Title: Integrating Neuromodulation-Induced Prehabilitation and Laser Interstitial Thermal Therapy in a Multimodal Treatment Strategy for Recurrent Glioblastoma: A Case Report

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Online Resources

Online Resource 1. Diffusion tensor imaging reconstruction of the corticospinal tract relative to recurrent right frontal lesion.

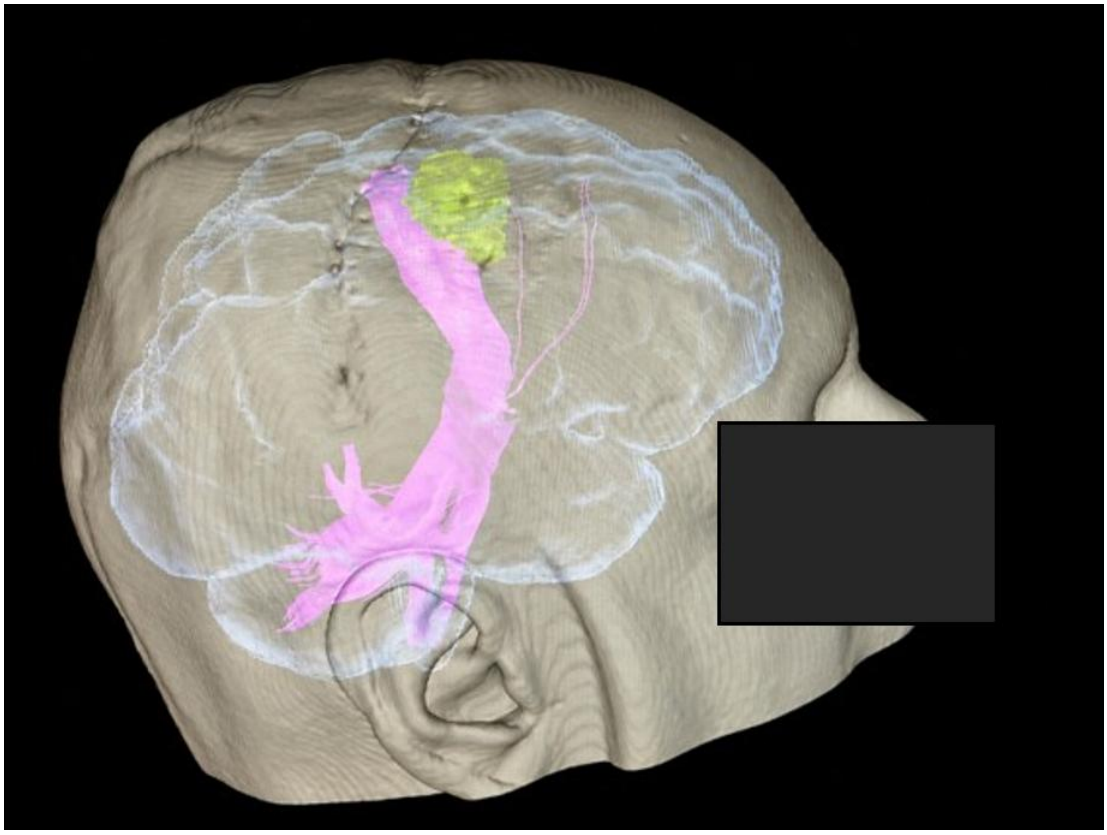
Online Resource 2. Clinical, functional, motor, and cognitive assessment scores across neuromodulation-induced prehabilitation cycles and surgical and ablative interventions.

Online Resource 3. Longitudinal motor-task fMRI activation metrics across two neuromodulation-induced prehabilitation cycles.

Online Resource 4. Structured neuromodulation-induced prehabilitation protocol.

Online Resource 5. CARE (CAse REports) checklist.

Online Resource 6. List of abbreviations



Online Resource 1. Diffusion tensor imaging reconstruction of the corticospinal tract relative to recurrent right frontal lesion. Three-dimensional fiber tractography showing the corticospinal tract in relation to the recurrent tumor. The reconstruction indicates intimate anatomical proximity between the motor pathway and tumor margin, with lateral displacement of the tract anticipated during surgical resection planning.

	NIP-Cycle 1 (Surgery)			NIP-Cycle 2 (MRIgLITT)	
Variable	**T1-S**	**T4-S**	**T6-S**	**T1-L**	**T4-L**
Overall functional status					
EORTC QLQ-C30 (physical functioning)	71	96	62	67	67
EORTC QLQ-C30 (symptom burden)	26	8	18	10	21
EORTC QLQ-C30 (global QoL)	58	100	33	25	58
EORTC QLQ-BN20 (motor dysfunction)	33	13	33	45	43
EORTC QLQ-FA12 (fatigue)	36	11	42	32	47
KPS (performance status)	90	90	60	70	60
NANO (neurological burden)	1	0	4	3	3
Clinical & motor assessment					
9-Hole Peg Test - affected (s)	21.94	21.16	27.99	45.6	49.35
9-Hole Peg Test - unaffected (s)	16.35	17.61	18.29	16.9	18.8
Brunel Balance Assessment	12	12	12	12	11
Fugl-Meyer Upper Extremity	66	66	61	59	58
Fugl-Meyer Lower Extremity	34	34	33	26	26
Hand Dynamometer - affected (kg)	23.7	27.43	25.53	20.06	25.53

Hand Dynamometer - unaffected (kg)	26.59	28.66	27.96	25.36	31.3
Reaction Time - CRT affected (ms)	577.5	525	550	741.5	726.5
Reaction Time - CRT unaffected (ms)	476.5	457	460	525.5	476.5
Reaction Time - SRT affected (ms)	316.5	364	333	546.5	487.5
Reaction Time - SRT unaffected (ms)	346	316.5	332	344.5	312.5
Six-Minute Walk Test - distance (m)	696	710	674	546	598
Six-Minute Walk Test - speed (m/s)	1.93	1.97	1.87	1.51	1.66
Cognitive assessment					
Hayling Test (behavioral regulation) (s)	1.30	1.2	2	1.2	1.2
Phonemic Fluency (words/60s)	54	55	49	55	62
RAVLT - delayed recall	12	13	14	14	14
RAVLT - recognition	14	14	14	14	14
RAVLT - total learning	57	64	68	61	61
TB-R (reading comprehension)	8	8	8	8	8
TB-R (verbal denomination)	6	6	6	6	6

TMT-A (visual attention; sequencing) (s)	34	22	27	35	29
TMT-B (attention; flexibility) (s)	75	53	57	75	90
WAIS-IV Block Design (executive function; raw)	44	45	46	40	41
WAIS-IV Digit Span (working memory; scaled)	11	13	10	11	11
WAIS-IV Digit Span Backward (working memory; raw)	4	4	3	2	5
WAIS-IV Digit Symbol-Coding (processing speed; raw)	78	83	76	67	66

Online Resource 2. Clinical, functional, motor, and cognitive assessment scores across neuromodulation-induced prehabilitation cycles and surgical and ablative interventions. Timepoints: T1-S, baseline before first NIP cycle; T4-S, immediately after first NIP cycle and before resection; T6-S, post-craniotomy. T1-L, baseline before second NIP cycle; T4-L, immediately after second NIP cycle and before MRIgLITT; T6-L, not performed due to clinical deterioration. Scoring direction: Higher scores indicate better status for EORTC QLQ-C30 physical functioning and global QoL, Fugl-Meyer assessments, Brunel Balance Assessment, hand dynamometer, and cognitive tests. Higher values indicate worse status for EORTC QLQ-C30 symptom burden, EORTC QLQ-BN20 motor dysfunction, EORTC QLQ-FA12 fatigue, NANO, and TMT time. Lower values indicate better performance for 9-Hole Peg Test, Reaction Time Task, and TMT. KPS is reported in 0-100 increments (higher = better independence).

	NIP-Cycle 1 (Surgery)			NIP-Cycle 2 (MRIgLITT)	
Variable	**T1-S**	**T4-S**	**T6-S**	**T1-L**	**T4-L**
Total suprathreshold voxels	1,315	4,403	13,536	29,100	1,110
Total fMRI volume (ml)	10.520	35.224	108.288	232.800	8.880
Main cluster extent (kE, voxels)	836	1,074	2,512	7,015	852
Main cluster volume (ml)	6.688	8.592	20.096	56.120	6.816
Affected hemisphere (RH) volume (ml)	6.688	17.920	59.976	123.536	7.352
Signed laterality index (LI)	−0.271	−0.017	−0.108	−0.061	−0.656
Lateralization % (RH)	63.57%	50.87%	55.39%	53.07%	82.79%
Relevance index (%)	63.57	24.39	18.56	24.11	76.76
Hemisphere dominance	RIGHT	BILATERAL	BILATERAL	BILATERAL	RIGHT
Peak fMRI anatomical region	Precentral_R	Precentral_L	Precentral_L	Precentral_R	Precentral_R
Peak coordinates (MNI x, y, z)	(42, −14, 60)	(−42, −8, 60)	(−44, −12, 60)	(42, −16, 62)	(42, −14, 58)
Peak T-statistic value	14.58	14.42	14.86	22.24	14.95
Number of suprathreshold clusters	2	10	12	14	3

Online Resource 3. Longitudinal motor-task fMRI activation metrics across two neuromodulation-induced prehabilitation cycles. Timepoints: T1-S, baseline before first NIP cycle; T4-S, post-NIP before surgical resection; T6-S, post-craniotomy follow-up. T1-L, baseline before second NIP cycle; T4-L, post-NIP before MRIgLITT. T6-L not performed due to clinical deterioration.

Session	Activities
Session 1	15 min piano - left hand; 15 min LEGO - bimanual, left-predominant; 15 min typing - bimanual
Session 2	20 min gait training in different directions with added dual task; 15 min monopodal BlazePods; 15 min Motek; 7 min HIIT
Session 3	15 min piano - left hand, bimanual, right hand; 15 min LEGO - bimanual, left-predominant; 15 min typing - bimanual; 10 min driving
Session 4	20 min gait training in different directions with added dual task; 15 min monopodal BlazePods; 15 min Motek; 7 min HIIT
Session 5	15 min piano - left hand, bimanual, right hand; 15 min LEGO - bimanual, left-predominant; 15 min typing - bimanual; 10 min driving
Session 6	20 min gait training in different directions with added dual task; 15 min monopodal BlazePods; 15 min Motek; 7 min HIIT
Session 7	15 min piano - left hand, bimanual, right hand; 15 min LEGO - bimanual, left-predominant; 15 min typing - bimanual; 10 min driving
Session 8	20 min gait training in different directions with added dual task; 15 min monopodal BlazePods; 15 min Motek; 7 min HIIT
Session 9	15 min piano - left hand, bimanual, right hand; 15 min LEGO - bimanual, left-predominant; 15 min typing - bimanual; 10 min driving
Session 10	20 min gait training in different directions with added dual task; 15 min monopodal BlazePods; 15 min Motek; 7 min HIIT
Session 11	15 min piano - left hand, bimanual, right hand; 15 min LEGO - bimanual, left-predominant; 15 min typing - bimanual; 10 min driving
Session 12	20 min ball-control/dribbling activities with different circuits; 20 min coordination circuits; 15 min HIIT
Session 13	20 min ball-control/dribbling activities with different circuits; 20 min coordination circuits; 15 min HIIT
Session 14	15 min piano - left hand, bimanual, right hand; 15 min LEGO - bimanual, left-predominant; 15 min typing - bimanual; 10 min driving
Session 15	15 min badminton using balloons; 15 min gait coordination + BOSU balance + active upper-limb movements; 10 min gait coordination; 15 min HIIT
Session 16	15 min badminton using balloons; 15 min gait coordination + BOSU balance + active upper-limb movements; 10 min gait coordination; 15 min HIIT
Session 17	15 min badminton using balloons; 15 min gait coordination + BOSU balance + active upper-limb movements; 10 min gait coordination; 15 min HIIT
Online Resource 4. Structured neuromodulation-induced prehabilitation protocol: 17-session physical activities preceding MRIgLITT. Activities progression: Alternating fine motor/cognitive (odd sessions: 1, 3, 5, etc.) and gross motor/balance/cardiopulmonary (even sessions: 2, 4, 6, etc.) training blocks. Protocol spans approximately 2 weeks with progressive intensity escalation; Sessions 12 - 17 introduce sport-specific coordination and high-intensity interval training. Target domains: left-hand dexterity, bimanual integration, gait stability, balance, dual-task cognitive-motor coupling, and cardiopulmonary endurance. Equipment: piano, LEGO construction, typing tasks, BlazePods (reaction-light training),	

Motek (computerized balance platform), BOSU (balance trainer), badminton using balloons.

Checklist adapted from https://www.care-statement.org/checklist		
Section	**Item**	**YES**
Title	Main diagnosis or intervention followed by "a case report"	**YES**
Keywords	2 to 5 keywords, including "case report"	**YES**
Abstract	Correct length and format (Introduction / Case presentation / Conclusion)	**YES**
Abstract: Introduction	Presents the novelty of the case	**YES**
Abstract: Case presentation	Main symptoms, signs, interventions and outcomes	**YES**
Abstract: Conclusion	Main lesson learned	**YES**
Introduction	Brief background referencing the most relevant literature	**YES**
Introduction	Statement that the CARE guidelines were followed	**YES**
Patient information	Demographic data without identifiers	**YES**
Patient information	Primary symptoms and relevant history	**YES**
Clinical findings	All relevant physical examination and clinical findings	**YES**
Diagnostic assessment	All relevant diagnostic tests and key findings	**YES**
Interventions	All interventions; key details of surgical procedures	**YES**
Outcomes / Follow-up	Outcomes of all interventions, including unanticipated events; follow-up findings	**YES**
Discussion	Comprehensive discussion of the most relevant literature, with references	**YES**
Discussion	Statements on strengths and limitations	**YES**
Conclusion	Main lesson learned	**YES**
Statements	Informed consent and authorship after the conclusion	**YES**

Online Resource 5. CARE (CAse REports) checklist.

Online Resource 6. List of abbreviations

9HPT: Nine-Hole Peg Test
BN20: Brain Neoplasm Module (EORTC)
BOSU: Both sides up balance trainer
CARE: Case Report guidelines
CDKN2A: Cyclin-dependent kinase inhibitor 2A
CRT: Choice reaction time
EGFR: Epidermal growth factor receptor
EORTC: European Organisation for Research and Treatment of Cancer
FA12: Fatigue Module (EORTC)
fMRI: Functional magnetic resonance imaging
GBM: Glioblastoma
HIIT: High-intensity interval training
IDH: Isocitrate dehydrogenase
KPS: Karnofsky Performance Status
LAANTERN: Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System
LITT: Laser interstitial thermal therapy
M1: Primary motor cortex
MGMT: O6-methylguanine-DNA methyltransferase
MRI: Magnetic resonance imaging
MRIgLITT: Magnetic resonance imaging-guided laser interstitial thermal therapy
NANO: Neurological Assessment in Neuro-Oncology
NIP: Neuromodulation-induced prehabilitation
QLQ-C30: Quality of Life Questionnaire (EORTC)
RAVLT: Rey Auditory Verbal Learning Test
RMT: Resting motor threshold
rTMS: Repetitive transcranial magnetic stimulation
SMA: Supplementary motor area
SRT: Simple reaction time
tb-fMRI: Task-based functional magnetic resonance imaging
TB-R: Barcelona Test - Revised
TMS: Transcranial magnetic stimulation
TMT-A/B: Trail Making Test - A/B
WAIS-IV: Wechsler Adult Intelligence Scale - Fourth Edition
WHO: World Health Organization