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Neuro-oncological superiority of supratotal resection in lower-grade gliomas

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Abstract

Background. Supratotal-resection (SpTR) is a promising surgical strategy in lower-grade gliomas (LGGs). SpTR assessment, feasibility and distinctive features, as well as clinical benefit at first and second surgery and on overall survival must be better characterized. The critical percentage of resection exceeding FLAIR margins to obtain clinical benefit and its impact on long-term functional performance are also undefined.

Methods. Included were 704 patients with primary and 439 with recurrent LGGs seen between 2010 and 2019, who underwent resection with brain-mapping technique (BMT) aimed at achieving a SpTR without any "a-priori" selection. Extent-of-resection, evaluated on 3D-FLAIR-MR and categorized according to residual tumor and cavity volume, was associated with progression-free survival (PFS) and malignant(M)PFS at first and second surgery and overall survival by univariate, multivariate, and propensity-score analysis. Functional performance was assessed by neuropsychological (NPS) evaluation.

Results. SpTR evaluation requires volumetric assessment enhanced by brain deformation measurement in parietal tumors; SpTR rate accounts on average for 50.2% and 35.7% at first and second surgery is higher in grade-2, frontal, and temporal locations (at expenses of total resection [TR]). Compared to TR, SpTR reduces and postpones first and second recurrences in all molecular subtypes and grades, delays MPFS without difference in rate, and prolongs overall survival (OS). A degree of SpTR > 120% associates with the lowest recurrence risk. SpTR associates with the best NPS longitudinal course.

Conclusions. This study supports the feasibility of SpTR in LGGs, its benefit at first and second surgery regardless of molecular subtypes, and on OS, significantly reducing recurrence when SpTR > 120%; SpTR also associates with the best patients' functional outcome.

Key Points

- SpTR is highly feasible in LGGs at first and second surgery; it reduces and postpones onset of first and second recurrence prolonging survival. Resection exceeding FLAIR borders ≥20% decreases recurrence risk. SpTR associates with the best functional outcome.

Lower-grade gliomas (LGGs) are primary brain tumors mainly affecting young patients, often causing seizures and high morbidity in a social and professional active population.[1,2] They appear at MRI as highly infiltrative, mostly nonenhancing, FLAIR lesions.[1,2] LGGs share IDH mutation and include Grade-2 and 3 astrocytomas or oligodendrogliomas.[3,4]

Complete resection of FLAIR anomaly is the currently favored initial approach, when feasible, improving survival

Importance of the Study

This is the largest study analyzing the benefit of supratotal resection (SpTR) on LGG outcome at first and second surgery and on overall survival (OS). This study provides a defined methodology for the SpTR assessment according to tumor locations and shows that SpTR is feasible in 50% of LGGs on average, especially in grade-2 and in frontal and temporal tumors (at expenses of total resection). The study confirms the powerful impact of SpTR in reducing and postponing the onset of first and second recurrences, regardless of tumor grade and molecular subtype; SpTR postpones malignant transformation and prolongs OS. The study shows that resection exceeding 20% of initial tumor volume dramatically reduces the risk of recurrence and provides the first evidence that SpTR associates with functional outcome. The implementation in daily practice requires the use of brain-mapping technique and intraoperative tasks to preserve high cognitive function networks.

regardless of molecular status.[5–8] When a functional surgical approach is used, resection continues until functional boundaries are encountered, possibly beyond FLAIR anomaly, safely maximizing excision with a supratotal resection (SpTR).[9–15] The rationale for SpTR grounds on evidence of LGGs infiltrating brain circuitry far beyond conventional MRI anomalies, leading to recurrences in apparently normal sorroundings.[9–15]

We previously reported SpTR general safety and feasibility at first surgery, showing very limited morbidity and comparable impact to total resection (TR) on short-term neuropsychological (NPS) outcome and quality of life.[11,12] We also previously demonstrated SpTR impact on first recurrence rate and PFS.[12] Despite this initial evidence, the current literature is limited, and many aspects of SpTR in LGGs remain to be clarified.[16–18] First, SpTR must be explicitly defined by means of a clear-coded, objective quantitative assessment of extent-of-resection beyond T2/FLAIR tumor borders, often confounded by possible cavity collapse contingencies.[17,18] Available methods are few and data on their daily-practice reliability are very limited.[11,14] A second issue regards SpTR feasibility and impact on first recurrence rate and PFS: available data refer to retrospective studies on limited patient samples or covering too few years, where larger samples and longer follow-up are advisable.[12,19] The impact in case of recurrence is currently unknown. A third issue regards the effect on survival, presently evaluated only on limited patient samples, allowing only unconfirmed conclusions, especially regarding molecular subtypes.[16] A further issue involves the amount of bordering tissue needing to be removed to translate into outcome differences, while considering safety risks and patient neurological and NPS outcomes.[17]

This study by investigating a large retrospective LGG–patient cohort sheds light on these issues and provides further evidence to neuro-oncological community about SpTR evaluation, feasibility, and clinical benefit, in general and regarding molecular subtype and grade.

Methods

Patients

Included were adult patients treated by our group (January 2010 to December 2019) with a histo-molecular diagnosis of LGGs (grade-2/3 IDH-mutant), undergoing resection. This study period partially overlaps with previous studies.[11,12] All procedures were approved by our Ethical Committee (Milano-Lombardia1-CET-1-L2093-AIRC-17842) and conducted according to the Declaration of Helsinki. Supplementary Figure 1A–B shows the flow diagram.

Imaging

MRI protocol included axial-3D-FLAIR-MR, postgadolinium-3D-T1-weighted MR, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC). Patients underwent both preoperative, immediate (within 48 h), and 1-month postoperative MRI.[20] Immediate postoperative DWI-MR were performed to rule out ischemia.[11,12] Follow-up imaging was subsequently acquired every 4–6 months (last follow-up: January 2024).

Surgery

Resection was accomplished according to functional boundaries to achieve SpTR whenever possible without any patient or tumor (size/location/extension) a-priori selection.[11,12] Brain mapping and monitoring techniques (BMT) under asleep–awake–asleep anesthesia were used to locate functional (language/cognitive/motor/visual) boundaries. Resection was extended until functional boundaries were reached, irrespective of their position according to MR-visible tumor borders.[11,12]

EOR Measurement and SpTR Degree

Extent of resection (EOR) was measured on volumetric-FLAIR. Any FLAIR-hyperintense signal abnormalities were included in the lesion load and reported in cm^3.[20] EOR was calculated on 1-month postoperative volumetric-FLAIR with manual segmentation using iPlan-Cranial-software-(BrainLAB) by 5 blinded investigators (MR, MCN, TS, LG, AG). EOR was classified based on residual tumor volume (RTV) as total-(TR,RTV = 0), subtotal-(SR,0 < RTV ≤ 5 mL), or partial-(PR,RTV > 5 mL).[11,12,20] SpTR was defined as complete removal of any signal anomalies with a postoperative cavity larger than preoperative tumor volume by modified Yordanova method,[11–14] implemented by our group in previous studies.[11,12] In Yordanova's original

method, the postsurgical cavity volume was calculated by measuring the major diameter in 3 orthogonal planes onto post and preoperative FLAIR-MR and by calculating tumor volume as an ellipsoid estimation.[13,14] We modified it,[11,12] by assessing postoperative cavity and tumor volume with manual segmentation computerized procedure (to increase accuracy), using pre- and postoperative (1-month)-3D-FLAIR-MR.[20] This resulted in a more refined SpTR definition. In this study, we investigated if cavity collapse/deformation, due to brain modifications following resection, CSF drainage or gravity, affected the quantitative SpTR estimation. To this aim, measurements were performed with 2 different methods, modified Yordanova and Schucht's,[21] and then compared. Schucht's method was originally described for assessing resection volumes in high-grade gliomas and considers brain deformation and CSF volume changes.[21]

Measurements were also obtained utilizing Schucht's method in a subset of representative patients[21] and compared with those by modified-Yordanova's. According to Schucht's, resection volumes were calculated by measuring the supra-tentorial brain volume prior and after surgery, subtracting CSF spaces with manual slice-by-slice correction to ensure accuracy. The ratio between surgical cavity and preoperative tumor volume defined the degree of SpTR.[11,12]

Clinical Factors

Patients underwent clinical, imaging, and NPS follow-up every 4–6 months. Progression was defined according to the RANO criteria.[22,23] Progression-free survival (PFS) was calculated from the surgery date till occurrence of progression, covering the lapse between initial surgery and first recurrence or between first and second recurrences. Malignant progression-free survival (MPFS) estimated the time between surgery and detection of malignant progression, based on biopsy confirmation or on occurrence of new/increased contrast enhancement on imaging judged as higher-grade upon multidisciplinary consensus.[11,12] Overall survival (OS) was calculated from first surgery until tumor-related death. Postsurgical management plan was designed by a multidisciplinary board and based on EOR class, patient clinical conditions, and tumor molecular subtype; it included either observation or adjuvant treatment (CHT/RT); observation was prescribed for most Grade-2 tumors subjected to TR/SpTR resection; Grade-3 tumors underwent observation or adjuvant treatment depending on patient clinical conditions (presence of symptoms), postoperative RTV, and histo-molecular profile: generally, symptomatic patients and/or with large RTV were submitted to postsurgical treatment. CHT included temozolomide (standard regimen) or, less frequently, procarbazine/lomustine; RT consisted in a dose of 54 (grade-2) or 60 (grade-3) Gy delivered in 2-Gy daily fractions.

We investigated the possible association with recurrence, PFS, MPFS, and OS of multiple factors as: (1) demographic (age/sex/preoperative seizures); (2) tumor-related factors (location/volume/side/corpus callosum involvement/well-defined vs irregular margins/molecular subtype/histological grade/malignant transformation of recurrence); (3) immediate (at 7 days) and permanent (after 3 months) postoperative deficits; (4) surgery-related factors (BMT and EOR); (5) postsurgical management (observation/RT/CHT). NPS profile was categorized according to 5 functional domains and reported as percentage of patients with pathological scores (e-methods).[24]

Pathological Analyses

Tumors were re-classified according to WHO-2021 criteria.[3,4] IDH1 status was determined by immunohistochemistry with mouse monoclonal anti-IDH1-pR132H(DIA-H09,Dianova) or, in case of negative expression, by mutational analysis (sequencing for IDH1-IDH2 alternate mutations); 1p/19q-codeletion by fluorescence in-situ hybridization (FISH); Alpha-thalassemia/mental-retardation-syndrome-X-linked-loss (ATRX), p53 mutation, and Ki67 by immunohistochemistry; CDKN2A/2B homozygous deletion by FISH.

Statistical Analysis

Continuous variables are summarized as mean ± SD (median, IQR), and differences among groups assessed by Student *t*-test or nonparametric Wilcoxon-rank sum test as appropriate. Categorical variables are presented as absolute values and percentages and differences assessed with Chi-square or Fisher's-exact test as appropriate. *P*-value was considered significant when <.05. PFS/MPFS/OS were analyzed by Kaplan–Meier and Log-rank. Association between variables and time to event was analyzed with simple and multiple Cox regression. Comparison between SpTR and TR in terms of OS and PFS at time of first and second recurrence was studied with a propensity-score-matched analysis. For propensity-score calculation, a logistic regression was used with EOR as dependent variable and relevant confounders as independent variables. A nearest-neighbor matching was used with variable caliper to better match the cohorts' width. A multivariable clustered Cox-regression was used to account for matched data.[11,12] The analysis was conducted using R-software.

Results

SpTR Estimation Reliability

SpTR is generally defined as a resection extending beyond MR-overt signal abnormalities. The objective quantitative SpTR assessment was performed by comparing modified-Yordanova's and Schucht's[21] methodology (e-methods). Results were evaluated in terms of feasibility (procedure and calculation time) and reliability, to identify the easiest, most effective methodology to apply clinical routine. The assessment was performed in 83 primary LGG patients undergone BMT-aided surgery aimed at achieving SpTR, during 2014–2015, in whom no signal abnormalities were detected at 1-month postoperative MR. Yordanova's calculation (7 min average), was easy to perform; Schucht's calculation required a longer learning curve, multiple passages, and a longer calculation time (45 min on average).

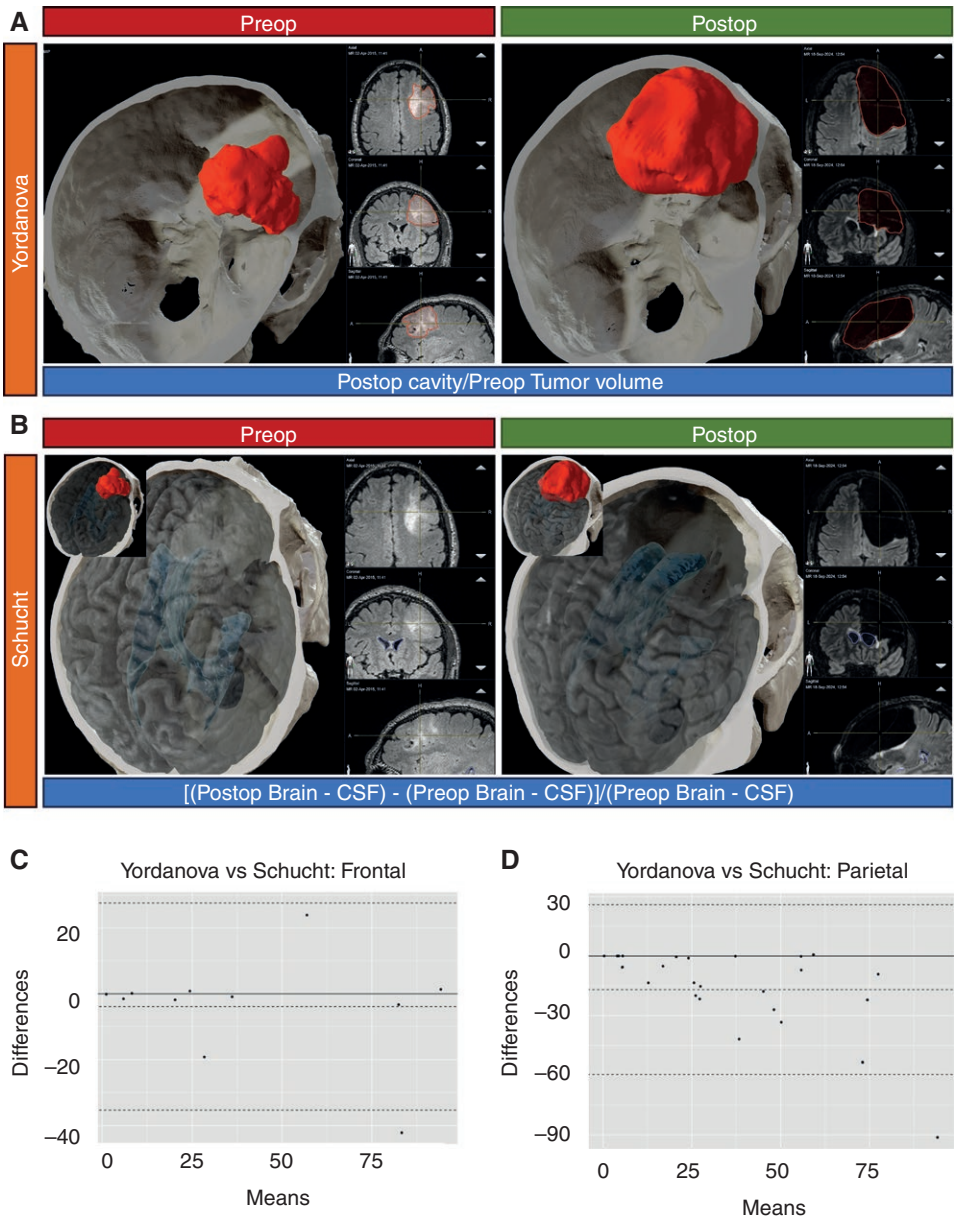

Figure 1. Assessment of SpTR. (A–B) measurement of SpTR: modified-Yordanova's and Schucht' s methods in a representative case of right frontal LGG. With modified-Yordanova's (A) the post-surgical cavity and the tumor volume are calculated by a semi-automated segmentation procedure applied to 1-month post- and preoperative 3D-FLAIR. In the Schucht's (B) the brain volume is calculated onto the preoperative 3D-FLAIR and 1-month post-3D-FLAIR, by a semiautomated segmentation procedure, considering the entire brain volume and subtracting the CSF space. In both cases, SpTR is achieved when the post-surgical cavity volume exceeds the tumor volume. C,D) comparison of the measurements obtained by modified-Yordanova's and Schutch's in frontal (C) and parietal (D) tumors; the superposition was good in case of frontal tumors; in parietal tumors modified-Yordanova's underestimated the cases of SpTR and 64% of cases judged as TR were re-considered as SpTR by Schucht's.

The coherence between the calculations methodologies was good for tumors in frontal, temporal or paralimbic/insular locations. In parietal tumors, Yordanova's underestimated SpTR extent (mean difference –16.93; limits of agreement: –59.67, 25.81) with 64% of cases initially classified as TR by Yordanova's re-classified as SpTR by Schucht's (Figure 1A,B). Consequently, modified-Yordanova' was used to assess SpTR in all locations except parietal where Schucht's was applied instead.

SpTR Feasibility: First vs. Second Surgery

Feasibility at first surgery was assessed in 704 LGG patients, who underwent primary resection using BMT in 2010–2019, aiming to achieve SpTR without any a-priori selection (Figure 2A,B). Two hundred and ninety-two were females (41.5%), 412 males (58.5%), with tumors mainly located in frontal (294, 41.8%) lobe; 417 (59.2%) were astrocytomas, 287 (40.8%) oligodendrogliomas, 539 (76.6%) Grade-2,

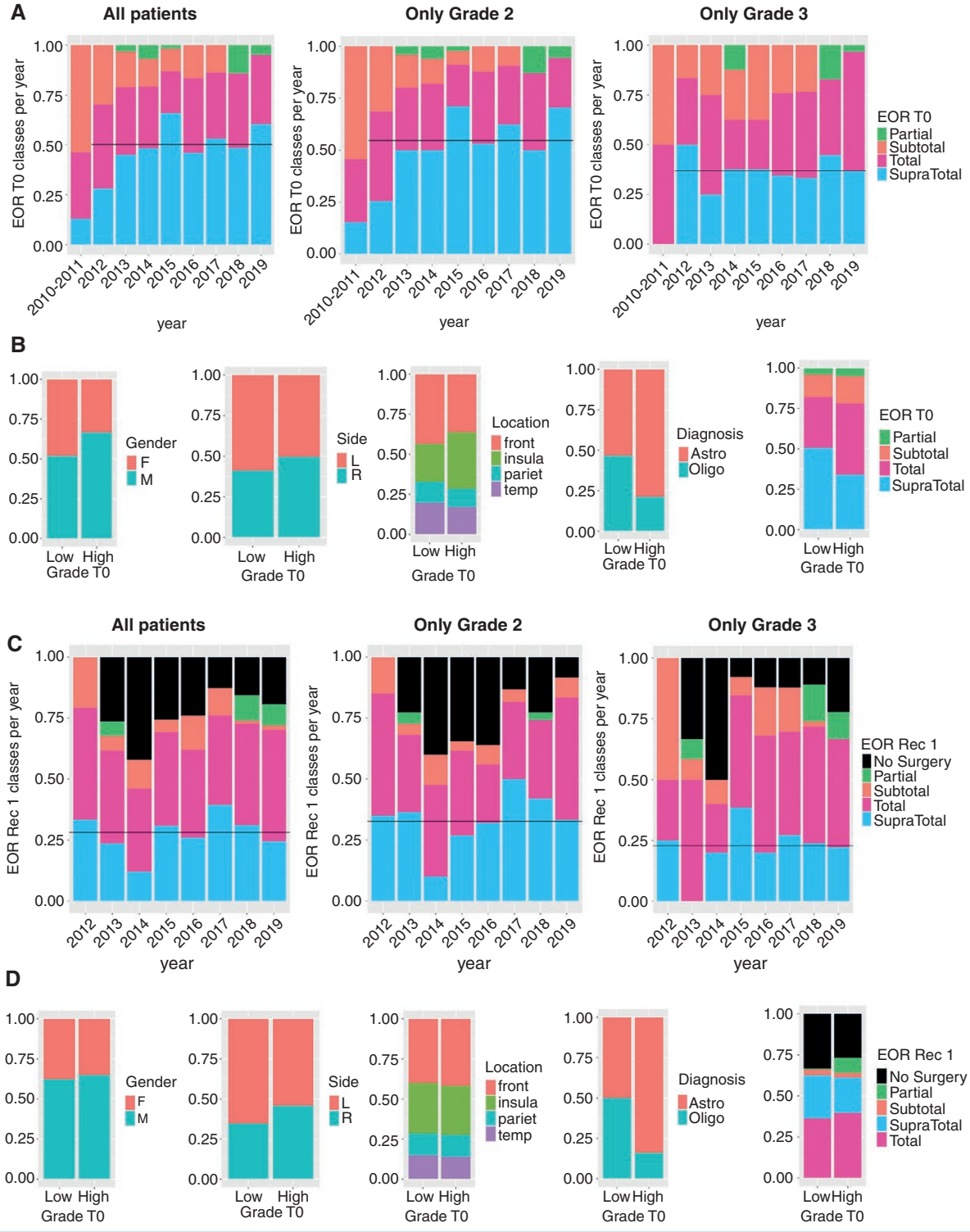

Figure 2. **Feasibility of SpTR**. Per-year incidence of EOR classes at first and second surgery presented for all patients, grade-2 LGG patients and grade-3 LGG patients. Incidence of EOR classes is reported as a percentage. (A) Per-year incidence of EOR classes at first surgery. All patients with a primary LGGs and submitted to resective surgery by using Brain Mapping technique aimed at achieving SpTR between 2010 and 2019 were included. Data are presented for all patients (N = 704)(left panel) and for those with a grade-2 (central panel) or grade-3 tumors (right panel) according to EOR classes reached at first surgery. (B) Distribution according to gender, side, location, molecular subtype, and EOR classes according to tumor grade. Grade T0 = tumor grade at first surgery; EOR T0 = EOR classes achieved at first surgery. (C) Per-year incidence of Treatment classes at first recurrence. All patients with a recurrent LGG and submitted to adjuvant treatment or to resective surgery by using Brain Mapping technique aimed at achieving SpTR between 2010 and 2019 were included. Data are presented for all patients (N = 439)(left panel)

and for those with a grade-2 (central panel) or grade-3 tumors (right panel) at first surgery, according to treatment classes (Treatment Rec1-First Recurrence = No Surgery, and EOR classes). (B) distribution according to gender, side, location, molecular subtype, and Treatment classes according to tumor grade. Grade T0 = tumor grade at first surgery; Treatment Rec1- First Recurrence (No Surgery and EOR classes).

165 (23.4%) Grade-3. SpTR was achieved in 329 patients (46.7%), TR in 242 (34.4%), subtotal in 104 (14.8%), and partial in 29 (4.1%). The overall population analysis was conducted according to surgery year, tumor location, side, molecular subtypes, and grade. SpTR was achieved in 26.5% cases on average in the early 2 years, increasing and stabilizing after 2012. When indeed looking at patients treated from 2012 to 2019 (602 patients, Supplementary Table 1), SpTR was performed in 50.2% of cases on average, with higher rates in frontal/temporal locations (at the expenses of TR), and lower in parietal (without differences with TR) and insular (where TR was predominant). SpTR and TR achievement rate did not differ according to side, but according to molecular subtype (slight prevalence of oligodendrogliomas) and tumor grade, as 81.5% of SpTR cases were Grade-2. Consequently, the analysis was repeated separately for Grade-2 and Grade-3 tumors. In 450 Grade-2 tumors, SpTR was achieved in 246 cases (54.7%), mainly in frontal and temporal locations, less frequently in insular (where TR was predominant) and parietal (as in TR), with no difference according to side and molecular subtype (Supplementary Table 1). In 152 Grade-3 tumors, SpTR dropped to 36.8% (56 patients), mostly achieved in frontal and temporal locations (at the expenses of TR), without differences in side or molecular subtype.

Feasibility at second surgery was evaluated in 439 patients seen from 2012 to 2019 for a recurrent tumor, 265 (60.4%) astrocytomas, 174 (39.6%) oligodendrogliomas, 243 (55.4%) initially Grade-2, 196 (44.6%) Grade-3 (Figure 2C,D); median PFS of first recurrence was 55 months (IQR: 24–77). Three hundred and forty-four underwent second surgery: SpTR was achieved in 123 (35.7%) cases, TR in 174 (50.6%, Figure 2C,D; Supplementary Table 2). SpTR achievement did not show differences according to year of surgery, locations, side, or molecular subtype, but it did relate to grade; SpTR was mostly achieved in recurrent patients with initial Grade-2 tumors (Supplementary Table 2). The analysis was therefore conducted separately for Grade-2 and Grade-3 tumors at first surgery; 184 recurrent Grade-2 tumors had a second surgery, and SpTR was achieved in 78 cases (42.4%), while TR in 89(48.4%), without differences in locations, side, and molecular subtype; 160 recurrent Grade-3 tumors underwent a second surgery and SpTR was achieved in 45 (28.1%), while TR in 85 (53.1%), without differences in locations, side and molecular subtype.

SpTR Feasibility: General Safety, Immediate and Permanent Morbidity

This analysis was carried out on 402 patients with primary and 282 patients with recurrent tumors, operated on during 2012–2017 (Supplementary Table 3A,B). They were extracted from the group of 602 primary LGGs and 439 recurrent LGGs treated in 2012–2019 (with comparable SpTR/year-rate), because of fully available clinical, imaging, intra-operative and histo-molecular data. Overall surgical and mapping (cortical/subcortical) time were comparable between SpTR and TR, without differences among first and second surgeries, side, and molecular subtype. During the awake surgeries (96.9% and 99.0% of cases at first and second surgery), patient fatigue was low and comparable in all groups, with no mapping abortion or differences among first or second surgeries. At first surgery, > 90% of patients in SpTR and TR cohorts experienced acute postsurgical functional deterioration (e.g. speech reduction, movement slowness), completely recovering within 1–2 weeks. Two patients experienced permanent deficits in SpTR and TR cohorts, no postoperative mortality was observed. At second surgery, transient postoperative deficits were observed in both cohorts. Two SpTR patients experienced permanent postoperative deficits (mild language impairment, 2.0%) and one TR patient (mild motor deficit, 0.7%). After first surgery, SpTR associated with better seizure control, reached with less AEDs (Supplementary Table 1A,B).

SpTR Feasibility: SpTR Patients' Distinctive Features

SpTR patients' distinctive features at first surgery were analyzed in 402 patients with primary tumors treated in 2012–2017. Analysis was performed globally and according to grade (Supplementary Table 3A). At first surgery, SpTR was achieved in 193 patients (48%), TR in 134 (33.4%). SpTR-achieving patients differed from TR-achieving for clinical history of generalized seizures, molecular subtype (slight predominance of oligodendrogliomas in SpTR: 51.8% vs 48.2% astrocytomas), and tumor grade (predominance of Grade-2). Other clinical, imaging, and intra-operative factors were irrelevant. The analysis was performed according to tumor grade. In 309 patients with Grade-2 tumors, 161 (52.1%) had SpTR and 97 (31.4%) TR. SpTR patients were characterized for clinical history of seizures, and slight predominance of oligodendrogliomas (57.8% vs 42.2% astrocytomas). In 93 Grade-3 tumors, SpTR was performed in 32 (34.4%), TR in 37 (39.8%), and only clinical history differed SpTR to TR patients.

The distinctive features of SpTR patients at second surgery were investigated in 282 recurrent tumors operated on between 2012 and 2017; 136 were initially treated by us using BMT (median PFS of first recurrence: 70 months [IQR: 34–93.75]); 146 patients were previously treated elsewhere with image-guided procedure and no BMT (median PFS: 29 months, IQR: 24–34.50 months); 101 (35.8%) had SpTR, 144 (51.1%) TR (Supplementary Table 3B). SpTR patients differed from TR patients for tumor grade at recurrence and adjuvant treatments received after first surgery: 19% of TR patients had RT after first surgery compared to 3% in SpTR group and 61.8% of tumors in TR group underwent malignant transformation

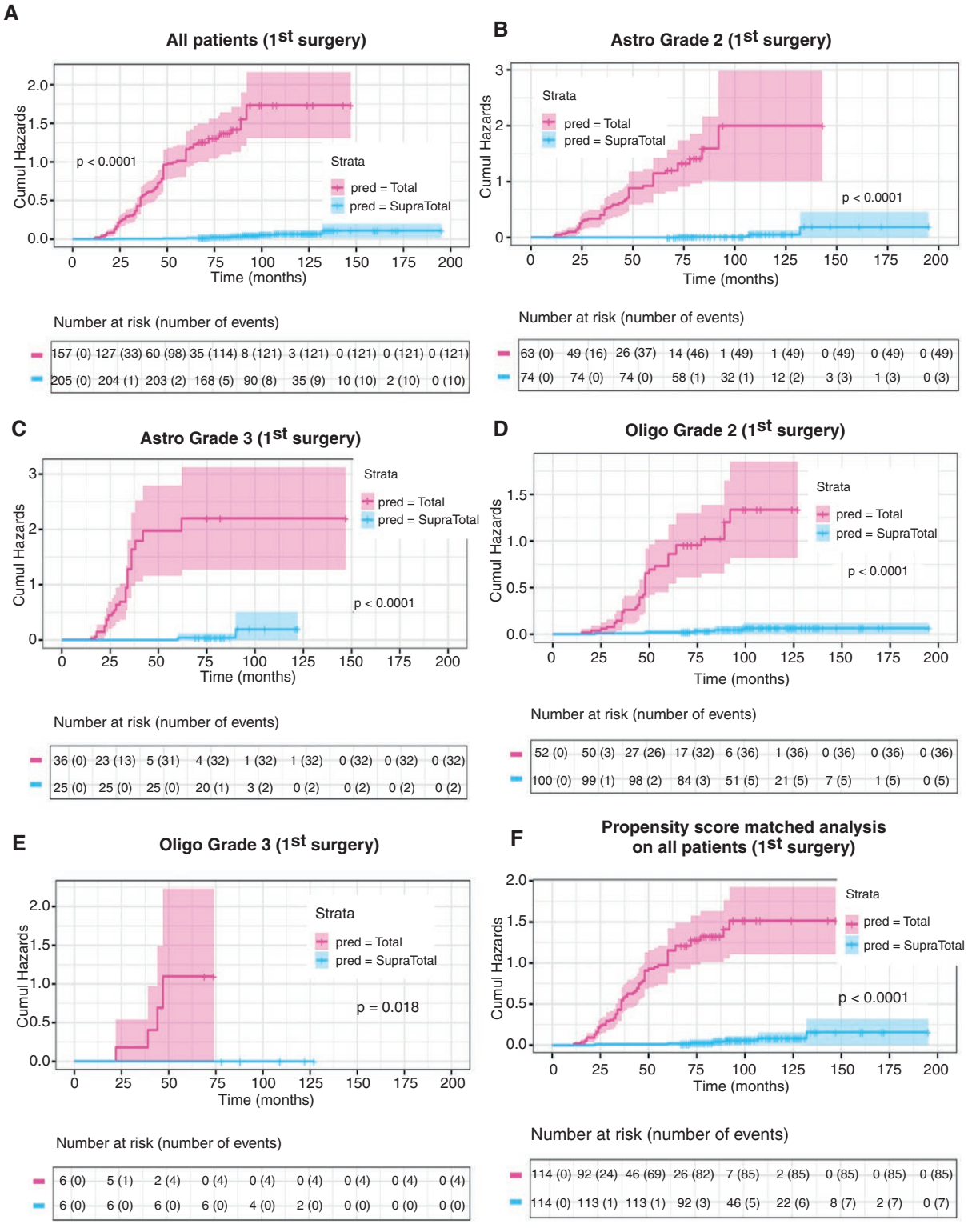

Figure 3. Cumulative-risk curve and number of events for PFS of first recurrence and EOR, in all patients and in molecular and tumor grade defined subtypes. A, Cumulative-risk curve and number of events for PFS of first recurrence and SpTR or TR EOR classes in all 466 primary LGGs; median PFS after SpTR not reached (95% CI NA-NA; HR 0.03, 95% CI 0.02–0.06), median PFS after TR 45 months (95% CI 37–48; HR 34.08, 95% CI 17.70–65.62). B, Cumulative-risk curve and number of events for PFS of first recurrence and SpTR or TR EOR classes in all primary Grade-2 astrocytomas; median PFS after SpTR not reached (95% CI NA-NA, HR 0.02, 95% CI 0.01–0.07), median PFS after TR 47 months (95% CI 36–60, HR 46.44, 95% CI 13.98–154.34). C, Cumulative-risk curve and number of events for PFS of first recurrence and SpTR or TR EOR classes in all Grade 3 primary astrocytomas; median PFS after SpTR not reached (95% CI NA-NA, HR 0.03, 95% CI 0.01–0.15), median PFS after TR 31.5 months (95% CI

24–34, HR 29.14, 95% CI 6.83–124.32). D, Cumulative-risk curve and number of events for PFS of first recurrence and SpTR or TR EOR classes in all Grade-2 primary oligodendrogliomas; median PFS after SpTR not reached (95% CI NA-NA; HR 0.04, 95% CI 0.02–0.11), median PFS after TR 51.5 months (95% CI 48–89; HR 24.33, 95% CI 9.46–62.58). E, Cumulative-risk curve and number of events for PFS of first recurrence and SpTR or TR EOR classes in all Grade-3 primary oligodendrogliomas: median PFS after SpTR not reached (95% CI NA-NA, HR 4.1e-10, 95% CI 0-Inf), median PFS after TR 45.5 months (95% CI 39-NA, HR 2.4e + 9, 95% CI 0-Inf). F, Cumulative-risk curve and number of events for PFS of first recurrence and SpTR or TR EOR classes in propensity-matched samples of patients with primary LGGs who underwent SpTR or TR; median PFS after SpTR not reached (95% CI NA-NA, HR 0.04, 95% CI 0.02–0.09), median PFS after TR 44.5 months (95% CI 36–50, HR 24.42, 95% CI 11.19–53.28).

versus 28.7% in SpTR. Out of 186 patients with recurrent Grade-2 tumors submitted to second surgery, 75 (40.3%) had SpTR and 93 (50.0%) TR; these patients differed mainly for malignant transformation rate at first recurrence, lower in SpTR (22.7% vs 55.9% in TR). Out of 96 patients with recurrent Grade-3 tumors, 26 (27.1%) had SpTR and 51 (53.1%) TR, differing for postsurgical management after first surgery and rate of malignant transformation at first recurrence.

Oncological Benefit of SpTR

Effect on first recurrence rate and PFS.

The analysis was conducted on 466 patients with primary tumors with fully available clinical, imaging, intraoperative, and histo-molecular data treated in 2010–2017 for long follow-up (median: 105 months, IQR: 81–145). They were extracted from the 704 primary tumor group patients treated within 2010–2019, by eliminating patients operated on after 2017 (Supplementary Table 4A). At univariate analysis, EOR at first surgery, molecular subtype, and grade associated with first recurrence rate and PFS (Supplementary Figure 2). First recurrence rate was 4.9% (10 patients) in SpTR and 77.1% (121 patients) in TR group. Median PFS after first surgery (PFS_t0) in overall population was 78 months (IQR: 53.8), 44 months (95%CI: 36–48) in TR group, not reached in SpTR group (95%CI:NA-NA) (Figure 3A). SpTR effect emerged in all molecular subtype and grade (Figure 3B–E), regardless of grade and molecular subtype (Supplementary Figure 3). Multiple Cox-regression confirmed SpTR, Oligodendroglioma and Grade-2 as protective-factors for first recurrence (Supplementary Table 5). This effect was confirmed by propensity score-matched analysis, run to rule out possible bias due to different risk-factors distribution between SpTR and TR patients (Figure 1,F); 2 groups of 114 patients each were created with similar distributions in all preoperative confounders (Supplementary Table 6).

Effect on second recurrence rate and PFS.

The analysis was conducted in 282 patients with recurrent Grade-2 and 3 tumors who underwent second surgery in 2012–2017. A second recurrence developed in 141 patients (median PFS 44 months, IQR:43). At univariate analysis, molecular subtype, EOR at second surgery, tumor grade at first surgery, and malignant transformation at first recurrence associated with onset of second recurrence (Supplementary Figure 4). Second recurrence occurred in 100 (69.4%) patients with TR at second surgery and in 5 (4.95%) with SpTR; median PFS was 48 months (95%CI: 44–55) for TR, not reached in SpTR (95%CI:NA-NA) (Figure 4A). SpTR effect emerged in all molecular subtypes and grade (Figure 4B–E) and was confirmed by multiple Cox-regression analysis (Supplementary Table 7). Grade-3 at first surgery and malignant transformation at first recurrence emerged as risk factors for second recurrence, further confirmed by propensity-matched analysis (Figure 4F). For the latter, 2 groups of 76 patients each with homogeneous distribution of pre- and intra-operative factors (Supplementary Table 8) were generated. The 2 groups differed in adjuvant treatments, both at first and second surgery.

Effect on malignant transformation at first and second recurrence.

Out of 139 SpTR and TR patients who developed a first recurrence, 80 (57.6%) had signs of malignant transformation, without difference between SpTR (5/10, 50%) and TR (71/121, 58.7%). MPFS in SpTR was longer than in TR (Supplementary Figure 5A). Molecular subtype (astrocytoma) and Grade-3 associated with malignant transformation at first recurrence (Supplementary Table 9). Out of 94 patients who developed a second recurrence, 80 (85.1%) had signs of malignant transformation at second recurrence, without difference between SpTR (2/5, 40.0%) and TR (78/100, 78.0%). MPFS in SpTR was longer than in TR (Supplementary Figure 5B). Malignant transformation at second recurrence associated with EOR at second surgery, grade at first surgery and malignant transformation at first recurrence (Supplementary Table 10).

Effect on OS.

Out of 370 patients who had SpTR or TR at first surgery, 50 (13.5%) died during follow-up: 47/157 (29.9%) in TR group and 1/205 (0.5%) in SpTR ($P < .001$). At univariate analysis, OS from first surgery associated with molecular subtype, grade, EOR, onset, and malignant transformation of first recurrence (Supplementary Figure 6). Median OS in overall population was 91 months (IQR: 41.8), 153 months(95%CI:153-NA) in TR group, not reached in SpTR (95%CI:NA-NA) (Figure 5A). SpTR at first surgery associated with OS in all molecular-defined tumor grade except Grade-3 oligodendrogliomas (only 12 cases were included) (Supplementary Figure 7A–D). When molecular subtype, grade, location, side, volume, EOR at first surgery, onset of recurrence, and malignant transformation at first recurrence were considered together by multiple Cox-model, tumor grade, onset of recurrence, and malignant transformation masked the other covariates (Supplementary Table 11A). The strong effect of onset of recurrence (95%CI reaching infinite) prevented significance. By removing recurrence from the multiple model (Supplementary Table 11B), SpTR ($P < .001$) and oligodendroglioma ($P = .009$) resulted as

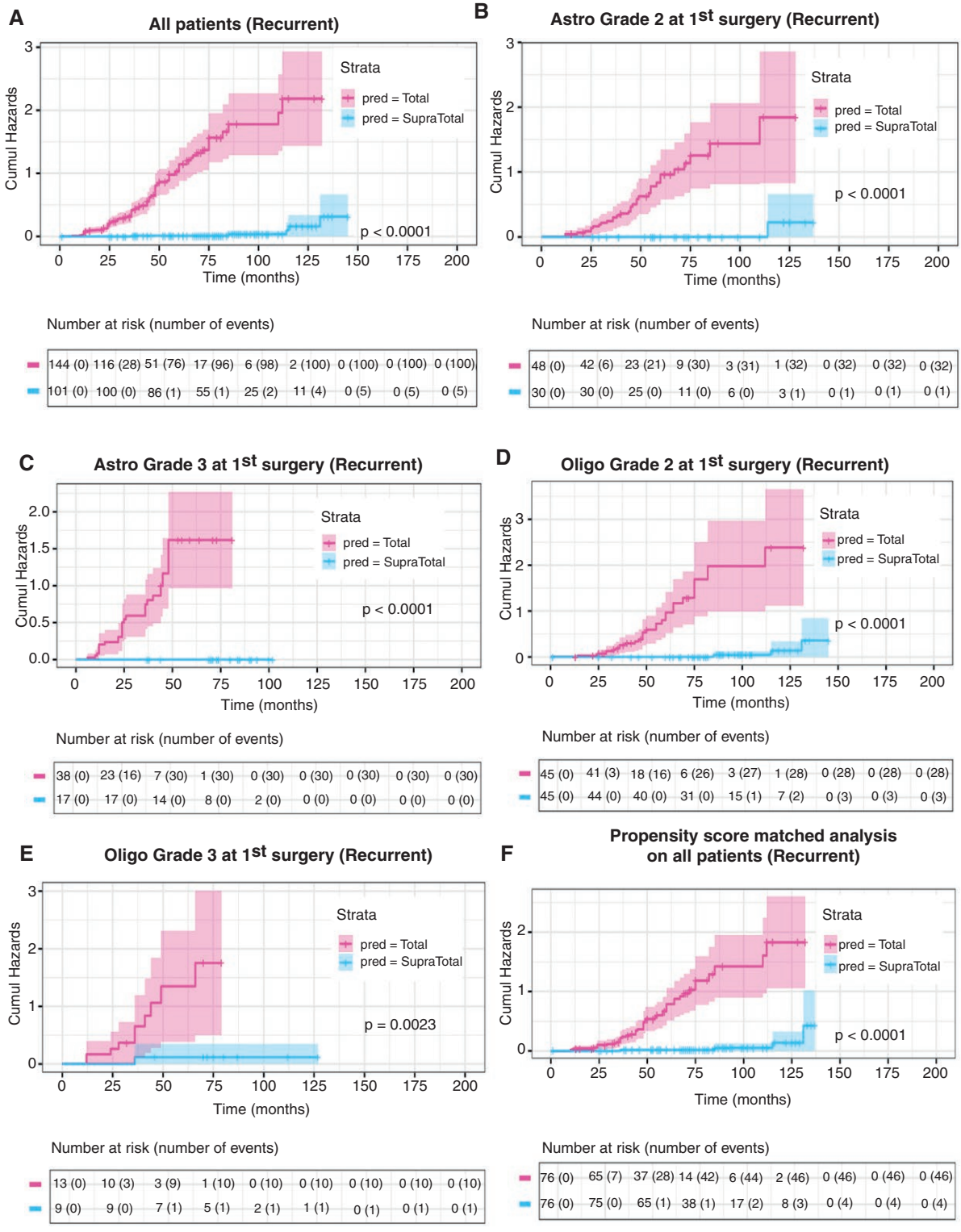

Figure 4. Cumulative-risk curve and number of events for PFS of second recurrence and EOR, in all patients and in molecular and tumor grade defined subtypes. Data are presented according to molecular subtype and grade at first surgery. A, Cumulative-risk curve and number of events for PFS of second recurrence and SpTR or TR EOR classes in all 377 recurrent LGGs: median PFS after SpTR not reached (95% CI NA-NA, HR 0.03, 95% CI 0.01–0.08), median PFS after TR 48 months (95% CI 44–55, HR 31.30, 95% CI 12.62–77.58). B, Cumulative-risk curve and number of events for PFS of second recurrence and SpTR or TR EOR classes in all Grade-2 recurrent astrocytomas (grade at initial surgery): median PFS after SpTR not reached (95% CI NA-NA, HR 0.03, 95% CI 0.00–0.21), median PFS after TR 55 months (95% CI 46–75, HR 34.94, 95% CI 4.72–258.73). C, Cumulative-risk curve and number of events for PFS of second recurrence and SpTR or TR EOR classes in all Grade-3 recurrent astrocytomas (grade at initial

surgery): median PFS after SpTR not reached (95% CI NA-NA, HR 2.0e-9, 95% CI 0-Inf), median PFS after TR 36 months (95% CI 24–48, HR 5.1e + 8, 95% CI 0-Inf). D, Cumulative-risk curve and number of events for PFS of second recurrence and SpTR or TR EOR classes in all Grade-2 recurrent oligodendrogliomas (grade at initial surgery): median PFS after SpTR not reached (95% CI 131-NA, HR 0.04, 95% CI 0.01–0.13), median PFS after TR 55 months (95% CI 48–69, HR 25.72, 95% CI 7.66–86.28). E, Cumulative-risk curve and number of events for PFS of second recurrence and SpTR or TR EOR classes in all Grade-3 recurrent oligodendrogliomas (grade at initial surgery): median PFS after SpTR not reached (95% CI NA-NA, HR 0.08, 95% CI 0.01–0.64), median PFS after TR 41 months (95% CI 28-NA, HR 12.33, 95% CI 1.56–97.47). F, Cumulative-risk curve and number of events for PFS of second recurrence and SpTR or TR EOR classes in propensity-matched samples of patients with recurrent LGGs who underwent SpTR or TR; median PFS after SpTR not reached (95% CI 131-NA, HR 0.05, 95% CI 0.02–0.13), median PFS after TR 60 months (95% CI 49–75, HR 21.37, 95% CI 7.64–59.74).

protective factors, while Grade-3 ($P = .001$) and insular location ($P = .036$) associated with increased risk of death.

Out of 245 patients receiving SpTR or TR at first recurrence, 71 (29.0%) died during follow-up: 70/144 (48.6%) in TR group and 1/101 (0.99%) in SpTR ($P < .001$). Median OS after first recurrence (OS-r1) calculated from second surgery was 68 months (IQR:45) for overall population, 74 months (95%CI:61-NA) in TR group, not reached in SpTR (Figure 5B). SpTR associated with OS in all molecular-defined tumor grade except Grade-3 oligodendrogliomas (only 20 cases were included) (Supplementary Figure 7E–H). At univariate analysis, molecular subtype, grade at first surgery, malignant transformation at first recurrence, onset and malignant transformation of second recurrence associated with OS (Supplementary Figure 8). When molecular subtype, grade at first surgery, EOR at second surgery, volume, malignant transformation of first recurrence, and onset and malignant transformation of second recurrence were considered together by multiple Cox-regression (Supplementary Table 12A), onset of second recurrence masked all other covariates, except for malignant transformation of first recurrence. The extreme effect of second recurrence (95%CI reaching infinite) prevented significance. By removing second recurrence (Supplementary Table 12B), SpTR remained as a protective factor ($P < .001$), while Grade-3 at first surgery ($P = .043$) and malignant transformation of first recurrence ($P < .001$) were risk factors for death.

SpTR Features Predictive of Recurrence Risk

SpTR associated with few recurrences, either at first or second surgery. To investigate associated risk factors, the distinctive features of SpTR patients developing or not a first or a second recurrence were analyzed. Risk factors at first surgery are given in Supplementary Table 13: preoperative tumor volume was significantly larger in patients experiencing recurrence. No risk factors at second surgery emerged (Supplementary Table 14).

To investigate if the amount of apparently normal brain parenchyma removed was linked with the risk of recurrence the SpTR degree was estimated in 95 representative patients with primary tumors who underwent SpTR at first surgery, inclusive of all 10 recurrent patients. Median degree was 147.30% (IQR:105.6). SpTR degree was plotted against the onset of recurrence (Figure 6A). In patients developing a first recurrence, median degree was 108.3% (104.6–152.6%) and 70% of patients were < 120%; patients not developing a recurrence had a median degree of 156% (105.2%–2538%). Patients who reached ≥120%SpTR (76.8% of the total) had a significantly lower recurrence risk (4.1% vs 31.8%–<120%, $P < .001$; median PFS not-reached, 95%CI:NA-NA, $P < .001$, Figure 6B). These patients showed only smaller initial tumor volumes (mean 40.7 ± 47.6cc vs 121 ± 67.4cc, $P < .001$, Supplementary Table 15). Upon multiple Cox-regression considering both tumor volume and SpTR degree, only the latter remained significant for first recurrence onset and PFS ($P = .009$, Supplementary Table 16). Interestingly, SpTR degree associated with molecular subtype: the protective threshold was higher in astrocytomas (140%, $P = .029$) than in oligodendrogliomas (110%, $P < .001$, Supplementary Figure 9).

Functional Outcome

The impact on functional performance was examined by looking at longitudinal course of NPS profile of primary LGG patients undergoing SpTR or TR at first surgery (period 2012–2017), categorized according to 5 functional domains and reported as percentage of patients with pathological scores (Figure 6C). SpTR patients had the longest and best performance, most of them improving each score up to "normal" in a 6/12 months period after surgery and maintaining them along the entire observation period, with only 3.9% patients with cognitive-function pathological scores. TR patients showed a remitting-relapsing performance, with improvement after first surgery followed by worsening upon first recurrence, a further improvement after its treatment (although never reaching "normal" scores) and a final worsening upon second recurrence. Most of the 3.9% of SpTR patients with cognitive-function pathological scores were treated before introduction, during 2013, of intraoperative cognitive tasks for guiding resection (Figure 6D). Since then, the percentage of pathological scores dropped to 1%.

Discussion

This is the largest study analyzing the assessment, feasibility, and clinical benefit of SpTR in LGGs, at first and second surgeries, and its impact on survival. The population studied, significantly larger and more representative of LGGs clinical and imaging features, comprises and expands the sample of our previous studies[11,12] and allows a better assessment of tumor resectability by reducing the influence of its size, location, and delineation on the decision to operate. The study includes cases with a confirmed

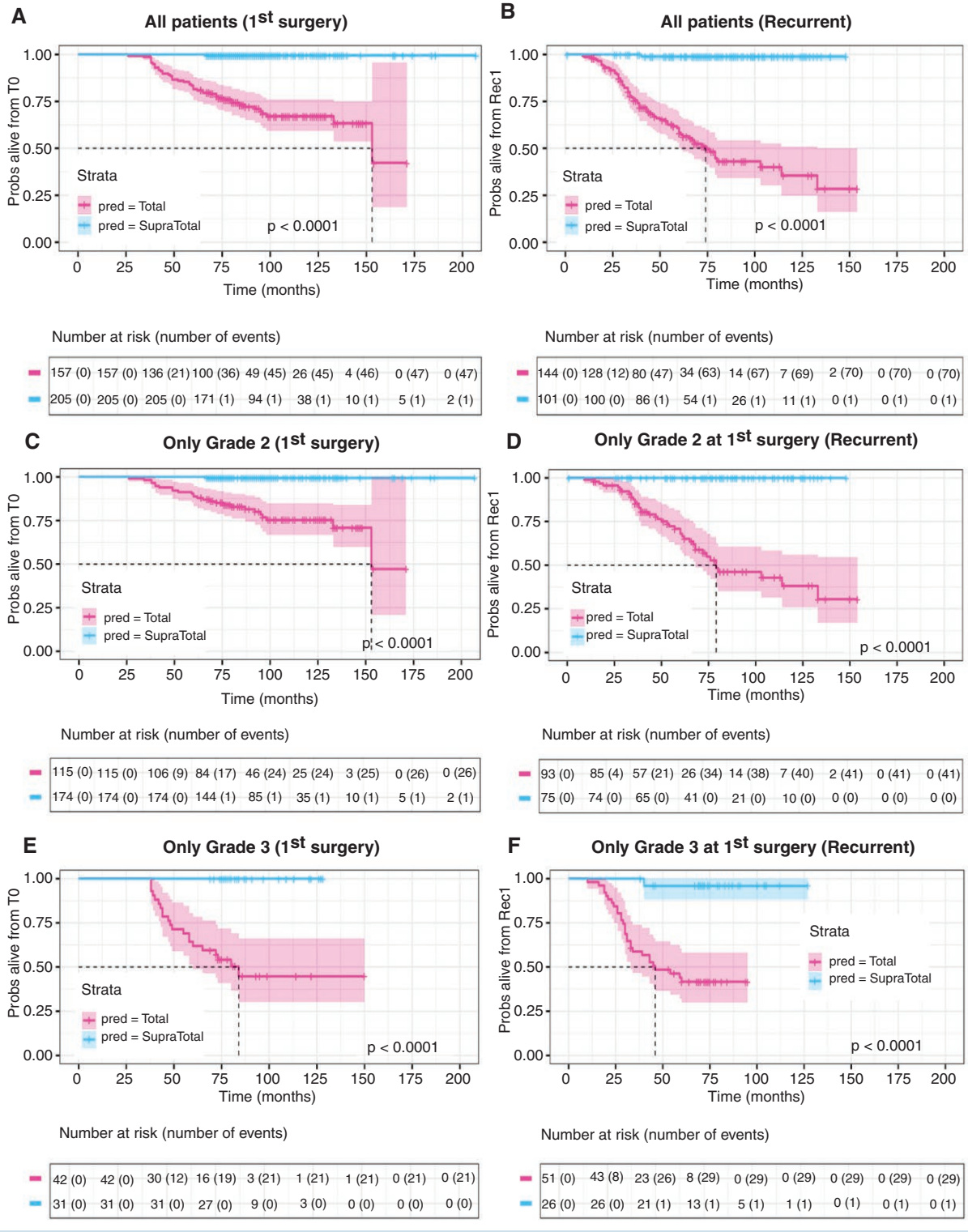

Figure 5. Probability of Overall survival (OS, Kaplan–Meier) curve and number at risk for death from first (A,C,E) or second surgery (B,D,F). Data are presented according to molecular subtype and grade at first surgery. A, OS probability curve and number of deaths from first surgery and EOR at first surgery in all patients with primary LGGs; median OS after SpTR not reached (95% CI NA-NA; HR 0.01, 95% CI 0.00–0.10), median OS after TR 153 months (95% CI 153-NA; HR 74.62, 95% CI 10.29–541.42). B, OS probability curve and number of deaths from second surgery and EOR at second surgery in all patients with recurrent LGGs; median OS after SpTR not reached (95% CI NA-NA; HR 0.01, 95% CI 0.00–0.10), median OS after TR 74 months (95% CI 61-NA; HR 72.22, 95% CI 10.02–520.56). C, OS probability curve and number of deaths from first surgery and EOR at firs surgery in all patients with Grade-2 primary LGGs; median OS after SpTR not reached (95% CI NA-NA,

HR 0.02, 95% CI 0.00–0.16), median OS after TR 153 months (95% CI 153-NA, HR 45.59, 95% CI 6.18–336.36). D, OS probability curve and number of deaths from second surgery and EOR at second surgery in all patients with Grade-2 (at T0) recurrent tumors; median OS after SpTR not reached (95% CI NA-NA, HR 1.4e-9, 95% CI 0-Inf), median OS after TR 79 months (95% CI 68-NA, HR 7.0e + 8, 95% CI 0-Inf). E, OS probability curve and number of deaths from first surgery and EOR at firs surgery in all patients with Grade-3 primary LGGs; median OS after SpTR not reached (95% CI NA-NA; HR 1.6e-9, 95% CI 0-Inf), median OS after TR 84 months (95% CI 60-NA; HR 6.1e + 8, 95% CI 0-Inf). F, OS probability curve and number of deaths from second surgery and EOR at second surgery in all patients with Grade-3 (at T0) recurrent tumors; median OS after SpTR not reached (95% CI NA-NA, HR 0.05, 95% CI 0.01-0.35), median OS after TR 46 months (95% CI 33-NA, HR 21.15, 95% CI 2.88–155.52).

histo-molecular diagnosis of LGG according to the WHO-2021 classification criteria.[3,4]

The first issue addressed was the development of a quantitative assessment of SpTR leading to a more precise definition. In previous studies, we defined SpTR as a surgical intervention resulting in a postsurgical cavity volume larger than tumor volume[11,12] and introduced a volumetric assessment of resection cavity and tumor volume to increase measurement accuracy.[11,12] This methodology, similar to that used for EOR evaluation in diffuse gliomas and familiar to many neurosurgeons and radiologists, does not rule out contingency of possible postsurgical cavity collapse, leading to miscalculation and SpTR-cases underestimation. This point was assessed by comparing feasibility and reliability of the above method with a second one (Schucht's), which is more laborious in that it considers brain deformation and CSF volume changes.[21] The practical point emerging is that our modified-Yordanova is just as accurate for tumors in all locations except for parietal lobe, where Schucht's is recommended for its higher accuracy. This allows for a faster evaluation of SpTR in most cases, limiting the time-consuming Schucht's method to parietal tumors only. This novel methodological finding has significant implication for the evaluation of any treatment response, including those of novel drugs.[25]

The second issue addressed is SpTR feasibility at first and second surgery. The analysis was conducted on a large patient sample treated over a 10-year period, considering overall population and SpTR achievement rate each year, from the first to the 10th. According to year-trend, after an initial increase, SpTR rate stabilized at 50.2% on average, mostly achieved in frontal and temporal locations (at the expenses of TR), less in parietal (not different from TR) and insular (TR predominant). The most interesting finding was the relation with tumor grade. SpTR at first surgery was mostly achieved in Grade-2 tumors accounting for 54.6% on average, while in Grade-3 it dropped to 36.8% on average, in both conditions regardless of molecular subtype. A similar result was found at second surgery, reaching 35.7% globally, without differences according to year, locations, side, or molecular subtype, but again, with remarkable difference in Grade-2 (42.3%) and Grade-3 (28.2%). Feasibility was confirmed by looking at intraoperative features, comparable between SpTR and TR, with very few complications. Considering that Grade-2 tumors represent > 70% of LGGs and frontal and temporal are the most frequent locations, these data indicate SpTR as highly feasible.

Closely related to the feasibility is the analysis of patient distinctive features predictive of successful SpTR achievement. At first surgery, SpTR is significantly predicted in patients with long clinical history of (generalized) seizures, frontal or temporal tumors, possibly Grade-2; at second surgery, SpTR achievement correlates with no history of radiotherapy and signs of malignant transformation at first recurrence. These findings suggest that the degree of brain functional re-organization at the individual patient level influences the ability to achieve (or not) SpTR. Functional reshaping is higher in slow-growing tumors (Grade-2), while it is considered reduced in faster growing ones (Grade-3) or very limited when RT is applied.[9,26]

The third point addressed regards the oncological benefit of SpTR. First recurrence rate and PFS strongly associated with SpTR with a strong protective effect compared to TR. Similarly, second recurrence rate and PFS associated with SpTR, tumor grade at first surgery, and malignant transformation at first recurrence. SpTR effect in reducing and postponing first and second recurrences was confirmed by propensity-match analysis. Furthermore, OS analysis performed on a large patient sample, confirmed SpTR as a protective factor against death in most tumor grade molecular-defined sybtypes, although the few Grade-3 oligodendroglioma cases included limited the power of the analysis in this subgroup. Finally, SpTR associated with better seizure control. These data expand the findings of previous studies confirming the oncological impact of SpTR.[11,12]

This conclusion raises the question about the amount of extra-tissue bordering visible tumor needing to be removed to translate into clinical benefit. The analysis of SpTR patients who developed recurrence showed 2 distinctive features: larger initial tumor volume and lower degree of SpTR (< 120%). SpTR degree measures the amount of tissue removed beyond FLAIR-MR tumor border.[11] Patients in this study undergoing ≥120% resection showed a lower risk of recurrence compared to those undergoing a < 120% resection. Patients in the ≥120% cohort had smaller initial tumor volume, allowing to foster resection far beyond FLAIR visible margins. SpTR degree correlates with tumor volume: resection cavity volume approaches tumor volume for large tumors, while for small ones the cavity is larger than tumor volume and shows high size variability.[11] Consequently, although initial tumor volume does not correlate per se with the chance of achieving SpTR,[11,12] it emerges as significantly associated with the amount of extra-tissue removed (degree), progressively decreasing in parallel with increasing tumor volume. Furthermore, the larger the tumor volume, the higher the number of functional circuits located at periphery, which in turn limits the chance of extending resection.[11] Interestingly, at multiple Cox-regression, only SpTR degree associated with onset of recurrence and PFS, supporting the importance of extending resection beyond FLAIR visible margins when functionally feasible. The protective SpTR degree threshold

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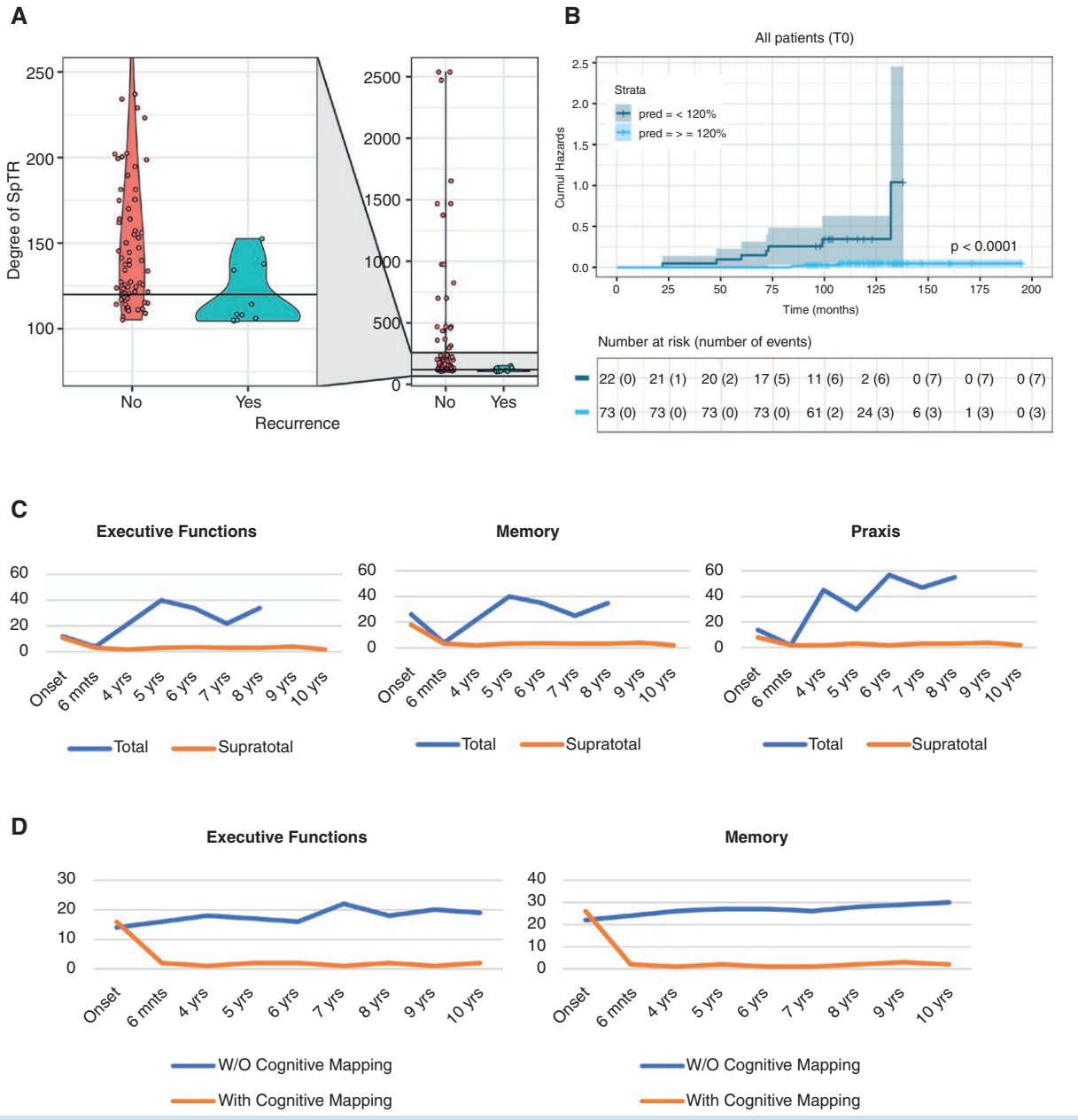

Figure 6. Association between amount of extra-tissue removed (degree of SpTR) and risk of recurrence (A–B); functional outcome of patients who underwent to SpTR or TR at first surgery (C–D). A, Association between degree of SpTR and risk of recurrence. the degree of SpTR (which expresses the amount of extra-tissue removed beyond 3D-FLAIR visible tumor borders) was calculated in a representative sample of 95 patients who underwent SpTR at first surgery and plotted according to the onset (or not) of first recurrence. In the group of patients who did not develop a first recurrence (No) the median degree was 156% (ranging between 105.2% and 2538.3%); in those who developed a first recurrence (Yes) the median was 108.3% (ranging between 104.6 and 152.6%) and the majority had a degree less than 150% (70% < 120%). A degree >=120% resulted to be protective toward the onset of a first recurrence as shown in (B): Cumulative-risk curve and number of events for PFS of first recurrence and SpTR degree: median PFS after SpTR >=120% not reached (95% CI NA-NA; HR 0.09, 95% CI 0.02–0.36), median PFS after SpTR < 120% 132 months (95% CI 132-NA; HR 11.08, 95% CI 2.81–43.65). **Longitudinal evolution of patients NPS profile**. C) Longitudinal evolution of patient score (as a percentage of pathological score) for Executive Functions (left panel), memory (central panel) and praxis functions (right panel) in the group of patients who underwent SpTR or TR at first surgery, reported at different time points of the follow-up. D) Longitudinal evolution of patient score (as a percentage of pathological score) for executive functions and memory, reported at different time points of the follow-up, in patients who received SpTR with and without the use of intraoperative cognitive mapping during the surgical procedure.

appeared also associated with molecular subtype, being higher in astrocytomas than in oligodendrogliomas, possibly reflecting differential growth properties and tumor–brain relationships. Furthermore, the limited amount of extra-tissue removed may also explain the similar rate of malignant transformation recorded in SpTR and TR recurrent patients, as limiting removal may also limit protection from acquisition of a more malignant phenotype. Nonetheless, the longer MPFS observed supports the hypothesis of SpTR beneficial effect.

The amount of extra-tissue removed raised an important fourth issue, that is, patients' functional performance. The current study expands our previous studies on short-term safety, by providing a long-term NPS outcome,[11,12,24] specifically focusing on cognitive functions. Notably, SpTR patients had the best outcome, with a progressive decrease in rate of pathological scores within 6 months of surgery, stabilizing in the following period to a low percentage of pathological scores. Differently, TR patients, after an initial improvement, worsened again with first recurrence, improved after treatment never regaining a normal performance. These results highlight a correlation between onset of recurrence and deterioration of patient functional performance. A possible interpretation may be that SpTR, by postponing any relapse, associates with the best long-term outcome. Only 3.9% of SpTR patients had cognitive pathological scores and most of them had been treated before the introduction of intra-operative cognitive tasks for guiding resection[27–32] which reduced the pathological score to 1%. These findings support the recommendation for using BMT, implemented with sophisticated intra-operative tasks to identify and preserve high cognitive functions circuits, and to functionally identify the boundaries where safely stopping resection.[9–12]

Despite including the largest LGGs population investigated to date, this study has limitations. Being a single-center and retrospective study, its conclusions should be confirmed in further large, independent cohorts, and validated from other neuro-oncological centers.[12] The implementation of SpTR in routine practice requires a well-trained team of dedicated neurosurgeons, neuropsychologists, neurophysiologists, and neuro-anesthesiologists to adapt the intra-operative tasks to the individual patient context, significantly reducing the risk of mapping abortion and optimizing the time required to perform resection.[9,12,24,27–31] Data on SpTR must be also confirmed onto a larger population. A further point of debate regards whether a trial may help in better clarify SpTR benefit and how to design it.

In conclusion, this study supports the feasibility of SpTR in LGGs, its benefit at first and second surgery and on patient OS, regardless of molecular subtype. SpTR requires the implementation of BMT and sophisticated intra-operative tasks in awake anesthesia to assure a high level of functional preservation.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

lower-grade gliomas | supratotal resection | recurrence | overall survival | neuropsychological evaluation

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Conflict of interest statement

None declared.

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Authorship Statement

Alberto Gallotti: study design, data collection and analysis, manuscript preparation and revision; Marco Rossi: manuscript preparation and revision; Marco Conti Nibali: data collection and analysis; Tommaso Sciortino: data collection and analysis; Lorenzo Gay: data collection and analysis; Guglielmo Puglisi; data collection, manuscript revision; Antonella Leonetti: data collection and manuscript revision; Francesco Bruno: data collection and manuscript revision; Roberta Rudà and Riccardo Soffietti: manuscript revision; Gabriella Cerri: study design, manuscript preparation and revision; Lorenzo Bello: study design, data collection and analysis, manuscript preparation and revision.

Data Availability

Data will be made available upon reasonable request by contacting the corresponding author

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