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CLINICAL STUDY

Effects of supra-total resection in neurocognitive and oncological outcome of high-grade gliomas comparing asleep and awake surgery

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Abstract

Purpose Awake surgery is an established technique for resection of low-grade gliomas, while its possible benefit for resection of high-grade gliomas (HGGs) needs further confirmations. This retrospective study aims to compare overall survival, extent of resection (EOR) and cognitive outcome in two groups of HGGs patients submitted to asleep or awake surgery.

Methods Thirty-three patients submitted to Gross Total Resection of contrast-enhancing area of HGGs were divided in two homogeneous groups: awake (AWg; N = 16) and asleep surgery (ASg; N = 17). All patients underwent to an extensive neuropsychological assessment before surgery (time_1), 1-week (time_2) and 4-months (time_3) after surgery. We performed analyses to assess differences in cognitive performances between groups, cognitive outcomes in each group and EOR. A comparison of overall survival (OS) between the two groups was conducted.

Results Statistical analyses showed no differences between groups at time_2 and time_3 in each cognitive domain, excluding selective attention that resulted higher in the AWg before surgery. Regarding cognitive outcomes, we found a reversible worsening of memory and constructional praxis, and a significant recovery at time_3, similar for both groups. Assessment of time_3 in respect to time_1 never showed differences (all ps > .074). Moreover we found a significant lower level of tumor infiltration after surgery for AWg ($p < .05$), with an influence on OS ($p < .05$). Indeed, patients of AWg showed a significant longer OS in comparison to those in the ASg ($p < .01$). This result was confirmed even considering only wildtype Glioblastoma ($p < .05$).

Conclusion These results indicate that awake surgery, and in general a supra-total resection of enhancing area, can improve OS in HGGs patients, preserving neuro-cognitive profile and quality of life.

Keywords Asleep surgery · Awake surgery · Cognitive outcome · Extent of resection · High-grade gliomas · Overall survival

Introduction

High grade gliomas (HGGs) (i.e. III and IV WHO) are the most frequent primitive brain tumors (incidence about 3–5/100.000 per year) [1]. These are tumors with an unfavorable prognosis [2], and overall survival (OS) is mainly influenced by these variables: patient and tumor features (histology and biological markers), and treatments [3]. Indeed, younger patients have longer OS [3], and grade III and/or expression of IDH1 mutation and MGMT methylation are positive prognostic factors [3–6]. Prognosis of HGGs is also strongly influenced by the extent of resection (EOR) [3, 6–10], classically the contrast-enhancing area, such as the volume of resection of T2/flair hyper-intensity in case of low-grade gliomas (LGGs) [11]. Recently, a negative impact of increased T2/flair hyper-intensity, as compared to the enhancement area, on survival of HGGs patients has been demonstrated [12]. Finally, considering the short time for neurological recovery before the mandatory post-operative treatments (radio- and chemo-therapy) [13, 14], the surgical strategy for resection of HGGs should be more

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and more tailored on an accurate balance between EOR and preservation of cognitive functions [15–20].

Awake craniotomy with intra-operative cortico-subcortical direct electrical stimulation (DES) is nowadays a worldwide spreading and recommended technique to reach the best balance between EOR and risks of permanent deficits in low-grade gliomas (LGGs) [9, 15, 20]. A recent study by Mandonnet et al. revealed that awake surgery for LGG and HGG leads to a good oncological, functional and employment outcome [17]. Gerritsen et al. already found a significant increased EOR after awake brain surgery for glioblastomas with respect to asleep surgery [21, 22]. However, to the best of our knowledge, no studies in literature compared an extensive neuropsychological and the oncological outcome between awake and asleep brain resections of HGGs.

Aim of this study is to compare two series of HGGs patients, 17 who underwent resection with asleep surgery and 16 submitted to awake surgery, in order to assess the impact of awake mapping in neuro-cognitive outcome, EOR and OS.

Materials and methods

Patients

We included in this retrospective study 33 (23 M; mean age: 53.1 ± 13.2) right-handed patients (at Edinburgh Handedness Inventory Test) [23] submitted to Gross Total Resection (i.e. complete removal of the enhancing area) [7] of HGGs at the Division of Neurosurgery of "Santa Chiara" Hospital (APSS Trento, Italy). All of them underwent surgery between 2013 and 2018. Every patient were also submitted to the same radio- and chemo-therapy regimen as proposed by Stupp [2], within 6 weeks after surgery. Seventeen (51%) were lesions infiltrating the left hemisphere. Demographical data are reported in Table 1. No patients had neurological deficits at conventional neurological examination before surgery. Onset symptoms, pre-operative steroid therapy and antiepileptic prophylaxis are reported in Online Resource 1. Patients were divided into two groups, depending on brain surgery technique: awake group (AWg, N = 16) and asleep group (ASg, N = 17). These populations were not randomized. Regardless tumor extension or location, awake surgery was proposed to the patients with: 1) adequate psychological profile and attitude for tolerating this procedure; 2) an expected high-level of cooperation in the operating room (as needed to perform a fine neuro-cognitive intra-operative assessment); 3) no language deficit, confusion and/or anxiety disorders [24, 25]; 4) no anesthesiologic contra-indication [26]. Patients gave their informed consent to the surgical procedure (asleep or asleep-awake-asleep) proposed after an accurate discussion of risks and benefits. This study respects the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194) and STROBE guidelines [27].

Neuropsychological assessment

Every patient underwent an extensive neuropsychological assessment (as previously reported by our Group) [7] before surgery (time_1), 1-week (time_2) and 4-months after surgery (time_3). Two weeks of post-operative specifically tailored cognitive and language rehabilitation were performed after neurosurgical discharge (mean hospital stay 6 days). No motor rehabilitation was needed.

Neuro-cognitive assessment included: Language functions [28, 29], Memory [30–32], Constructional praxis [32], Attention, [33, 34] Executive functions [35, 36]. See Online Resource 2 for a complete description.

Pre-operative planning and MRI acquisition

All patients underwent a detailed pre-operative MRI including perfusion and diffusion-weighted imaging (DWI) for tractography. A T1-weighted volumetric sequence (with gadolinium) and a volumetric T2/Flair merged with the tractography reconstructions [1.5 GE scanner; 60 directions; single shot multislice spin echo–echo planar sequence (40 slices; slice thickness: 2.6 mm; matrix 256 × 256; TR: 10 000; TE: 92.7; and flipangle: 90); constrained spherical deconvolution algorithm] of the critical pathways neighboring the tumors were used for every patient.

The neurosurgeon performing the surgery (SS) tracked all the critical pathways neighboring the tumor with Trackvis (https://www.trackvis.org/). All patients underwent early post-operative MRI with gadolinium (24 h after surgery).

Volumetric analysis

The volumetric ROIs of pre-operative enhancing (i.e. target for tumor resection) area, overall hyper-intensity area, volume of post-operative surgical cavity and residual hyper-intensity area were collected on pre- and post-operative T1 with gadolinium and T2/Flair sequences by a neurosurgeon (LA) with MRIcron (https://www.nitrc.org/projects/mricron). Both T1 and T2 ROIs were co-registered using FLIRT (FMRIB's Linear Image Registration Tool) as previously reported by our Group [37, 38].

Finally, a ratio reflecting only the tumor infiltration (hyperintensity) areas (TuI) was calculated (T2-hyperintensity lesion volume/T1-gadolinium lesion volume), for both pre- (TuI_pre) and post-operative (TuI_post) MRI. The more TuI index score is close to 1, the less tumor infiltration (hyperintensity) is relevant in respect to the contrast-enhancing portion.

Table 1 Demographic and clinical features of HGG patients

Group	Patient	Sex/age (years)	Lesion side and localization	Survival (days)	Tumor histology	IDH1 mutated	MGMT	Treatment
ASg	P1	M/67	L/Temporal	567*	GBM	No	Yes	S + r + c
	P2	M/54	R/Fronto-parietal	470*	GBM	No	No	S + r + c
	P3	M/56	R/Temporal	335	GBM	No	No	S + r + c
	P4	M/56	L/Mesial-temporal	722	GBM	No	No	S + r + c
	P5	M/46	L/Parietal	646	GBM	No	No	S + r + c
	P6	F/74	R/Frontal	614	GBM	No	Yes	S + r + c
	P7	M/63	R/Parieto-temporal	565	AA	No	Yes	S + r + c
	P8	M/33	R/Frontal	744	AA	No	No	S + r + c
	P9	M/62	L/Mesial-temporal	685	GBM	No	No	S + r + c
	P10	M/40	L/Frontal	361	GBM	No	Yes	S + r + c
	P11	M/59	R/Mesial-temporal	912*	GBM	No	Yes	S + r + c
	P12	M/32	R/Frontal	2508*	AA	Yes	Yes	S + r + c
	P13	F/36	L/Frontal	891*	GBM	Yes	Yes	S + r + c
	P14	F/60	L/Frontal	630	GBM	No	Yes	S + r + c
	P15	M/60	L/Temporo-parietal	344	GBM	No	No	S + r + c
	P16	F/75	L/Frontal	149	GBM	No	Yes	S + r + c
	P17	M/65	R/Fronto-temporal	478	GBM	No	No	S + r + c
AWg	P18	M/53	L/Parietal	407	AA	No	No	S + r + c
	P19	F/56	L/Frontal	723*	GBM	No	Yes	S + r + c
	P20	M/41	L/Parietal	933*	AA	Yes	No	S + r + c
	P21	M/32	L/Frontal	1269*	GBM	No	No	S + r + c
	P22	F/50	R/Frontal	1147*	GBM	No	Yes	S + r + c
	P23	M/63	R/Frontal	720*	AA	No	No	S + r + c
	P24	F/66	L/Frontal	1874*	AA	Yes	Yes	S + r + c
	P25	M/43	R/Temporal	1602*	AA	Yes	No	S + r + c
	P26	M/37	R/Frontal-insular	1337*	AA	Yes	Yes	S + r + c
	P27	M/53	L/Temporal	1021	GBM	No	Yes	S + r + c
	P28	F/64	L/Frontal	1052	GBM	No	No	S + r + c
	P29	F/47	R/Mesial-temporal	1206	GBM	Yes	No	S + r + c
	P30	F/36	L/Temporo-insular	835	AA	Yes	Yes	S + r + c
	P31	M/66	R/Mesial-frontal	140	GBM	No	No	S + r + c
	P32	M/37	R/Temporal	182*	GBM	No	No	S + r + c
	P33	M/74	R/Frontal	205*	GBM	No	No	S + r + c

ASg Asleep surgery group; *AWg* Awake surgery group; *M* male; *F* female. *L/R* left/right lesion side; *BM* Glioblastoma; *AA* anaplastic astrocytoma; *S* surgery; *r* radiotherapy; *c* chemiotherapy

*patient still alive

Surgical procedure

Total intravenous anesthesia with Remifentanil and Propofol infusion was administrated. Initial intubation with laryngeal mask was performed for the patients submitted to asleep-awake-asleep procedures. A regular oro-tracheal intubation was utilized for full asleep surgeries. Neuronavigation with volumetric T1 (with gadolinium) and T2/Flair merged with the tractography reconstructions of the critical pathways neighboring the tumors was used in all cases.

The cortical and subcortical mapping was performed with 60 Hz, 1 ms and amplitude ranging between 2-4 mA, according to the protocol previously reported [39–41]. The threshold for both cortical and subcortical mapping was set eliciting speech arrest at the level of the ventral pre-motor cortex, regardless tumor laterality.

Resection stopped when functional responses were elicited at cortical and subcortical stimulation of the eloquent structures: different intraoperative neuropsychological tests were selected and utilized in each case depending on lateralization and location of the lesions and the extensive neuropsychological pre-operative assessment. According to previous report by our Group, during awake surgery we performed: counting test (0–10)

[18, 39, 42, 43] and complex motor task (superior and/or inferior limb) [43]; object naming (in the Italian version, known also as Laiacona-Capitani) and verb generation test for the different aspects of language elaboration (semantic, phonologic, syntactic) [18, 19, 42–44]; Pyramids and Palm Tree Test (PPTT) for non-verbal semantic comprehension disorders [42, 43]; object naming in opposite quadrants for monitoring positive and negative functional responses during visual pathways mapping [45]; line bisection test for spatial awareness [42]; the modified version of "reading the mind in the eyes" test for emotion recognition (also known as mentalizing) [37, 46]; Stroop test for attention; reading test for monitoring eventual alexia.[37, 38] In the asleep procedures, the resection stopped after the complete resection of the enhancing area and until reaching the tractography reconstructions with 5 mm of safety margin. No patients experience post-operative neurological deficits at conventional examinations or surgical complications.

Statistical analyses

Analyses have been performed using R v3.6.1 and SPSS v20.0 software. Considering the limited number of patients, non-parametric analyses were conducted. Balance between groups for patients and clinical features has been assessed with chi square (χ^2) analysis and Mann–Whitney U test; Odds Ratio (OR) with 95% of Confidence Intervals (C.I.) was also reported. Mann–Whitney U test was run to assess statistical differences between AWg and ASg neuropsychological scores at time_1, time_2 and time_3.

Friedman repeated measures ANOVA (rmANOVA) separated for both AWg and ASg has been conducted with time_1 (baseline, pre-op), time_2 (post-op) and time_3 (FU) as factors, to verify the trend of cognitive outcome inside each group. Post-hoc analyses were measured using Wilcoxon rank paired T-test.

Differences between groups in pre-operative tumors-enhancing volume (T1_pre), surgical cavity (T1_post), hyperintensity (T2_pre and T2_post) and TuI index (TuI_pre and TuI_post) were assessed with permutation test (10,000 interactions). A longitudinal assessment of the same volumes before and after surgery were conducted with Wilcoxon rank paired T-test, separated for groups.

Factors potentially influencing the OS were assessed using univariate Cox proportional hazard regression model. Hazard ratio (HR) and 95% confidence limits on HR were reported. Multivariate analysis wasn't performed due to number of patients and events [46, 47].

Finally, in order to evaluate difference in OS, the Kaplan–Meier method with Log-rank test was applied.

Results

Differences in patients and clinical features between AWg and ASg

No statistical differences emerged between AWg and ASg (all ps > 0.085): groups resulted balanced for age, sex, tumor grade and lateralization, presence/absence of IDH mutation and MGMT methylation. Full results are reported in Online Resource Table 1.

Overall cognitive and neurological outcome comparison in AWg and ASg

The full results of rmANOVA are reported in Online Resource Table 2. For ASg, analyses showed a significant difference in long-term verbal memory (REY, $p < 0.001$), improving at FU (40.2% of words recalled) as compared to post-surgery (22.2%; $p < 0.01$). Regarding constructional praxis (OST_copy, $p < 0.05$), ASg patients performed a lower score after surgery (71.4% of accuracy) as compared to baseline (84.2%, $p < 0.05$) with a significant improvement at FU (86.1%; $p < 0.05$). Finally, long-term visual memory showed a significant improvement (OST, $p < 0.01$) at FU (41.2% of accuracy) as compared to baseline (27.1%, $p < 0.01$). No other differences were found (all ps > 0.074).

For AWg a difference was found in verbal learning (REY_rep, $p < 0.01$), with a worsening after surgery (33.1% of accuracy) compared to baseline (49.6% $p < 0.01$) and a significant improvement at FU (51%, $p < 0.001$). As before, a difference in long-term verbal memory was found (REY, $p < 0.01$), with a decrease of scores after surgery (23.8%) as compared to baseline (39.3%, $p < 0.05$) and an improvement at FU (42% of accuracy) in comparison to post-surgery ($p < 0.01$). Finally, in constructional praxis task (OST copy, $p < 0.01$), AWg patients showed impairment immediately after surgery (73.1% of accuracy) as compared to baseline (90.7%, $p < 0.01$). No other differences were found (all ps > 0.233).

Graphics of results are reported in Fig. 1.

None of the 33 patients included in the study experienced post-operative neurological deficits at conventional neurological examination, and we did not experience intra-operative troubles during awake surgery (e.g. delay in cooperation after removal of laryngeal mask, scarce cooperation during awake phase, brain swelling, etc.) despite the adoption of a classical anesthesiologic protocol (i.e. propofol and remifentanil infusion during asleep phase).

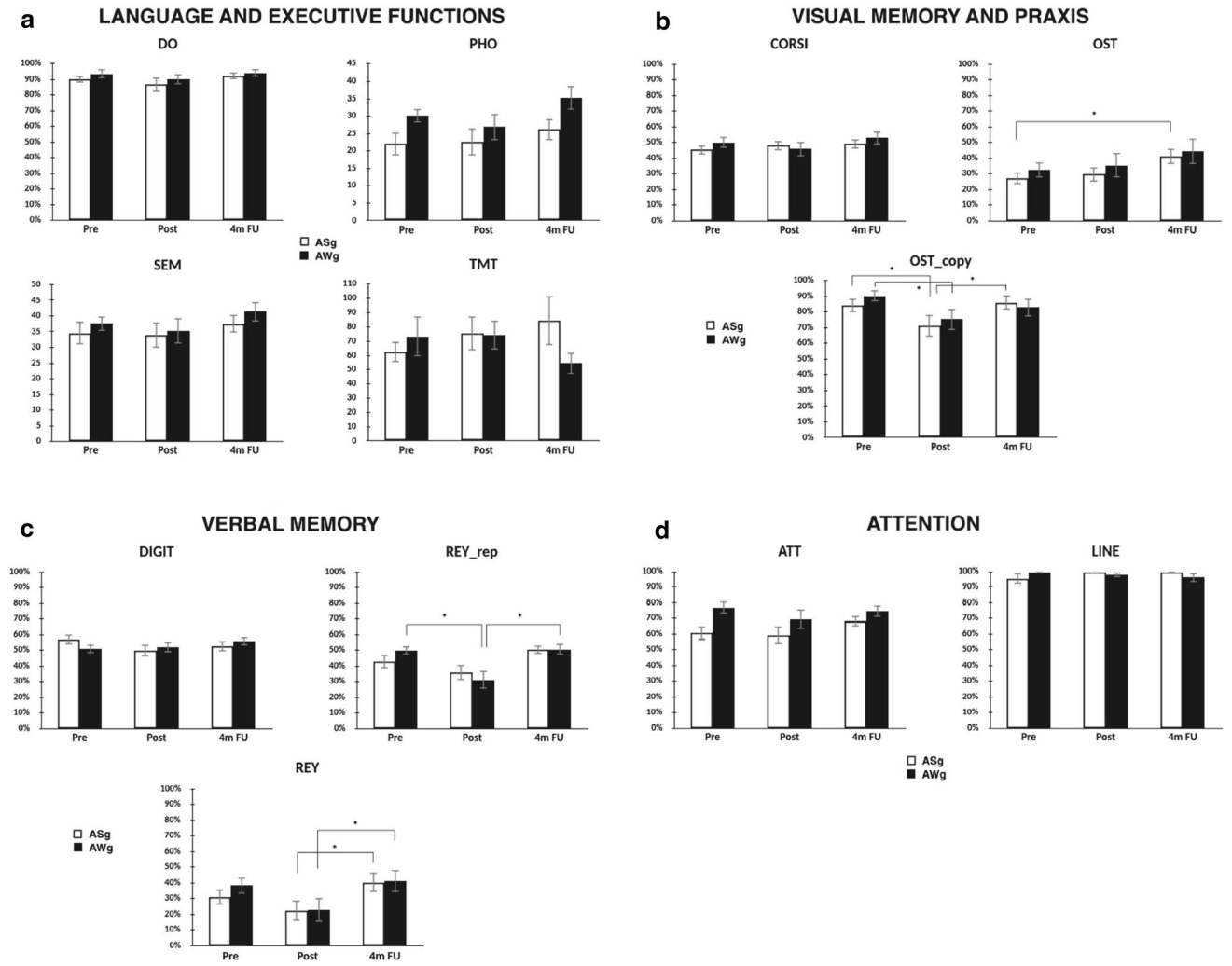

Fig. 1 Results of Friedman rmANOVA test, separated by group. *ASg* Asleep surgery Group; *AWg* Awake surgery Group. **a** Language and executive functions; *DO* object denomination, *PHO* phonemic fluency, *SEM* semantic fluency, *TMT* Trial Making Test (for this test higher values correspond to worse performance). **b** Visual memory and praxis; *CORSI* Corsi span, OST delayed recall of complex figure, *OST_copy* copy of complex figure. **c** Verbal memory; *DIGIT* digit span, *REY*_rep Rey's 15 word list immediate recall, *REY* Rey's 15 word list delayed recall. **d** Attention; *ATT* attentional matrix; *LINE* line cancellation test. *p < .05

Cognitive functions of ASg and AWg pre-surgery, post-surgery and 4 months FU

Results of analysis, mean scores at neuropsychological tests and percentage of deficits are reported in Table 2. Considering the pre-surgical level, a significant difference between ASg and AWg emerged for selective attention test ($p < 0.01$): patients of AWg have a better performance in selective attention (76.8% of targets detected) before surgery compared to patients of ASg (60.7%). No other differences were found (all $ps > 0.063$).

Regarding the post-surgical assessment and the 4 months follow up assessment, no differences have been found between patients operated in general anesthesia (ASg) and in awake surgery (AWg), (respectively all $ps > 0.087$ for Time_2 and all $ps > 0.058$ for Time_3).

Volumetric analyses

Results of permutation test and cm^3 tumors volume (T1_pre), surgical cavity (T1_post), pre-surgery and post-surgery hyperintensity (T2_pre and T2_post) and TuI (TuI_pre and TuI_post) are reported in Online Resource Table 3. ASg showed more flair hyperintensity before surgery (mean volume = 117 cm^3) as compared to AWg (mean volume = 57.5 cm^3; $p < 0.05$). Tumor infiltration index resulted significantly lower after surgery for AWg (mean volume = 2.5 cm^3) as

Table 2 Results of Mann–Whitney U test, average scores in neuropsychological tests and percentage of deficit for every assessment

Test	Time of assessment	Group	Mean scores	% of deficit	p-value
Object Denomination (DO)	Pre	ASg	72.1	5.9	.146
		AWg	75.1	6.3	
	Post	ASg	69.4	17.6	.510
		AWg	72.6	12.5	
	4 m follow up	ASg	73.9	5.9	.817
		AWg	75.1	6.3	
Phonemic fluency (PHO)	Pre	ASg	22	47.1	.063
		AWg	30.7	6.3	
	Post	ASg	22.6	35.3	.465
		AWg	27.4	25	
	4 m follow up	ASg	26.2	23.5	.074
		AWg	34.1	6.3	
Semantic fluency (SEM)	Pre	ASg	34.5	23.5	.345
		AWg	38.4	12.5	
	Post	ASg	34	23.5	.845
		AWg	36.3	25	
	4 m follow up	ASg	37.5	17.6	.581
		AWg	40.5	0	
Digit span (DIGIT)	Pre	ASg	5.1	11.8	.345
		AWg	4.8	12.5	
	Post	ASg	4.5	23.5	.709
		AWg	4.8	12.5	
	4 m follow up	ASg	4.7	11.8	.488
		AWg	5.1	6.3	
Corsi span (CORSI)	Pre	ASg	4.1	29.4	.179
		AWg	4.5	12.5	
	Post	ASg	4.3	11.8	.958
		AWg	4.2	18.8	
	4 m follow up	ASg	4.4	11.8	.533
		AWg	4.7	12.5	
15 Rey's word list: immediate recall (REY_rep)	Pre	ASg	31.9	29.4	.157
		AWg	37.2	12.5	
	Post	ASg	26.7	47.1	.683
		AWg	24.8	43.8	
	4 m follow up	ASg	37.6	17.6	1
		AWg	38.3	12.5	
15 Rey's word list: delayed recall (REY)	Pre	ASg	4.6	52.9	.168
		AWg	5.9	25	
	Post	ASg	3.3	70.6	.763
		AWg	3.6	62.5	
	4 m follow up	ASg	6	41.2	.845
		AWg	6.3	31.3	
Rey's complex figure: copy (OST_copy)	Pre	ASg	30.3	29.4	.231
		AWg	32.7	18.8	
	Post	ASg	25.7	47.1	.929
		AWg	26.3	50	
	4 m follow up	ASg	31	17.6	.606
		AWg	30	25	

Table 2 (continued)

Test	Time of assessment	Group	Mean scores	% of deficit	p-value
Rey's complex figure: delayed recall (OST)	Pre	ASg	9.8	52.9	.260
		AWg	12.3	31.3	
	Post	ASg	10.6	47.1	.817
		AWg	12.4	43.8	
	4 m follow up	ASg	14.8	29.4	.845
		AWg	15.3	25	
Line cancellation (LINE)	Pre	ASg	57.2	29.4	.231
		AWg	59.8	6.3	
	Post	ASg	59.5	11.8	.958
		AWg	58.9	12.5	
	4 m follow up	ASg	59.7	5.9	.986
		AWg	57.9	18.8	
Attentional matrix (ATT)	Pre	ASg	36.4	17.6	< .01**
		AWg	46.1	6.3	
	Post	ASg	35.5	29.4	.087
		AWg	42.1	6.3	
	4 m follow up	ASg	40.8	17.6	.058
		AWg	45.7	6.3	
Trial Making Test (TMT)	Pre	ASg	62.2	0	.851
		AWg	70.4	7.1	
	Post	ASg	75.5	10	.974
		AWg	69.5	0	
	4 m follow up	ASg	84.5	0	.317
		AWg	53.6	0	

Pre pre-surgery assessment; *post* post-surgery assessment; 4 *m follow up* assessment 4 months after surgery. *ASg* Asleep surgery Group; *AWg* Awake surgery Group

** p-value < .01

compared to ASg (mean volume = 7.79 cm^3; $p < 0.05$). No other differences were found (all ps > 0.075).

Moreover, we compared the same pre and post-operative volumes, separated for both groups, in order to verify longitudinal differences. ASg patients showed a significant decrease of hyperintensity after surgery [T2_pre (117.28 cm^3) vs T2_post (71.98 cm^3), $p < 0.01$]. No other differences were found [T1_pre (27.14 cm^3) vs T1_post (14.2 cm^3), $p = 0.124$; TuI_pre (13.94 cm3) vs TuI_post (7.79 cm^3), $p = 0.619$]. Regarding AWg results showed decrease of both hyperintensity [T2_pre (57.49 cm^3) vs T2_post (41.62 cm^3), $p < 0.01$], and importantly of TuI after surgery [TuI_pre (36.84 cm^3) vs TuI_post (2.5 cm^3), $p < 0.01$]. No differences for tumor volume and surgical cavity emerged [T1_pre (12.61 cm^3) vs T1_post (17.77 cm^3), $p = 0.088$].

Variables influencing OS

In our cohort age (HR = 1.051; 95% C.I. = 1.009 – 1.096; $p < 0.05$) and IDH mutation (HR = 0.129; 95% C.I. = 0.03—0.641; $p < 0.05$) emerged as factors capable of influencing OS; no other significant values were found (all ps > 0.101). Complete results of every factor, including volumetric analysis, are reported in Online Resource Table 4. In order to assess the maximum value of residual tumor infiltration (TuI_post) associated with survival, this variable was dichotomized in increments of 1. The value of this ratio capable to influence OS, in our cohort, was 9 (HR = 4.31; 95% C.I. = 1.25 – 14.87; $p < 0.05$) (Online Resource Fig. 1). Kaplan–Meier curve showed a lower mean survival (558 days) in patients with residual hyperintensity > 9 (i.e. TuI_post = T2_post / T1_post > 9) compared to those with ratio < 9 (1357 days as mean survival, Log-rank test $p < 0.05$) (Online Resource Fig. 2). Moreover, a χ^2 test showed that patients with residual tumor infiltration index < 9 were significantly distributed in AWg ($\chi^2 = 4.28$, $p < 0.05$).

Survival

The Kaplan–Meier method showed a significant longer overall survival rates for patients of AWg in respect to those of ASg (Log-rank test $p < 0.01$). According to previous analyses, showing a possible influence of IDH mutation and age on survival, we performed a Kaplan–Meier curve on a restricted group of patients, including only wild-type glioblastoma (i.e. grade IV WHO and no IDH mutation), excluding 4 patients from ASg and 8 patients from AWg. These new groups resulted balanced for age ($U = 38.5$, $p = 0.336$) and sex ($\chi^2 = 0.505$, $p = 0.477$). Results still showed a significant longer survival for patients of AWg compared to ASg (Log-rank test $p < 0.05$). Full results are reported in Fig. 2 and Table 3.

Discussion

Nowadays, EOR is considered a critical prognostic factor for delaying the progression of the disease and improving OS for both LGGs and HGGs [48]. Considering the proved benefit of a radical surgical approach, a main criteria in selecting the surgical strategy should be the preservation of the neurocognitive profile and, as a consequence, of the QoL [16, 51].

We studied two homogenous populations of patients with HGGs who underwent two different surgical strategies: asleep versus asleep-awake-asleep surgery. Our goal was to verify whether the surgical procedure has an effect on cognitive outcome, EOR and OS.

In order to avoid possible conceptual and statistical biases, groups were balanced for age, sex, left/right tumor location, grade and biomolecular pattern. Moreover, all the patients received the same treatments (complete resection of enhancing areas and post-operative radio- and chemotherapy). It is worth noting that they did not differ in cognitive performance before surgery, with the exception of a selective attention task. Interestingly, even if it was not a pre-set cut off for awake surgery, this result confirms that the selection criteria (mainly based on good expected cooperation in the intra-operative setting, no anxiety disorder, good clinical conditions and compliance) were concordant with this cognitive item.

A first interesting result is the absence of worsening in the overall cognitive outcome at 4 months FU after surgery in both groups, demonstrating a full restoration of the cognitive

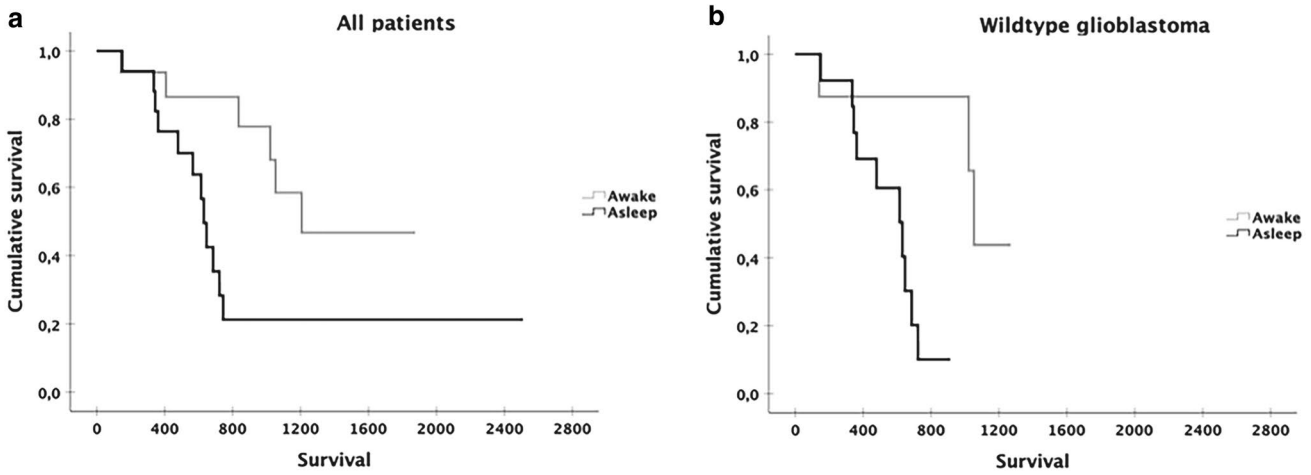

Fig. 2 Kaplan–Meier curves for all patients (**a**) and for wildtype glioblastoma (**b**)

Table 3 Data of survival and Log-rank test

Patients	Group	N	Survival mean (days)	Standard error	Survival median (days)	Standard error	Log-rank test
All	ASg	17	955.28	213.81	630	28.85	$\chi^2 = 6.73$
	AWg	16	1328.81	164.44	1206	0	$p < .01$ **
Wildtype Glioblastoma	ASg	13	557.774	58.68	630	11.853	$\chi^2 = 6.03$
	AWg	8	1026.56	128.97	1052	32.09	$p < .05$ *

ASg Asleep surgery group; *AWg* Awake surgery group

*p-value < .05; **p-value < .01

functions assessed without significative differences in the rate of cognitive impairment (Fig. 1, a complete description of cognitive outcome is reported in Online Resource 3).

At a more fine-grained observation, awake surgery produces transitory and reversible cognitive deficits immediately after surgery, as largely reported for LGGs [13]. This is probably due to the intrinsic feature of this technique, focused on reaching cortical and subcortical functional structures as limit of resection [8, 44]. The full recovery at 4 months after surgery, i.e. 1 month after the end of the radio-therapy, compared to the pre-surgical assessment, is particularly worth noting considering also the supposed intrinsic negative effect of this post-operative treatment. [14, 52]. Interestingly, no increased neurocognitive impairment in the ASg were revealed, demonstrating a preservation of the critical cortical epicenters and subcortical pathways probably related to an accurate pre-surgical planning. On the other hand the asleep approach, mainly focused on the resection of the tumor-enhancing area, leads to different results in respect to both EOR and OS.

Indeed, a second interesting point regards the comparison of OS. We found a significantly longer OS, in patients of AWg [mean = 955 days (about 32 months) for ASg vs 1329 days (about 44 months) for AWg]. Considering the different grades (i.e. III and IV, WHO) and biomolecular profiles (in particular, IDH mutation), and their effects on the expected OS [3–6], we a stratification of these data, considering only wild-type Glioblastoma. Interestingly, excluding patients with grade III tumor and IDH mutation from both groups, AWg patients still have a significant longer survival [mean = 1026 days (34 months) as compared to the 558 days (about 18 months) of the ASg] (Fig. 2). It is worth noting that our data on ASg are in line with those reported by the most recent revision of the WHO classification of brain tumors (15 months for wild-type glioblastoma, 31 months for IDH mutated) [5], but our median survival for AWg is longer than commonly reported.

Considering these differences in the OS and the recent data regarding the negative impact on survival of larger Flair hyper-intensity area at post-operative MRI [12, 22], we tested the hypothesis of possible more aggressive (i.e. beyond the contrast-enhancing area) resections in the AWg analyzing the OS in respect to the EOR. In this cohort no differences between groups in volumes of enhancing-tumor, surgical cavity and T2/flair post-surgery hyper-intensity volumes were revealed. ASg patients showed a greater hyperintensity before surgery compared to AWg, even if Cox regression demonstrated no influence of this variable on patients' OS. Importantly, the value of tumor infiltration index (i.e. a ratio between T2/flair and T1 lesion volumes) was significantly lower after surgery (i.e. close to 1) in AWg patients, revealing larger surgical cavities and smaller residuals of tumor infiltration. Comparing these volumes before and after surgery, separated for groups, we found a significant decrease of volumes of post-operative T2/Flair hyperintensity in both AWg and ASg, but a significant and notable decrease of tumor infiltration index in respect to the pre-operative MRI only in the AWg. Finally, the results of this surgical series suggest that patients with a residual hyperintensity 9 times bigger than the surgical cavity (i.e. tumor infiltration index > 9) had significant lower OS (Online Resource Fig. 2), and interestingly they were more distributed in ASg. These results together suggest that awake resection with cortico-subcortical mapping probably leads the resection beyond the classical estimated limits (i.e. tumor-enhancing area), reducing the area of tumor infiltration, that was demonstrated influencing the OS [12].

The main limitations of this study are sample size and the retrospective design. Nevertheless, the extensive neuropsychological follow-up provided, the homogeneity of patients' and tumors' features, the methods and results constitute an encouraging statistical background for future studies focused on the definition of a reliable advantage of awake surgery in the resection of HGGs. A second point is related to the selection criteria for asleep or awake surgery. As highlighted before, we did not adopt location, lateralization or volume of the tumors as selection criteria. Considering that patients had no neurological deficit, the main selection criterion was the objective and subjective ability of patients to be cooperating at best of the surgical team needs. Finally, considering we provided two extensive neuro-cognitive post-operative assessments and no patients experienced post-operative neurological deficits (i.e. by definition KPS was always ≥ 80), we did not report here KPS scores and data regarding the patients' perceived QoL.

Conclusion

To the best of our knowledge, this is the first study comparing asleep and awake resections of HGGs, suggesting that awake surgery leads to the same cognitive outcome in comparison to asleep surgery, reducing the residual tumor infiltration and improving, at the same time, the OS.

In conclusion, these data demonstrated as the supra-total resection of enhancing area, allowed in this series by awake surgery with cortico-subcortical mapping during neuropsychological monitoring, provides a benefit in the neuro-oncological outcome of patients submitted to resection of HGGs. Particularly, we demonstrated a longer overall survival for awake compared to asleep patients, with a significant decrease of post-operative residual tumor infiltration and no significant differences in the neuro-cognitive profile and, as a consequence, in the quality of life.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This retrospective study respects the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194).

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