

Supplementary Material: Lesion-function analysis from multimodal imaging and normative brain atlases for prediction of cognitive deficits in glioma patients

Martin Kocher, Christiane Jockwitz, Philipp Lohmann, Gabriele Stoffels, Christian Filss, Felix M. Mottaghy, Maximilian I. Ruge, Carolin Weiss Lucas, Roland Goldbrunner, Nadim J. Shah, Gereon R. Fink, Norbert Galldiks, Karl-Josef Langen, Svenja Caspers

Table S1: Patient characteristics

	n	%
Gender (male/female)	73/48	60/40
Age (years, upper limit) 25/30/40/50/60/70/80	5/17/28/40/23/8	4/14/23/33/19/7
Performance Status (ECOG Scale) 0/1/2/3	58/56/6/1	48/46/5/1
Tumor Type		
Glioblastoma, <i>IDH wildtype/mutant/NOS</i>	67/10/4	56/8/3
Anaplastic astrocytoma, <i>IDH wildtype/mutant/NOS</i>	5/16/ 7	4/13/ 6
Anaplastic Oligodendroglioma, <i>IDH mutant, 1p/19codel.</i>	12	10
Tumor Location		
Frontal left/right	31/28	26/23
Parietal left /right	7/8	6/7
Temporal left/right	22/16	18/13
Occipital left /right	5/4	4/3
Primary Treatment ^a		
Resection + RT + TMZ/CCNU/PC	93	77
Biopsy + RT + TMZ/CCNU/PC	12	10
Resection + RT	6	5
Resection + TMZ	3	2
Resection alone	6	5
Biopsy + RT	1	1
Total Number of Oncologic Interventions ^b		
1 / 2 / 3 / 4 / 5 / 6 / 7-9	6/6/79/11/11/5/3	5/5/65/9/9/4/3
Corticosteroids no/ yes	91/30	25/75
Anticonvulsants no/ yes	49/72	40/60
Recurrence diagnosed by clinical FET PET no/ yes	63/58	52/48
Neurological Symptoms		
None	40	33
Paresis	29	24
Aphasia	17	14
Fatigue	19	16
Visual Field Defect, Diplopia	12	10
Vertigo, confusion	4	3
Employed no/yes	45/76	37/63
	Median/ Mean	Range
Imaging follow-up interval (months)	14.4/ 30.4	0.6 – 213.7
Lesion Volume (ml)		
Resection Cavity (n= 90) ^c	20.9/ 35.8	0.3 – 172.5
T2/FLAIR abnormalities (n=121) ^c	53.4/ 70.1***	3.4 – 252.9
T1-Contrast Enhancing (n= 95) ^c	8.3/ 17.9	0.01 – 122.9
FET-PET positive (n= 79) ^d	30.3/ 39.5	2.6 – 227.8
Radiation Dose (Gy)	60.0/ 59.3	40.1 - 62.0

ECOG: Eastern Cooperative Oncology Group, IDH: Isocitrate Dehydrogenase, NOS: Not otherwise specified, RT: Radiotherapy, TMZ: Temozolomide, CCNU: Chloroethyl-Cyclohexyl-Nitroso-Urea = Lomustin, PC: Procarbacin plus CCNU. ^areceived until the date of imaging, ^bincluding biopsy, resection, radiotherapy series, systemic therapy courses. ^cNumber of patients affected, ^dincluding patients with no recurrence according to clinical PET criteria. *** p<0.001, 2-sided Kruskal-Wallis test

Table S2: Correlation analysis for cognitive scores and age, education or total volume of lesion types

Cognitive Function Domain/ Test	Age	Edu- cation	Resect. cavity volume	T2/ FLAIR volume	T1-CE Tumor volume	FET-PET Tumor volume
Attention, Processing Speed (TMT-A)	0.46**	- 0.20*	- 0.19*	0.34**	0.28**	0.27**
Processing Speed/ Executive Function (TMT-B)	0.42**	- 0.33**	- 0.17	0.27**	0.20*	0.21*
Executive Function (TMT-B/A ratio)	0.06	-0.34**	0.05	- 0.05	- 0.11	- 0.08
Language Processing (Number Transcoding)	- 0.26**	0.26**	0.04	- 0.03	0.02	- 0.01
Verbal Working Memory (Digit span forward)	- 0.16	0.23*	0.07	- 0.14	- 0.07	- 0.02
Verbal Working Memory (Digit span backward)	- 0.30**	0.28**	0.16	- 0.16	- 0.12	- 0.07
Visual Working Memory (CBT forward)	- 0.40**	0.24**	0.13	- 0.29**	- 0.18*	- 0.15
Visual Working Memory (CBT backward)	- 0.34**	0.33**	0.13	- 0.20*	- 0.24**	- 0.28**
Verbal Episodic Memory (Word list, immediate recall)	- 0.25**	0.26**	0.18*	- 0.29**	- 0.25**	- 0.24**
Verbal Episodic Memory (Word list, delayed recall)	- 0.38**	0.24**	0.26**	- 0.21*	- 0.19*	- 0.20*

Spearman rank correlation coefficients between age, educational level and total volume of lesion types and neurocognitive test scores in different domains. Increasing age and lesion volumes are expected to increase the time needed for TMT-A/B and decrease the scores for the other tests, while educational levels are assumed to act in the opposite way. Unexpectedly, this opposite pattern was also observed for the total volume of the resection cavities. *p < 0.05, **p < 0.01 (2-sided); Resect. Cavity: volume of resection cavity; T2/FLAIR: volume of T2/FLAIR image changes; T1-CE: volume of contrast-enhancing tumor in T1-weighted MR-images; FET-PET: volume of FET-PET positive tumor

Table S3: Correlation analysis for cognitive scores and clinical variables

Cognitive Function Domain/Test	Interval	Surgical Proced.	Radioth. Series	Chemoth. Courses	Total Intervent.	Gender f/m	Anticonv. no/yes	Glioma Grade III vs. IV	Glioma MolType AA-wt/-mut/ OD
Attention, Processing Speed (TMT-A)	- 0.17	- 0.13	0.00	- 0.04	- 0.04	45.1/48.7	47.0/47.5	39.1/51.2*	51.9/40.8/32.9*
Processing Speed/ Executive Function (TMT-B)	- 0.13	- 0.11	-0.04	0.00	- 0.04	110.0/122.6	117.9/117.5	100.3/126.1	126.3/109.4/84.2
Executive Function (TMT-B/A ratio)	0.11	0.00	- 0.02	0.05	- 0.01	2.5/2.6	2.5/2.6	2.6/2.5	2.5/2.7/2.6
Language, Word Fluency (Supermarket)	- 0.02	- 0.02	- 0.02	- 0.09	- 0.06	20.8/19.7	20.7/19.8	21.0/19.7	20.1/19.2/22.1
Language Processing (Number Transcoding)	- 0.06	- 0.06	- 0.05	- 0.08	- 0.08	3.5/3.3	3.3/3.3	3.3/3.3	3.3/3.4/3.6
Verbal Working Memory (Digit span forward)	- 0.04	- 0.04	- 0.08	- 0.03	- 0.05	7.2/7.5	7.5/7.3	6.9/7.6	7.5/7.0/6.9
Verbal Working Memory (Digit span backward)	0.20*	0.16	0.08	0.14	0.15	6.4/6.6	6.6/6.5	7.1/6.2	6.3/6.7/7.3
Visual Working Memory (CBT forward)	- 0.01	- 0.02	- 0.16	- 0.11	- 0.12	6.8/6.4	6.6/6.6	7.1/6.3	6.3/6.9/7.7
Visual Working Memory (CBT backward)	0.03	0.05	0.04	0.02	0.03	4.9/4.8	4.6/4.9	5.3/4.5	4.5/5.2/5.6
Verbal Episodic Memory (Word list, immediate recall)	- 0.06	0.03	- 0.02	- 0.08	- 0.04	12.0/11.6	12.1/11.5	12.0/11.6	11.5/11.8/13.1
Verbal Episodic Memory (Word list, delayed recall)	- 0.02	0.08	0.04	- 0.09	- 0.02	4.6/4.5	4.9/4.2	4.7/4.4	4.1/5.2/5.6

Spearman rank correlation coefficients between therapy interval, number of surgical procedures, number of radiotherapy series, number of chemotherapy courses and total number of oncologic interventions and neurocognitive test scores in different domains; mean neurocognitive scores in groups of differing gender, anticonvulsant use, glioma grade and molecular glioma type (AA-wt: anaplastic astrocytoma/ glioblastoma IDH wild-type, -mut: IDH mutated, OD: anaplastic oligodendroglioma); Mann-Whitney-U and Kruskal-Wallis tests, *p < 0.05, (2-sided)