Connectome-Informed Single-Isocenter Multi-Target SRS Planning
A Pilot Feasibility Study

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ABSTRACT

Purpose: To evaluate the feasibility of connectome-informed single-isocenter, multi-target (SIMT) fractionated stereotactic radiosurgery (fSRS) planning for patients with multiple brain metastases.

Methods: Five adults with multiple brain metastases (2–13 lesions per patient) who had previously undergone cranial fSRS using multiple isocenters were retrospectively replanned using SIMT SRS with and without functional-network sparing. All patients underwent pre-radiotherapy T1-weighted, T2-FLAIR, resting-state functional MRI (rs-fMRI; approximately 13 minutes), and diffusion tensor imaging (DTI; b = 0 and 1,000 s/mm², 30 directions). Patient-specific functional and structural connectomes were generated using the Quicktome platform (Omniscient Neurotechnology). White-matter tracts connecting the triple-network system (the default mode, salience, and central executive networks) were delineated as functional organs at risk (fOARs) and co-registered with the planning CT. For each patient, two plans were generated: (A) a standard anatomy-based OAR plan and (B) a connectome-informed plan incorporating tract avoidance. Target coverage and tract dosimetry were compared between plans.

Results: Connectome-informed SIMT fSRS planning reduced dose to the selected white-matter tracts, with relative reductions in V5 Gy of 1.4%–59.5%, V10 Gy of 28.3%–71.2%, V15 Gy of 27.5%–32.2%, V20 Gy of 0%–22.2%, V25 Gy of 0%–13.4%, V30 Gy of 0%–85.7%, Dmax of 0.5%–14.5%, and Dmean of 13.0%–40.7%. Clinically required target coverage was maintained in all connectome-informed plans, with PTV Dmin >90% of the prescription dose and PTV V100% >98%.

Conclusion: Connectome-informed SIMT fSRS planning was technically feasible and produced clinically acceptable plans while selectively reducing dose to cognition-related white-matter pathways beyond that achieved with conventional anatomy-based OAR optimization.

INTRODUCTION

Cognitive impairment remains a clinically significant toxicity of intracranial radiotherapy. Although SRS reduces neurocognitive decline compared with whole-brain radiotherapy, 52%–64% of patients treated with SRS alone for multiple brain metastases still experience cognitive deterioration [1]. This finding suggests that focal irradiation may impair cognition through direct or indirect injury to cognition-critical neural substrates. Cognition is increasingly understood as a network-level function supported by distributed cortical hubs and interconnecting white-matter pathways. The triple-network model provides a relevant framework, comprising the default mode network (DMN), salience network (SN), and central executive network (CEN), which collectively support memory, salience detection, attention, executive control, and adaptive behavior. Injury to the white-matter tracts interconnecting these networks may therefore disrupt cognitive function even when conventional anatomical OAR constraints are met. Single-isocenter, multi-target (SIMT) SRS is an efficient strategy for treating multiple brain metastases; however, its complex dose distributions may overlap with patient-specific cognitive networks. This feasibility study evaluated whether SIMT SRS plans could be optimized to reduce dose to tracts connected to the DMN, SN, and CEN while maintaining target coverage, overall plan quality, and conventional OAR constraints.

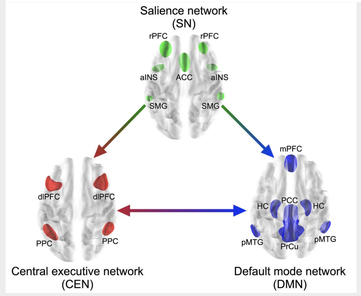

Fig 1. Triple network model. The anti-correlated relationship between the central executive network (CEN; red regions) and default mode network (DMN; blue regions), which are regulated by the salience network (SN; green regions). rPFC rostral prefrontal cortex, ACC anterior cingulate cortex, aINS anterior insula, SMG supramarginal gyrus, dlPFC dorsolateral prefrontal cortex, PPC posterior parietal cortex, mPFC medial prefrontal cortex, HC hippocampus, PCC posterior cingulate cortex, pMTG posterior middle temporal gyrus, PrCu precuneus (from Ref. [2]).

METHODS AND MATERIALS

Under institutional review board approval (IRB No. 21-0008), we retrospectively identified five patients with pre-treatment connectome imaging. Neuroimaging was acquired on a Siemens MAGNETOM Vida 3.0-T scanner using the protocol described in Ref. [3]. Diffusion and functional MRI data were processed using the Quicktome platform described in Ref. [4], generating individualized structural and functional connectomes. Structural connectivity was derived using constrained spherical deconvolution based tractography and resting-state fMRI maps were incorporated for all patients with usable functional imaging.

SRS plans were generated for an HD120 MLC-equipped TrueBeam linear accelerator using (MAT. Treatment planning was performed in Eclipse v16.1 using Photon Optimizer v16.1.0 and the AAA v16.1.2, with a 1.0 × 1.0 × 1.0 mm³ dose-calculation grid. For each patient, a standard plan was created according to institutional planning directives. A network-sparing plan was then generated with the objective of reducing dose to white-matter tracts supporting the triple-network system. fSRS Rx consisted of 9 Gy × 3 fractions or 8 Gy × 3 fractions.

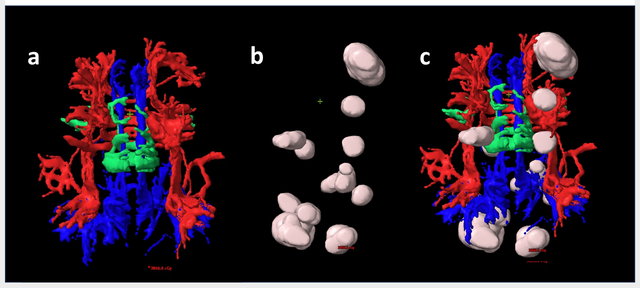

Fig 2. Case 5. (a) Patient-specific connectome showing white-matter tracts associated with CEN (red), DMN (blue), and SN (green). (b) Thirteen lesions identified on post-contrast T1-weighted MRI. (c) Co-registration of the triple-network tracts with the lesions.

RESULTS

Dose Distribution Comparisons

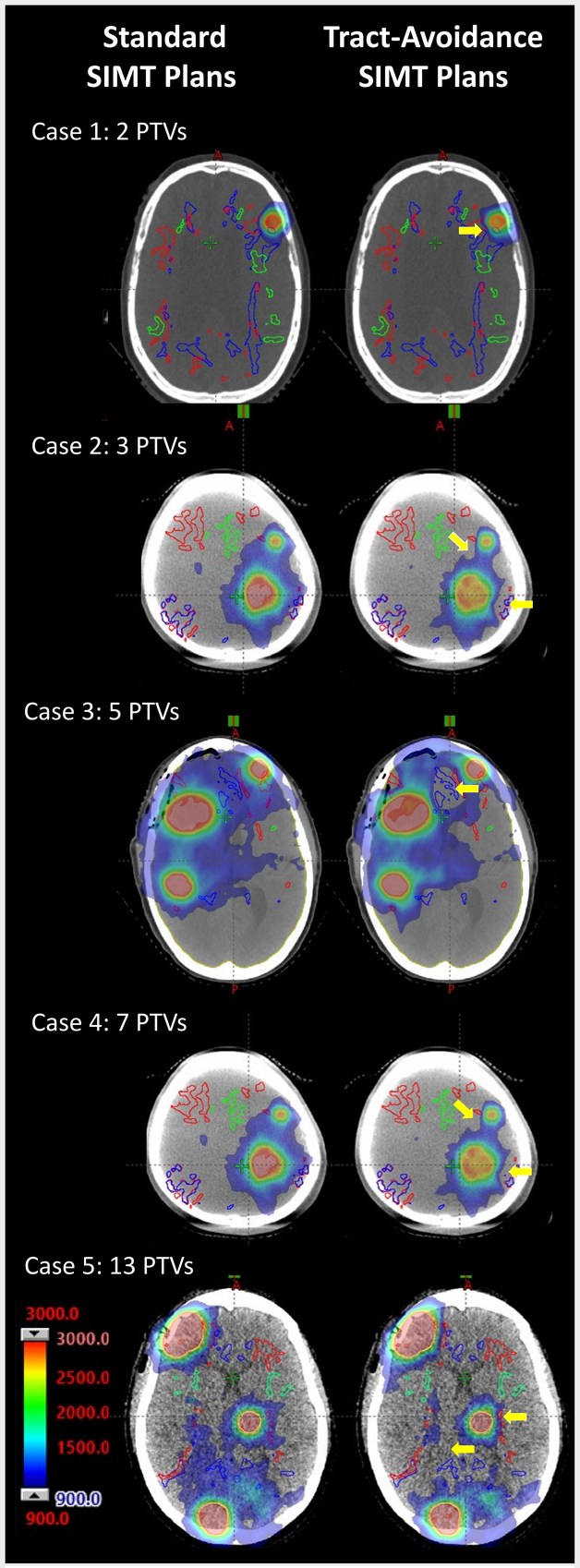

Fig 3. Representative axial dose distributions from the standard plans (left) and tract-avoidance plans (right). Patient-specific triple-network tracts are shown in red (CEN), blue (DMN), and green (SN). The number of intracranial lesions ranged from 2 to 13, representing a spectrum of clinical SIMT SRS cases. Yellow arrows indicate regions of dose redistribution associated with tract avoidance.

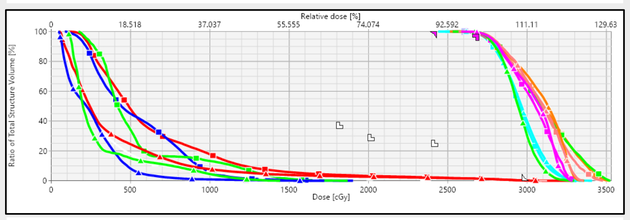

Fig 4: Case 3. DVH comparison of standard and tract-avoidance SIMT SRS plans.

PTV Coverage Comparisons

	PTV	Dmin>90%		V100%>98%	
		Standard	TripleN	Standard	TripleN
Case 1	1	93.8	96.3	98.0	99.0
	2	92.2	92.7	98.1	98.0
Case 2	1	95.5	92.4	98.7	98.0
	2	92.8	90.7	99.2	99.1
	3	90.0	91.9	99.2	98.5
Case 3	1	92.0	91.6	98.1	99.0
	2	93.6	93.3	98.3	98.1
	3	95.1	92.9	99.5	99.4
	4	94.4	94.8	98.6	98.9
	5	93.7	94.1	98.5	98.5
Case 4	1	96.4	98.1	99.2	99.9
	2	95.3	97.2	99.6	99.8
	3	99.5	99.5	100.0	99.9
	4	97.9	97.0	98.0	98.0
	5	97.8	98.0	98.3	99.9
	6	98.9	98.7	100.0	99.9
	7	98.5	99.9	98.7	100.0
Case 5	1	91.8	92.8	98.4	98.7
	2	90.2	92.4	99.0	99.4
	3	96.8	96.9	99.3	99.5
	4	90.6	90.2	98.9	99.2
	5	92.2	95.0	98.6	99.0
	6	90.0	90.0	98.6	99.0
	7	92.9	94.6	98.4	99.1
	8	95.0	93.8	98.8	99.3
	9	90.8	91.8	98.5	99.2
	10	94.8	94.9	99.2	99.3
	11	93.7	95.0	98.8	99.5
	12	93.4	94.4	98.8	99.2
	13	94.6	95.1	99.5	99.8
Δ mean (sd)		**0.4 (1.4)**		**0.3 (0.5)**	

Network Dose Reduction

	STANDARD							
	Dmax(%)	Dmean(%)	V5(cc)	V10 (cc)	V15 (cc)	V20 (cc)	V25 (cc)	V30 (cc)
Case 1	115.60	6.90	10.79	4.59	2.40	1.35	0.67	0.05
Case 2	139.00	15.90	19.41	4.18	1.43	0.76	0.44	0.28
Case 3	130.50	22.10	43.90	11.80	3.80	2.30	1.70	0.70
Case 4	121.10	13.30	17.89	1.11	0.19	0.05	0.02	0.00
Case 5	126.40	31.40	50.24	13.52	3.35	1.28	0.47	0.10
	TripleN Spare							
	Dmax(%)	Dmean(%)	V5(cc)	V10 (cc)	V15 (cc)	V20 (cc)	V25 (cc)	V30 (cc)
Case 1	115.00	6.00	8.99	3.29	1.74	1.05	0.58	0.05
Case 2	118.80	13.50	14.66	2.02	0.97	0.60	0.41	0.14
Case 3	116.00	13.10	17.80	5.30	2.70	2.10	1.70	0.10
Case 4	120.50	10.70	7.86	0.32	0.13	0.05	0.02	0.00
Case 5	125.20	27.30	50.92	4.36	2.27	1.10	0.41	0.09
	DIFFERENCE							
	Dmax(%)	Dmean(%)	V5(cc)	V10 (cc)	V15 (cc)	V20 (cc)	V25 (cc)	V30 (cc)
Case 1	-0.5%	-13.0%	-16.7%	-28.3%	-27.5%	-22.2%	-13.4%	0.0%
Case 2	-14.5%	-15.1%	-24.5%	-51.7%	-32.2%	-21.1%	-6.8%	-50.0%
Case 3	-11.1%	-40.7%	-59.5%	-55.1%	-28.9%	-8.7%	0.0%	-85.7%
Case 4	-0.5%	-19.5%	-56.1%	-71.2%	-31.6%	0.0%	0.0%	0.0%
Case 5	-0.9%	-13.1%	1.4%	-67.8%	-32.2%	-14.1%	-12.8%	-10.0%

CONCLUSION

Connectome-informed SIMT SRS planning was technically feasible and reduced dose to cognition-supporting networks while maintaining PTV coverage and overall plan quality.

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