Re-irradiation of Brain Targets: What have we learned and where do we need to go?

Workshop – Current Challenges of Patient Re-irradiation

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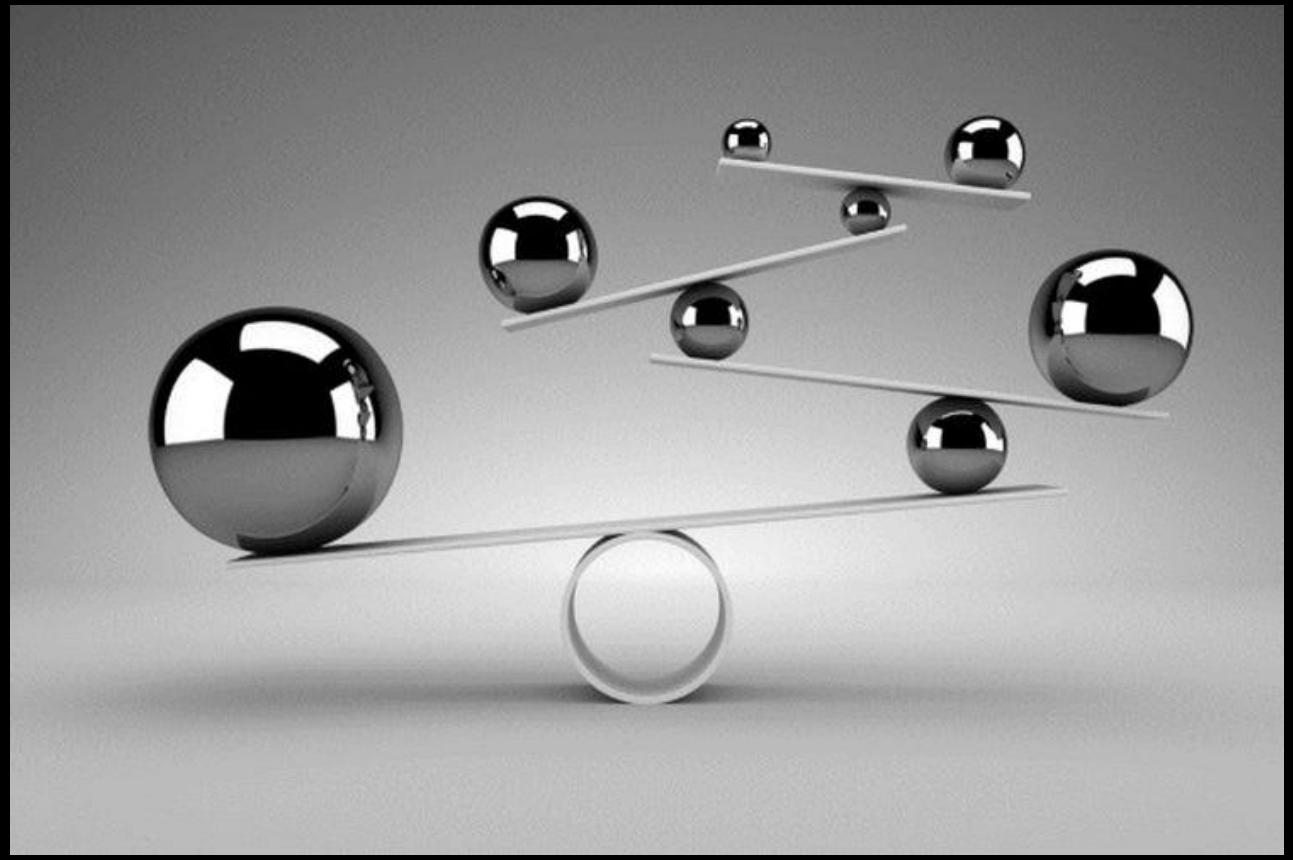
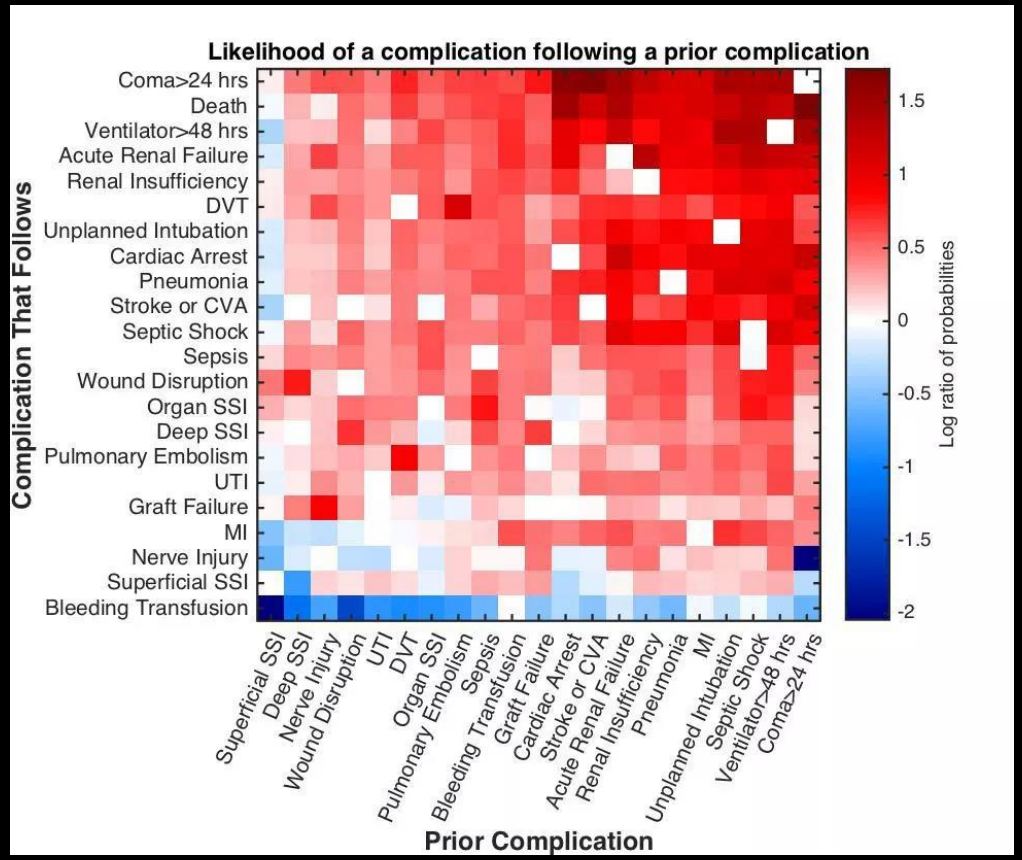
Clinical Decision-making around Re-Irradiation: It's all about balancing probabilities of benefit vs. harm





What is the critical information for safe and effective delivery of re-irradiation?

- Details of prior RT: dose,fractionation, spatial distribution
- Behavior of tumor/target:
  - Tumor histology, biology/molecular/genetic
  - Response to initial RT: speed and duration
- Response of normal structures to RT:
  - Existing changes that may predict future RT sensitivity or functional outcomes
  - Pathophysiology of radiation injury
- Overall Status of the Patient

How are we doing at gathering this information?

Looking back at Re-irradiation of Primary Brain Tumors

Brachytherapy			
Scharfen *et al.* 1992 (36)	66 GBM	Brachytherapy I-125 64.4 Gy	11.3 months
Sneed *et al.* 1997 (37)	66 GBM	Brachytherapy I-125 64.4 Gy	11.7 months
	45 WHO III		12.3 months
Simon *et al.* 2002 (38)	42 GBM	Brachytherapy Ir-192 40-60 Gy	50 weeks
Gabayan *et al.* 2006 (39)	81 GBM	Glissite brachytherapy 60 Gy at 10 mm	35.9 weeks
	14 WHO III		43.6 weeks
Tselis *et al.* 2007 (40)	84 GBM	Brachytherapy Ir-192 40 Gy	37 weeks
Fabrini *et al.* 2009 (41)	18 GBM	HDR brachytherapy 18 Gy	8.0 months
	3 WHO III		
Kickingereder *et al.* 2014 (42)	98 GBM	Brachytherapy I-125 60 Gy	10.4 months
Schwartz *et al.* 2015 (43)	40 GBM	Brachytherapy I-125 50 Gy	13.4 months
	28 WHO III		
Stereotactic radiosurgery			
Shrieve *et al.* 1995 (44)	86 GBM	Stereotactic radiosurgery 13 Gy	10.5 months
Cho *et al.* 1999 (45)	46 GBM	Stereotactic radiosurgery 17 Gy	11.0 months
Combs *et al.* 2005 (46)	32 GBM	Stereotactic radiosurgery Median 15 Gy (10-20 Gy)	10.0 months
Combs *et al.* 2005 (47)	54 GBM	Stereotactic radiotherapy	8.0 months
	39 WHO III	36 Gy (15-62 Gy) 5×2 Gy conventional fractionation	16.0 months
Kong *et al.* 2008 (48)	65 GBM	Stereotactic radiosurgery 16 Gy	13.0 months
	49 WHO III		26.0 months
Patel *et al.* 2009 (49)	36 GBM	Stereotactic radiosurgery 18 Gy	8.5 months
		Fractionated stereotactic radiotherapy 36 Gy in 6 fractions	7.4 months
Martinez-Carrillo *et al.* 2014 (50)	46 GBM	Stereotactic radiosurgery	7.5 months
	41 WHO III	Median 18 Gy (14-20 Gy)	17.0 months
Bir *et al.* 2015 (51)	29 GBM	Stereotactic radiosurgery 10-20 Gy	7.9 months
Pinzi *et al.* 2015 (52)	128 High-grade	Stereotactic radiosurgery or hypofractionated Hypofractionated stereotactic radiotherapy	11.5 months
Shepherd *et al.* 1997 (53)	33 GBM	Hypofractionated conformal radiotherapy Escalation 20-50Gy	11.0 months
Lederman *et al.* 2000 (54)	88 GBM	Stereotactic hypofractionated radiotherapy Median 24 Gy in 4 fractions	7.0 months
Grosu *et al.* 2005 (55)	44 GBM	Stereotactic hypofractionated radiotherapy 36 PET/SPECT 30 Gy	9.0 months
		8 CT/MRI (6×5 Gy)	5.0 months
Fokas *et al.* 2009 (56)	53 GBM	Stereotactic hypofractionated radiotherapy 30 Gy in 10 fractions	9.0 months
Fogh *et al.* 2010 (57)	105 GBM	Stereotactic hypofractionated radiotherapy	11.0 months
	42 WHO III	Median 35 Gy in 10 fractions	10.0 months
Dincoglan *et al.* 2015 (58)	28 GBM	Stereotactic hypofractionated radiotherapy 25 Gy in 5 fractions	10.3 months

Conventionally fractionated (stereotactic) radiotherapy			
Arcicasa *et al.* 1999 (59)	31 GBM	Fractionated conventional 2D-radiotherapy 34.5 Gy in 23 fractions (1.5Gy/F)	13.7 months
Cho *et al.* 1999 (45)	25 GBM	Conventional fractionated radiotherapy 37.5 Gy in 15 fractions	12.0 months
Koshi *et al.* 2007 (60)	11 GBM	Stereotactic radiotherapy	11.0 months
	14 WHO III	22 Gy in 8 fractions/8F (+ hyperbaric oxygen)	19.0 months
Combs *et al.* 2008 (61)	8 GBM	Stereotactic radiotherapy	9.0 months
	10 WHO III	36 Gy in 2 Gy per fraction	
	7 low-grade	(+ Temozolomide 50mg/m^2)	
Lee *et al.* 2016 (62)	21 GBM	Conventional fractionated radiotherapy	10.0 months
	8 WHO III	(median dose 45 Gy)	Not reported
	7 low-grade		Not reported

- Limitations of available data:
  - Variable reporting of
    - Target volumes
    - OAR definitions
    - Dosimetric reporting
    - Outcomes reporting
  - Variable patient selection
  - +/- pathological confirmation

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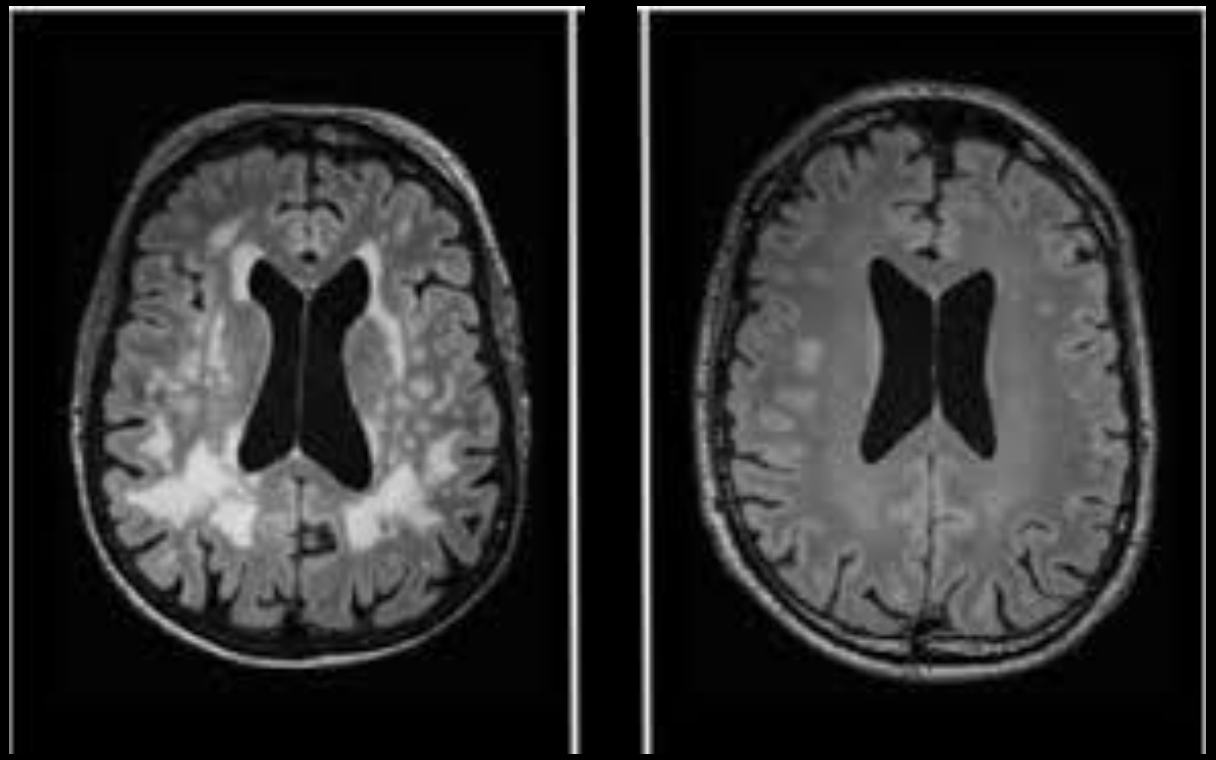
Patient Selection: Factors associated with RT toxicity

Age

Vascular comorbities

Metabolic comorbities

Smoking history



Current functional status

Baseline cognitive function

Imaging may reveal signs of patient-specific tolerance to RT

Phase II trial of Re-RT (3D-CRT) + TMZ in recurrent gliomas

Purpose: To assess the response rate, survival benefits and toxicity profile of TMZ then Re-RT (3D-CRT) for treatment of recurrent high grade glioma.

Eligibility:

- **unequivocal evidence of tumour recurrence as shown by gadolinium-enhanced MRI** after failing conventional RT +/- chemotherapy (only 6 prior TMZ treated)
- Histology included recurrent anaplastic astrocytoma, glioblastoma multiforme.

Interventions: (1) TMZ 200 mg/mÇ/day for chemonaïve and 150 mg/mÇ/day to previously treated patients, for 4-5 cycles (2) Then Re-RT 30-40 Gy by3D-CRT

Response: Measured on MR 2-3 wks post-RT

Ann Transl Med 2014;2(5):44

J Neurooncol. 2017 Sep;134(3):495-504. doi: 10.1007/s11060-017-2375-2. Epub 2017 Apr 5.

Pseudoprogression, radionecrosis, inflammation or true tumor progression? challenges associated with glioblastoma response assessment in an evolving therapeutic landscape.

Ellingson BM[1,2,3], Chung C[4], Pope WB[5], Boxerman JL[6], Kaufmann TJ[7].

	RECIST	Macdonald	RANO
Measurement	1D CE disease	2D CE diseaes	2D CE + FLAIR
Progression	≥ 20% increase in sum of lesions	≥ 25% increase in product of perpendicular diameters	≥ 25% increase in product of perpendicular diameters
Response	≥ 30% decrease in sum of lesions	≥ 50% decrease in produce of perpendicular diameters	≥ 50% decrease in produce of perpendicular diameters
Durablity of Response	Optional	Yes (≥ 4 wks)	Yes (≥ 4 wks)
Definition of measurable dz	Yes	No	Yes
No. Target Lesions	Up to 5	Not specified	Up to 5
T2/FLAIR	No	No	qualitative
Steroids	No	Yes	Yes
Clinical status	No	Yes	Ye
Pseudo-progression	No	No	Yes

Current criteria only use conventional T1-gad (T2/FLAIR qualitative)

3D volume is recommended but need standardized approach

Growing interest in advanced imaging, particularly to differentiate tumor progression vs. pseudo-progression and radionecrosis

Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

Benjamin M. Ellingson, Martin Bendszus, Jerrold Boxerman, Daniel Barboriak, Bradley J. Erickson, Marion Smits, Sarah J. Nelson, Elizabeth Gerstner, Brian Alexander, Gregory Goldmacher, Wolfgang Wick, Michael Vogelbaum, Michael Weller, Evanthia Galanis, Jayashree Kalpathy-Cramer, Lalitha Shankar, Paula Jacobs, Whitney B. Pope, Dewen Yang, Caroline Chung, Michael V. Knopp, Soonme Cha, Martin J. van den Bent, Susan Chang, W.K. Al Yung, Timothy F. Cloughesy, Patrick Y. Wen, Mark R. Gilbert, and the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee

We need to standardize MRI acquisition protocols

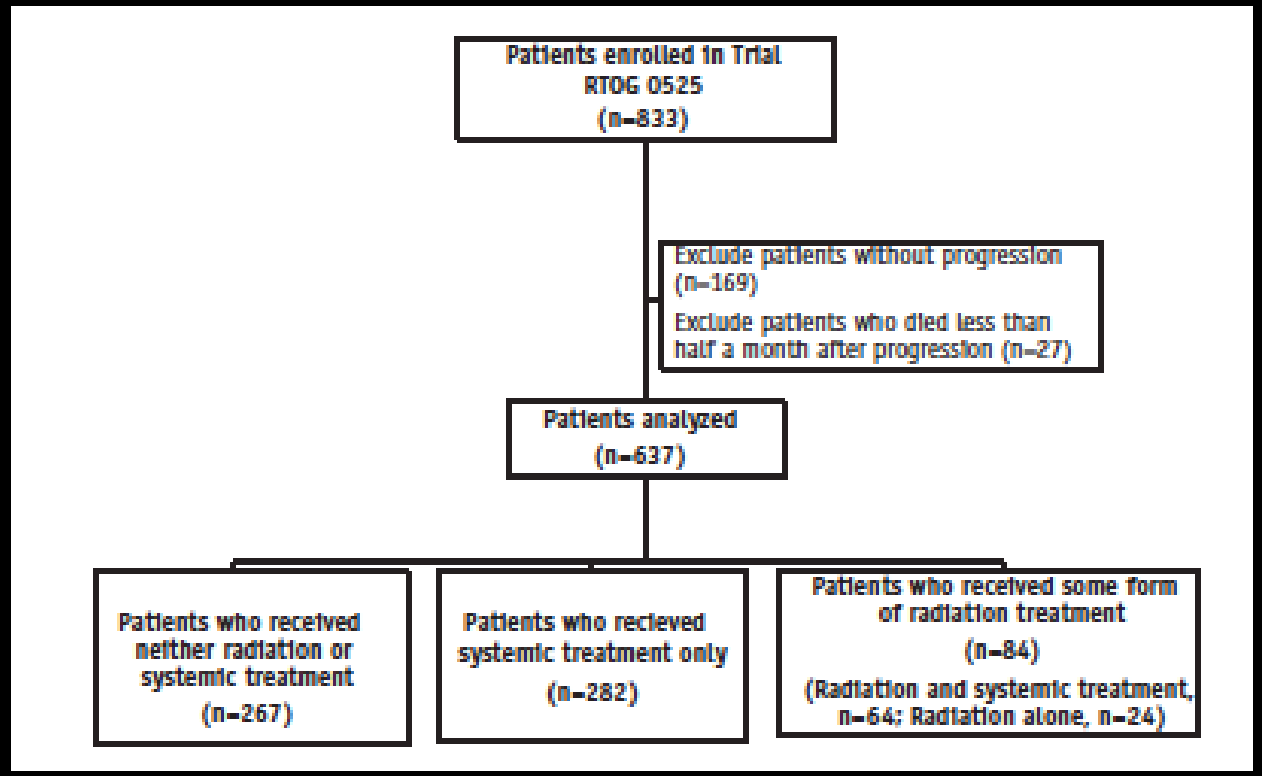
- Lesion contrast is highly dependent on sequence parameters
- Lesion size is subjective due to ability for reader (or algorithm) to generalize across levels of image quality

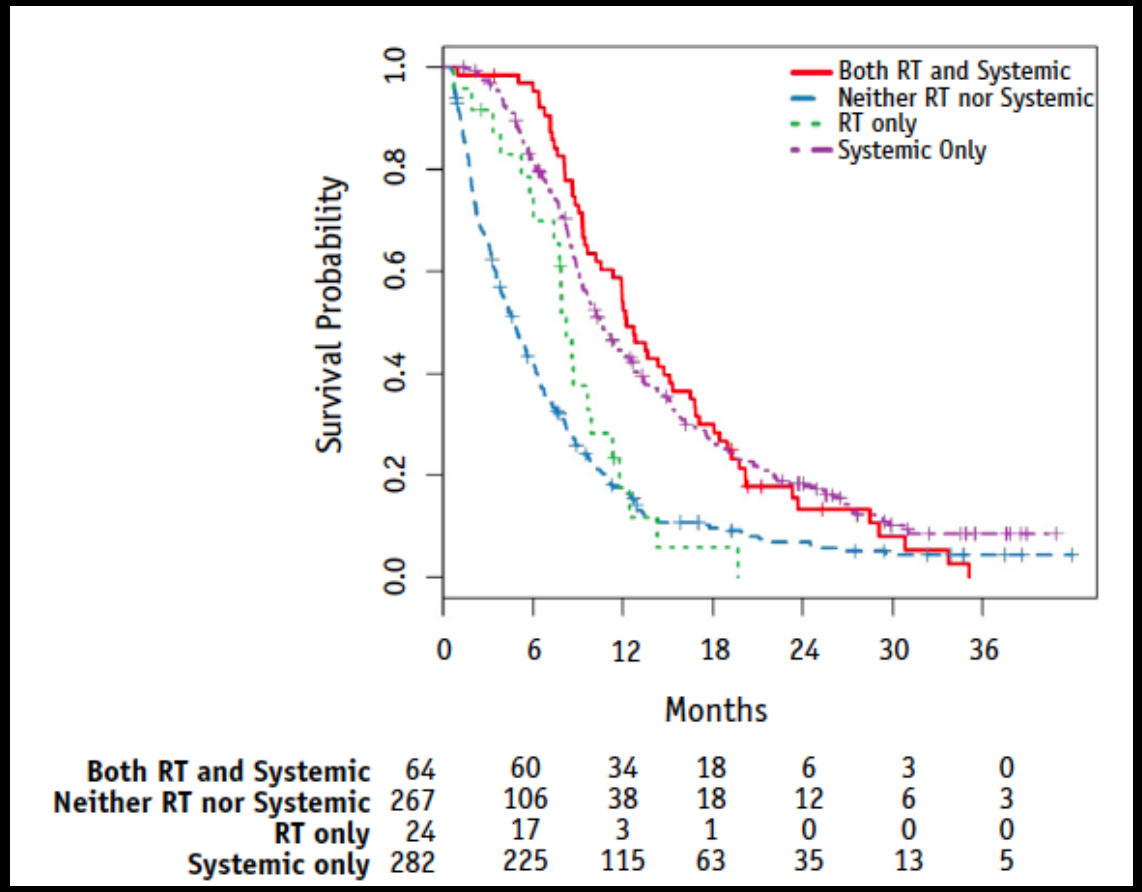
Impacts:

- Diagnosis of recurrence
- Radiation Target delineation
- Measurement of treatment response

Neuro-Oncology 2015

RTOG 0525: Management at tumor recurrence
RT regimen used for Re-RT is widely variable





Patients received a variety of re-RT regimens (stereotactic radiosurgery, FSRT, or brachytherapy).

Different dose & fractionations used, but details were not available for analysis

Phase II trial of Re-RT (3D-CRT) + TMZ in Recurrent High Grade Gliomas

Radiation: Re-RT 30-40 Gy by 3D-CRT

Target Definition:

- T1-images on MRI were used to define GTV.
- T2-weighted and FLAIR images were used to define CTV.
- **PTV was defined by adding 1 cm to the GTV + surrounding oedema. The PTV was reduced in areas near organ at risks (OARs).**

- Limited info on OAR constraints

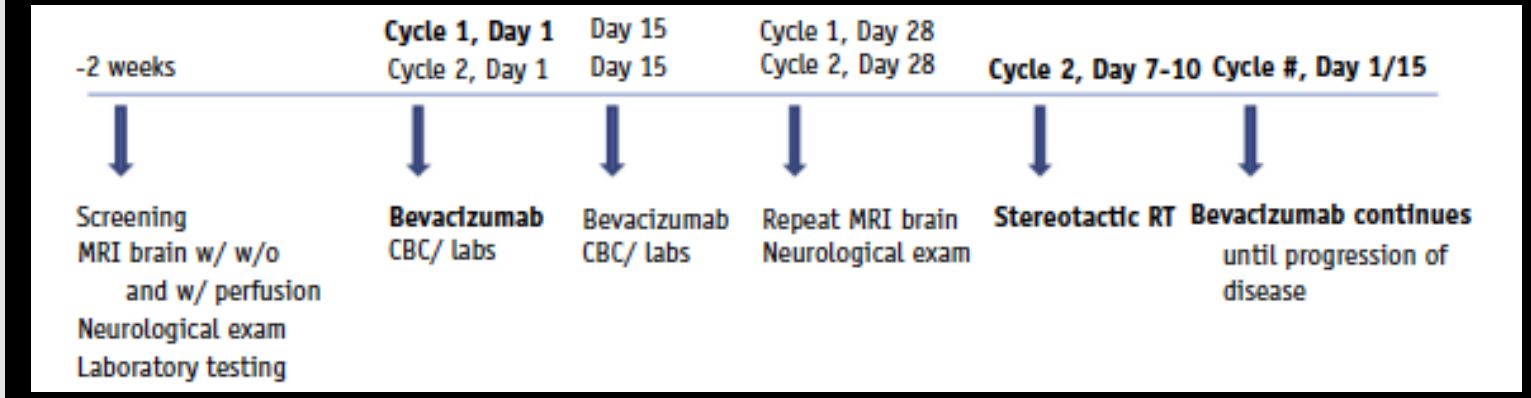
Ann Transl Med 2014;2(5):44

Multi-center Ph I Dose Escalation of Hypofractionated SRT for Recurrent High Grade Gliomas

Table 1 Patient characteristics

Characteristics (n = 15)	Value
Sex	
Men	12 (80)
Women	3 (20)
Age (y)	
Median (range)	63 (50-73)
<60	5 (33)
≥60	10 (67)
Histology	
Glioblastoma	10 (67)
Anaplastic astrocytoma	5 (33)
KPS, median score (range)	90 (70-100)
MGMT methylation status	
Unknown	7 (47)
Unmethylated	6
Methylated	2
Prior salvage chemotherapies	
Median (range)	2 (1-3)
1 prior treatment, n	6
2 prior treatments, n	8
3 prior treatments, n	1
Mean (range) tumor size at largest diameter (cm)	2.65 (1.8-5.37)

Abbreviation: KPS = Karnofsky performance status.
Values are number (percentage) unless otherwise noted.



GTV = T1-gad enhancing disease (post cycle 1 MR) +/- mass-like T2/FLAIR abnormality, discretion of treating RO

PTV = GTV + 2-5mm margin

3 patients: 9 Gy x 3, 5 patients: 10 Gy x 3 , 7 patients: 11Gy x 3 [MTD based on 1 DLT - Gr3 fatigue and cognitive decline]

IJROBP, Vol. 99, No. 4, pp. 797e804, 2017

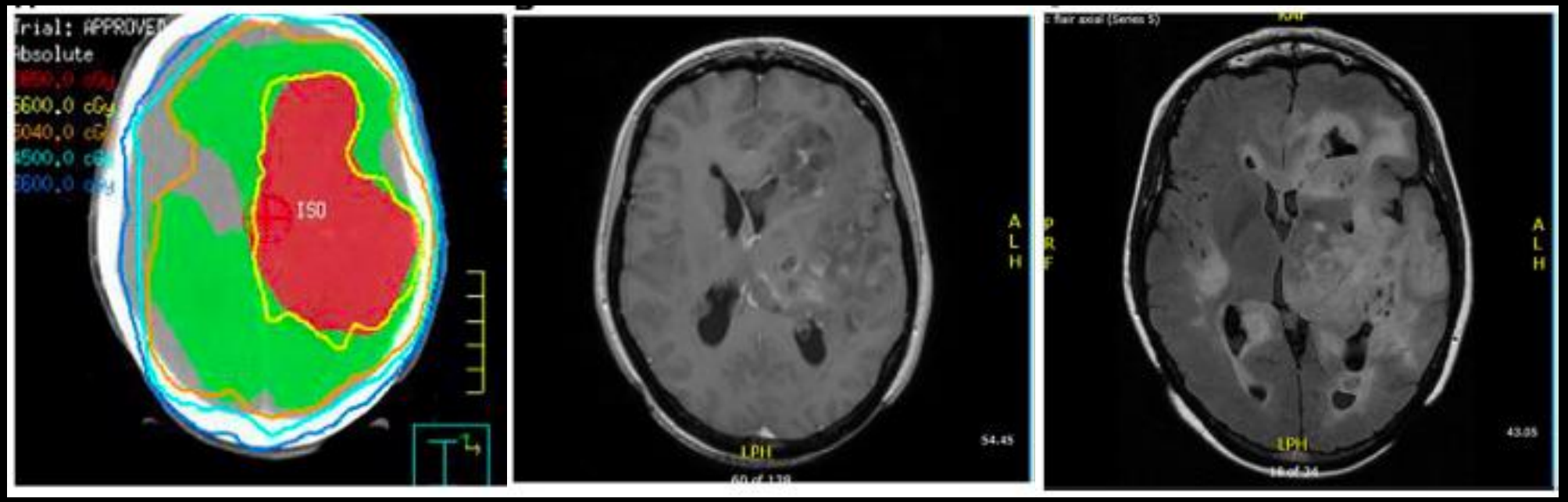
IMRT with Pulsed Reduced Dose Rate for Re-RT

Target Volume Definition:

GTV = defined on FLAIR/T2 MRI + 1-2 cm CTV margin + 3 mm PTV margin

Rx dose: 54 Gy (range, 38 to 60 Gy) delivered in 30 fractions (1.8 or 2 Gy),

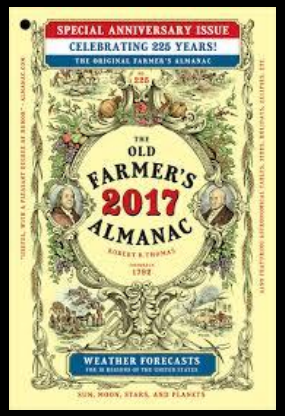
Allowed full RTOG dose constraints to OARs



Median FU: 5.2 months – no increased toxicity such as radionecrosis noted

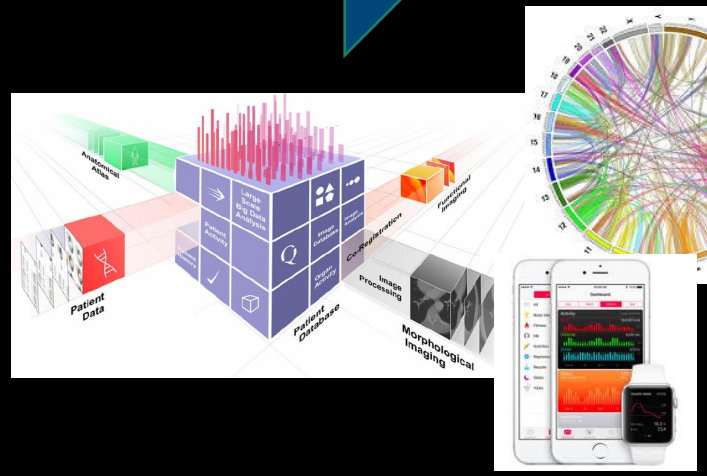
Practical Radiation Oncology (2017) 7, e391-e399

We need to bring the Medical Profession into the Data-Driven Era



'Practice of Medicine' → **Data-driven Clinical Optimization**

INCREASING STANDARDIZATION

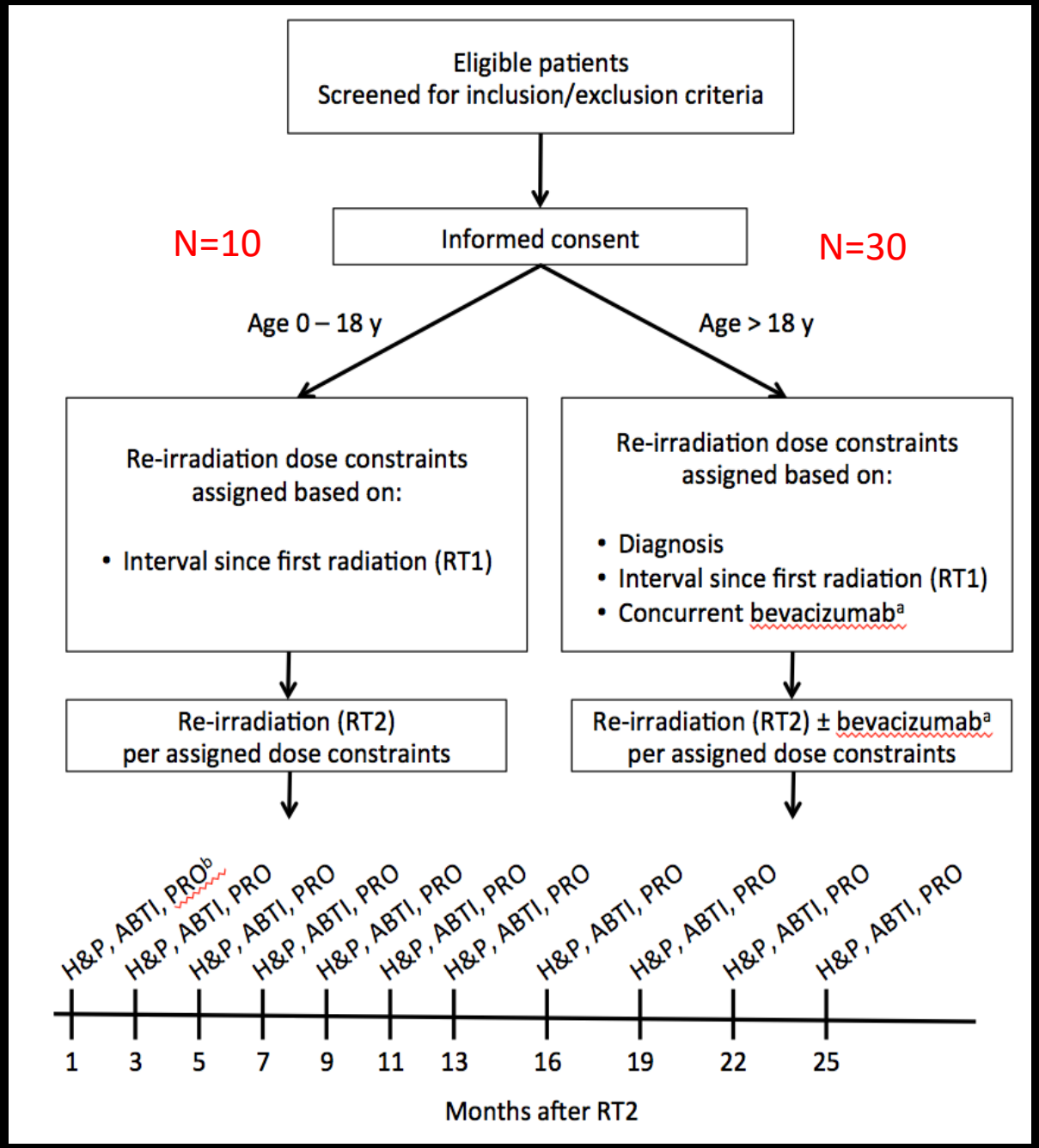


Pilot trial of dose-volume constraints for reirradiation of recurrent brain tumors

(PI: S. McGovern, MDACC)

Eligibility:

- Previous pathologic confirmation of a brain tumor treated with RT >6 months prior to Re-RT with imaging findings consistent with recurrent tumor
- Prior course of RT delivered at 1.5 – 2.5 Gy/fraction
- Prior 3D DVH data for OARs must be available



Pilot trial of dose-volume constraints for reirradiation of recurrent brain tumors

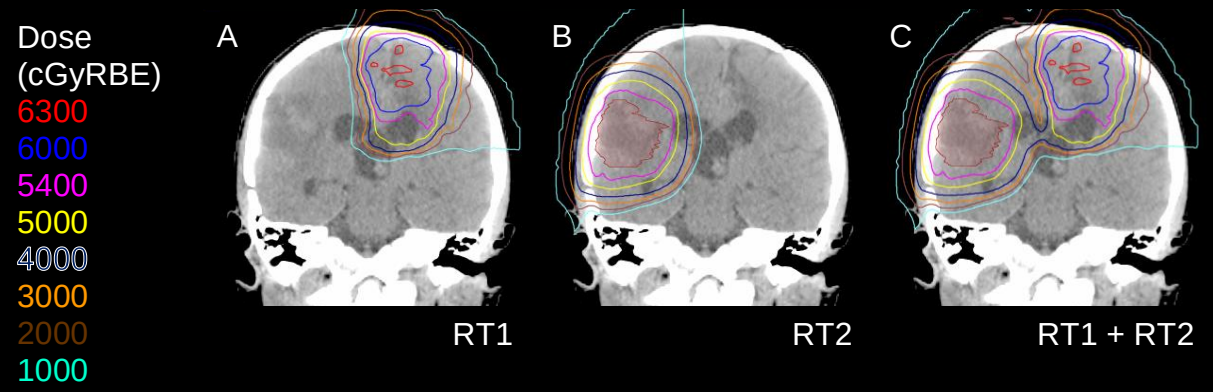
Primary Objective:

- To estimate the rate of ≥ Gr3 CNS necrosis 6 months after Re-RT of the brain for recurrent tumor.

Secondary Objectives:

- To evaluate acute and late toxicities of re-RT
- To evaluate longitudinal changes in symptom burden of patients undergoing re-RT.
- To use Advanced Brain Tumor Imaging (ABTI) to evaluate changes in the brain after re-RT (progression,RN, pseudoprogression)
- To estimate PFS and OS following reirradiation.

Dose-Volume Constraints for Re-RT



RT2 Dose constraints:

OAR	Max D0.03cc (Gy or GyRBE)
Optic nerves (ON)	55
Optic chiasm (OC)	56
Brainstem	60
Eye, including retina	50

[a]GBM = glioblastoma or gliosarcoma

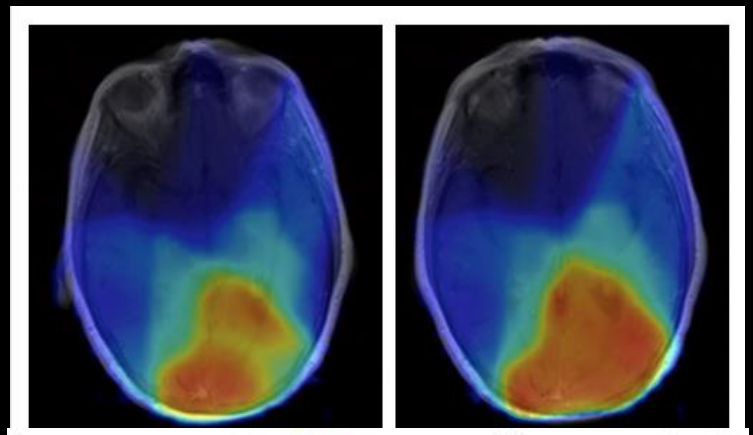
[b]Bevacizumab must be given concurrently with RT2.

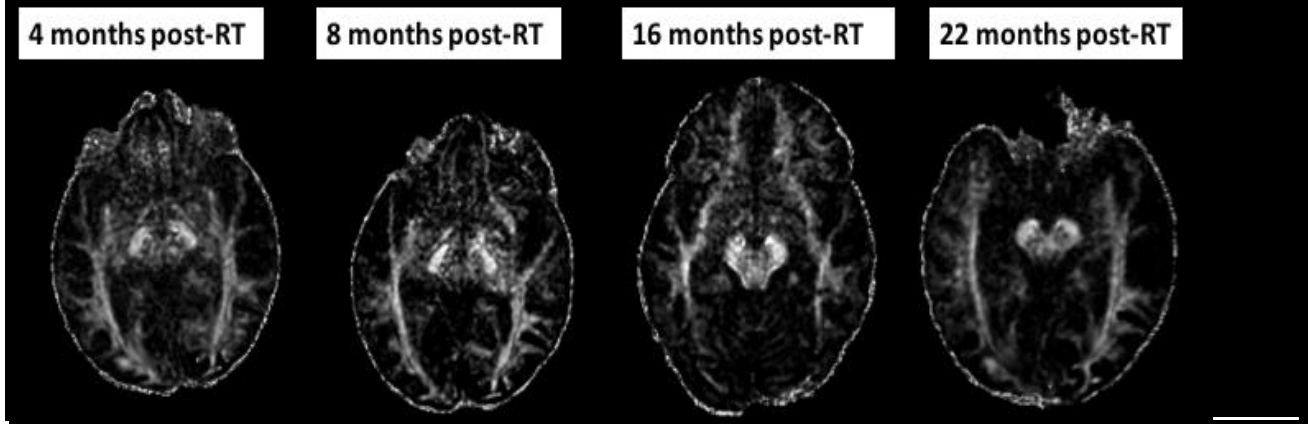
[c][Brain – PTV] = [Whole brain – (PTV + OC + RON + LON + Brainstem)]

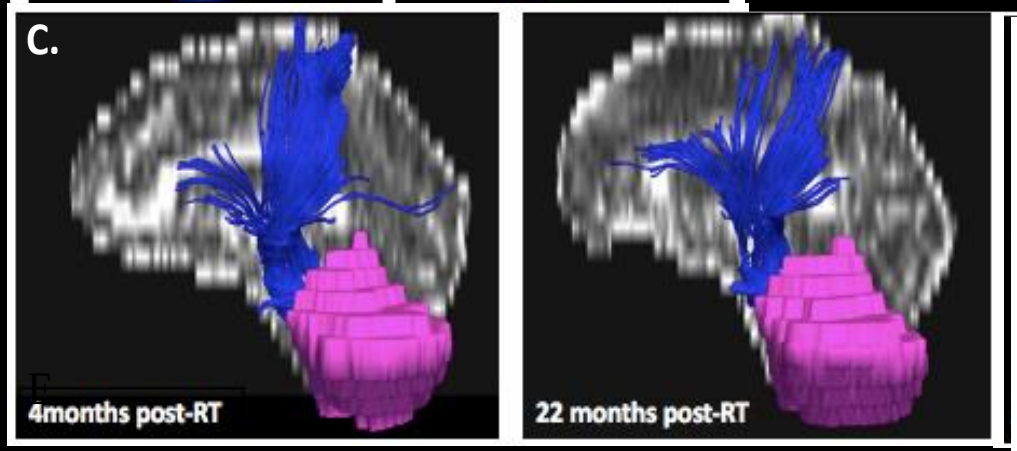
RT1 + RT2 Dose constraints:

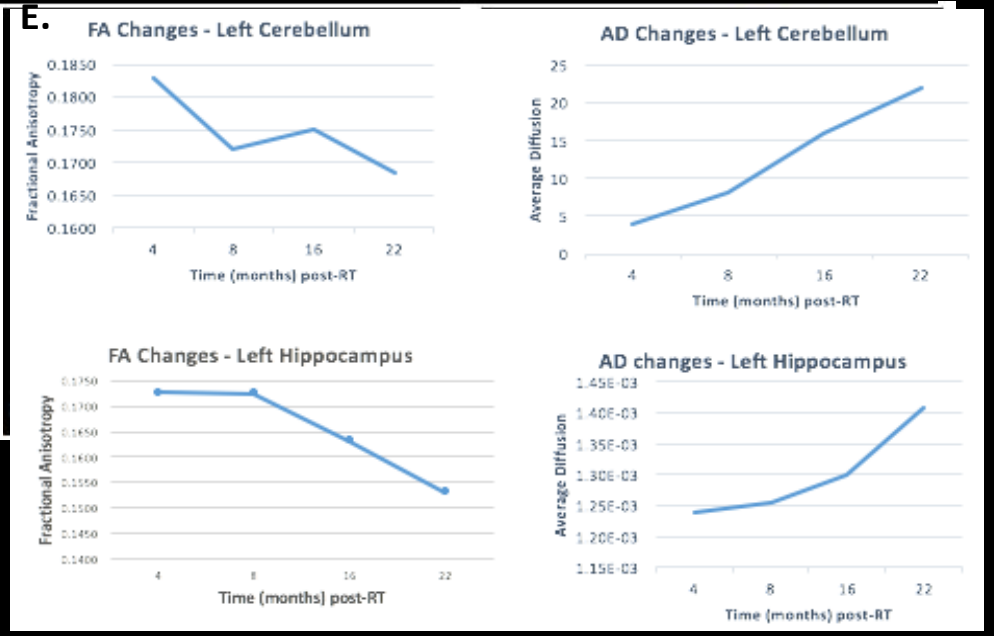
Group	Age at RT2 (y)	Current Diagnosis	Time since RT1	Max D0.03cc [Brain – PTV][c] (Gy or GyRBE)	Max D1cc [Brain – PTV][c] (Gy or GyRBE)	Max D0.03cc ON, OC (Gy or GyRBE)	Max D1cc Brainstem (Gy or GyRBE)
1	0 - 18	Any	6 mo – 3 y	95	90	60	70
2	0 - 18	Any	> 3 y	100	95	70	80
3	> 18	Any except GBM[a]	6 mo – 3 y	100	95	65	70
4	> 18	Any except GBM[a]	> 3 y	105	100	75	80
5	> 18	GBM[a] without Bev	> 6 mo	105	100	75	80
6	> 18	GBM[a] with Bev[b]	> 6 mo	110	105	80	85

Serial Changes on DTI MR: Clinical & Dosimetric Correlation



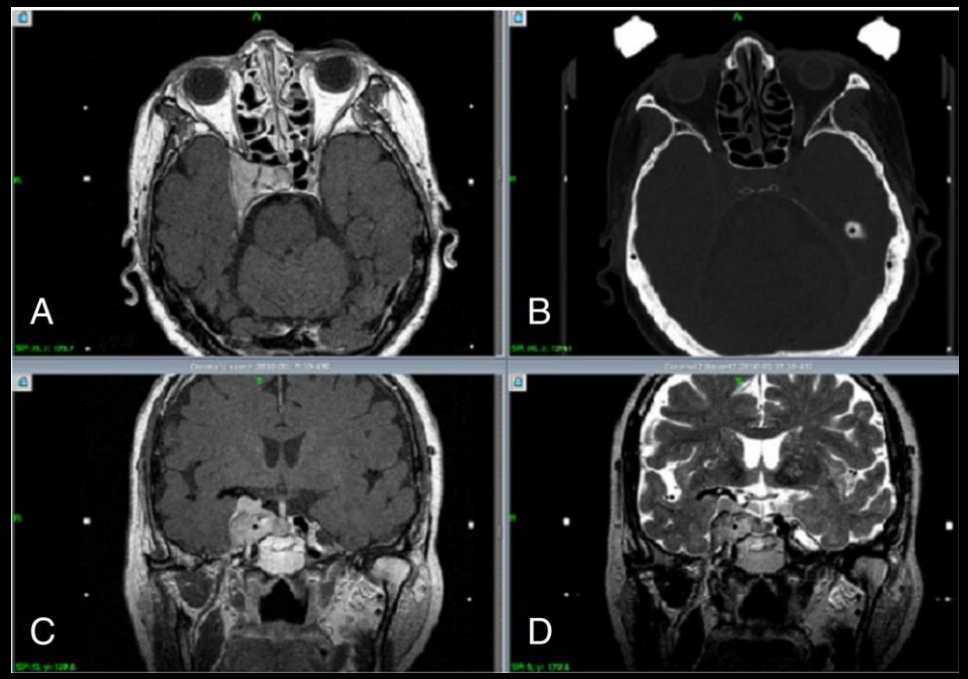


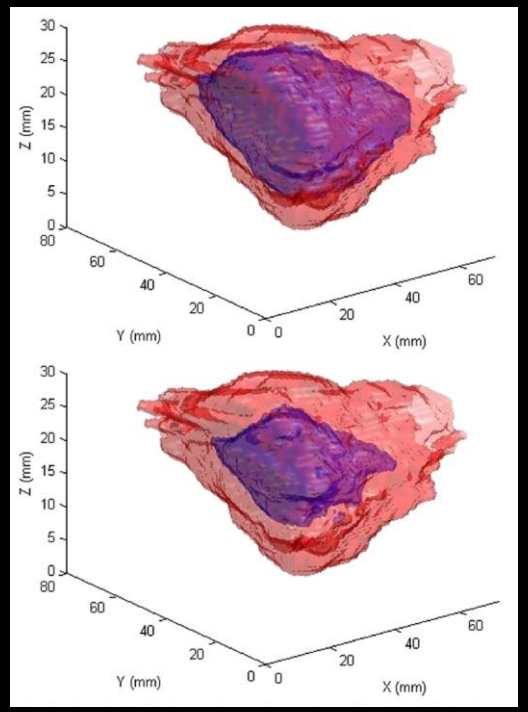




Target Definition – Humans are inconsistent

- 16 participating GK centers
- Axial and coronal T1-w, coronal T2-w and CT (bone-window) images were provided for target delineation





AV_{50}

$V_{encompassing}$

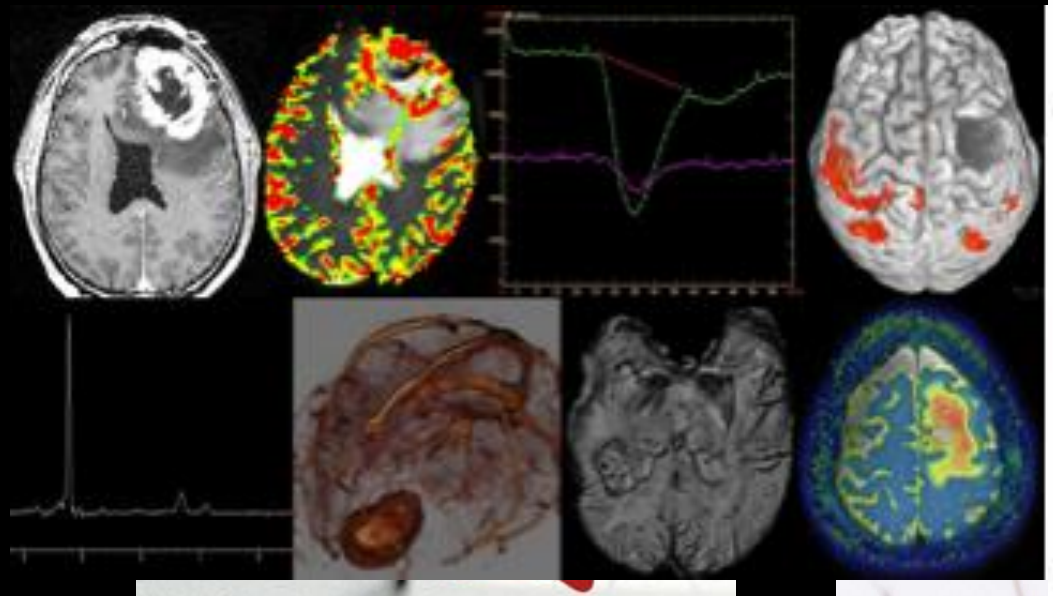
AV_{100}

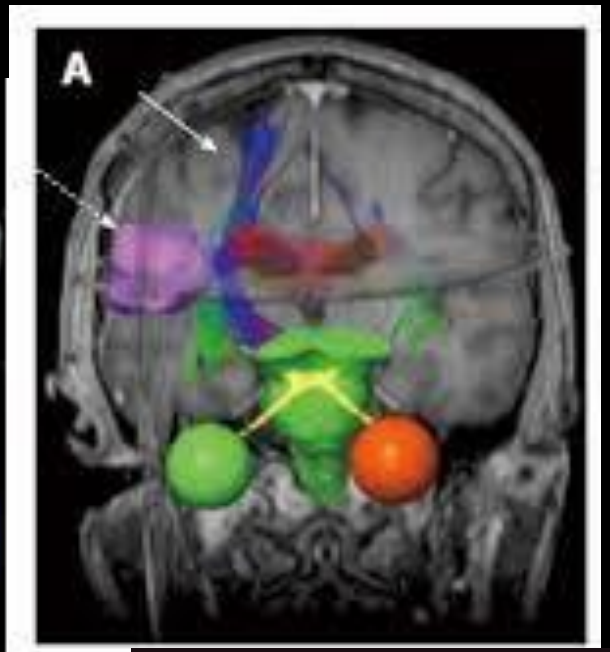
$V_{encompassing}$

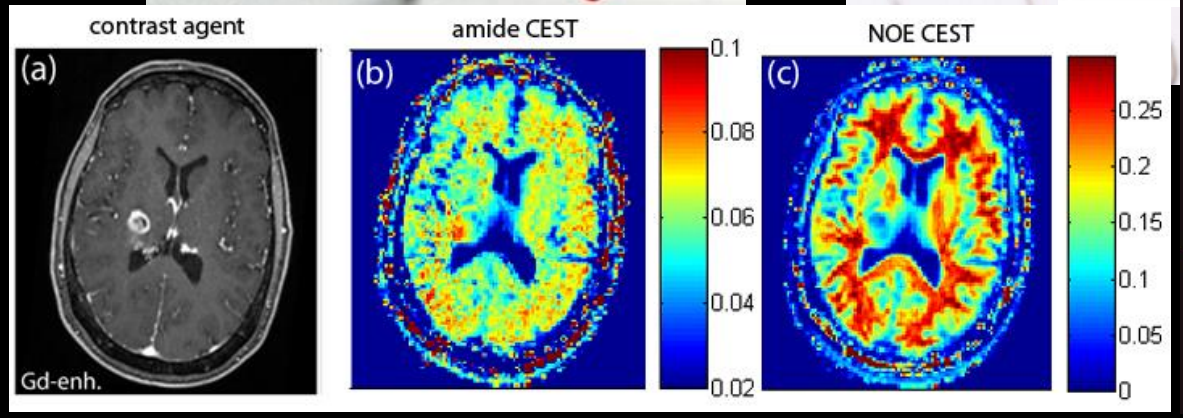
We need better understanding of what we are visualizing

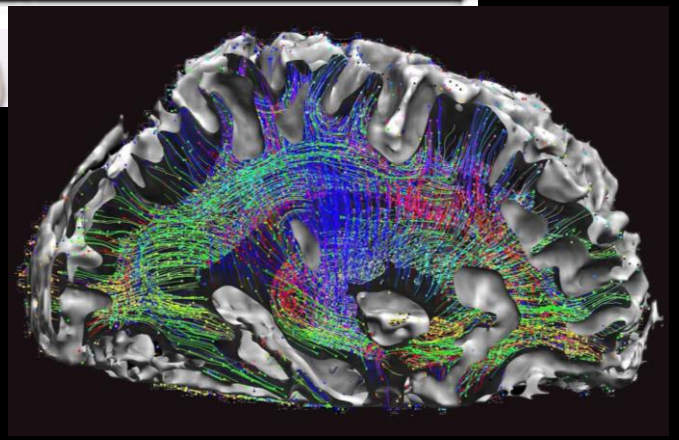
Sandstrom-Acta Neurochir 2014

Multiparametric Imaging for Brain







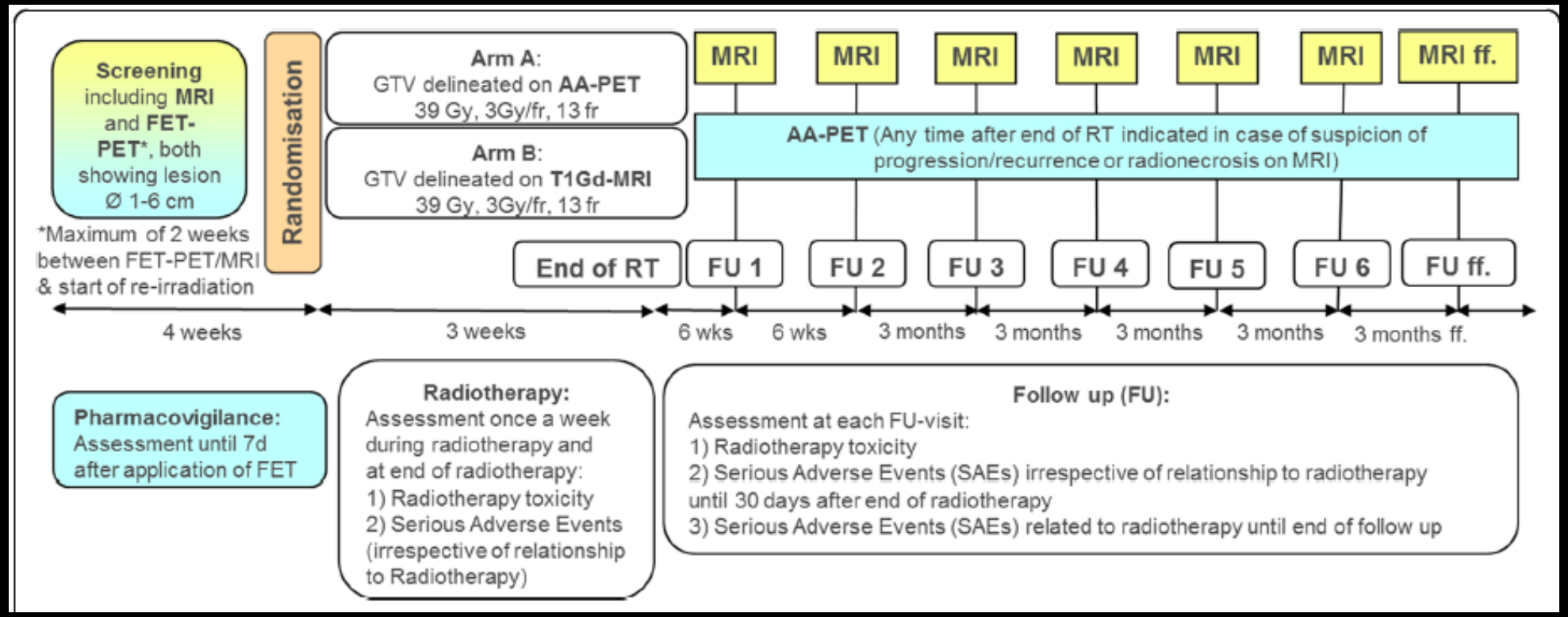


Need to effectively integrate imaging data for RT planning

Improving Target Definition

Amino-acid PET versus MRI guided re-irradiation in patients with recurrent GBM (GLIAA) protocol of a randomized Ph II trial (NOA 10/ARO 2013-1)

Target n=200 (1:1 randomization)



Oehlke et al. BMC Cancer (2016) 16:769

Utilization of Imaging: Moving Beyond the Art

Qualitative

'Relative'

Quantitative

'Absolute'

Dependent on human expertise

Increasing potential for automation/standardization

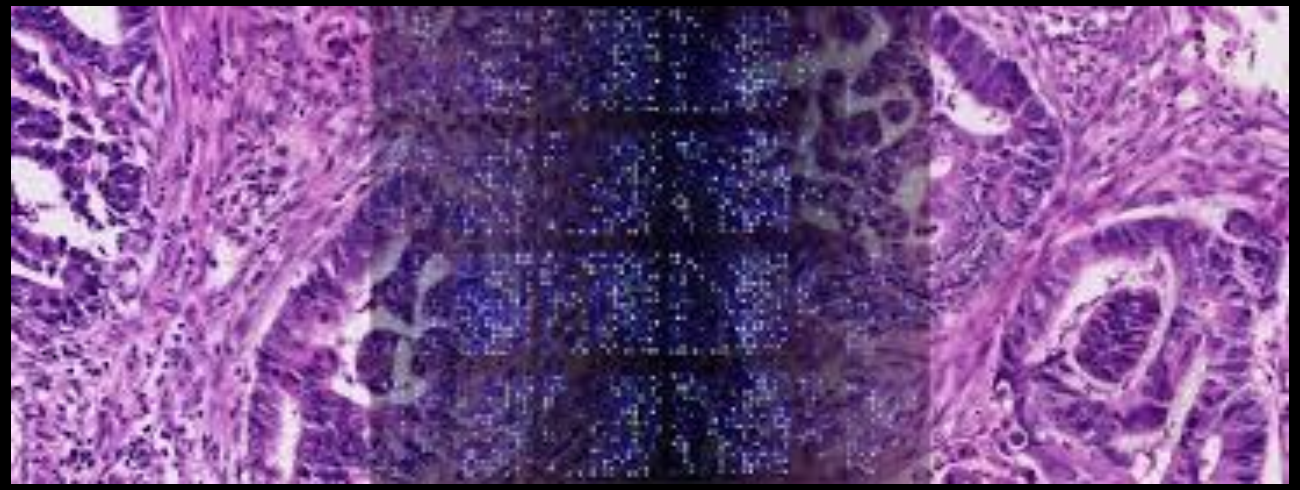
Major Challenge: Defining goals

Defining ground truth

Working towards the ’Ground Truth’ in Imaging

- Collaborative effort between therapy (RO, SO, MO, IR), diagnostic imaging and pathology

Digital pathology

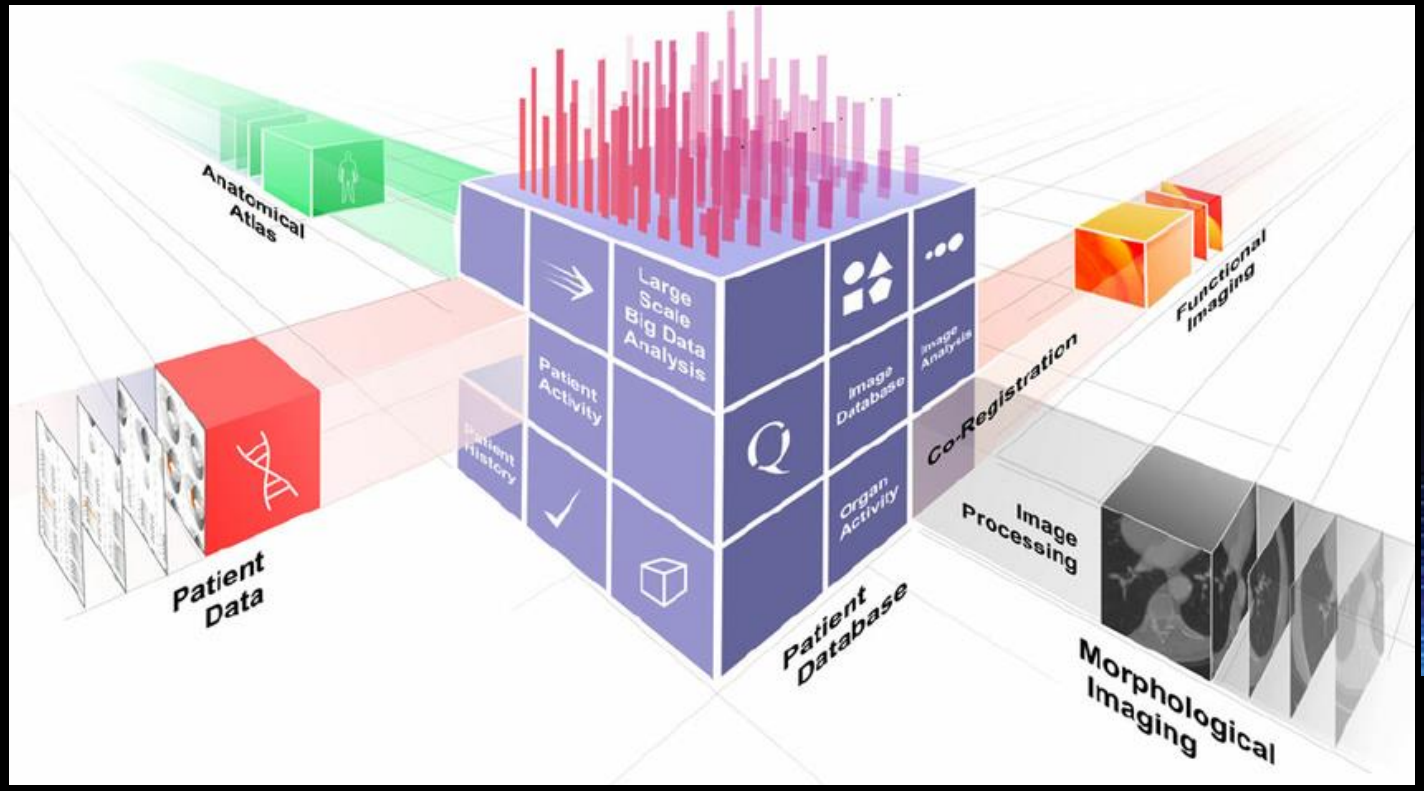


Anatomical/Functional Imaging

- Target Definition for RT
- Enable serial non-invasive biological imaging interpretation for personalized therapy adaptation

Big Data is Critical for Data-Driven Re-Irradiation

Each case is so unique, a personalized approach is critical.



To learn from unique treatment approaches,
we need to share a common reporting framework

hank you

cchung3@mdanderson.org