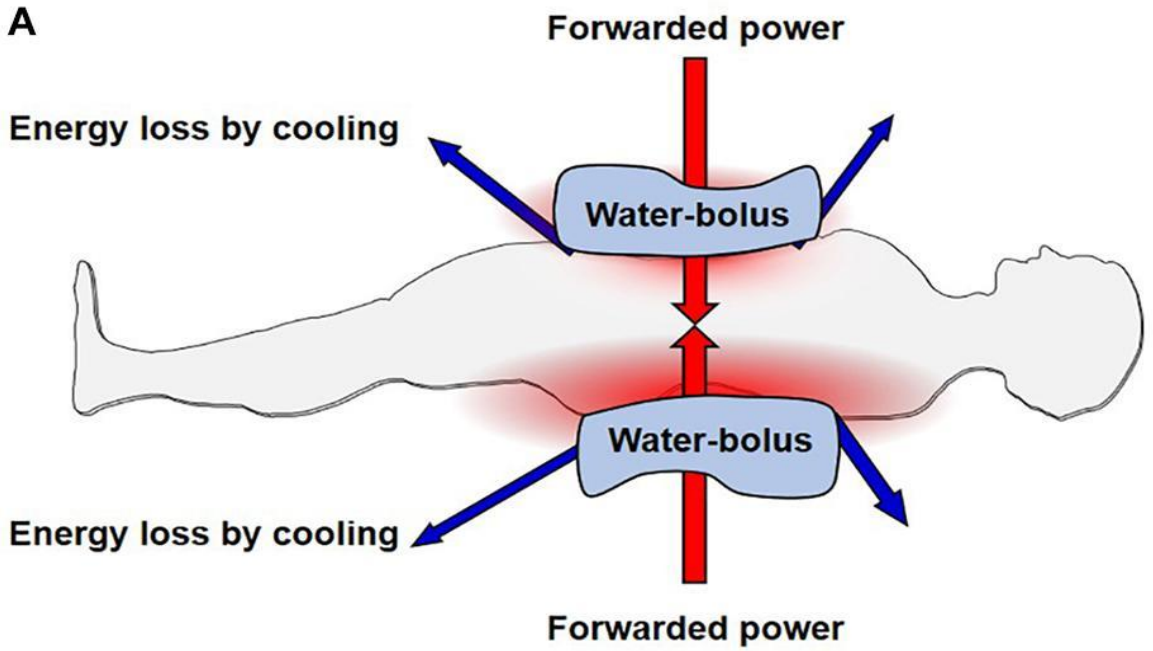
Plaatselijke behandelingen zonder 'snijden'

- Radiotherapie
  - Fotonen
  - Protonen
  - FLASH
- HIFU en FUS
- Hyperthermie



Hyperthermie

- Samen met radiotherapie
- Koorts opwekken
- Boven 41 graden
- Cel herstel geblokkeerd
- Geen patent



https://doi.org/10.3389/fonc.2020.01690

https://www.kanker.nl/soorten-behandelingen/hyperthermie/algemeen/wat-is-hyperthermie

Hyperthermie

- Nog niet voor hersenen

Master's Thesis Announcement Nov. 2022

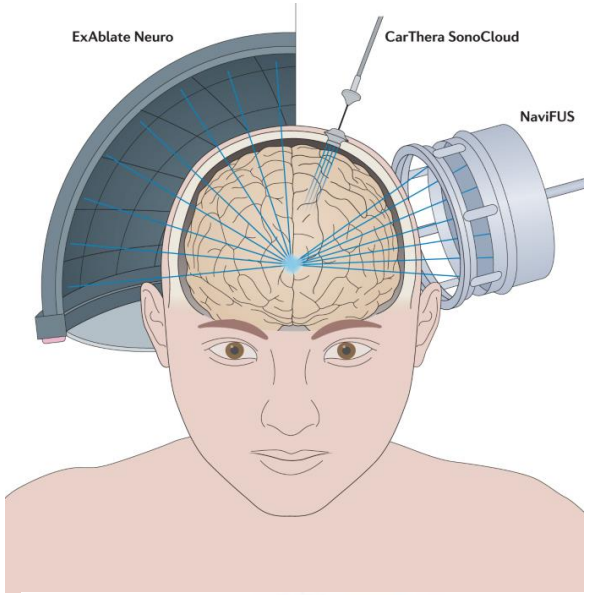
Efficient High-Power Amplifier for Hyperthermia Treatment Applicator

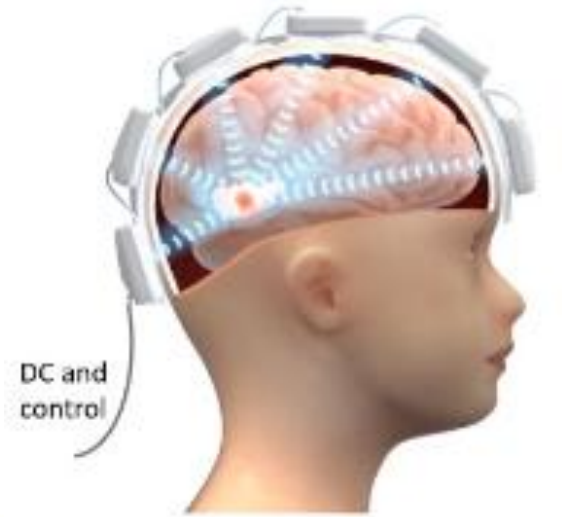
Assist. Prof. Gregor Lasser, gregor.lasser@chalmers.se , MC2, Microwave Electronics Lab

Figure 1 Comparison of state-of-the-art commercial (a) and envisioned compact, efficient, and reconfigurable hyperthermia treatment system (b).

Plaatselijke behandelingen zonder 'snijden'

- Radiotherapie
  - Fotonen
  - Protonen
  - FLASH
- HIFU en FUS
- Hyperthermie





Publieksdag
Hersentumoren

Zaterdag 26 November 2022

Online event

In samenwerking met:

Modality-specific CNS injury following proton vs photon beam radiotherapy in glioma

Sebastian F. Winter,[1-3,*] **Melissa Gardner**,[1,4] **Michael W. Parsons**,[1,4] **Clemens Grassberger**,[5] **Marc Bussière**,[5] **Felix Ehret**,[3,6] **David Kaul**,[6] **Wolfgang Boehmerle**,[2] **Matthias Endres**,[2] **Helen A. Shih**,[1,5] **Jorg Dietrich**[1]

[1] *Division of Neuro-Oncology, MGH Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA;* [2] *Department of Neurology and Experimental Neurology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany;* [3] *Berlin Institute of Health at Charité – Universitätsmedizin Berlin, BIH Biomedical Innovation Academy, BIH Charité Junior Clinician Scientist Program, Berlin, Germany;* [4] *Department of Psychiatry, Psychology Assessment Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA;* [5] *Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA;* [6] *Department of Radiation Oncology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany;* ***Correspondence: sfwinter@mgh.harvard.edu***

Introduction

- CNS injury following brain-directed radiotherapy (RT) is common, may mimic disease progression, and difficult to diagnose and manage.
- Dosimetric advantages of protons (PRT) over photons (XRT) minimize radiation to healthy brain (**Figure 1**), potentially limiting radiotoxic sequelae.
- We characterized CNS radiotoxicity i.e., radiation-induced leukoencephalopathy (RIL), brain tissue necrosis (TN), and cerebral microbleeds (CMB), during progression-free survival (PFS) periods in glioma patients irradiated with PRT or XRT.

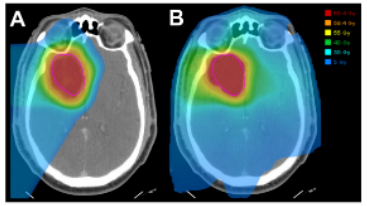


Figure 1. *Dosimetric comparison of proton (**A**) and photon (VMAT) (**B**) radiation treatment plans in a patient with a WHO grade 3 IDH1 mutant astrocytoma, illustrating equal target coverage with relative sparing of most of the contralesional hemisphere achievable by proton therapy.*

Materials and Methods

- Retrospective analysis of 34 patients with grade 2/3 gliomas treated by partial cranial RT.
- Patients were stratified by RT modality [XRT(n=17) vs PRT(n=17)] and matched on 11 criteria [age, sex, tumor type/location/laterality, mutational status (IDH; 1p19q deletion), concurrent/adjuvant chemotherapy, radiation dose/fractions].
- Radiotoxicity was characterized longitudinally until 3 years post-RT via analysis of serial MRI T2/FLAIR- (RIL), T1+Contrast- (TN), and gradient-echo T2* (CMB)-weighted sequences.
- RIL was rated using a novel scoring system with embedded Fazekas scale at global (whole-brain) and hemispheric levels (**Figure 2, Table 1**).
- Patient RT dose distribution plans were spatially correlated to each CMB and/or TN lesion to extrapolate radiation dose exposure at individual lesion level, using MiM medical imaging software.

Figure 2. *Evolution of RIL severity (grades 1 – 3) on axial T2/FLAIR MRI, demonstrating hyperintensities in the periventricular (P-WMH), deep (D-WMH), and resection cavity (RC-WMH) white matter.*

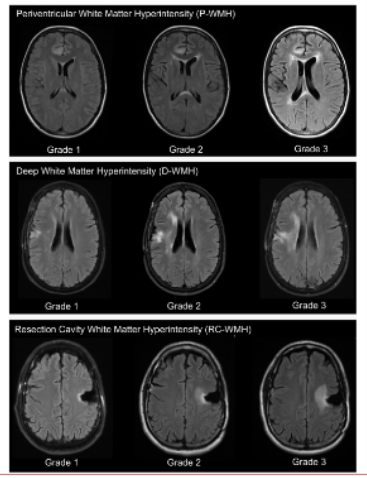


Table 1. *Summary of the novel RIL scoring system, depicting calculation of RIL score and corresponding RIL grade, at both hemispheric and global (=whole-brain) levels.*

Score Type	P-WMH (≤10mm from ventricle)	D-WMH (>10mm from ventricle or isolated lesions)	RC-WMH (resected tumors only)
Grade 0	absent	absent	no WMH
Grade 1	caps or thin line	punctate foci	non-tumor related WMH present at post-RT baseline
Grade 2	smooth halo	beginning confluence	increase <50% of RC size
Grade 3	Extension into DWM (>10mm)	large confluent areas	increase of >50% of RC size
Hemispheric Level: RIL Score (= RIL Grade)	0 (= absent; 0) 1 – 2 (= mild; 1) 3 – 4 (=moderate; 2) 5 – 6 (=severe; 3)		
Hemispheric Level: RIL Score (= RIL Grade)	0 (= absent; 0) 1 – 3 (=mild; 1) 4 – 6 (=moderate; 2) 7 – 9 (=severe; 3)		
Global Level: RIL Score (= RIL Grade)	Left + Right Hemispheric RIL Grade = Global RIL Score (0 – 6), whereby 0 (= absent; 0) ≥1 (= mild; 1) >2 or any moderately affected (grade 2) hemisphere (= moderate; 2) >4 or any severely affected (grade 3) hemisphere (= severe; 3)		

Results

I. Patient Characteristics & Treatment Specifics

- 34 patients (56% males; median age 39.9 years) with newly diagnosed (n=22) or recurrent (n=12) grade II (67%) or III (33%) gliomas, irradiated with partial cranial XRT (n=17) or PRT (n=17) (**Table 2**).
- Pathologies included astrocytoma (50%), oligoastrocytoma (23.5%), and oligodendroglioma (20.6%); tumors were mostly located in frontal (50.0%) or temporal (32.3%) lobes and predominantly (78.8%) IDH-1 mutated.
- Median Karnofsky performance status (KPS) prior to RT was high (90/100); most patients (>60%) had ≥1 cardiovascular comorbidities at time of RT.
- Median progression free survival (PFS) was 5 years (4.7 [XRT] vs 5.1 [PRT]); recurrence rate post-RT was 41.2% (52.9% [XRT] vs 29.4% [PRT]), with a median follow-up time of 9.8 and 5.5 years, respectively.

Table 2. *Summary patient treatment specifics.*

Treatment specifics	Total (N=34)	XRT (N=17)	PRT (N=17)	p value for difference
Extent of resection				X^2=5.727, p=0.126
% GTR (N)	8.8 (3)	5.9 (1)	11.8 (2)	
% NTR (N)	17.6 (6)	0 (0)	35.3 (6)	
% STR (N)	32.4 (11)	29.4 (5)	35.3 (6)	
% PR (N)	17.6 (6)	17.6 (3)	17.6 (3)	
% Biopsy only (N)	23.5 (8)	41.2 (7)	5.9 (1)	X^2=5.1, p=0.024
RT Regimen				N/A
% Photons (N)	50 (17)	100 (17)	N/A	
% IFRT (N)		53.3 (8/15)	N/A	
% IMRT (N)		33.3 (5/15)	N/A	
% VMAT (N)		13.3 (2/15)	N/A	
% Protons (N)	50 (17)	N/A	100 (17)	
Median Dose in Gy (range)	54 (9)	59.4 (9)	54(RBE) (5.4)	
Median No. Fractions (range)	30 (5)	33 (5)	30 (3)	
Median Fraction size in Gy	1.8	1.8	1.8(RBE)	
Systemic Treatment				
% w/ neoadjuvant Ctx (N)	14.7 (5)	17.6 (3)	11.8 (2)	X^2=0.234, p=0.628
% w/ concurrent Ctx (N)	26.5 (9)	23.5 (4)	29.4 (5)	X^2=0, p=1
% w/ adjuvant Ctx (N)	67.6 (23)	58.8 (10)	76.5 (13)	X^2=1.209, p=0.271
% Bevacizumab use (N)	33.3 (11/33)	41.2 (7/17)	25.0 (4/16)	X^2=0.971, p=0.325
% Steroid use (N)	15.4 (4/26)	33.3 (3/9)	5.9 (1/17)	X^2=3.406, p=0.065

II. Radiation-induced leukoencephalopathy: injury burden & dynamics

- The novel RIL scoring system was reliable (intraclass correlation coefficient >0.9).
- Longitudinal analysis identified a significant increase in global RIL in both XRT [$F(3, 57)=8.63$, $p< 0.001$] and PRT [$F(3, 61)=4.69$, $p< 0.005$] groups over time, relative to baseline (6 weeks post-RT) (**Figure 3 A**).
- Most patients [62% (XRT) and 72% (PRT)] developed moderate or severe RIL within 3 years, with the ipsilesional hemisphere more severely affected (**Figure 3 C, E**).
- PRT was associated with greater ipsilesional injury at baseline [average RIL grade: 0.8 (XRT) vs. 1.1 (PRT), t=2.379, p<0.03)] but this observation was not significant at subsequent timepoints.
- Analysis of RIL injury dynamics, measured as average % change between 1 and 3 years post-RT, identified no significant intergroup differences at global level [34.4% (XRT) vs. 29.4% (PRT)] (**Figure 3 B**).
- Notably, analysis of RIL injury dynamics at hemispheric level identified radiation modality-specific differences: XRT resulted in greater contralesional hemispheric injury than PRT [37.5 % (XRT) vs. 7.8% (PRT), t=2.175; p=0.037] (**Figure 2 F**). This effect was not observed in ipsilesional hemispheres (**Figure 2 D**).

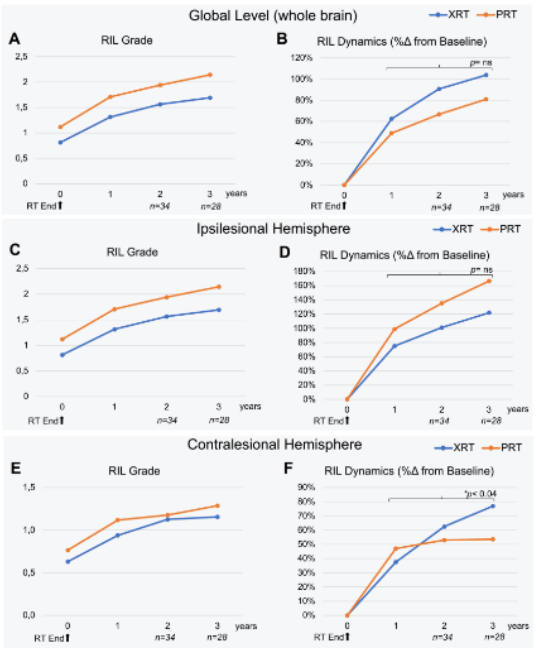


Figure 3. ***Panels A, C, E:*** *Evolution of average RIL grade in XRT (blue lines) and PRT (orange lines) groups at global (**A**) and ipsilesional (**C**) and contralesional (**E**) hemispheric levels. In both groups, global and hemispheric RIL grade increases significantly from baseline up until 3-years post-RT. The PRT group exhibits slightly greater average RIL grade across all timepoints (finding only significant at baseline).* ***Panels B, D, F:*** *Analysis of RIL injury dynamics (average % change between 1 and 3 years post-RT) in XRT (blue lines) and PRT (orange lines) groups at global (**B**) and ipsilesional (**D**) and contralesional (**F**) hemispheric levels, demonstrating an association of XRT with significantly greater RIL injury dynamics in the contralesional hemisphere.*

III. Cerebral microbleeds: prevalence, burden, distribution pattern

- Longitudinal radiographic analysis of CMB was reliable (intraclass correlation coefficient >0.9), and a total of 362 CMB [213 (XRT); 149 (PRT)] were identified and included in the analysis.
- At 3 years post-RT, cumulative prevalence of CMB was 73.5% (n=25/34), with an average number of 4.2 (SD, 5.0) lesions per patient (**Figure 4 A, B**).
- CMB typically manifested as numerous small round hypointense lesions on gradient-echo T2*-weighted MRI sequences, occurring in lobar (>60%), deep territorial (>30%), or, rarely, infratentorial (<5%) brain regions (**Figure 4 C**) typically in ipsilesional hemispheres (75%) and within the main RF (>60%)
- Median latency from RT completion to first CMB manifestation was 17 (range, 1 – 55) months. In all cases, individual CMB remained traceable longitudinally on serial MRIs, persisting throughout the entire follow-up period.
- XRT was associated with earlier CMB onset [median time to first CMB, 7 (XRT) vs 17.5 (PRT) months, p=ns] and greater CMB burden in remote, contralesional hemispheres [31.5% (XRT) vs 16.8% (PRT), p=ns]
- CMB-to-RF correlation identified significant intergroup differences (**Figure 4 D – F**): PRT was associated with preferential CMB clustering at the RF margin (70 – 89% target dose) [14% (XRT) vs 26% (PRT)], whereas XRT resulted in greater remote CMB development outside the main RF (<70% target dose) [25% (XRT) vs 11% (PRT)] (X^2=14.697, p<0.001).

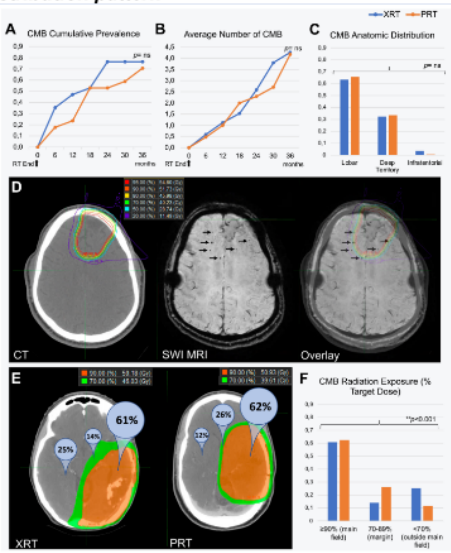


Figure 4. *Intergroup comparison of CMB cumulative prevalence (**A**), average number per patient (**B**), and anatomic distribution (**C**), demonstrating no significant differences between XRT (blue color) and PRT (orange color) groups. (**D**): Correlative spatial analysis in a patient irradiated with PRT, depicting the CT-based RT dose distribution plan (left panel), an axial SWI MRI (middle panel) displaying CMB lesions (black arrows), and a corresponding overlay (right panel) which demonstrates preferential enrichment of CMB along the radiation field margin. (**E-F**): Schematic (**E**) and graphical (**F**) illustration of significant intergroup differences in CMB distribution (i.e., in the main radiation field (RF), at the RF margin, or remote to the RF), suggesting preferential clustering of CMB at the RF margin following PRT and greater remote CMB development following XRT.*

IV. Brain tissue necrosis: incidence & distribution pattern

- TN at 3 years post-RT was enriched following PRT (17.6%; n=3) vs. XRT (5.9%; n=1) (**Figure 5 A**). This trend was even stronger at 5 years post-RT [23.5% (PRT) vs. 5.9% (XRT)] but did not reach statistical significance (X^2=2.1103, p=0.146).
- TN lesions occurred at a median of 18 (10 – 30) months post-RT as *de novo* contrast-enhancing, round (2-30mm diameter) periventricular (n=2), subcortical (n=1), or resection cavity adjacent (n=1) lesions. TN was mostly (75%) asymptomatic, persisting for a median of 31.5 months until radiographic resolution.
- All (100%) TN lesions were located in the main RF (>90% of target dose), in two instances (50%) with close proximity to the RF margin (**Figure 5 B**)

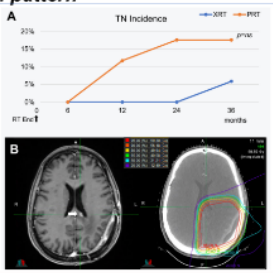


Figure 5. ***(A)*** *Cumulative TN incidence following PRT vs XRT up until 3 years post-RT.* ***(B)*** *T1+ contrast MRI (left) demonstrating a small nodular focus of enhancement (white arrow) located in the left periventricular white matter (splenium), manifesting at 10 months after PRT, consistent with TN. RT dose distribution overlay on axial computed tomography (right) demonstrates prior exposure of this region of interest to the main radiation field (56.2 Gy; orange line) and proximity to the distal fall-off region.*

Discussion & Conclusions

- *CNS radiotoxicity following brain-directed RT is common, often diagnostically challenging, progressive, and associated with a range of quantifiable clinic-radiographic sequelae in brain tumor patients.*
- *Injury patterns suggest radiation modality specificity as RIL, CMB, and possibly TN appear to exhibit unique spatiotemporal features following XRT vs PRT, likely reflecting underlying dosimetric differences.*
- *The impact of such sequelae on cognition is subject of current investigation. Characterizing radiation-induced CNS injury may improve prevention, diagnosis, and treatment of CNS radiotoxicity, with the goal to preserve long-term neurocognitive function in patients treated with cranial RT.*

Radiation-induced Contrast Enhancement (RICE) following Proton Radiotherapy for Low-Grade Glioma depends on Tumor Characteristics and is rarer in Children than Adults

Tanja Eichkorn, MD[1-3,5], Julia Bauer, PhD[1-2,5], Emanuel Bahn, PhD[4], Jonathan W. Lischalk, MD[7], Eva Meixner, MD[1-3,5], Elisabetta Sandrini, MD[1-3,5], Sebastian Regnery, MD[1-3,5], Thomas Held, MD[1-3,5], Juliane Hörner-Rieber, MD[1-5], Markus Alber, PhD[4], Klaus Herfarth, MD[1-3,5], Jürgen Debus, MD, PhD[1-6], Laila König, MD[1-3,5]*, Semi Harrabi, MD[1-3,5]*

*The senior authors Laila König and Semi Harrabi contributed equally.

1. Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany
2. Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Germany
3. National Center for Tumor diseases (NCT), Heidelberg, Germany
4. Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
5. Heidelberg Ion-Beam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany.
6. German Cancer Consortium (DKTK), partner site Heidelberg, Germany
7. Department of Radiation Oncology, Perlmutter Cancer Center at New York University Langone Health at Long Island, New York, NY, USA

Background and purpose:

Proton beam radiotherapy (PRT) is used in the treatment of low-grade glioma (LGG) to mitigate long-term sequelae.

Following PRT, increased rates of radiation-induced contrast enhancements (RICE) are suspected but poorly understood.

Patients and Methods:

We analyzed consecutive 227 patients (42 children and 185 adults) treated with PRT (54Gy RBE) for LGG from 2010 to 2020 and followed with serial clinical exams and magnetic resonance imaging for in median 5.6 years.

Results:

Tumors were graded WHO 1 in a minority (n = 22, 12%) of adults, but a majority of children (n = 29, 69%). In contrast, tumors were graded WHO 2 in the majority (n = 160, 87%) of adults and a minority of children (n = 10, 24%). The risk of RICE was 5-fold more frequent in adults (25%) versus children (5%) (p = 0.0043). In children and adults, RICE were symptomatic in 50% and 55% (n=1 and 26) of cases with CTCAE grade 0 in 47% (n=23), grade 1 in 25% (n=12), 0% grade 2 (n=0) and 29% grade 3 (n=14), respectively. In adults, RICE risk was associated to WHO grading (8% in WHO grade 1 vs. 24% in WHO grade 2, p = 0.026), independent of age (p=0.44) and irradiation dose (p=0.005), but not independent of IDH mutational status.

Figure 1: RICE-free Survival stratified by children and adults

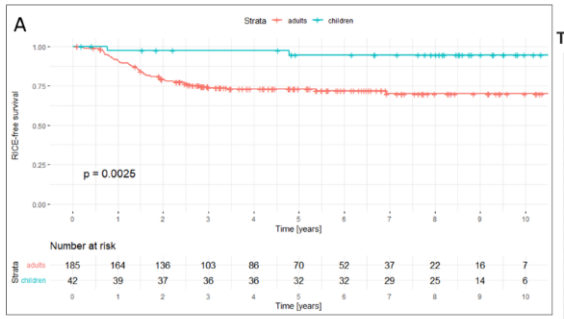


Figure 2: Four examples of RICE.

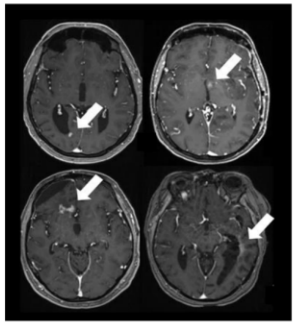


Table 1: RICE in the overall, adult and pediatric cohort.

	overall cohort n=227 [%]	adults n=185	children n=42
RICE occurrence			
yes	49 [21.6]	47 [25.4%]	2 [4.8%]
no	178 [78.4]	138 [74.6%]	40 [95.2%]
time radiotherapy end to first occurrence of RICE (months)			
median	16.9	16.9	33.2
minimum - maximum	1.7 - 57.2	1.7 - 40.9	9.1 - 57.2
RICE CTCAE grading			
CTCAE grade 0	23 [46.9%]	22 [44.9%]	1 [50.0%]
CTCAE grade 1	12 [24.5%]	11 [23.4%]	1 [50.0%]
CTCAE grade 2*	0 [0%]*	0 [0%]*	0 [0%]
CTCAE grade 3	14 [28.6%]	14 [28.6%]	0 [0%]
CTCAE grade >3	0 [0%]**	0 [0%]**	0 [0%]
RICE clinical symptoms			
none	23 [46.9%]	22 [44.9%]	1 [50.0%]
mild	12 [24.5%]	12 [24.5%]	1 [50.0%]
moderate	14 [28.6%]	14 [28.6%]	0 [0%]
severe	0 [0%]	0 [0%]	0 [0%]
RICE treatment needed	**n=49 [%]**	**n=47 [%]**	**n=2 [%]**
no treatment needed	35 [71.4%]	34 [69.4%]	1 [50.0%]
treatment needed	14 [28.6%]	13 [26.5%]	1 [50.0%]
steroids only	5 [10.2%]	4 [30.8%]	1 [100.0%]
bevacizumab (anti-VEGF antibody)	9 [18.4%]	9 [69.2%]	0 [0%]

Fazit:

These data demonstrate effectiveness of PRT for LGG in both children and adults. The RICE risk is lower in children which are a main target group for PRT and differs with WHO grading

Eichkorn et al., Radiotherapy & Oncology (2022)

Iatrogenic Influence on Prognosis of Radiation-Induced Contrast Enhancements in Patients with Glioma WHO 1-3 following Photon and Proton Radiotherapy

Tanja Eichkorn*[1-3,5], Jonathan W. Lischalk[7], Elisabetta Sandrini[1-3,5], Eva Meixner[1-3,5], Sebastian Regnery[1-3,5], Thomas Held[1-3,5], Julia Bauer[1,2,5], Emanuel Bahn[4], Semi Harrabi[1-3,5], Juliane Hörner-Rieber[1-6], Klaus Herfarth[1-3,5], Jürgen Debus[1-6], Laila König[1-3,5]

1. Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany
2. Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Germany
3. National Center for Tumor diseases (NCT), Heidelberg, Germany
4. Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
5. Heidelberg Ion-Beam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany.
6. German Cancer Consortium (DKTK), partner site Heidelberg, Germany
7. Department of Radiation Oncology, Perlmutter Cancer Center at New York University Langone Health at Long Island, New York, NY, USA

Background and purpose:

Radiation-induced contrast enhancement (RICE) is a common side effect following radiotherapy for glioma, but both diagnosis and handling are challenging. Due to the potential risks associated with RICE and its challenges in differentiating RICE from tumor progression, it is critical to better understand how RICE prognosis depends on iatrogenic influence.

Patients and Methods:

We identified 99 patients diagnosed with RICE who were previously treated with either photon or proton therapy for World Health Organization (WHO) grade 1-3 primary gliomas. Post-treatment brain MRI-based volumetric analysis and clinical data collection was performed at multiple time points for in median 5.6 years.

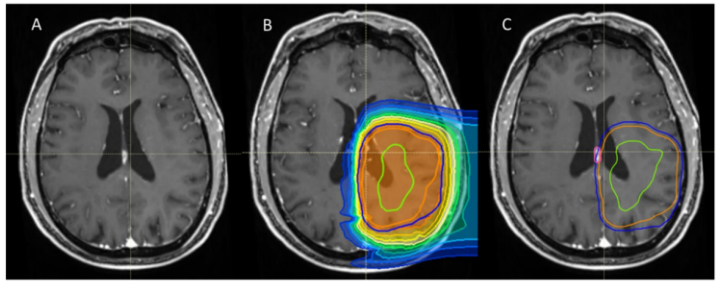
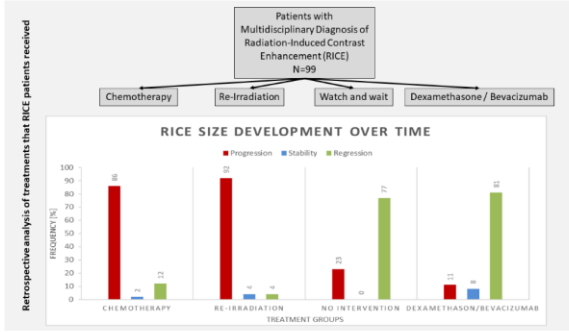


Figure 1: An example of a radiation-induced contrast enhancement (RICE) at the interface between the periventricular region (A) and the dose peak/steep dose falloff (B) as the most common predilection site. Delineation of RICE (pink), GTV (green), CTV (orange) and PTV (blue) is demonstrated in (C)

Results:

The most common histologic subtypes were astrocytoma (50%) and oligodendroglioma (46%). In 67%, it was graded WHO grade 2 and in 86% an IDH mutation was present. RICE first occurred after 16 months (range: 1 - 160) in median. At initial RICE occurrence, 39% were misinterpreted as tumor progression. A tumor-specific therapy including chemotherapy or re-irradiation led to a RICE size progression in 86% and 92% of cases, respectively and RICE symptom progression in 57% and 65% of cases, respectively. A RICE-specific therapy such as corticosteroids or Bevacizumab for larger or symptomatic RICE led to a RICE size regression in 81% of cases with symptom stability or regression in 62% of cases.

Figure 2: Radiation-induced contrast enhancements (RICE) size development in response to the received treatment.



Conclusion:

While with chemotherapy and re-irradiation a RICE progression was frequently observed, anti-edematous or anti-VEGF treatment frequently went along with a RICE regression. For RICE, correct diagnosis and treatment decisions are challenging and critical and should be made interdisciplinarily.

Eichkorn et al., Radiotherapy & Oncology (2022)