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ORIGINAL ARTICLE - TUMOR - GLIOMA

Hotspots of small strokes in glioma surgery: an overlooked risk?

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Abstract

Background Small deep infarcts constitute a well-known risk of motor and speech deficit in insulo-opercular glioma surgery. However, the risk of cognitive deterioration in relation to stroke occurrence in so-called silent areas is poorly known. In this paper, we propose to build a distribution map of small deep infarcts in glioma surgery, and to analyze patients' cognitive outcome in relation to stroke occurrence.

Methods We retrospectively studied a consecutive series of patients operated on for a diffuse glioma between June 2011and June 2017. Patients with lower-grade glioma were cognitively assessed, both before and 4 months after surgery. Areas of decreased apparent diffusion coefficient (ADC) on the immediate postoperative MRI were segmented. All images were registered in the MNI reference by ANTS algorithm, allowing to build a distribution map of the strokes. Stroke occurrence was correlated with the postoperative changes in semantic fluency score in the lower-grade glioma cohort.

Results One hundred fifteen patients were included. Areas of reduced ADC were observed in 27 out of 54 (50%) patients with a lower-grade glioma, and 25 out of 61 (41%) patients with a glioblastoma. Median volume was 1.6 cc. The distribution map revealed five clusters of deep strokes, corresponding respectively to callosal, prefrontal, insulo-opercular, parietal, and temporal tumor locations. No motor nor speech long-term deficits were caused by these strokes. Cognitive evaluations at 4 months showed that the presence of small infarcts correlated with a slight decrease of semantic fluency scores.

Conclusion Deep small infarcts are commonly found after glioma surgery, but their actual impact in terms of patients' quality of life remains to be demonstrated. Further studies are needed to better evaluate the cognitive consequences—if any—for each of the described hotspots and to identify risk factors other than the surgery-induced damage of microvessels.

Keywords Strokes · Glioma · Surgery · Cognitive outcome

Introduction

If survival benefits of surgical glioma resection are no longer debated [1], acquired neurologic deficiency can affect quality of life [2]. In order to limit the risk of neurological deficits, techniques were developed that help the surgeon to extend tumoral resection up to functional borders. Hence, thanks to intraoperative cortical and axonal mapping performed in an awake patient, glioma surgery can be successfully achieved, even in highly eloquent areas [3]. The principle of sparing cortical and axonal sites eliciting transient functional disturbance during direct electrical stimulation is now well established and the reliability of the technique greatly contributed to its wide spreading [4]. Yet, permanent neurological deficits still occur in a small percentage of patients, mostly related to small deep infarcts [5]. This holds especially true for glioma located in the insula (deep stroke due to perforating arteries running in the depth of the cavity) or in the operculum.

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While such strokes are feared due the risk of motor sequel, very little is known about the functional risk in other locations, like prefrontal lobe, temporal lobe, and parietal lobe.

In this paper, we propose to determine the occurrence rates of small strokes in a consecutive series of 115 glioma patients and to draw the distribution map of these strokes. Furthermore, their impact on cognitive functioning was analyzed for the lower-grade glioma subgroup.

Methods

Inclusion criteria

Patients operated on by the senior author for a glioma between June 2011 and June 2017 were retrospectively and consecutively included. Histopathological diagnosis was made according to the 2007 WHO classification, and WHO grades II to IV glioma were included. We grouped the grade II and grade III as "lower-grade glioma." Patient's age was greater than 18 years of age. Patients diagnosed on biopsy sample were excluded from the study.

Surgical techniques

The senior surgeons applied principles of glioma surgery, with subpial dissection and minimal use of bipolar coagulation [6]. Visualization was achieved by naked eyes, surgical loops, or microscope, depending on the steps of the resection and the location of the tumor. Awake surgery with functional mapping was performed whenever feasible, as previously detailed [7].

Imaging

Diffusion imaging and 3D T1 was acquired within 2 days after surgery. Between June 2011 and 1 July 2014, a 1.5 T GE Medical System (GE Healthcare, Chicago, Illinois) was employed to acquire DWI of the entire head with an anterior-posterior phase of acquisition. DWI parameters consisted of a total field of view of 128 × 128 mm. DWI was acquired with a weighting $b = 2000$ s/mm^2. Additionally, non-weighted ($b = 0$) was also acquired. Echo time (TE) was set at 84 ms and repetition time (TR) at 9000 ms. 3DT1 parameters consisted of a total field of view of 256 × 256 mm. Echo time (TE) was set at 1.73 ms and repetition time (TR) at 7.29 ms.

Between 1 July 2014 and June 2017, a 3 T Siemens Skyra system (Siemens, Erlangen, Germany), was employed to acquire DWI of the entire head with an anterior-posterior phase of acquisition. DWI parameters consisted of a total field of view of 220 × 220 mm. DWI was acquired with a weighting $b = 2000$ s/mm^2. Additionally, non-weighted ($b = 0$) was also acquired. Echo time (TE) was set at 64 ms and repetition time (TR) at 5600 ms. 3DT1 parameters consisted of a total field of view of 256 × 256 mm. Echo time (TE) was set at 1.73 ms and repetition time (TR) at 7.29 ms.

Small deep infarcts were defined by a strong decrease of ADC, concomitantly to a clear hypersignal on the $b = 2000$ diffusion sequence, excluding restricted diffusion related to methemoglobin (hyperintense T1 signal and/or hypointense T2*) and very thin rims (< 3 mm) at the border of the operative cavity. The ischemic nature was further investigated on the 3D-SPGR T1 sequence of the late MRI (4-months postoperatively), looking for the typical aspect of encephalomalacia. Extent of resection was also assessed on the late postoperative MRI, with the following definitions of complete resections:

- No residual contrast enhanced area for glioblastoma,
- No residual hypersignal flair for lower-grade glioma.

Distribution map of strokes

DICOM images were first converted to Nifti format using the academic software dicom2nii (https://www.nitrc.org/projects/mricron/). The area affected by strokes was segmented, based on b2000 hypersignal and ADC hyposignal, using the software MI-brain [8] (Imeka, Sherbrooke, Canada). For each subject, the ADC was spatially resampled to a 1 mm isotropic voxel size and then registered to a T1-weighted image with six degrees of freedom (rigid) using mutual information metric. T1 image was nonlinearly registered to the MNI 2009c Nonlinear Asymmetric T1w template using a cross-correlation metric. Both registrations were performed by the Ants registration software [9]. Transformations were subsequently applied to the segmentations performed in diffusion space, resulting in area affected by the strokes aligned within the MNI template. Once all subjects were registered in a common space with their binary segmentation of the stroke, a probability map was created by doing a voxel-wise addition of all the binary segmentation followed by a division of the total amount of subjects with a stroke. The resulting probability values are between 0 and 1, a region with a value of 0 means that none of the stroke subjects was affected in this region while a value of 1 means that all stroke subjects had strokes in the region. Hence the number of cases with a stroke in a voxel is obtained by multiplying the probability in that voxel with the total number of patients with a stroke. The map can then be visualized in the MNI template, in order to see the anatomical regions associated or not with strokes.

Cognitive assessments

All patients with lower-grade glioma (WHO grade II and III) were cognitively assessed, as previously detailed [7], just

before and 4 months after the surgery. All these patients benefited from intensive cognitive rehabilitation with a speech therapist, started right after the surgery. In this first attempt to correlate cognitive outcome with stroke occurrence, we only selected the semantic fluency testing, which consists of giving, within 2 min, the highest number of words belonging to a given semantic category (here chosen to be animals). The same modality was applied pre- and postoperatively. It has been indeed shown that this is a very sensitive measure of global cognitive functioning in glioma patients [10, 11], as this test taps several cognitive aspects, including language ability, executive functions, and speed of information processing. Moreover, it allows to overcome the bias of tumor location, as decrease in semantic fluency has been shown to be unrelated to a specific lesion location [12]. Last but not the least, this test is very easy to implement, explaining why most teams make use of this test [13, 14].

Statistical methods

Marginal associations between single variables (age, gender, tumor grade and location, extent of resection, anesthesia type) and ischemia were assessed by a Wilcoxon rank-sum test for quantitative variables and the chi-square test for qualitative variables. Statistical analysis of cognitive changes made use of the Wilcoxon rank-sum test, with the presence or absence of stroke as categorical variables, and the variation Δ (Δ = postop − preop) in semantic fluency scores as continuous variables (either expressed as absolute values or as standard deviations). $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R statistical software (The "R" Foundation for Statistical Computing, Vienna, Austria), implemented under Rstudio (version 1.0.143).

Results

Patients and tumor characteristics

Our population was made of 115 patients, 40.9% female and 59.1% male. Median patient age was 50 years (mean = 50.5, range 24–86) (see Table 1).

The lower-grade population (76% grade II, 24% grade III) was made of 54 patients with 39% female and 61% male. Median patient age was 44 years (mean = 45; range = 24–76). Initial symptom was seizure in 75.9%. Follow-up was 23.17 months on average. Tumor localization was fontal (25.6% right/33.3% left), insular (3.6% right/7.7% left), opercular (5.5% left), parietal (5.5% right/5.5% left), temporal (11.2% left), and occipital (1.8% left). Median tumoral volume was 41.2 cm^3 (mean = 45.4, range = 0.7–157). Awake surgery was performed in 98.1%. Removal was complete in 88.9%. Ischemia was diagnosed on postoperative MRI in 27 cases (50%,) with confirmation of encephalomalacia on late postoperative MRI in all cases but one. In this latter case, the late postoperative MRI was difficult to assess, due to important distortion of brain tissue surrounding the cavity after chemoradiation therapy. Complete pre- and postoperative cognitive assessments were available in 92.6% patients.

Table 1 Patient characteristics

	GBM ($N = 61$)	LGG ($N = 54$)
Median age at tumor diagnosis, *year*	55	44
Gender, *N* (%)		
Male	35 (*57.4%*)	33 (*61.1%*)
Female	26 (*42.6%*)	21 (*38.8%*)
Extent of surgery, *N* (%)		
Total and sub-total resection	44 (*72.1%*)	48 (*88.9%*)
Partial resection	17 (*27.9%*)	6 (*11.1%*)
Awake surgery, *N* (%)		
Yes	35 (*57.4%*)	53 (*98.1%*)
No	26 *(42.6%)*	1 (*1.9%*)
Neuropsychological evaluation, *N* (%)		
Yes	21 (*34.4%*)	50 (*92.6%*)
No	40 (*65.6%*)	4 (*7.4%*)
Average survival, *month*	13.7	23.17
Ischemia		
Yes	25 (*41%*)	27 (*50%*)
No	36 (*59%*)	27 (*50%*)

GBM glioblastoma, *LGG* lower grade glioma

The GBM population was made of 61 patients with 42.6% female and 57.4% male. Median patient age was 56 years (mean = 56, range = 28–86). Follow-up was 13.8 months on average. Initial symptom alternated between headaches (11.4%), seizures (31.1%), and neurologic deficits (31.1%). Tumor localization was frontal (19.7% right/24.6% left), parietal (8.2% right/8.2% left), temporal (12.1% right/18% left), insular (3.3% right/1.6% left), and occipital (4.9% left). Median tumor volume was 25.9 cm^3 (mean = 35.2, range = 0.7–118.9). Awake surgery was performed in 57.3%. Removal was complete in 72.1%. Ischemia was diagnosed on postoperative MRI in 41% of cases. The diagnosis of stroke was confirmed by typical aspect of encephalomalacia on late postoperative MRI in 21 out of the 25 patients (84%). In two patients, the late postoperative MRI was difficult to interpret because of strong distortion of brain tissue after chemoradiation therapy, and in two patients, the late postoperative MRI was not available.

Age, gender, tumor grade and location, extent of resection, and type of anesthesia did not correlate with stroke occurrence (see Table 2).

Table 2 Comparison of the characteristics of the two groups (stroke versus no stroke)

	No stroke ($N = 63$)	Stroke ($N = 52$)	p value
Age *(year)*	48 ± 14	48 ± 12	1
Female gender	28 (44.4%)	19 (36.5%)	0.24
Tumor type			0.32
LGG	36 (*57.4%*)	25 (*48.1%*)	
HGG	27 (*42.6%*)	27 (*51.9%*)	
Tumor location			0.58
Frontal	35 (*55.5%*)	53 (*46.1%*)	
Temporal	19 (*30.1%*)	15 (*28.8%*)	
Parietal	*2* (*3.3%*)	2 (3.8%)	
Insulo-opercular	7 (11.5%)	11 (21.1%)	
Complete resection	46 (73%)	46 (85.2%)	0.19
Awake surgery	47 (74.6%)	41 (78%)	0.89

GBM glioblastoma, *LGG* lower grade glioma

Distribution map of strokes

Ischemia was diagnosed on postoperative MRI in 52 patients (45%): 27 (50%) in the lower-grade population and 25 (41%) in the GBM population. Median volume of strokes was 1.6 cc (mean 2.2, range 0.02–10.00).

Qualitative analysis of distribution map revealed five clusters of deep strokes: callosal (see Fig. 1a), prefrontal white matter (see Fig. 1b), external capsule and anterior arm of internal capsule (see Fig. 1c), stratum sagittal (see Fig. 1d), and white matter of the anterior temporal lobe (see Fig. 1e), corresponding respectively to tumors located in fronto-mesial, lateral prefrontal, insulo-opercular, parieto-temporal, and anterior temporal tumors.

Functional outcome and correlation with stroke occurrence

None of the patients had a new motor or speech deficit at the 4-months postoperative neurological examination. Visual field defects were observed in patients with temporal and parietal tumors, but the retrospective nature of this study did not allow to analyze the correlation with stroke occurrence (only few objective evaluations of visual fields were available).

In the lower-grade group, the postoperative change in semantic fluency statistically differed between the two groups with and without strokes: the absolute score decreased by 4 units in the stroke subgroup, whereas it increased by 1 unit in the intact subgroup ($p = 0.04$). However, when scores were expressed in terms of standard deviations for each patient, this difference did not reach statistical significance (− 0.2 SD in the stroke subgroup versus 0.1 SD in the intact subgroup, $p = 0.37$).

Discussion

Almost half of patients were diagnosed with neurologically silent small area of ischemia, as detected by decreased ADC on MRI within 2 days after glioma surgical resection. Ischemic cartography revealed a non-random distribution. Considering tumor localization, five specifics hotspots were highlighted.

Comparison of occurrence rates and stroke volumes with current literature

Occurrence rate of postoperative abnormality on diffusion-weighted MRI in the present study was in the low average of results presented in literature. Previous studies found variable rates: 70% cases of glioblastoma [15], 64% cases after resection of newly diagnosed gliomas [16], 51.2% cases in a selected series [17], 31% in a group of newly diagnosed glioma [5], 19% in another one [18]. In this latter study, stroke volumes were not reported, but authors specified that small marginal areas of enhanced DWI hypersignal were not considered as abnormal and subsequently not included in the study. This might explain such a low rate compared to other series. Median volume was 1.6 cm^3 in our study, in agreement with previous studies. Stroke volumes reported by Smith et al. ranged from 4.5 to 11.4cm^3. Median volume reported by Jakola et al. was 1.08 cm^3 in a subgroup of patients with newly acquired neurological deficits. Mean stroke volume was 14.6 cm^3 by Ulmer et al. [15].

Functional consequences of small deep strokes in glioma surgery

The functional impact of these radiologically-detected small strokes is well known regarding tumors of insulo-opercular location. In this subgroup of tumors, long lasting new motor deficits have been clearly linked to deep strokes in the corona radiate [19–23], in keeping with damage to perforators of M1, M2, or M4 branches. Other studies without focus to specific tumor locations also reported a correlation between new postoperative motor or speech deficits and DWI abnormality [5, 15, 17, 18]. On the contrary, some authors reported that areas of reduced ADC seem to be most of the time clinically silent [16, 17], with for example 40% of DWI abnormality in the control group without any new motor or speech deficit [17]. But as acknowledged by these authors, "standard clinical assessments of deficits from brain surgery are presumably insensitive. Although DWI changes in non-eloquent locations may not cause motor or language deficits, there are presumably no silent brain regions." As a first attempt to address this issue, our study is, to our knowledge, the first one to report a correlation between stroke occurrence and mid-term impact on cognitive functioning, as broadly evaluated by the semantic

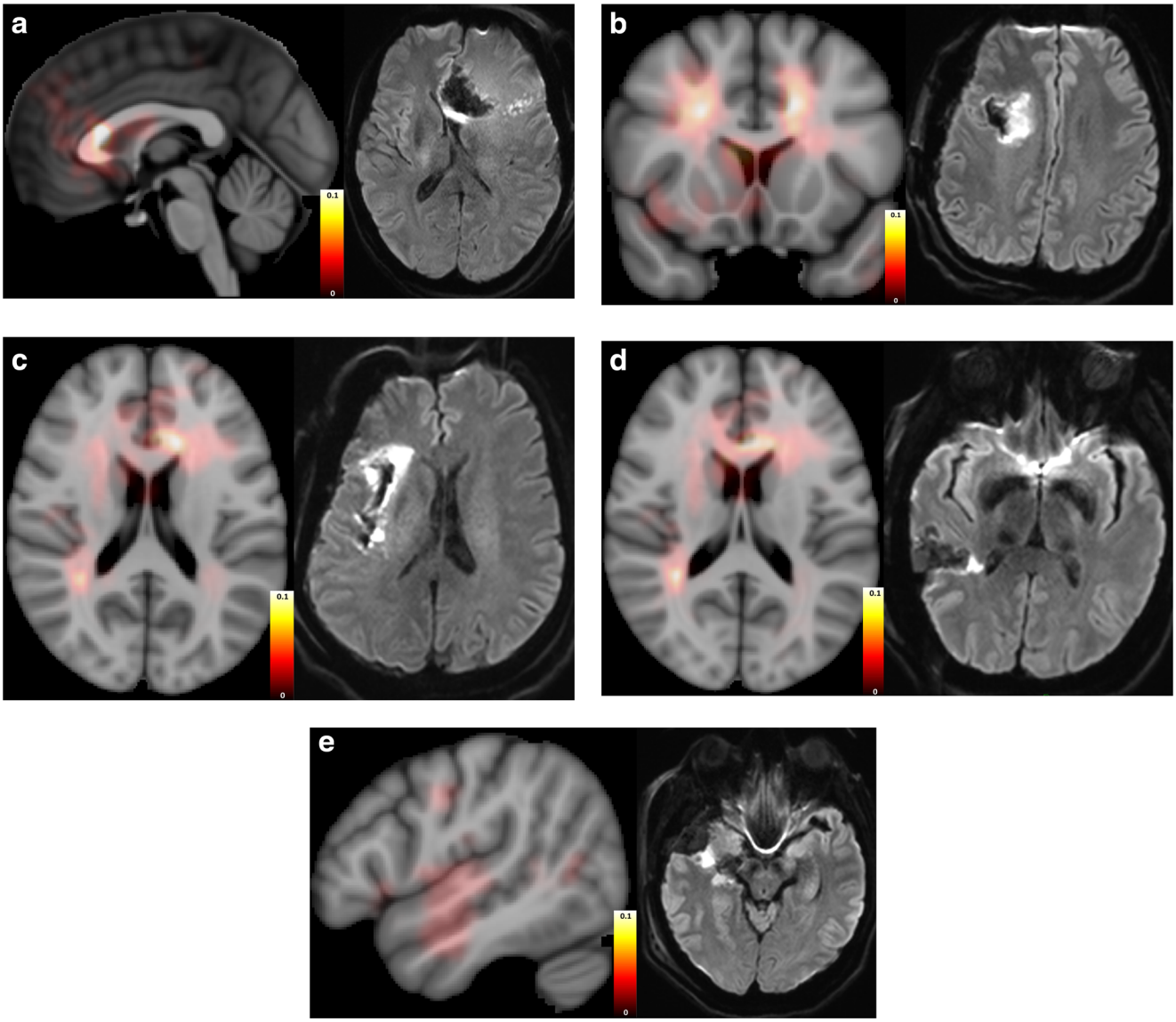

Fig. 1 Spatial distribution of strokes. Left: average map. The color intensity gives the probability. A maximum of 0.09 was noted, corresponding to a net number of 5 cases. Right: typical case. **a** Hotspot in the corpus callosum. **b** Prefrontal hotspot. **c** External capsule hotspot. **d** Parietal hotspot. **e** Temporal hotspot.

fluency score. However, the decrease in absolute scores of semantic fluency was very mild and likely to be without any actual impact on patients' quality of life (difference of only 0.3 standard deviations between the two groups).

Factors of small deep stroke occurrence and considerations for avoidance

We could not identify in the present study any risk factors of stroke occurrence. Previous studies also failed to identify factors that correlated with the occurrence of DWI hypersignal: age, sex, tumor grade and location, histopathological subtypes, and surgical techniques were not associated with a higher risk of strokes [16]. However, several authors reported the importance of subpial resection and bipolar coagulation avoidance for optimal preservation of vessels [6, 24]. Despite the senior author complied with these rules (except in most early cases), their application did not warrant to obtain postoperative MRI free of DWI hypersignal spots. Based on our current knowledge of microvascular anatomy of cerebral cortex and white matter arteries [25–27], we now propose to analyze the anatomy of the disrupted vessels in the five stroke hotspots highlighted by the present study.

The anterior temporal pattern of strokes (see for example Fig. 5 and also Fig. 3 in Ulmer & al. [15]) might be preventable. When removing the anterior temporal lobe, it seems natural to coagulate the sulcus separating the superior and middle temporal gyrus at the posterior limit of the resection, or to coagulate the surface of the anterior superior temporal gyrus. By this way, temporal M4 branches that run in an antero-posterior direction

over the superior temporal gyrus towards the superior temporal sulcus, are coagulated, depriving downstream temporal areas from blood supply (see Fig. 2). This illustrates that corticectomies of superior temporal gyrus and middle temporal gyrus should be handled separately, preserving the entire sulcus by subpial dissection on both sides and preserving any artery passing through the surface of the gyrus. After removal on both sides, the sulcus becomes flexible and can be easily pushed away from the operative corridor.

The prefrontal pattern is much more challenging. Indeed, when the tumor arches around the fundus of a sulcus, tumor removal will inevitably destroy small distal arteries that are leaving the depth of the sulcus to run radially towards the ventricle (see Fig. 3). In that situation, even subpial resection on both sides of the sulcus will not enable to preserve perforators leaving the depth of the sulcus. The only solution would be to keep a small sheet of white matter in the continuation of the plane of the sulcus, with the hope to preserve the radial perforators within it.

In insular tumors, deep strokes can arise by two distinct mechanisms (lenticulo-striate arteries or perforators arising from the M2-M3 junction at the level of the superior insular sulcus). A good way to avoid LSA injury is to stop before reaching this level that is within the white matter of the external capsule [28]. To this end, functional mapping is very helpful, as stimulation of IFOF generates language disturbances on the dominant side (perseveration, semantic paraphasia, anomia, asemantism) and semantic troubles on the right non-dominant side (asemantism). The other danger is the long perforators arising from the junction between M2 and M3 branches at the level of the superior insular sulcus. Subpial resection performed under the insular surface (through the opercular approach) is not always protective, depending on the exact level at which the perforators leave the M2 or M3 branch [29]. If it is before reaching the superior insular sulcus, as previously suggested, then the perforator is necessarily taken out during the subpial resection. This calls for new tools for better preoperative identification of micro-vascular architecture [30–32]. The very same issue will be observed for opercular tumors. Here, the subpial removal is performed « on the other side » of the insular surface. Hence, if the perforator is leaving the M3 branch after the turning back of M3, there would be a risk of damage. Moreover, some authors suggested that the ischemia in the corona radiata can be observed as a consequence of long medullary arteries terminating the M4 branches. The subpial dissection that is started around the M4 segment on the lateral surface of the operculum does not fully prevent damage to these very thin long medullary arteries, which are originating from the terminal end of the M4 segment, through distal branches leaving the depth of the precentral and central sulcus towards the underlying white matter. However, in the present series, no ischemia was observed in opercular tumors (3 cases), except for 1 case, where perforators of M3 were voluntarily coagulated and cut (as they were invaded by the glioblastoma), after verifying that transitory clipping of the vessels did not result in any speech disturbance.

For the callosal and stratum sagittal hotspots, we currently lack knowledge about the microvascular anatomy of these regions, precluding any discussion about avoidance.

Last but not the least, it can be hypothesized that if surgery-induced damage to microvasculature was the sole factor of stroke occurrence, we would expect a 100% occurrence rate. The 50% rate observed in this and other studies suggest the

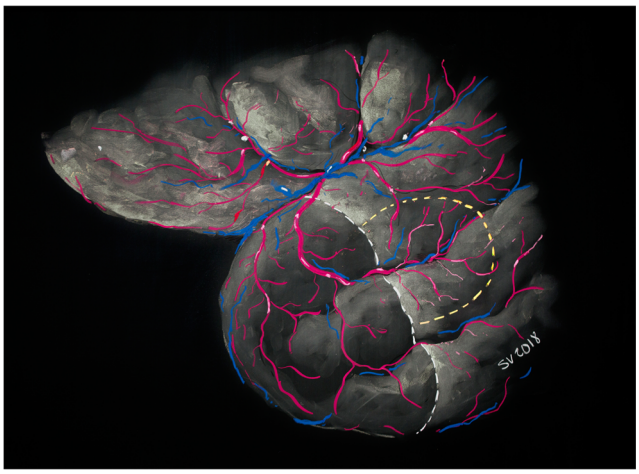

Fig. 2 Illustration of downstream strokes following anterior temporal lobectomy. Such stroke could be avoided by preserving M4 branches all along their trajectory, from their exit at the level of the lateral fissure up to the superior temporal sulcus

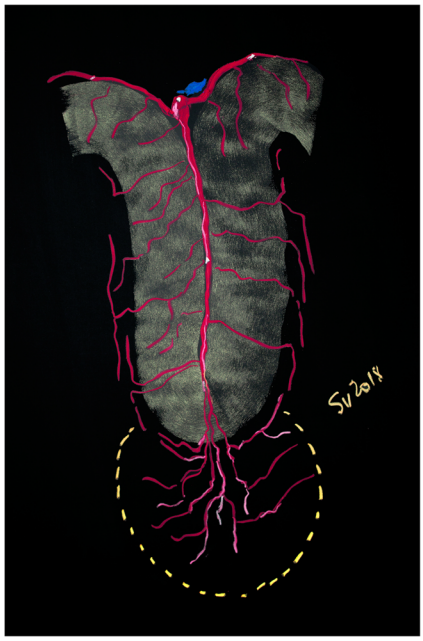

Fig. 3 Illustration of deep strokes in the depth of the superior frontal sulcus. If the tumor is invading the white matter in the depth of the sulcus, perforators are inevitably damaged, potentially causing a small deep stroke in the white matter

existence of another cause. For example, a prolonged period of lowered blood pressure in the course of the surgical resection could compromise the physiological compensation of blood flow (thanks to anastomotic microarteriolar network) in the neighborhood of a damaged perforating artery. Such investigations are underway in our institution.

Conclusion

We found five hotspots of ischemia after glioma surgery. It is confirmed that such small strokes do not result in motor nor speech deficits, but they might have an impact on cognitive functioning. Any slight cognitive deterioration would be even more critical in the context of resecting incidentally discovered low-grade glioma. In such situation, the bar is set very high in terms of functional results. Further studies are thus needed to better delineate the actual cognitive impact of each hotspot of small strokes in a larger population of diffuse low-grade glioma patients.

The importance of preserving any small artery cannot be overemphasized. Still, preservation of deep perforators remains a real challenge, with well-known risk of noisy neurological deficit in the insulo-opercular region, but with a potential risk of cognitive deficits in prefrontal, temporal and parietal regions. Patients should be informed about these risks during the preoperative counseling interview.

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Compliance with ethical standards

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

Informed consent All patients signed a written informed consent for retrospective analysis of their clinical and radiological data, although due to the retrospective nature of the study, formal consent is not required.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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