



Advancements in Radiation Treatment for CNS Tumors

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Learning Objectives

- Clinical applications/paradigm shifts in radiation treatment for CNS tumors
- Approaches to improving RT-CNS outcomes
- Brain metastasis SRS and Immunotherapy outcomes
- Introduction to proton therapy for CNS tumors
- RT and neurocognitive function
- Example cases

Neuro-Radiation Oncology at




- One of 25 centers in US with proton therapy
- One of 45 centers selected for the National Stereotactic Radiosurgery Database (AANS-ASTRO)
- One of the largest SRS outcomes databases in the world with >2000 metastases treated with median FU >3 yrs, with concurrent systemic therapy and volumetric response data
- 18 presentations at national/international meetings since 2016 on CNS/proton research
- Co-author ASCO guidelines for breast cancer brain metastasis treatment

A pivotal time in cancer treatment

- Fundamental Advances:
 - Immunotherapy
 - Targeted Therapies
 - Personalized Therapies
 - Advanced Radiotherapy
 - Radiosurgery
 - Proton Therapy
- Patients are living longer with fewer side effects from treatment
- Requires re-assessment of treatment paradigms and treatment techniques for best possible outcomes

Radiation for benign/low grade CNS tumors

- Effective in definitive/adjuvant/recurrent setting
 - Vestibular schwannoma*
 - Gr. I Meningioma
 - Craniopharyngioma*
 - Pituitary Adenoma
- Improved PFS
 - Low grade glioma



Associated with 85-95% long term local control

**Paradigm shift- shift to greater reliance on RT/SRS to avoid surgical toxicity*

Radiation for malignant CNS tumors

- Established benefit in survival and *local control* in upfront and recurrent setting
 - Gliomas grade III-IV
 - Medulloblastoma*
 - Pineoblastoma
 - *Atypical and malignant meningiomas*

**Paradigm shift-in progress?*
molecular subtyping potentially
redefining role of RT

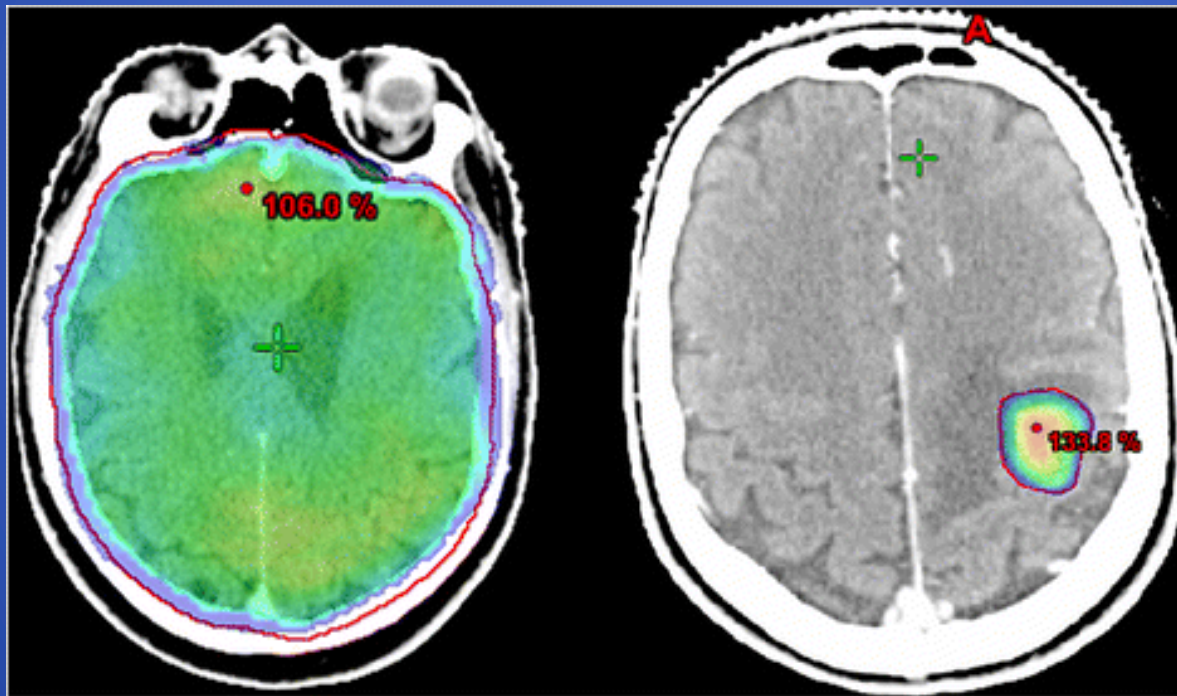
Radiation for CNS metastases

- SRS effective as ablative local therapy with improved QOL/neurocognitive preservation vs WBRT*, with increased distant brain failure
 - NSCLC
 - Breast
 - Melanoma
 - Renal
 - Colorectal

****Paradigm shift**- shift to greater reliance on SRS in setting of improved systemic therapy, longer survival with metastatic cancer, and appearance of CNS active therapies which may mitigate increased rate of distant brain failure.*

Distant brain failure-a new frontier

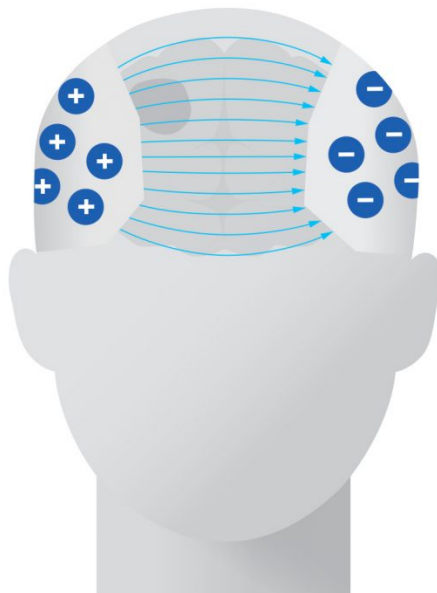
- WBRT-----→SRS

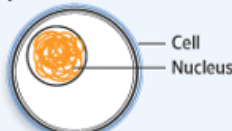
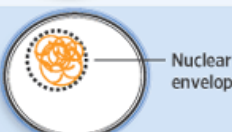


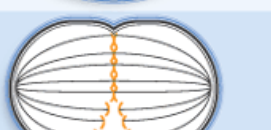





**SRS results in improved local control /QOL,
but increased rate of distant brain failure**

EF-25 METIS trial

- Randomized phase III trial of SRS+/- TTF for newly diagnosed NSCLC brain metastases



Disrupting Cancer-Cell Division		
Normal Cell Division (Mitosis) The cell DNA is doubled in preparation for division.		Mitosis with Device The device delivers alternating electrical fields to the cancer cells by means of insulated electrodes on the surface of the scalp. Healthy brain cells don't divide, and the electrical fields generated by the device don't affect them. The electrical field interferes with the production of spindle fibers...
The cell's nuclear envelope disintegrates.		
Spindle fibers form.		
Chromosomes align in the center of the cell and attach to the spindle fibers.		...and disrupts the even distribution of the chromosomes...
Chromosomes move toward the two poles and the cell begins to cleave.		
Two identical 'daughter cells' are formed.		...causing structural disruption and cell fragmentation.
Source: NovoCure		

Disease-specific approaches to brain metastasis management

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: American Society of Clinical Oncology Clinical Practice Guideline

Naren Ramakrishna, Sarah Temin, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Sharon H. Giordano, Ana M. Gonzalez-Angulo, Jeffrey J. Kirshner, Ian Krop, Jennifer Levinson, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Eric P. Winer, and Nancy U. Lin

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Orlando, FL

All brain metastases are not alike and our approach is now differentiating and evolving along disease-specific lines

Prognostic factors:

Age, KPS, ECD status, # brain mets

bRAF mutation status

negative \longleftrightarrow unknown \longleftrightarrow Positive

What is the median OS of a melanoma brain metastasis patient?

Gaspar- RPA (1997)	2.1-----7.1 m
Sperduto- DS-GPA (2012)	3.4-----13.2m
Sperduto-molGPA (2017)	4.9-----34.1m

Prognosis is changing rapidly!

Immunotherapy Checkpoint Inhibitor Type:
CTLA-4 PD1

Immunotherapy Timing:
Before \longleftrightarrow Before and After \longleftrightarrow After

Melanoma brain metastases treated 2008-2017 at single institution

Initial SRS

SRS X

Neurologic death

Overall Survival

Overall Survival
Cause-specific Survival
following SRS for melanoma brain mets

Study population

- Single institution
- 68 patients
- 230 metastases
- 11/2008- 2/2017
- Median FU
 - 29.05 months censored patients

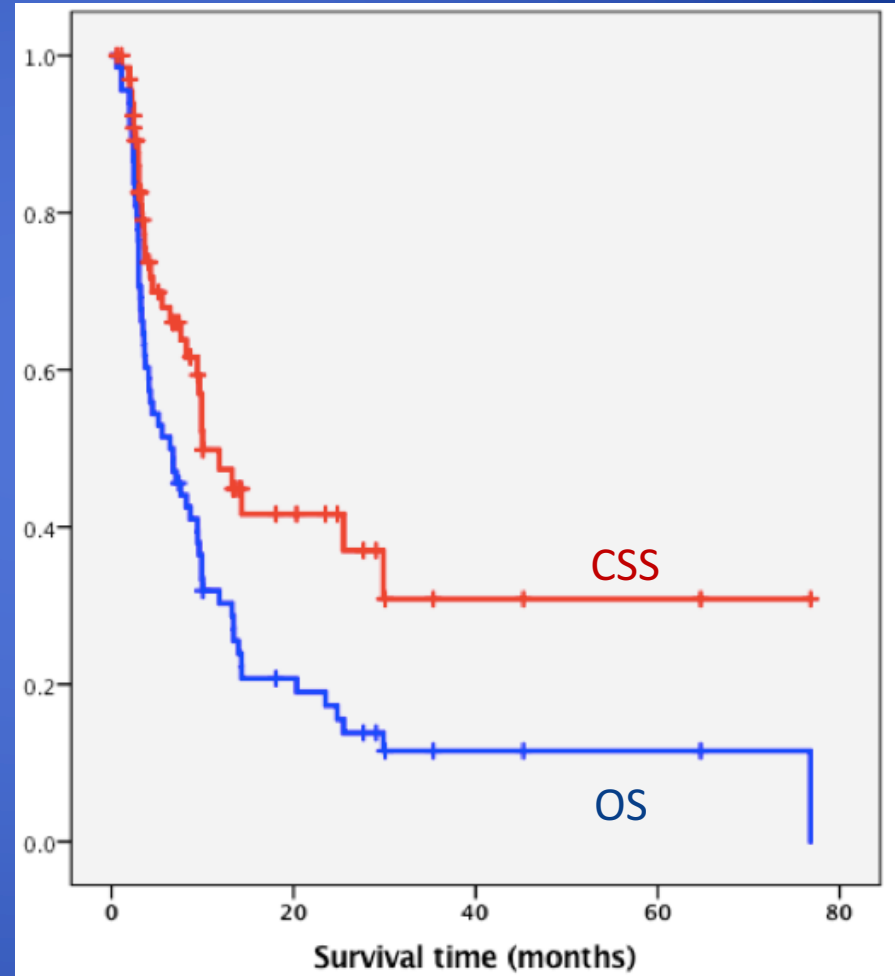
**Includes primary disease, visceral metastases, and osseous metastase*

***Sperduto et al. IJROBP 2017*

Table 1. Patient characteristics (N=68)	
	No. of patients (%)
Gender	
Female	23 (33.8)
Male	45 (66.2)
Age at initial SRS	
<60 years	35 (51.5)
≥60 years	33 (48.5)
KPS at initial SRS	
<70	12 (17.6)
≥70	56 (82.4)
Extracranial disease control at initial SRS*	
Controlled	20 (29.4)
Not controlled	48 (70.6)
Patient received any WBRT	
No	45 (66.2)
Yes	23 (33.8)
BRAF mutation status	
Unknown	35 (51.5)
Negative	21 (30.9)
Positive	12 (17.6)
2017 molGPA score at initial SRS**	
0 – 1.0	6 (8.8)
1.5 – 2.0	24 (35.3)
2.5 – 3.0	28 (41.2)
3.5 – 4.0	10 (14.7)

Survival- all cohorts

- Median overall survival
– 6.43 months
- Median cause-specific survival (neurologic death)
– 10 months



OS vs. Immunotherapy

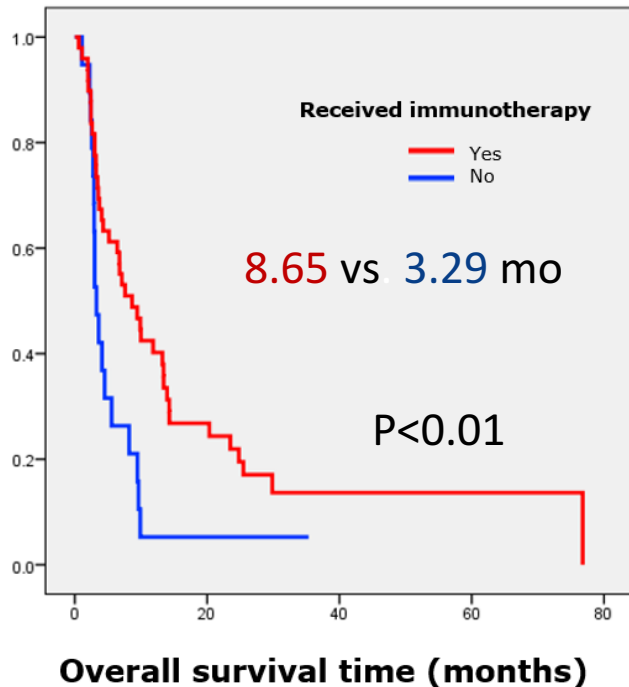
	MS (months)	95% CI	Log-rank <i>p</i> - value
Received immunotherapy			
No	3.29	2.55-4.02	0.01
Yes	8.65	4.48-12.81	

Immunotherapy subgroups

Ipilimumab without PD1-inhibitors	6.43	2.86-10.00	<0.001
PD1-inhibitors with or without ipilimumab	23.51	5.15-41.87	
No immunotherapy	3.29	2.55-4.02	

Survival post SRS by immunotherapy class

Overall survival by immunotherapy status



Overall survival by checkpoint inhibitor class

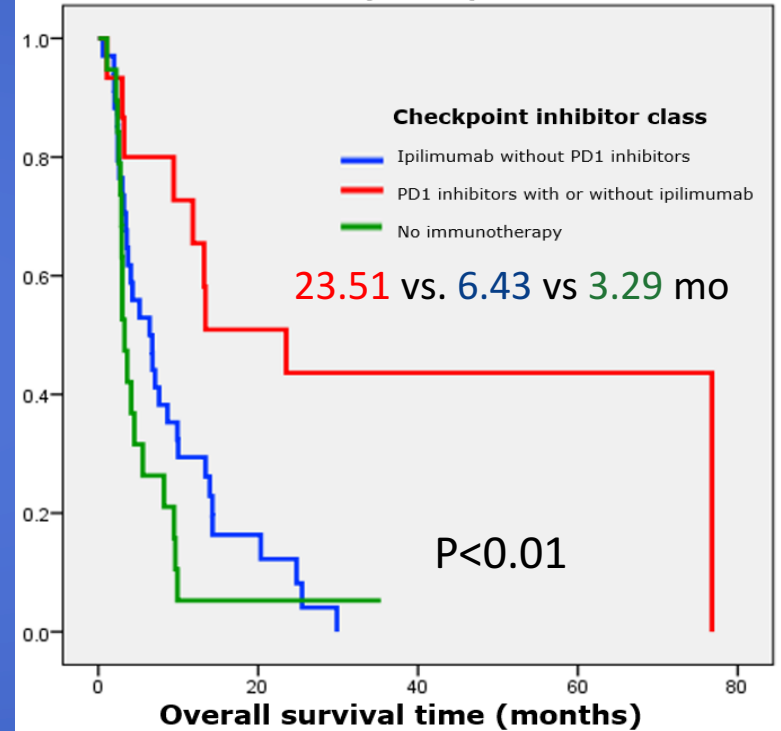


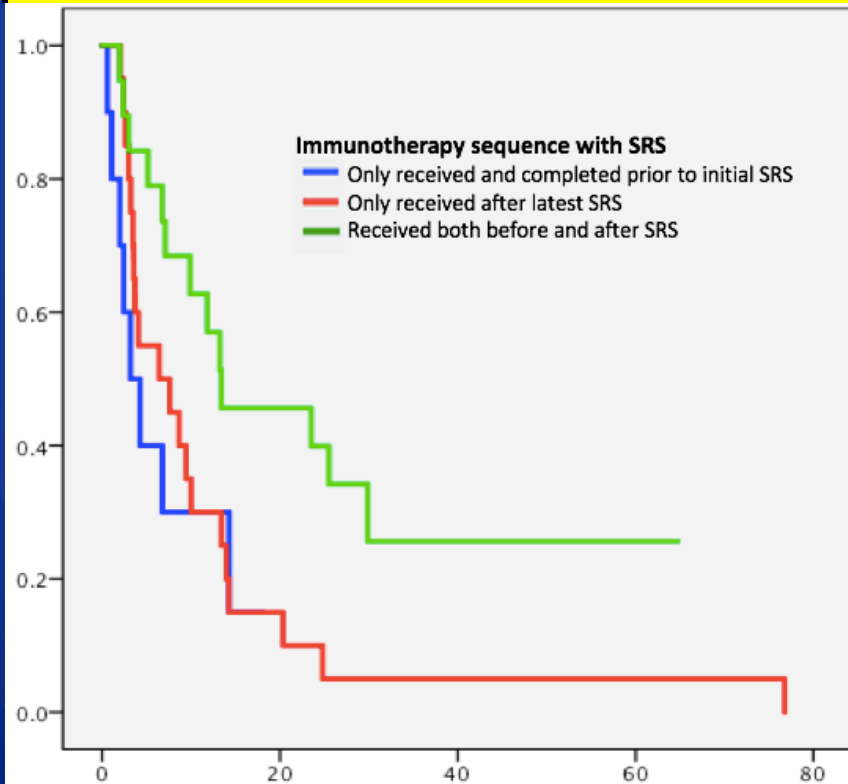
Table 5. Cox proportional hazards model for overall survival (entire cohort)

	HR (95% CI)	P-value
Immunotherapy subgroups		
No immunotherapy	-	-
Ipilimumab without PD1-inhibitors	0.25 (0.10-0.67)	<0.01
PD1-inhibitors with or without ipilimumab	0.09 (0.03-0.30)	<0.01

PD-1 immunotherapy results in longer overall survival, median OS 23.51 months

Immunotherapy Sequence and OS

	MS (months)	95% CI	Log-rank <i>p</i> -value
Immunotherapy sequence	MS		p
Completed prior to initial SRS	3.19	0.34-6.04	0.04
Only received after latest SRS	6.43	-	
Received both before and after SRS	13.40	-	



On univariate analysis only, association between median OS and immunotherapy(IPI/PD1) sequence

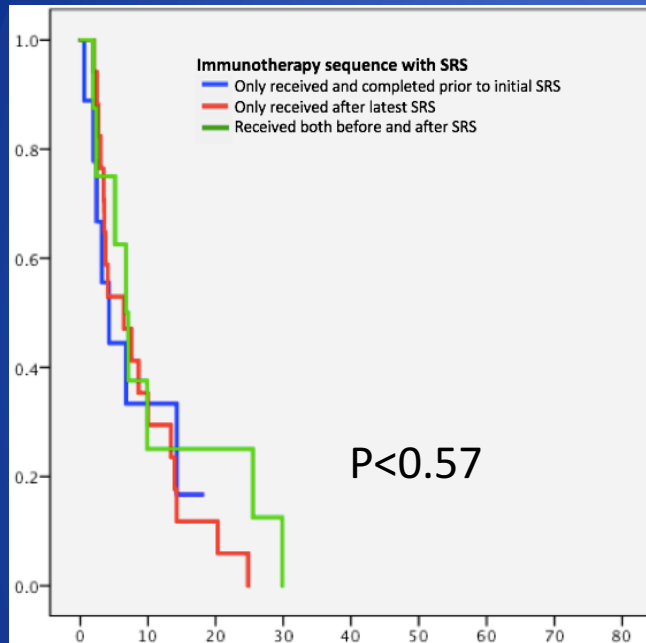
Table 5. Cox proportional hazards model for overall survival (entire cohort)

	HR (95% CI)	<i>P</i> -value
Sequence of immunotherapy with SRS		
Received and completed prior to initial SRS	-	-
Only received after latest SRS	1.38 (0.51-3.72)	0.52
Received both before and after SRS	0.60 (0.21-1.74)	0.35

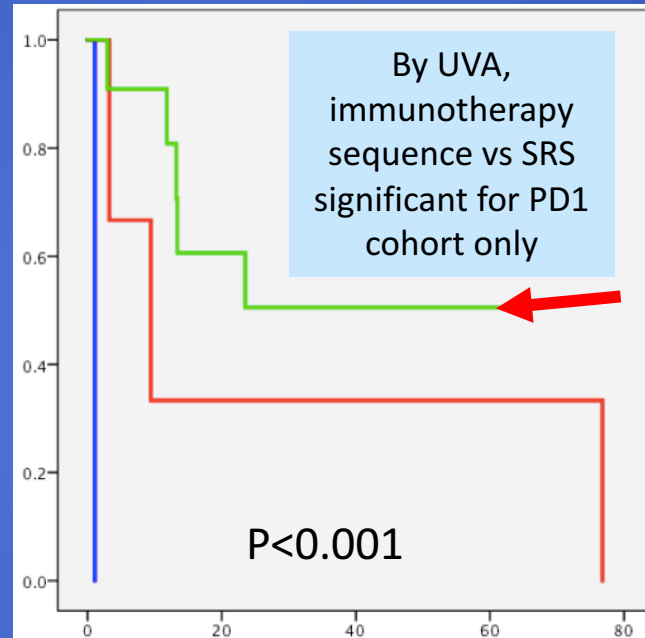
Overall Survival (months)

Immunotherapy sequence : by class

Ipilimumab-only cohort



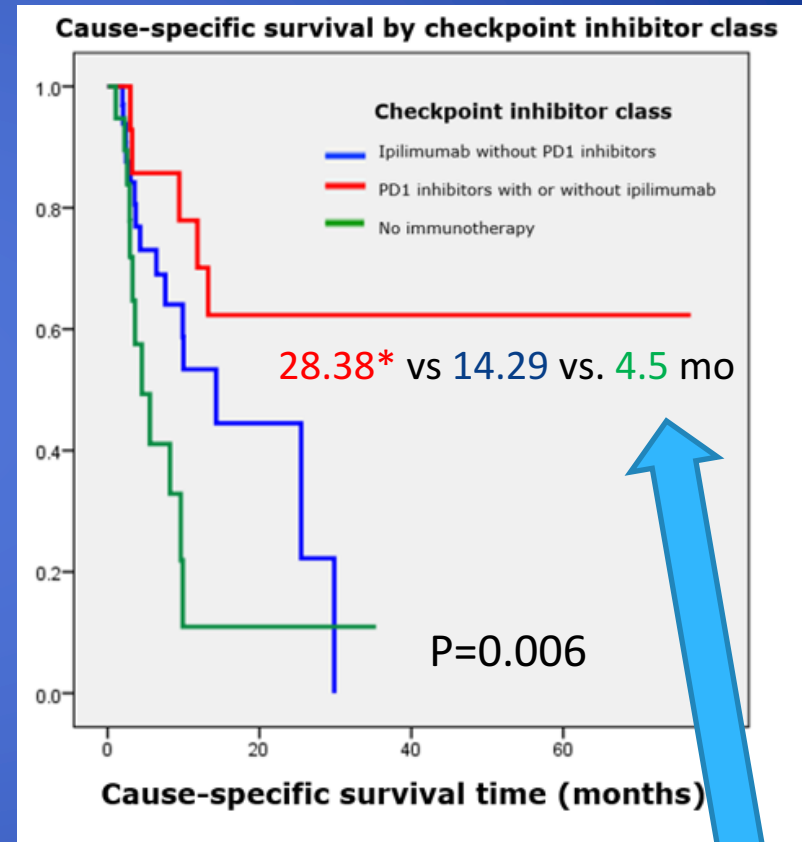
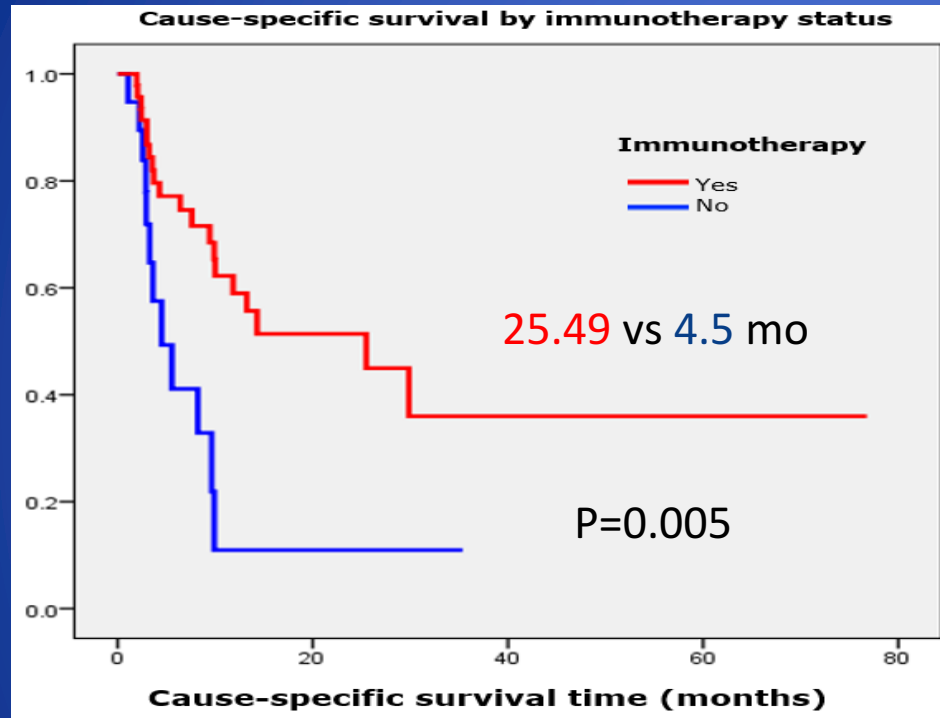
PD1 inhibitor cohort



****Median OS not reached for PD1 before+after cohort at 30.01 month FU**

	Ipilimumab only (n=53)		PD1 inhibitors (n=15)	
	MS in months (95% CI if applicable)	Log-rank <i>p</i> -value	MS in months (95% CI if applicable)	Log-rank <i>p</i> -value
Sequence of immunotherapy* with respect to SRS				
Only received and completed prior to initial SRS	4.27 (n=9)	0.57	1.08 (n=1)	0.001
Only received after latest SRS	6.43 (n=17)		9.44 (n=3)	
Received both before and after SRS	6.75 (n=8)		30.01 (n=11)**	

Neurologic death post-SRS +/- immunotherapy



Kaplan-Meier estimate of cause-specific survival		
	MS (months)	95% CI
Received immunotherapy		
No	4.50	1.46-7.55
Yes	25.49	3.71-47.27
Immunotherapy subgroups		
Ipilimumab without PD1-inhibitors	14.29	7.10-21.48
PD1-inhibitors with or without ipilimumab	28.38*	-
No immunotherapy	4.50	1.46-7.55

***Median survival not reached for PD1-treated patients at 28.38 months FU**

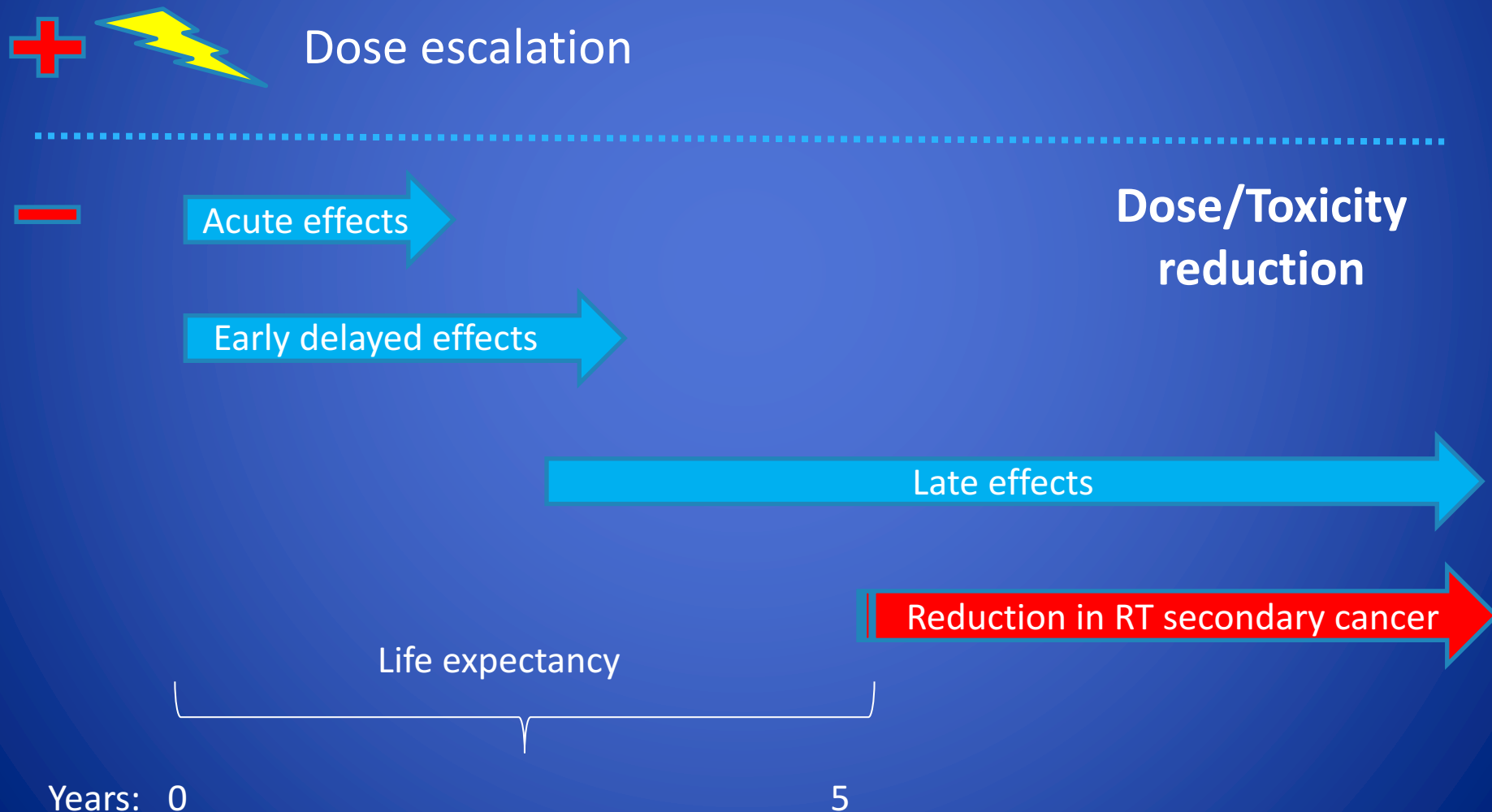
Summary

- Dramatic increases in overall and cause-specific survival for melanoma brain metastasis patient cohort treated with SRS with PD-1 class immunotherapy relative to non-immunotherapy/ipilimumab cohorts.
- Improved overall survival among PD-1 cohort for those receiving immunotherapy before and after SRS
- Prospective clinical trial in progress to validate retrospective results

Improving CNS RT outcomes:

- I. **More dose** to target where dose escalation is potentially beneficial
 - Chordoma/chondrosarcoma
 - Atypical and malignant meningiomas
 - Glioblastoma?
 - AVM
- II. **Less dose** to surrounding brain
 - Decrease neurocognitive sequelae
 - Decrease treatment-related chronic fatigue
 - Decrease vascular sequelae
 - Decrease long term effects on vision, hearing, balance, neuro-endocrine function

Visual Rubric for clinical benefit



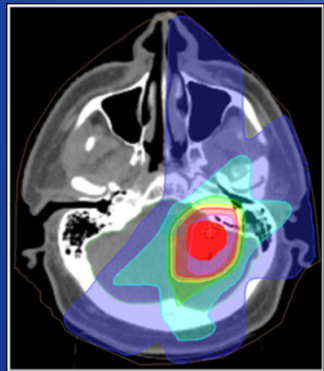
X-ray treatment is mainstay of Radiation Oncology



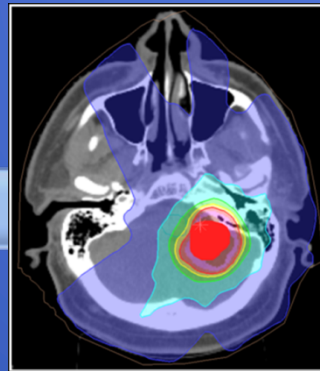
More precise and focused treatment using X-rays with technology such as IMRT (intensity modulated radiotherapy), 3D image-guidance and robotic positioning

X-rays → Protons

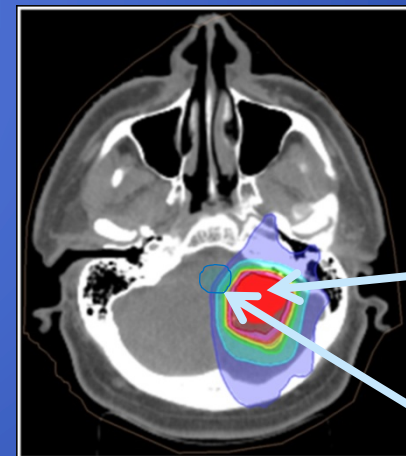
Protons represent a fundamental advance in dose delivery to tumors, which in many cases delivers less dose to normal tissue thereby potentially reducing the side-effects of treatment.



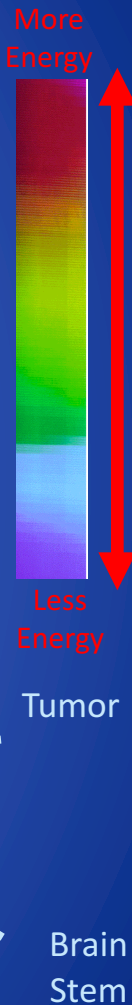
X-rays
3D Conformal 5 Field



X-rays
IMRT

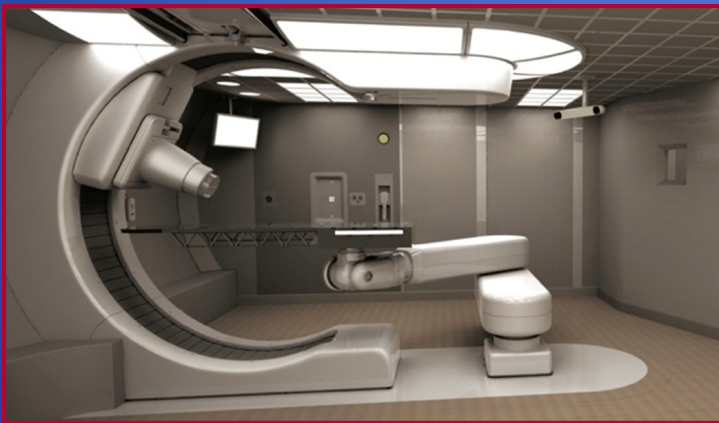


Proton 1 Field



Proton therapy comes to Orlando Health

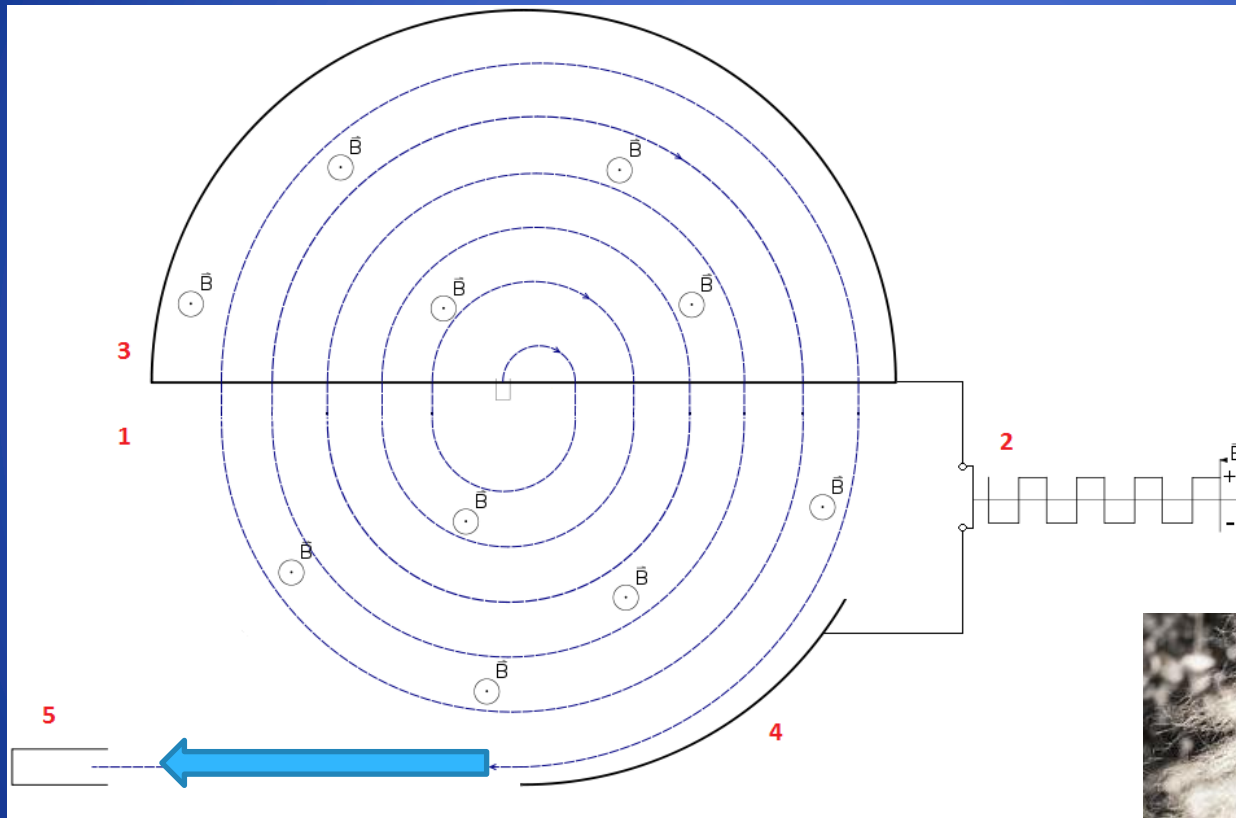
- One of 60 worldwide
- One of 25 in the nation



- Opened April 2016
- Over 300 patients treated



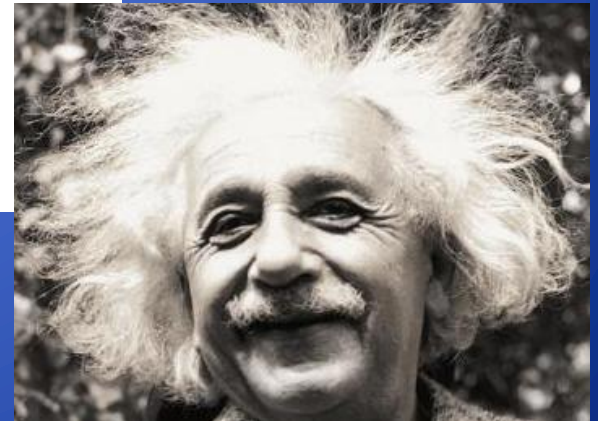
Protons – a different form of RT



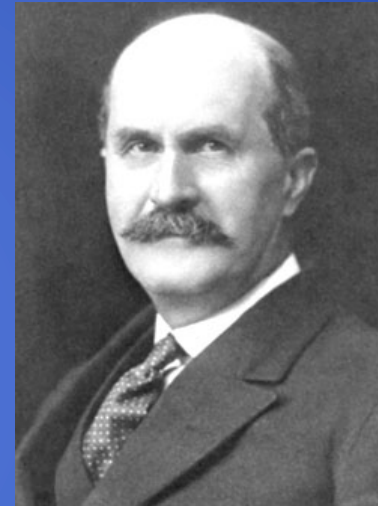
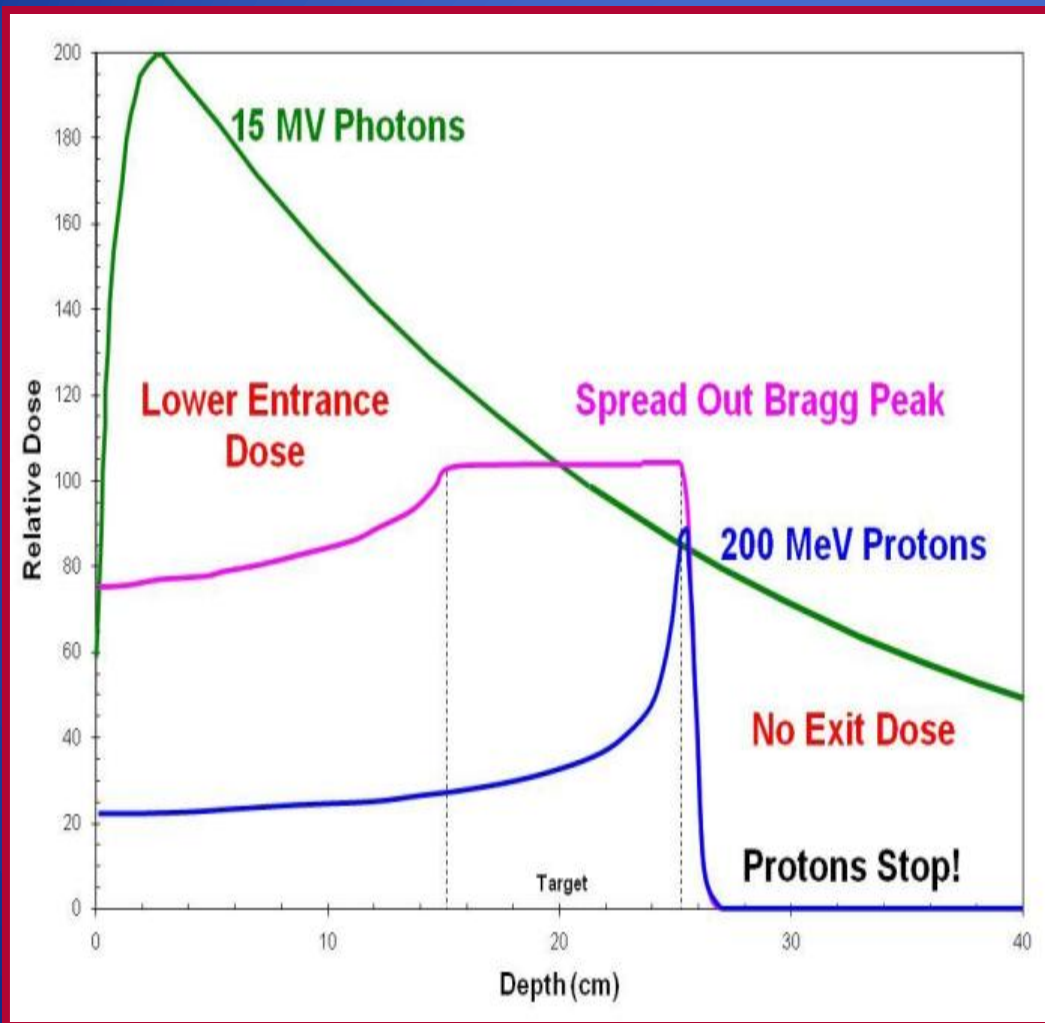
Protons extracted
from Hydrogen
atoms

Accelerated in
devices such as
synchrocyclotron

Protons race around wider orbits at higher and higher speeds, reaching $0.6 \times$ speed of light before exiting towards the target



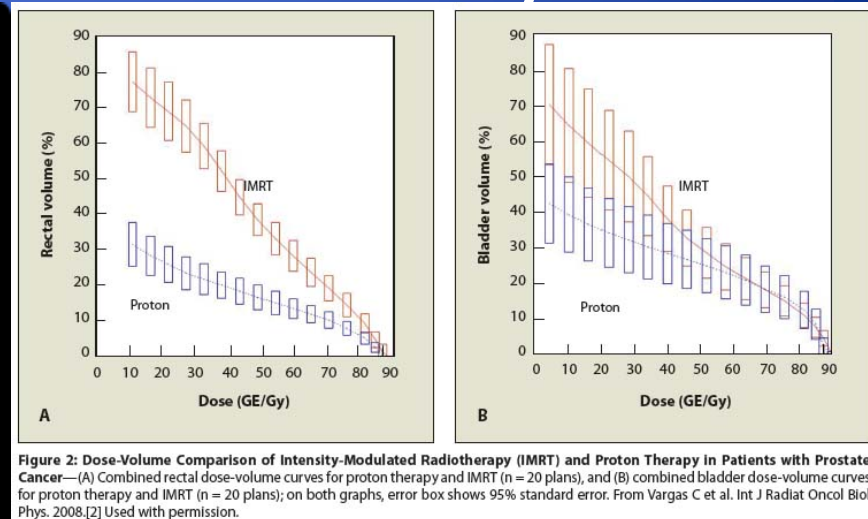
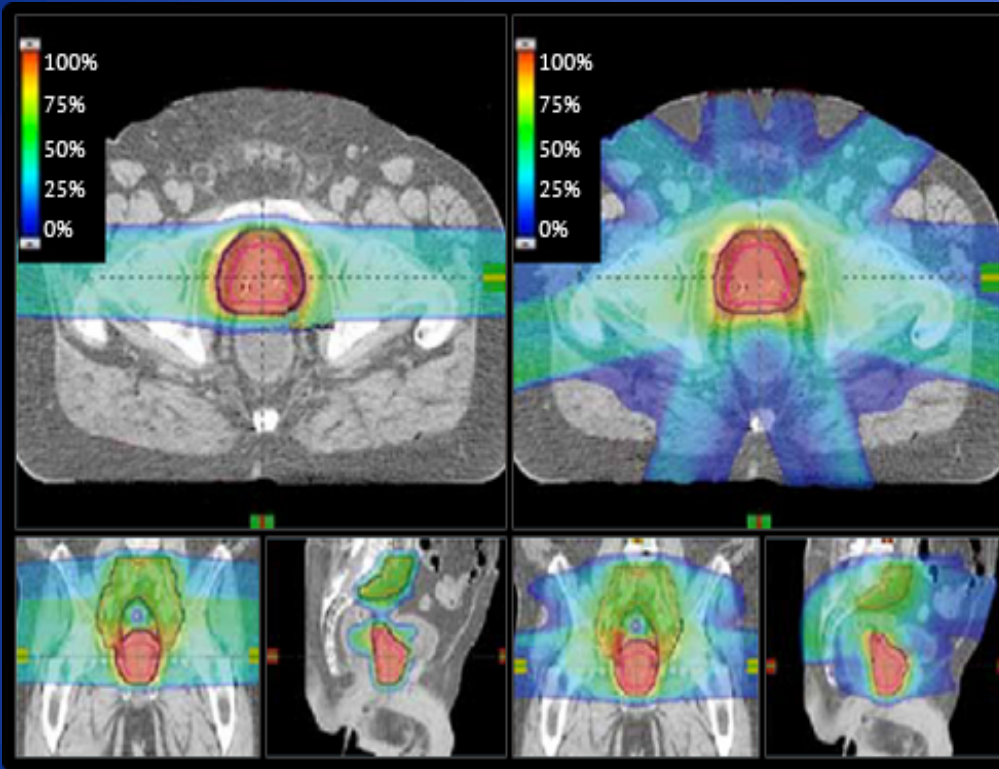
Proton dose deposition: Bragg Peak



X-rays deposit high dose on their way to tumor and high dose on their way past the tumors.

Protons deliver less dose on their way in and NO Dose on their way out.

Proton integral dose: less overall normal tissue dose than X-rays



Reduction in the volume of tissue receiving both high dose and low dose radiation is beneficial to organ-related toxicity and for reduction of risk of secondary malignancies

Protons decrease the risk of secondary cancers caused by radiation

A 2008 MGH study determined that protons decrease the risk of patients developing a secondary cancer by 50%⁽¹⁾

Protons decrease the risk of secondary malignancies in prostate cancer treatment over 5 year period

“According to the study, 6.4 percent of patients who underwent proton therapy developed a secondary cancer while 12.8 percent of patients who had photon treatment [X-Rays] developed another type of cancer.”

Modality	Risk of Induced Tumor ⁽²⁾
Conventional	10%
IMRT	20%
Protons	5%

1) CS Chung, N Keating, T Yock, N Tarbell, “Comparative Analysis of Second Malignancy Risk in Patients Treated with Proton Therapy versus Conventional Photon Radiation,” International Journal Radiation Oncology Biology Physics 72 (2008): S8.

2) Estimated Risk of Radiation-Induced Malignancies 5 years After Radiation Therapy. Conventional radiation risk is measured against surgery in McGee et al., “Comparison of Second Cancer Risk in Prostate Cancer Patients Treated with Neutron/Photon Irradiation, Photon Irradiation, or Prostatectomy,” Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 3 S318-S319, 2006. IMRT risk is measured from relative risk of IMRT and conventional radiation from Eric J. Hall’s, “Intensity-Modulated Radiation Therapy, Protons, and the Risk of Second Cancers,” Int. J. Radiation Oncology Biol. Phys. Vol. 65, No. 1 pp. 1-7, 2006. Proton therapy secondary malignancy risk is measured from the relative risk of protons and conventional radiation from, Chung et al., “Comparative Analysis of Second Malignancy Risk in Patients Treated with Proton Therapy versus Conventional Photon Therapy,” Int. J. Radiation Oncology Biol. Phys. Vol. 72, No. 1 S8, 2008.

Cognitive Domains Compromised by Radiation: *a rationale for less dose*

- Learning
- Memory
- Processing Speed
- Attention
- Executive Function

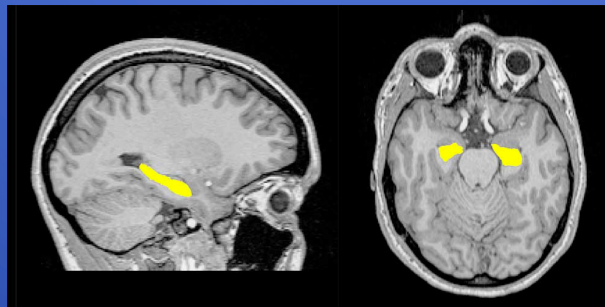
Critical for CNS patient quality of life

Cognitive function and RT dose

- Acute declines in verbal memory seen after 1-3 fractions WBRT (Welzel IJROBP 72;5, 2008)
 - Suggests highly sensitive compartment in brain.
- Loss in IQ correlates to temporal lobe dose (Merchant et al IJROBP 65:1, 2006)
- Preclinical murine data:
 - Depletion of cells with radiation doses $\leq 10\text{Gy}$ in the dentate gyrus linked to deficits in spatial-temporal learning/memory.

Hippocampal-sparing: Rationale

- Preclinical and clinical evidence support hypothesis that neural stem cell compartment in hippocampus is central to pathogenesis of neurocognitive defects.
- Neural stem cells anatomically clustered within dentate gyrus of hippocampus



Effects of RT on mature neurons

- RT interferes with neurogenesis (stem cells)
 - But the fraction of neurogenic cells in the brain is extremely small
- What are effects of RT on mature neurons?
 - Mature neurons are capable of significant structural and synaptic plasticity- what are the effects of radiation on these properties?
- Stem cells populations are sensitive to radiation but so are mature neurons which may display profound alterations in morphology, with significant functional implications.

Effects of Radiation on neuronal morphometry

- Neural networks require formation and establishment of precisely regulated complexes of dendritic arbors and spines, as well as synaptogenesis.
- Dendritic complexity, spine morphology and synaptic density are critical determinants for learning and memory.
- A pronounced decrease in dendritic spines is seen in Huntington's disease, Alzheimer's, and HIV-dementia.

Radiation reduces neuronal and dendritic complexity

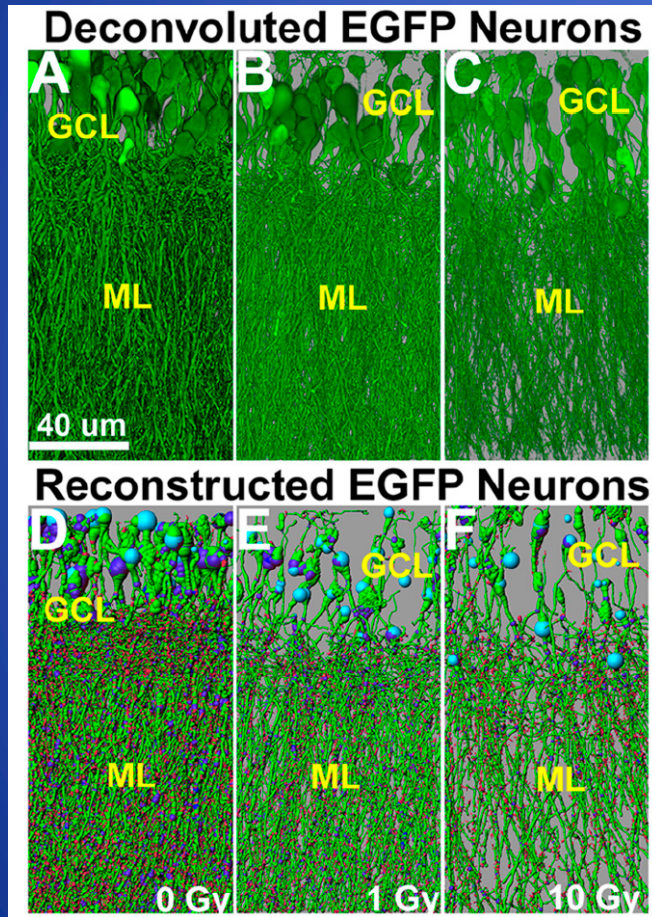


Fig. 1. Reduced dendritic complexity of GCL neurons 30 d after irradiation. (A–C) Examples of deconvoluted EGFP⁺ GCL neurons showing dendrites orientated vertically and traversing the ML. (D–F) Deconvoluted 3D reconstructed images of A–C, respectively, with dendrites containing spines projecting into the ML (sky blue, cell body; green, dendrites; blue, branch points; red, spines).

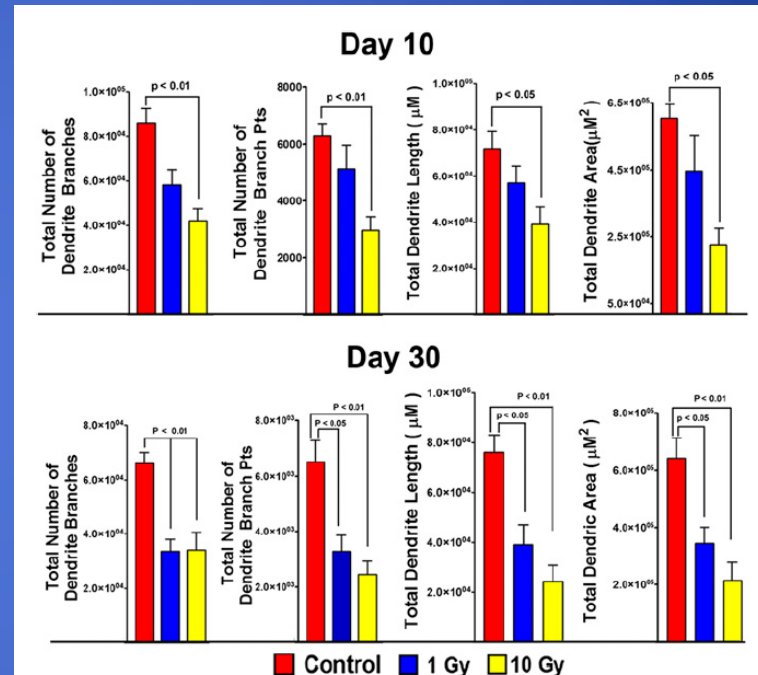
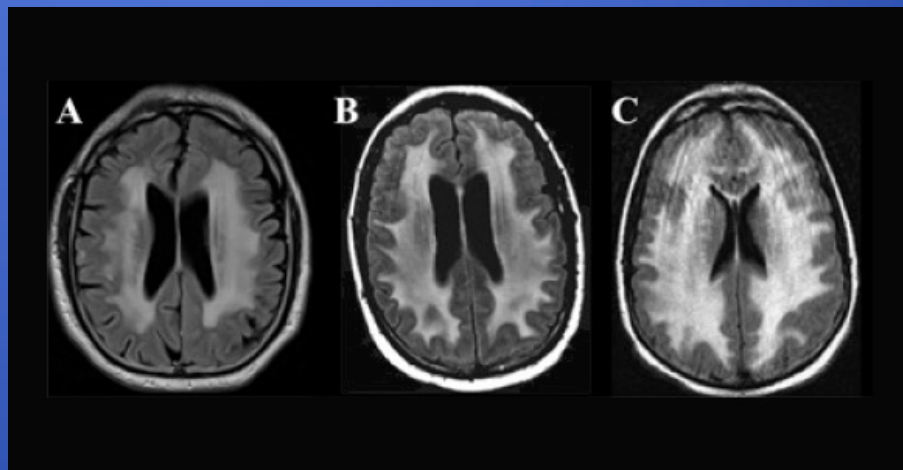


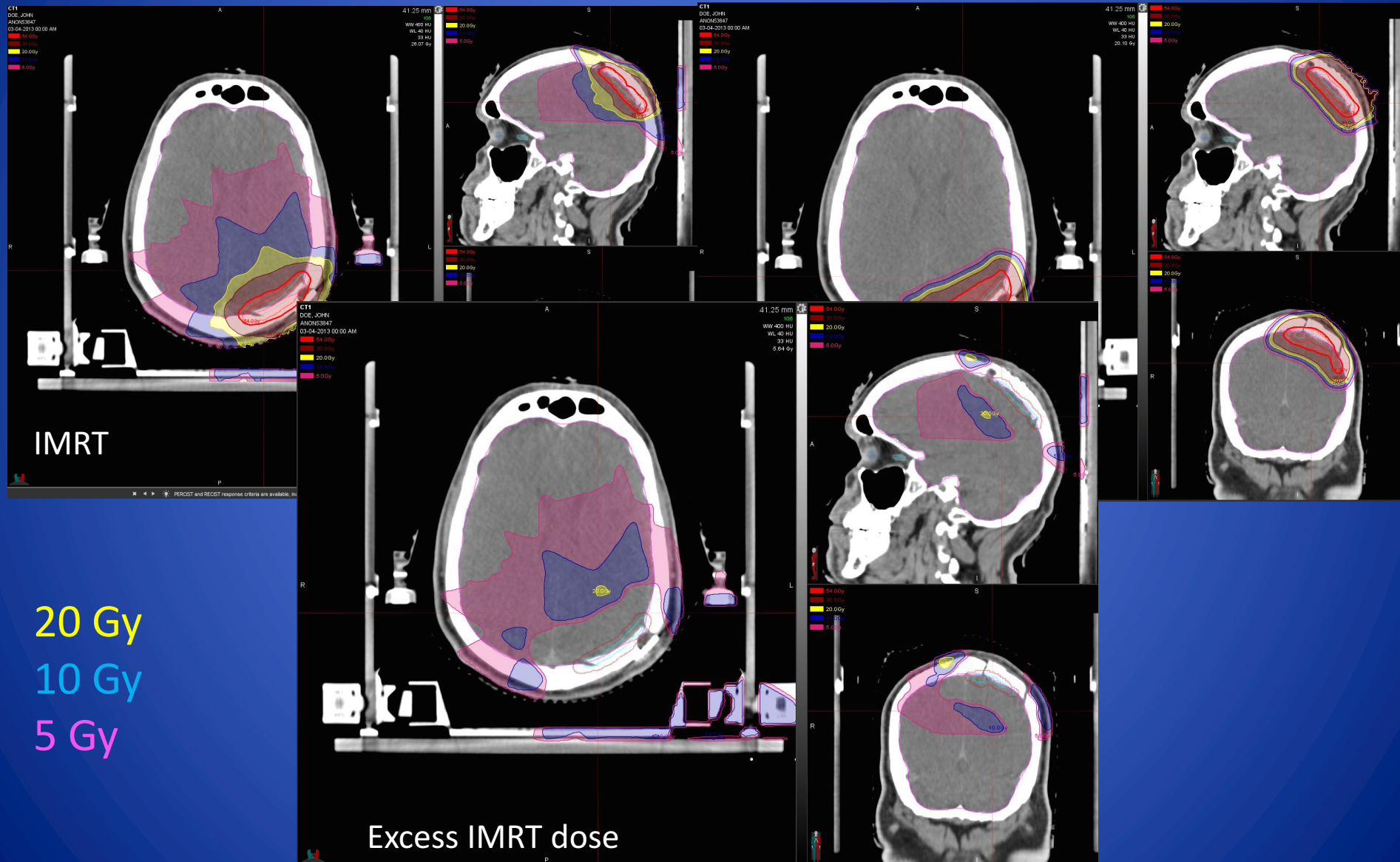
Fig. 2. Quantification of morphometric parameters 10 and 30 d after irradiation. Quantified morphometric parameters of dendritic complexity including dendrite branching, branch points, dendrite length, and dendrite area 10 d (*Upper*) and 30 d (*Lower*) after irradiation.

Benefits of Less Dose: Vascular hypothesis of radiation injury

- Vascular insufficiency and increased infarctions post radiation
 - Radiation-induced accelerated atherosclerosis
 - Radiation-induced mineralizing microangiopathy
 - Similar to small vessel disease seen with vascular dementia



Meningioma: IMRT/Proton dosimetry



We don't need more dose for LGG

Table Contemporary Trials of Adjuvant Therapy for Low-Grade Glioma*

Trial	Adjuvant Therapy	5-y PFS (%)	5-y OS
EORTC 22844	45 Gy	47	58%
	59.4 Gy	50	59%
NCCTG 86-72-51	50.4 Gy	55	72%
	64.8 Gy	52	64%
EORTC 22845	Observation	35	66%
	54 Gy	55	68%
RTOG 9802	Observation (nonrandomized low-risk arm)	48	93%
	54 Gy	72	63%
	54 Gy + PCV	84	72%
RTOG 0424	54 Gy/TMZ (nonrandomized)	46	60%
EORTC 22033	50.4 Gy/TMZ (12 cycles)		
RTOG 0925	Observation (nonrandomized low-risk arm only)		

Abbreviations: CCNU, vincristine, OS, overall survival; PCV, procarbazine.

TMZ, temozolomide delivered daily and concurrently with fractionated radiation therapy.

QOL critical in Low grade gliomas

- Proton RT results
 - No decline in neurocognitive function

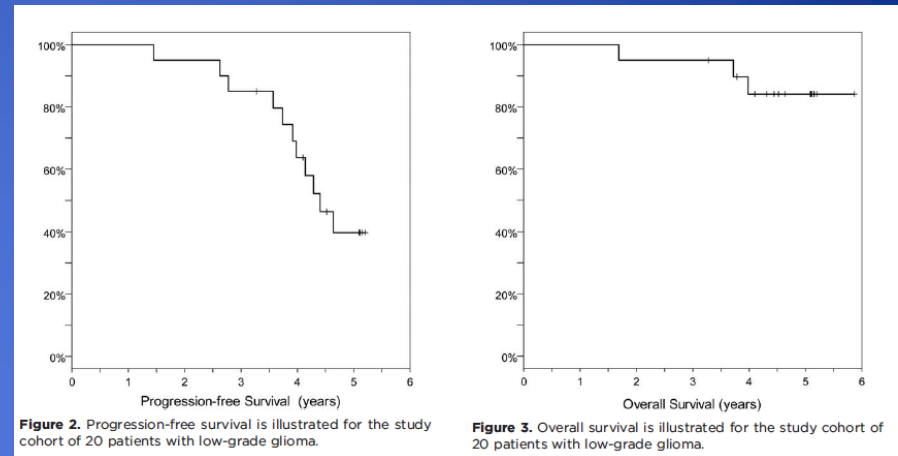
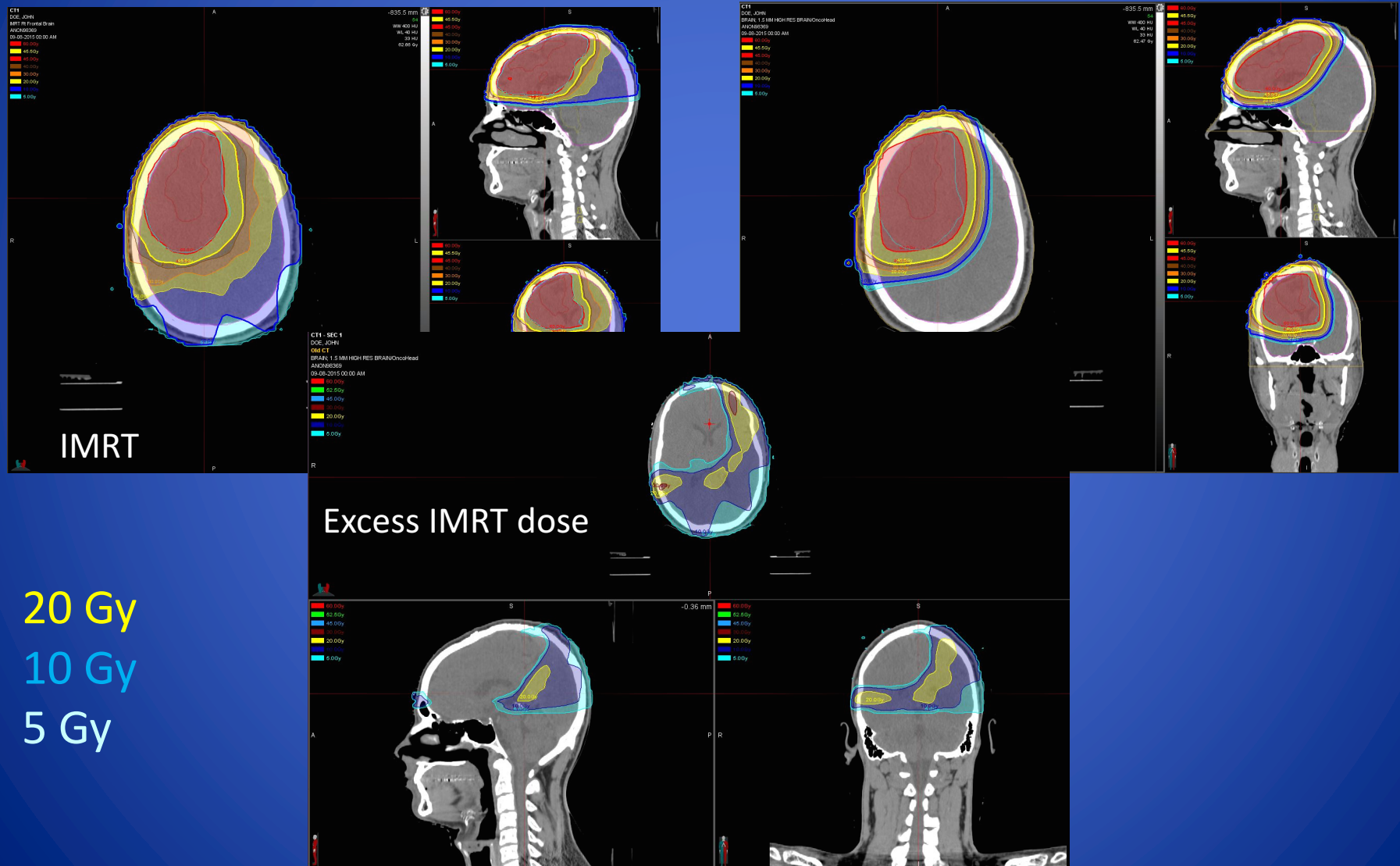


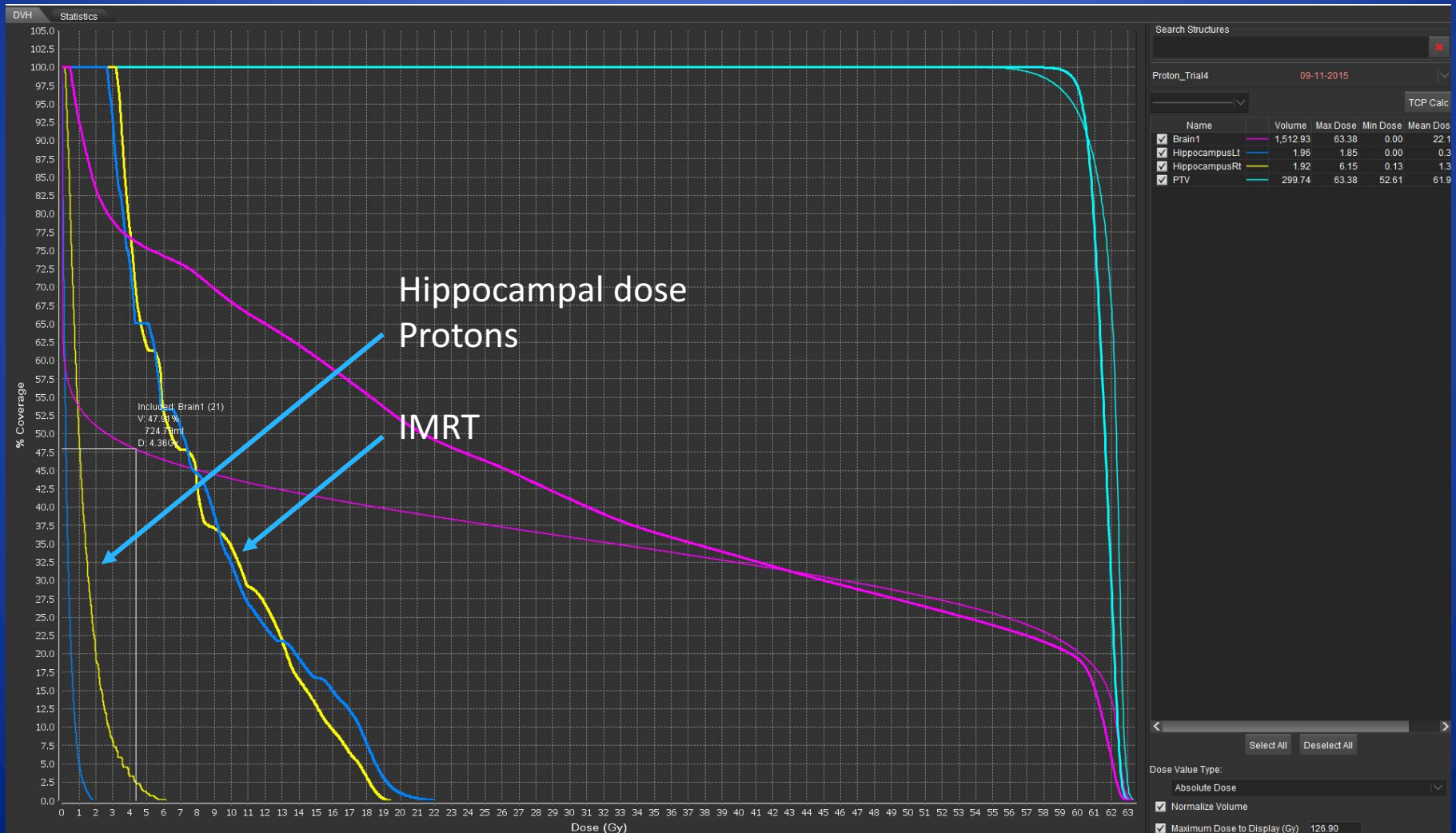
TABLE 2. Neurocognitive and Quality-of-Life Outcomes

Domain	Tests	Baseline Score: Mean \pm SD (Range)	Average Score Change per Year: Average \pm SE	P
Intellectual Visuospatial Language	WAIS-III Full Scale IQ	0.47 \pm 0.56 (–0.47, –1.40)	0.07 \pm 0.04	.1400
	WAIS-III Perceptual Organization Index	0.54 \pm 0.69 (–0.60, –2.33)	0.13 \pm 0.05	.0187
	WAIS-III Verbal Comprehension Index, Boston Naming Test, Auditory Naming Test	–0.50 \pm 2.19 (–5.72, –1.00)	0.07 \pm 0.09	.4462
Attention and working memory	WAIS-III Working Memory Index and Spatial Span; Continuous Performance Test: Inattention Score and Vigilance Score	0.24 \pm 0.49 (–0.37, –1.58)	0.04 \pm 0.04	.3292
Processing speed	WAIS-III Processing Speed Index; Trail Making Test A	0.06 \pm 0.83 (–1.86, –1.33)	0.10 \pm 0.07	.1679
Executive function	Trail Making Test B; Controlled Oral Word Association Test F-A-S; Wisconsin Card Sorting Test; Continuous Performance Test Impulsivity Score	–0.18 \pm 0.62 (–1.18, –0.77)	0.12 \pm 0.06	.0501
Verbal memory	HVLT-R: Total Recall, Delayed Recall, and Retention	–0.72 \pm 1.19 (–2.67, –0.93)	0.04 \pm 0.07	.5316
Visual memory	BVMT-R: Total Recall and Delayed Recall	–0.81 \pm 1.41 (–3.00, –1.05)	–0.003 \pm 0.06	.9644
Clinical trials battery	HVLT-R Total Recall; WMS-III Trails A and Trails B; Controlled Oral Word Association Test F-A-S	–0.35 \pm 0.78 (–1.57, –1.13)	0.11 \pm 0.06	.0742
Emotional ^a	Beck Anxiety Inventory	8.9 \pm 8.0 (0–25)	–0.50 \pm 0.36	.1870
	Beck Depression Inventory	12.71 \pm 9.85 (0–31)	–0.05 \pm 0.54	.9212
Quality of life	FACT-G Total Score	77.0 \pm 18.4 (39–102)	0.41 \pm 0.58	.4919
	FACT-Fatigue Score	32.7 \pm 14.8 (8–52)	1.05 \pm 0.44	.0265
	FACT-Br Total Score	131.0 \pm 28.5 (84–174)	1.47 \pm 0.89	.1154

Oligodendroglioma: 41 yo

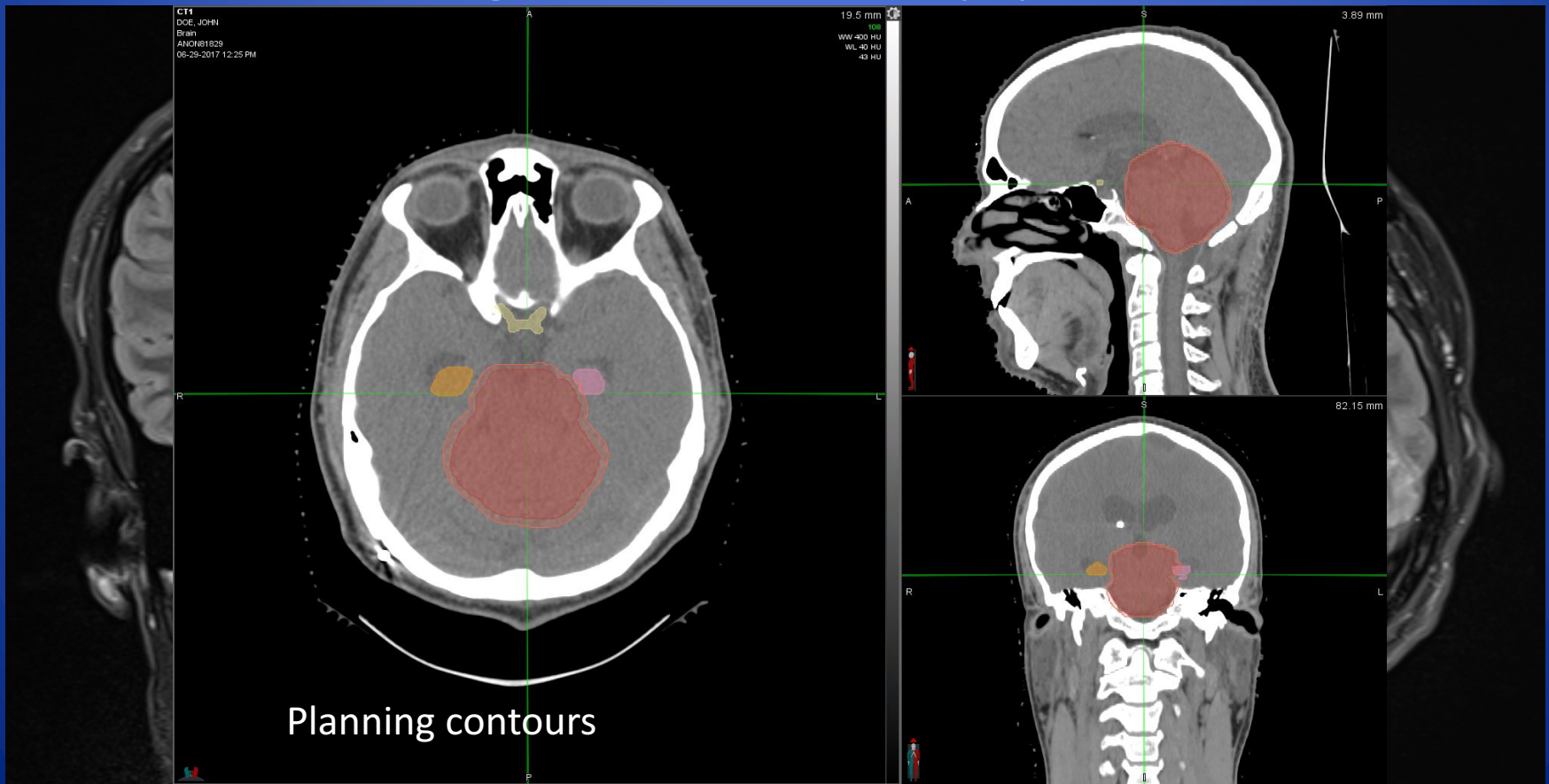


Hippocampal sparing with protons

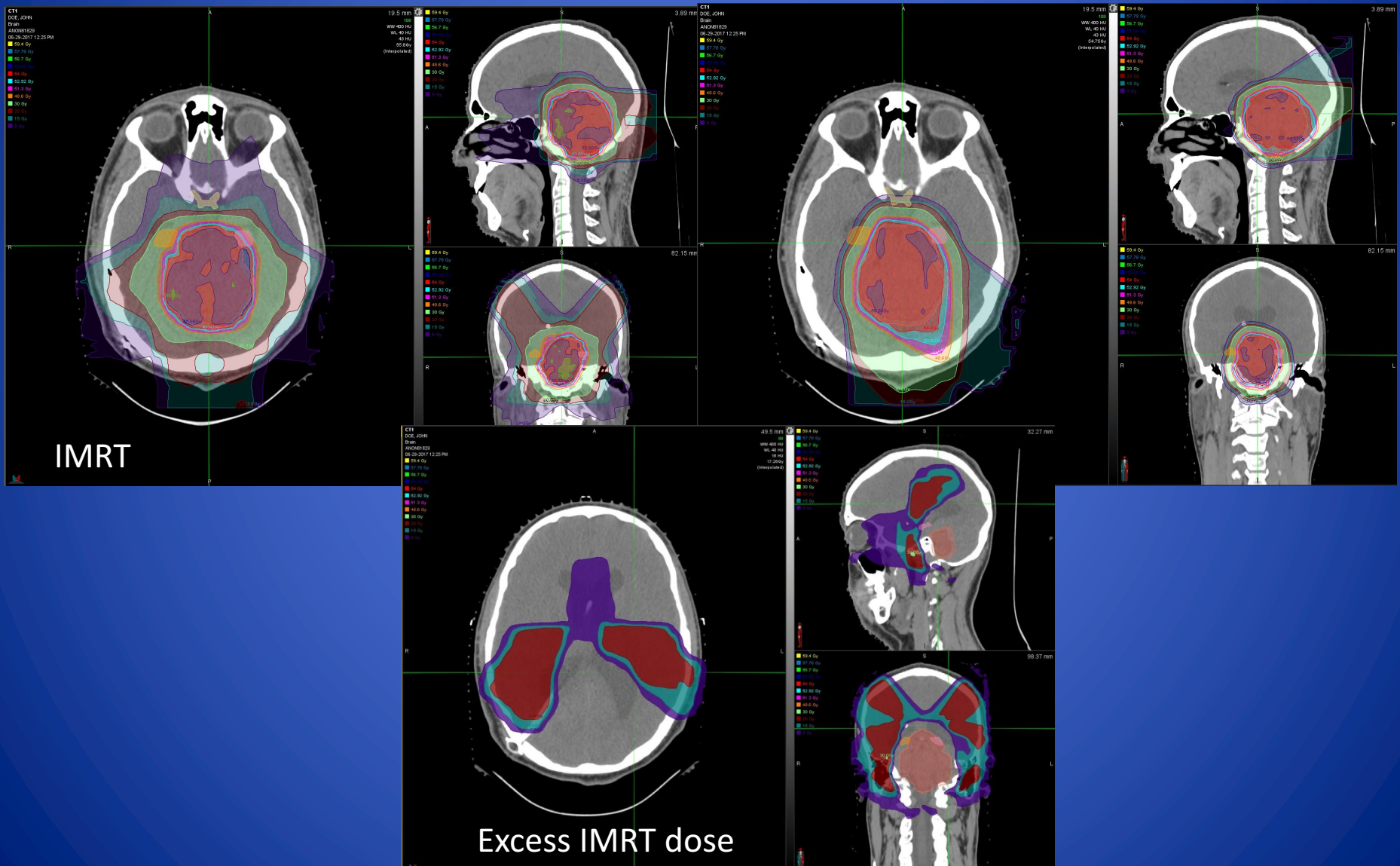


Diffuse Midline Glioma

- 32 year old presented left facial numbness, mild incoordination/gait imbalance- biopsy H3K27M mutation



Proton-IMRT dose comparison



Dose escalation for GBM: revisited

NRG-BN001

Randomized Phase II Trial Hypofractionated Dose-Escalated IMRT or Proton Therapy vs. Conventional Photon RT with TMZ in Newly Diagnosed Glioblastoma

PIs: Minesh Mehta, MD (UMaryland), and Vinai Gondi, MD (Cadence)

Protons: Anita Mahajan MD (MDACC), Helen Shih, MD (MGH)

Physics: Kevin Teo, PhD (UPenn), Jim McDonough, MD (UPenn)

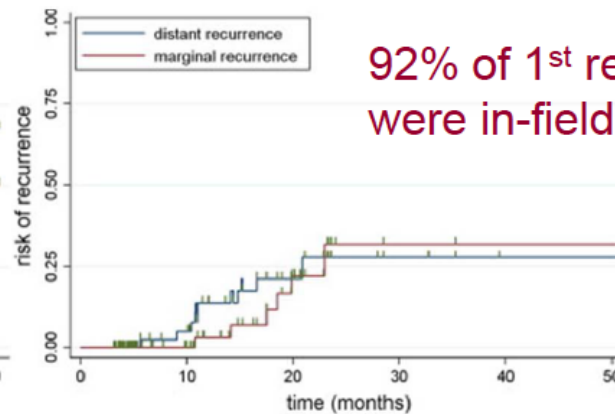
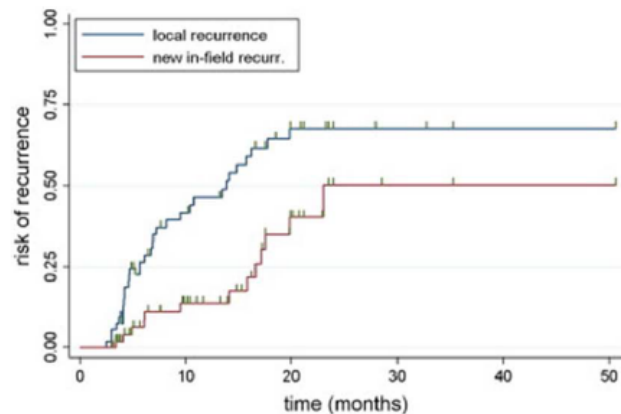
Neuro-Oncology: Mark Gilbert, MD (MDACC), Antonio Omuro, MD (MSKCC)

QOL: Terri Armstrong, PhD (MDACC); Neurocog: Jeffrey Wefel, PhD (MDACC)

Imaging: Christina Tsien, MD (WashU); TRP: Erik Sulman, MD (MDACC)

Rationale for Local Therapy Intensification

- Majority of relapses occur in high-dose RT field
 - N=54, analysis of newly dxed GBM txed with TMZ-RT to 60 Gy



92% of 1st recurrences were in-field (95% IDL)

- Central recurrence: arising from surgical cavity
- In-field recurrence: new lesion in 95% isodose line
- Marginal recurrence: new lesion crossing 95% isodose line
- Distant recurrence: new lesion entirely outside 95% isodose line
 - If relative to 90% IDL, 4 of 8 distant recurrences would be reclassified as marginal

Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation With Concomitant and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

SCHEMA (8/7/15)

Group I: Photon IMRT Centers

Proton Centers: Please see schema on next page.

STEP 1 REGISTRATION

Central Pathology Review for confirmation of histology and adequacy of tissue for MGMT analysis
NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.



STEP 2 REGISTRATION

STRATIFY

RPA Class: III, IV, or V

MGMT Status: Methylated, Unmethylated, or Indeterminate

RANDOMIZE*



Arm A1: Reference Arm

Photon irradiation using 3DCRT or IMRT:
46 Gy in 23 fractions followed by a sequential
boost for an additional 7 fractions to 60 Gy
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles



Arm B: Experimental Arm

Photon dose-intensified irradiation using IMRT:
50 Gy in 30 fractions with a simultaneous
integrated boost to 75 Gy in 30 fractions.
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

Group II: Proton Centers

All proton centers must be able to deliver photon therapy or partner with a photon therapy site for patients randomized to Arm A2. It is recommended that proton sites not able to deliver photon therapy discuss logistics for a treatment partnership with partnering sites prior to registering patients, See the beginning of Section 12 for data submission logistics pertinent to this partnership.

NOTE: IF YOUR SITE IS CREDENTIALLED FOR PROTONS FOR THIS TRIAL YOU **MUST** REGISTER TO GROUP II ONLY.

STEP 1 REGISTRATION

Central Pathology Review for confirmation of histology and adequacy of tissue for MGMT analysis
NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.



STEP 2 REGISTRATION

STRATIFY

RPA Class: III, IV, or V

MGMT Status: Methylated, Unmethylated, or Indeterminate

RANDOMIZE*



Arm A2: Reference Arm

Photon irradiation using 3DCRT or IMRT:
46 Gy in 23 fractions followed by a sequential
boost for an additional 7 fractions to 60 Gy
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles



Arm C: Experimental Arm

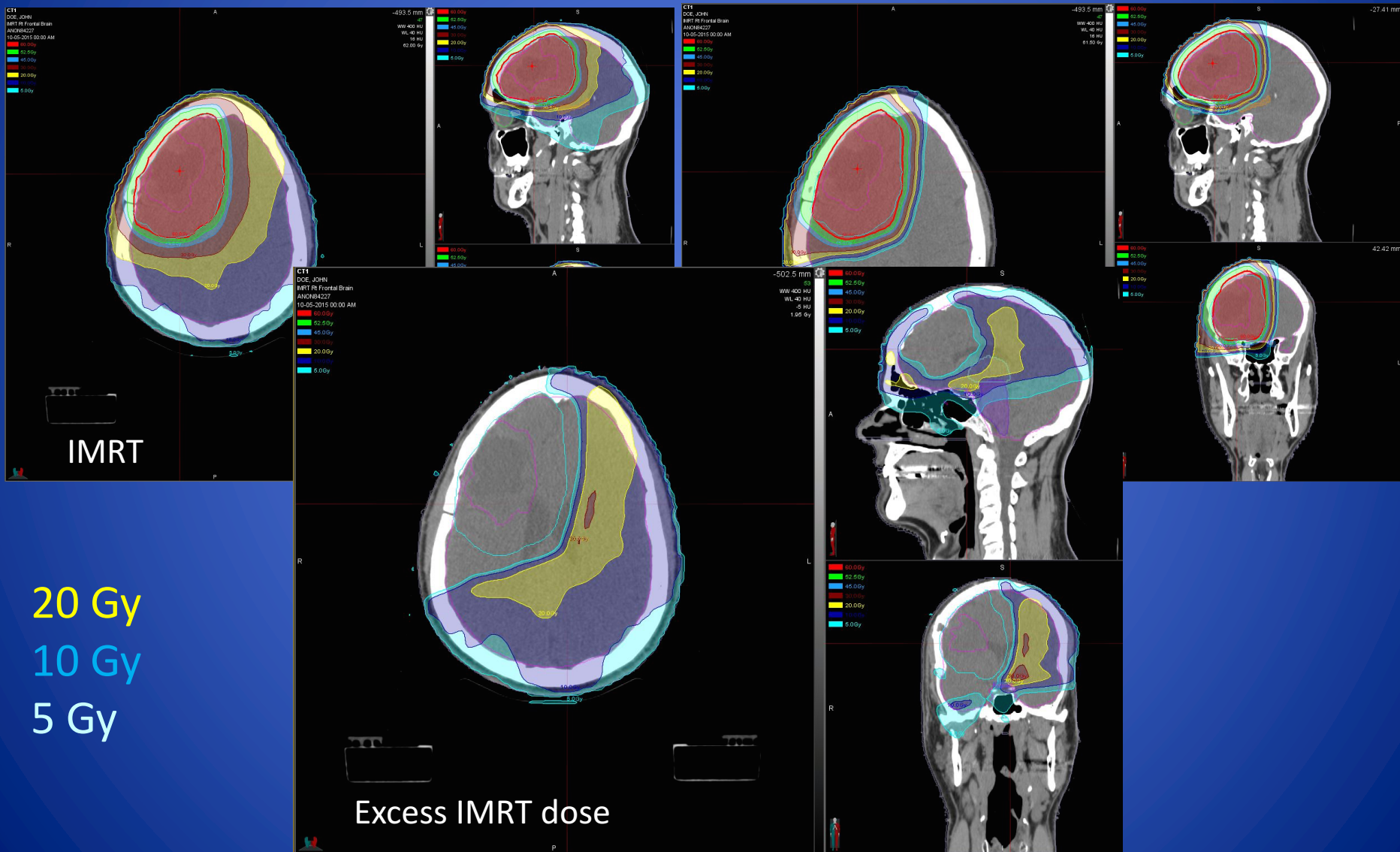
Proton dose-intensified irradiation using passive
scattered, uniform scanning beam, PBS or IMPT:
50 Gy(RBE) in 30 fractions with a simultaneous
integrated boost to 75 Gy(RBE) in 30 fractions.
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:

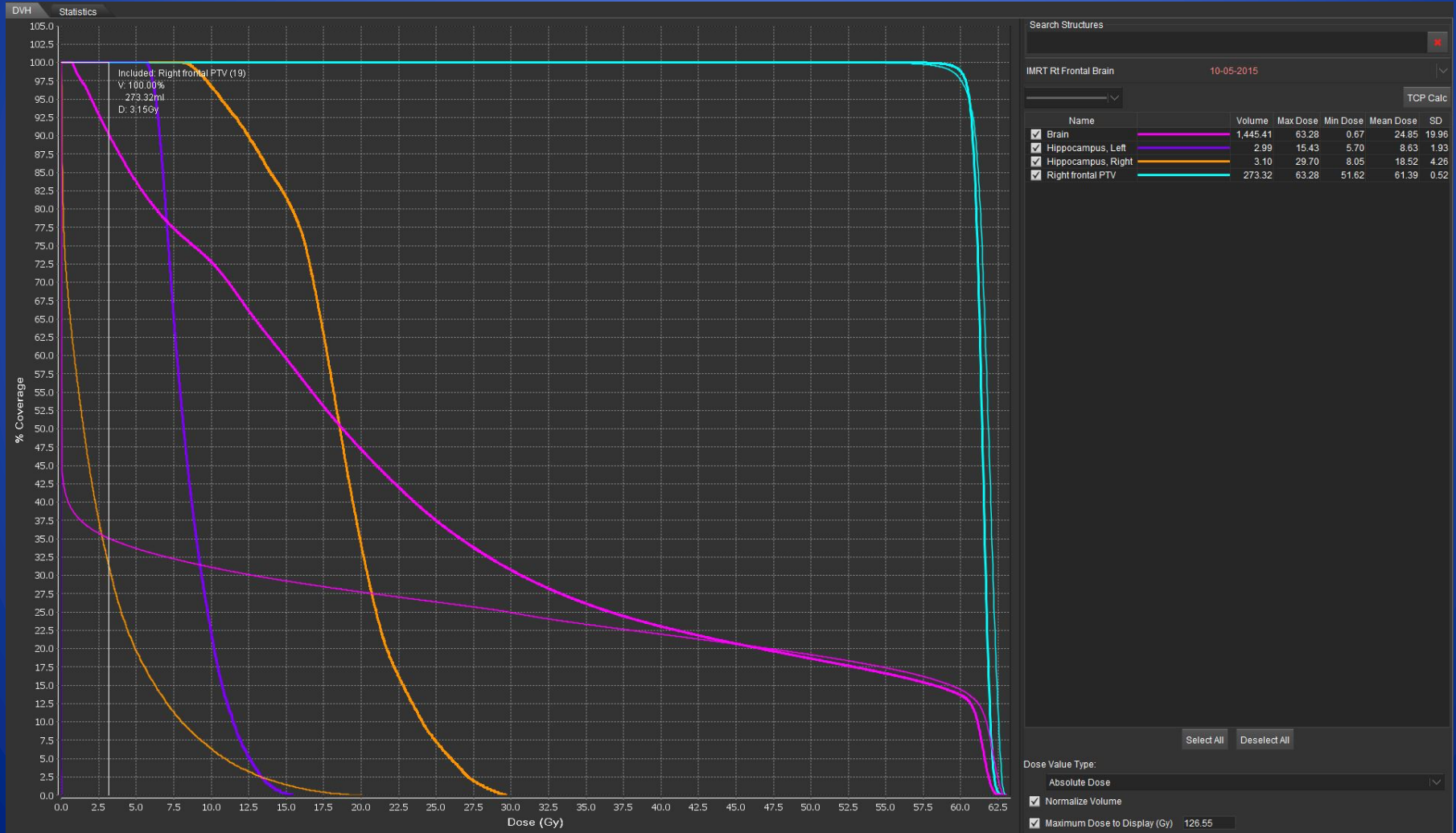
Adjuvant temozolomide x 6-12 cycles

*Randomization is 1:2 in favor of the experimental arm.

Glioblastoma: 40 yo



GBM: Comparative DVH



Problems with Protons

- Range uncertainty
 - Far greater effect on protons than X-rays
 - Sensitive to small changes in tissue density that may result from motion or variable anatomic compartments
- Neutron production
 - Protons interact with material in beamline and tissue to produce high energy neutrons

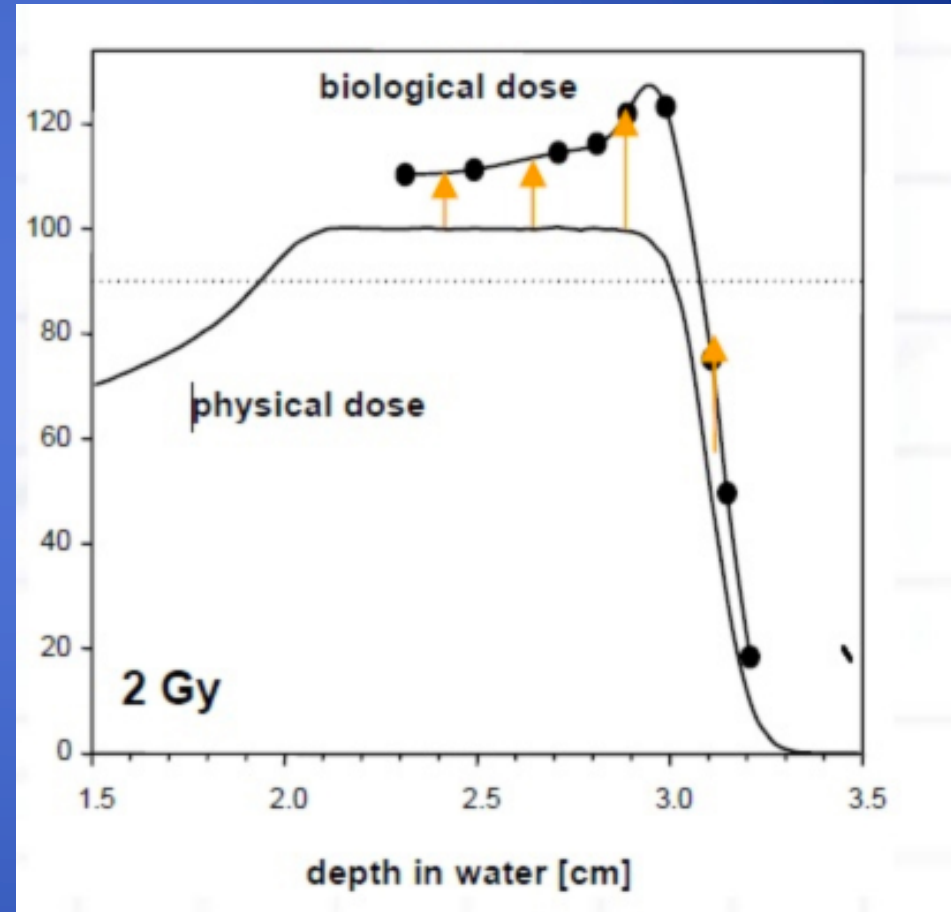


Captain, what should I do with these unwanted neutrons?

Biological effects at the leading edge:

Unknown

- The relative biological effect/dose varies with depth of the proton dose (spread out Bragg Peak) with increased biological dose at the distal edge
 - Increased effects on normal/tumor cells



Summary

- Radiation treatment is an important modality for management of CNS tumors
- The paradigms for best RT treatment for primary and metastatic cancer is evolving along with advances in systemic therapy.
- There is considerable interest in advancing CNS RT treatment technology for the purpose of reduction in treatment-related toxicity and improved tumor control.