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CLINICAL STUDY

Feasibility of fluorescence-guided resection of recurrent gliomas using five-aminolevulinic acid: retrospective analysis of surgical and neurological outcome in 58 patients

Anne-Katrin Hickmann · Minou Nadji-Ohl · Nikolai J. Hopf

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Abstract Five-aminolevulinic-acid (5-ALA) is known for its benefits in surgery of primary gliomas, but has only been cautiously used in recurrent gliomas dreading over-resection, insufficient or false-positive fluorescence in adjuvantly treated tumors. We evaluated intraoperative fluorescence based on tumor pathology, pretreatment as well as surgical and neurological outcome in patients with recurrent gliomas. Patients who underwent fluorescence-guided surgery for recurrent gliomas between 6/2010 and 2/2014 at our institution were retrospectively selected. Degree of surgical resection, neurological status, pathology results, intraoperative fluorescence and follow up status were analyzed. Patients who underwent repeat surgery without 5-ALA were selected as controls. 58 patients with high grade gliomas (°III and °IV) were included. 10 of 63 tumors (15.9 %) failed to fluoresce intraoperatively of which nine (90 %) had been adjuvantly treated prior to recurrence, as were 46 of the 53 fluorescing tumors (86.8 %). Non-fluorescing tumors were IDH mutated significantly more often ($p = 0.005$). 30 tumors (47.6 %) were located eloquently. 51 (80.9 %) patients showed no new neurologic deficits postoperatively. 13 patients (20.6 %) showed no signs of recurrence at their latest follow up. Eight patients were lost to follow up. Overall survival was significantly longer in the 5-ALA group ($p = 0.025$). Fluorescence-guided surgery in recurrent gliomas is safe and allows for a good surgical and neurological outcome in a difficult surgical environment, especially when used in combination with neuronavigation and intraoperative ultrasound to prevent over-resection. Adjuvant therapy did not significantly influence fluorescing properties.

Keywords Five-aminolevulinic acid · Intraoperative fluorescence · Recurrent glioma · Repeat-surgery · Outcome · Controlled · Retrospective

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Introduction

Recurrence is a matter of time when treating gliomas [1–4]. Reoperations may be beneficial for the course of the disease [3, 5–8], despite the increased risk of neurological deterioration [8]. During repeat surgeries, surgeons often have to face a different, sometimes more challenging environment due to scar tissue from previous surgeries and adjuvant treatment, distorted anatomical landmarks and even more diffuse tumor borders.

However, the goal of any surgery should be to remove the tumor completely while ensuring neurological integrity of the patient as this is known to improve survival and quality of life [2, 5, 8–13].

To visualize tumor borders intraoperative imaging such as ultrasound, intraoperative magnetic resonance imaging (iMRI) or computed tomography (iCT) can be of help [14–17]. Results of navigated transcranial magnetic stimulation (nTMS) can be incorporated into navigational systems [18–21] and electrophysiological monitoring should be used during the course of resection [22, 23] to maintain neurological integrity.

Furthermore five-aminolaevulinic acid (5-ALA) is known to aid in visualization of the tumor and its infiltration zone [24–27]. Even though its advantages for primary surgery have been studied and reported extensively, not much is known about previously treated tumors [28–30]. We therefore evaluated our patient population who underwent repeat glioma surgery using 5-ALA to investigate the safety and feasibility of 5-ALA-guided repeat surgery.

Methods

We retrospectively reviewed our surgical database and selected all patients who underwent repeat glioma sugery using 5-ALA between June 2010 and February 2014 at our institution. Their files were reviewed for pre- and postoperative neurological deficits, 5-ALA side effects, overall survival (OS), progression free survival (PFS), and histopathological grading. Images where analyzed for pre- and postoperative tumor volume (Volumetry, Navigation Software, Brainlab, Feldkirchen, Germany), and contrast enhancement. Surgical reports were reviewed for intraoperative fluorescence properties and extend of resection (EOR) as well as reasons for subtotal resection. Complete resection (CR) was defined according to the RANO-criteria [31]. Accordingly contrast enhancing tissue in enhancing/hyperintense tissue in non-enhancing tumors was measured with individually drawn regions of interest (ROIs) on pre- and postoperative images. The difference was defined as residual tumor. To evaluate the effect of EOR on PFS and OS a cutoff of 98 % was chosen [10]. Patients who underwent repeat glioma surgery without 5-ALA between January 2006 and February 2014 were identified as control group from the hospital's database. Their files were reviewed for OS, PFS and histopathological grading.

Statistical analysis [descriptive, Mann-Whitney-*U*-Test, Kruskall-Wallis-Test, Kaplan–Meier-Analysis (Log Rank, Breslow)] was performed using SPSS 20.0 (IBM Corp, worldwide). $p < 0.05$ was considered statistically significant.

This analysis was conducted in accordance with national law, institutional ethical standards and the Helsinki Declaration.

Results

Patients

63 repeat surgeries with 5-ALAwere performed in 58 patients for recurrent gliomas between June 2010 and February 2014 (5-ALA group). 65 patients were selected for the control group (repeat surgery without 5-ALA, WHO °III and °IV). Six patients survived more than 5 years after the index surgery (n = 4 WHO °III, n = 2 WHO °IV). Patient and tumor characteristics are listed in Table 1.

Intraoperative fluorescence

Positive fluorescence was seen in 53 of the 63 surgeries (84.1 %). Fluorescent tumors were significantly more often contrast-enhancing on MRI and more often Grad IV tumors (Table 2). No significant differences in fluorescent properties were seen when comparing tumors, which were adjuvantly treated after primary surgery versus no adjuvant treatment prior to recurrence and in tumors with secondary malignancy versus primary malignant tumors. Tumor characteristics of non-fluorescent tumors are listed in Table 3. All tumors with positive contrast enhancement on preoperative MRI and negative intraoperative fluorescence showed oligodendroglial differentiation (n = 5)/progressed from a tumor with oligodendroglial differentiation (n = 1). All, but one non-contrast enhancing, non-fluorescing tumors were oligodendriglial tumors (n = 3) (Table 3).

No significant difference in age and gender distribution was seen.

Surgical outcome

Resection of more than 98 % of tumor volume [10] was achieved in 36 surgeries (57.1 %). Tumors infiltrating eloquent areas (basal ganglia, corpus callosum, primary somatosensory cortex, speech-relevant areas) were intended for partial resection only. The overall mean EOR was 91.1 % (range 17.5–100 %). Mean tumor volume preoperatively was 21.8 cm^3 (range 0.31–112.4 cm^3). Postoperatively, tumor volume ranged from 0 to 56.9 cm^3 (mean 3.4 cm^3).

In cases with fluorescent tumors surgeons tended to achieve an EOR ≥98 % more often (58.5 vs. 50 %, p = 0.622) with smaller tumor remnants (Table 4). EOR ≥98 % was associated with a trend towards longer PFS and significantly increased OS (mean PFS 11.3 vs. 9.8 months, p = 0.363; mean OS 20.3 vs. 13.7 months, p = 0.015) as depicted in Fig. 1a, b (Breslow Test: p = 0.042). In a subgroup analysis based on tumor grading EOR only significantly improved OS in °IV tumors (p = 0.019).

In the group with EOR <98 %, tumors tended to be eloquently located more often (59.3 vs. 38.9 %, p = 0.112).

CR of all fluorescent tissue was achieved in 34 surgeries (64.1 %) and associated with a significantly greater mean EOR (96.8 vs. 85.7 %, p = 0.014, range 70.6–100 vs. 17.5–100 %). However, preoperative tumor volume did also differ significantly as depicted in Table 4. Resection

Table 1 Patient and tumor characteristics

	5-ALA		w/o 5-ALA	
	n/mean	%/range	n/mean	%/range
Demographics				
Patients total	58		63	
Surgeries total	63		65	
Male	36	62.1	44	69.8
Female	22	37.9	19	30.2
Age (years)	50.3	26.3–75.3	47.8	26.3–75.3
Follow up (FU)				
FU period (months)	16.2	0.7–50.7	22.1	0.6–93.4
LFU	8	12.7	8	12.3
LFU after recurrence	7	11.1	7	10.9
Death w/o FU-MRI	3	4.8	4	6.2
No recurrence yet	13	22.4	2	3.1
Survival >5 years	0	0	6	9.2

Imaging (5-ALA)	n/mean	%/range
Contrast-enhancement	55	84.1
Tumor volume preop (cm^3)	21.8	0.3–112.4
Tumor volume postop (cm^3)	3.6	0–56.9

Tumor localisation (5-ALA)	n	%
Frontal	25	39.7
Temporal	16	25.4
Parietal	13	20.6
Central	6	9.5
Occipital	3	4.8
Eloquent	30	47.6

Histopathology	5-ALA		w/o 5-ALA	
	n	%	n	%
WHO °III	38	60.3	21	32.3
WHO °IV	25	39.7	44	67.7
Glioblastoma multiforme (°IV)	38	60.3		
Oligoastrocytoma (°III)	9	14.3		
Anaplastic Oligoastrocytoma	8	12.7		
anapl. Oligodendroglioma (°III)	4	6.3		
anapl. Astrocytoma (°III)	12	19.0		
Secondary malignancy	20	31.7		

Adjuvant treatment (5-ALA)	n	%		n	%
Adjuvant treatment before recurrence	55	87.3			
Stupp	15	23.8	Cleopatra	1	1.6
Stupp+[a]	11	17.5	Centric	2	3.2
Radiation + chemotherapy[b]	5	7.9	APG-101	1	1.6
Temozolomide (TMZ) alone	8	12.7			
PCV + TMZ	1	1.6			
Radiation alone	6	9.5			
39 Gy	1	1.6			
54 Gy	5	7.9			
Multiple[c]	5	7.9			

w/o Without, *FU* follow up, *LFU* lost to follow up, *MRI* magnetic resonance imaging

[a] Stupp-protocol with prolonged TMZ and/or intensified TMZ (one week on/one week off)

[b] Radiation and chemotherapy other than TMZ

[c] Multiple adjuvant treatment protocols (Radiation + PCV/ACNU/BCNU/TMZ) in various combinations

Table 2 Fluorescing and non-fluorescing tumors: characteristics based on intraoperative fluorescence

	Fluorescent tumors		Non fluorescent tumors		p value
	n	%	n	%	
Contrast-enhancement on MRI	49	92.5	6	60	0.005
No contrast-enhancement on MRI	4	7.5	4	40	
WHO °III	17	31.1	8	80	0.005
WHO °IV	36	67.9	2	20	
IDH mutation[a]	24	51.1	10	100	0.005
IDH wild-type[a]	23	48.9	0	0	

[a] Missing: n = 6

tended to be more complete in non-eloquently located tumors (eloquent vs. non-eloquent CR: 46.7 vs. 63.6 %, p = 0.179; mean EOR 89.4 vs. 94.2 %, p = 0.143).

CR of all fluorescent tissue was associated with a longer PFS (mean 11.5 vs. 7.8 months, p = 0.529) and OS (mean 19.9 vs. 13.5 months, p = 0.123). In the Kaplan–Meier-Analysis a significant increase in OS was seen for patients with CR of all fluorescent tissue (Log Rank: p = 0.038) (Fig. 1c, d). No significant difference in age and gender distribution was seen.

Neurological outcome

Thirty tumors (47.6 %) were located eloquently. All of these patients were operated on using continuous electrophysiological monitoring (MEP, SSEP), direct cortical stimulation (DCS) and neuronavigation with integrated functional data from preoperative nTMS. Three patients showed neurological improvement after surgery (4.8 %). New focal neurological deficits (nFND) were observed in 12 patients postoperatively (19.1 %). In 8 patients (15.1 %)

Table 3 Fluorescing and non-fluorescing tumors: characteristics of non-fluorescent tumors

Patient	Sex	Age	Primary diagnosis	Repeat surgery	CE on MRI	Histopathology (primary)	Histopathology (recurrence)	Adjuvant treatment prior to repeat surgery w/5-ALA
P. H.	M	53	1994	02/2011	Yes	Oligoastrocytoma °III	Glioblastoma multiforme °IV	2002 Radiation (54 Gy) 2009 Temozolomide 5/28 (6 cycles) 2010 Temozolomide 5/28 (7 cycles) 2010 ACNU (2 cycles)
G. K.	M	31	2007	10/2011	Yes	Oligodendroglioma °III	Anaplastic oligodendroglioma °III	2007 PCV (4 cycles) 2010 Temozolomide 5/28 (12 cycles)
S. G.	M	29	2010	01/2012	No	Astrocytoma °III	Anaplastic astrocytoma °III	2010 Temozolomide 5/28 (10 cycles)
A. M.	M	49	2002	06/2012	No	Oligoastrocytoma °II	Anaplastic oligoastrocytoma °III	2002 Radiation (54 Gy)
S. D.	F	32	2010	11/2012	No	Astrocytoma °III	Anaplastic astocytoma °III	2010 Stupp protocol
R. D.	F	60	1999	06/2013	Yes	Astrocytoma °II	Glioblastoma multiforme °IV with oligodendroglial differentiation	2000 Radiation (54 Gy) 2009 Temozolomide 5/28 (12 cycles) 2011 Stupp Protocol 2012 Temozolomide 5/28 (17 cycles)
G. K.	M	62	2012	06/2013	Yes	Oligodendroglioma °III	Anaplastic oligodendroglioma °III	2012 Temozolomide 5/28 (7 cylcles)
G. K.	M	33	2007	06/2013	Yes	Oligodendroglioma °III	Anaplastic oligodendroglioma °III	2007 PCV (4 Cycles) 2010 Temozolomide 5/28 (12 cycles) 2011 Radiation (60 Gy) 2012 Temozolomide 5/28 (12 cycles, reduced dose)
C. Z.	M	42	2009	10/2013	No	Oligoastrocytoma °II	Anaplastic oligodendroglioma °III	No
P. C.	M	27	2011	02/2014	Yes	Oligoastrocytoma °III	Anaplastic oligoastrocytoma °III	2011 Temozolomide 5/28 (6 cycles)

Primary diagnosis ⇒ year of initial diagnosis, repeat surgery ⇒ month/year of index surgery

CE Contrast enhancement, *MRI* magnetic resonance imaging

Table 4 Surgical outcome

	Positive fluorescence	Negative fluorescence	p value
EOR ≥98 % [n/%]	31/58.8	5/50	0.622
Mean EOR [%] (range)	92.8 (17.51–100)	87.1 (32.19–100)	0.42
Mean tumor volume preop [cm^3] (range)	22.0 (0.31–112.43)	20.7 (3.56–81.03)	0.88
Mean tumor volume postop [cm^3] (range)	2.9 (0–56.91)	6.4 (1.2–25.8)	0.47
	CR of fluorescent tissue	ICR of fluorescent tissue	p value
Mean EOR [%] (range)	96.8 (70.59–100)	85.7 (17.51–100)	0.014
Mean tumor volume preop [cm^3] (range)	16.4 (0.31–58.81)	32.2 (0.86–112.43)	0.012
Mean tumor volume postop [cm^3] (range)	1.1 (0–10.37)	6.11 (0–56.91)	0.016

EOR Extend of resection, *CR* complete resection, *ICR* incomplete resection

the deficits improved over time (n = 5 improvement within 7 days, 7.9 %), which results in only 4 patients (6.3 %) with permanent nFND. In all cases with nFND, the tumor did fluoresce intraoperatively compared to 80.4 % fluorescing tumors in patients with no nFND (p = 0.097). There was no significant difference in nFND based on

fluorescence ($p = 0.097$). Patients with °IV-tumors tended to experience nFND more often (83.3 vs. 54.9 %, $p = 0.072$). With greater EOR nFND tended to occur more often (CR vs. incomplete resection: 20 vs. 17.9 %, $p = 0.831$). Patients with postoperative nFND tended to have lower PFS (mean 4.6 vs. 12.1 months, $p = 0.098$) and OS (mean 11.1 vs. 19 months, $p = 0.064$) as depicted in Fig. 1e, f. No significant difference in age and gender distribution was seen.

Influence of 5-ALA on survival

When excluding long term survivors (>5 years) to adjust for follow up, patients in the 5-ALA group had a similar mean PFS (10.7 vs. 10.6 months, $p = 0.4$) with a trend towards a longer OS (mean 17.6 vs. 14.6 months, $p = 0.26$). The Kaplan–Meier-Analysis (Log Rank) showed a significant influence of the use of 5-ALA during repeat surgery on OS ($p = 0.025$), while PFS was not significantly influenced ($p = 0.267$) (Fig. 1g, h).

Discussion

The value of 5-ALA in glioma surgery is well known and has been studied extensively [25–27, 32]. However, only little is known about its role in recurrent and adjuvantly treated gliomas [28–30].

This retrospective analysis of patients harboring recurrent gliomas showed, that 5-ALA is equally valuable in recurrent gliomas. In concordance with Tykocki et al. and Nabavi et al. we did not observe any negative influence of adjuvant therapies on the capability of 5-ALA in detecting tumor tissue [28, 30]. Tumor tissue could be distinguished well from scar tissue and surrounding edema under blue light in general according to the surgeons' impression, even though in 7 cases false positive fluorescence was observed when comparing intraoperative impression and postoperative MRI. Due to the retrospective character of this analysis and the fact that there were no separate histological samples available from the margins of fluorescing area, determination of the actual sensitivity and specificity in this series was not possible. However, the intraoperative impression was, that in several cases distinguishing tumor from surrounding scar tissue would not have been possible using white light only. In the majority of fluorescent tumors ($n = 30$, 56.6 %) further resection was performed after inspection under white light did not show residual tumor (Fig. 2). Additionally, since the surgeons switched from white to blue light intermittently during all surgeries, positive fluorescence could have assisted in achieving greater EOR throughout. Despite the positive intraoperative impression it has to be noted that there are limitations as with all adjuncts. Even though only a minority showed no residual fluorescence at the end of white light resection, in 57 % of them tumor was left behind (Fig. 2).

Positive fluorescence improved the extent of resection (mean 92.8 vs. 87.1 %) with a significantly greater EOR in cases with CR of all fluorescent tissue compared to patients with residual fluorescent tissue (mean EOR 96.8 vs. 85.7 %, $p = 0.014$). Resection of all fluorescent tissue was also associated with a trend towards longer PFS and OS in this population (mean PFS 11.46 vs. 7.8 months, $p = 0.529$; mean OS 19.87 vs. 13.5 months, $p = 0.123$), whereby the difference in OS reached statistical significance in the survival analysis ($p = 0.038$) (Fig. 1d).

In accordance with previous studies [10, 12, 33] OS was significantly improved with greater EOR (EOR ≥98 vs. EOR <98 %: 20.3 vs. 14.2 months, $p = 0.015$).

Overall median OS after index surgery (11.5 months) in this cohort of patients was better than that reported by other authors performing repeat surgeries [4–7], which might be due to the effect of 5-ALA on the EOR as well as improved multimodal adjuvant therapies. Furthermore when comparing patients who underwent repeat surgery with 5-ALA ($n = 63$) to historical controls ($n = 65$) at our institution a significant improvement of OS could be seen ($p = 0.025$), underlining the possible positive effect of 5-ALA on OS. But one has to keep in mind that options for adjuvant treatment have also changed over the past decade, which might improve OS as well.

Tumors with positive intraoperative fluorescence were significantly more often contrast-enhancing on preoperative MRI ($p = 0.005$) and more often °IV-tumors ($p = 0.005$). But preoperative contrast enhancement and tumor grade is no independent predictor for intraoperative fluorescence. Five contrast-enhancing tumors (50 % of all non fluorescent tumors) did not show any intraoperative fluorescence, as did two glioblastomas. The only similarity amongst all contrast-enhancing, non-fluorescing tumors was their oligodendroglial origin/differentiation (Table 3), which has not been described in that way before, even though others have found non-fluorescing tumor tissue in highly malignant contrast enhancing tumors [34] (necrosis, secondary malignancy). Additionally all non-enhancing tumors showed IDH-1- ($n = 8$) or IDH-2-mutations ($n = 2$), which might be associated with a different pattern of endothelial proliferation interfering with 5-ALA passing the blood–brain-barrier as suggested by Stummer et al. [34]. Further evidence of malignant cells behaving differently under blue light after exposure to 5-ALA was also given by Duffner et al. who were able to show different fluorescence intensity in different glioma stem cell lines in vitro [35].

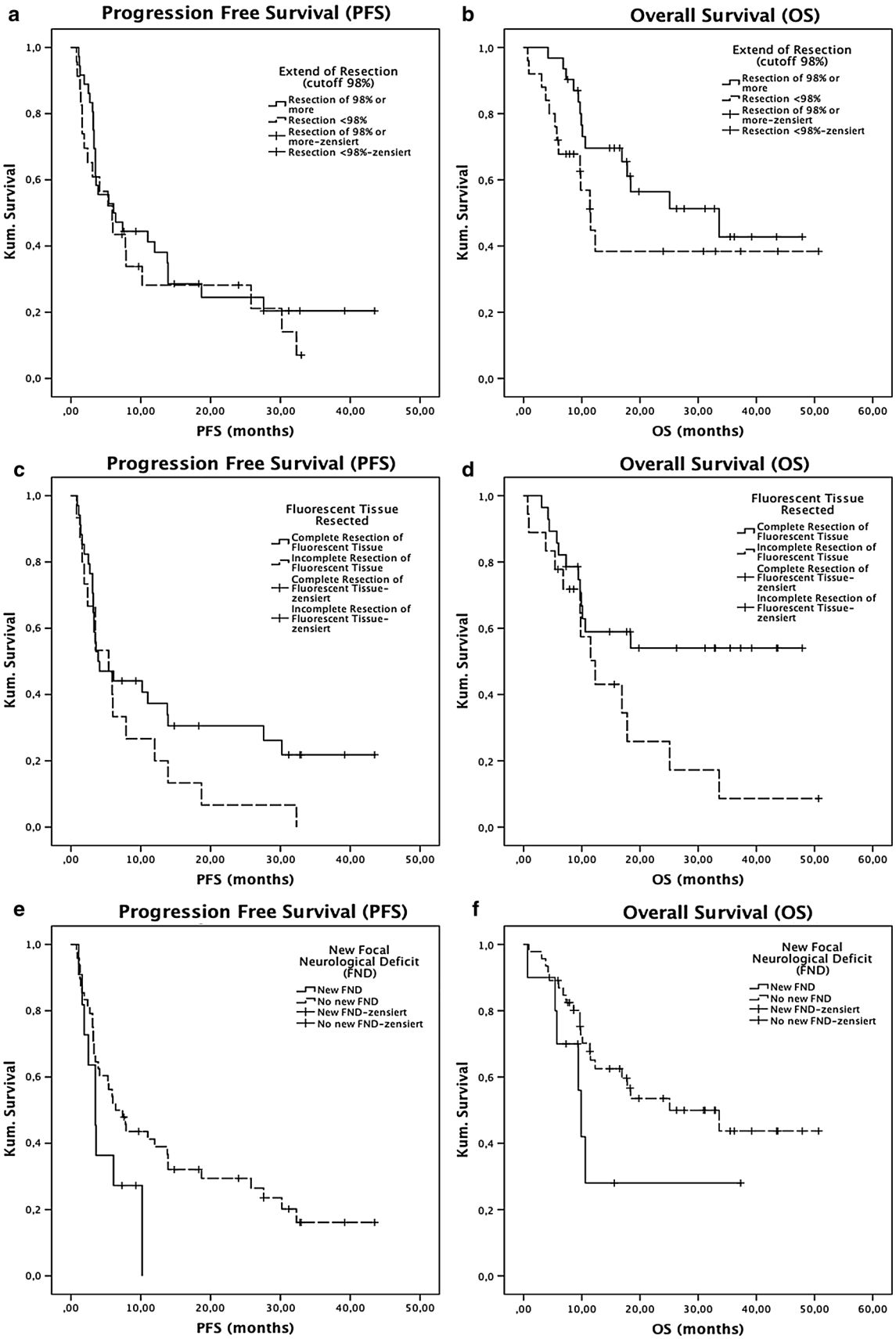
Interestingly seven tumors with residual intraoperative fluorescence were completely resected based on

postoperative MRI [31] (n = 1 residual fluorescence in scar tissue, n = 1 residual fluorescence toward edematous tissue beyond contrast-enhancement on navigation, n = 2 residual fluorescence towards basal ganglia/CST, n = 3 residual ventricular wall fluorescence). Three of these patients had a longer PFS compared to the mean of the subgroup (patients with residual fluorescence) (mean 7.8 months, patients: 12, 13.9, 18.7 months) and four had a longer OS (mean 13.5 months, patients: 28.3, 25.1, 20.3, 16.9 months). These findings are in contrast to the assumption of possible early recurrence due to infiltrating tumor cells causing residual fluorescence undetected by gadolinium. However, Utsuki et al. and Panciani et al. were able to demonstrate that edema and scar tissue might show weak false positive fluorescence due to inflammation after radiation and leakage of 5-ALA [28, 36, 37]. Furthermore, auto-fluorescence of normal tissue may cause false positive fluorescence in rare cases [37]. The patient in our series survived 16.9 months after repeat surgery supporting the theory of false positive fluorescence. On the other hand adjuvant treatment (APG-101) [38, 39] may have prolonged survival. Without separate histological samples taken from the residual fluorescing area it remains unclear whether the cause was scar tissue or residual cells. Of three patients with residual fluorescence in the ventricular wall, 2 experienced a long PFS and OS (#1: 12, 28; #2: 18.7, 25.1 months) whereas the third patient showed early recurrence (1.6 months) and died quickly (5.9 months). This supports the theory of Tejada et al. who found residual ventricular wall fluorescence not to be an independent predictor for poor outcome, but periventricular tumor location itself [40]. One possible reason for residual ventricular wall fluorescence not being a predictor for fast progression or recurrence may be the presence of neuronal precursor cells in the subventricular zone, which show antitumoral activity [41] and may thus inhibit progression of possible residual tumor cell within the ventricular wall. The patient with rapid progression showed leptomeningeal tumor infiltration, which may have caused early recurrence and fast progression, rather than residual cells in the ventricular wall. Patients with residual fluorescence in eloquent areas (basal ganglia/CST) and within edematous appearing tissue showed early recurrence probably due to residual tumor cells undetected by postoperative MRI. Even though fluorescence was weak, it supports the theory of Utsuki et al. who recommend resection of all weakly fluorescing areas in recurrent glioma [36] and Stummer et al. who showed a PPV of 95 % of weakly fluorescing tissue [42].

Intraoperative resection of all fluorescent tissue was found to be associated with a significantly greater EOR (mean 96.8 %). However, it did not always correspond with CR on MRI (range 70.6–100 %). This is not plausible due to the biological mechanism of 5-ALA, the diffuse infiltrating tumor architecture and is in contrast to the findings by Coburger et al. [43]. It may be caused by hidden fluorescent tissue covered by blood or non-infiltrating, overhanging margins after partial resection and collapse of the surrounding tissue [34, 44, 45]. Furthermore, inadequate illumination with blue light of the resection cavity due to a small corticotomy as routinely performed at our institution may have led to false negative fluorescence [45]. Another reason may be photo bleaching, although not of great relevance in brightly fluorescing tumor tissue [45, 46], it may have been responsible for fading of fluorescence particularly in weakly-fluorescing areas (infiltration zones) as described in early publications by Stummer et al. [34] and Tonn et al. [45]. Since the extent of resected fluorescent tissue was based on the surgeon's impression at the end of the surgery, there may have been a bias concerning CR. When reviewing the surgical reports it was also noted that the surgeons often reported more inhomogeneous fluorescence in recurrent and adjuvantly treated tumors than in primary gliomas [28], which may have led to missing of weakly fluorescing tissue.

In 6.3 % of all cases (n = 4) a permanent nFND was noted postoperatively with 47.4 % eloquently located tumors. The overall rate of nFND was 19.1 % (n = 12), which is comparable to the neurological complication rates reported by others (8.2–18 %) [8, 47] after repeat glioma surgery. In accordance with others we believe from our results that the advantages of operating with 5-ALA can be used in eloquently located tumors as long as a good functional outcome is a major goal of surgery and attempted by using continuous intraoperative electrophysiological monitoring [48, 49]. Functional borders should be respected even though residual fluorescent tissue may be left behind (Fig. 2). In accordance with others good neurological outcome is relevant for PFS (mean 12.1 vs. 4.6 months, p = 0.098) and OS (mean 19 vs. 11.1 months, p = 0.064) [8, 11, 12]. Patients with partially resected fluorescent tissue show longer PFS (mean 7.8 vs. 4.6 months) and OS (mean

Fig. 1 Kapplan-Meier-Curves. **a** Progression free survival EOR ≥98 ▶ versus EOR <98 % (Log Rank: p = 0.411, Breslow: p = 0.376), **b** overall survival EOR ≥98 versus EOR <98 % (Log Rank: p = 0.146, Breslow: p = 0.042), **c** progression free survival: complete versus incomplete resection of all fluorescent tissue (Log Rank: p = 0.154, Breslow: p = 0.425), **d** overall survival: complete versus incomplete resection of all fluorescent tissue (Log Rank: p = 0.038, Breslow: p = 0.153), **e** progression free survival: new focal neurological deficit versus no new focal neurological deficit postoperatively, (Log Rank: p = 0.097, Breslow: p = 0.175), **f** overall survival: new focal neurological deficit versus no new focal neurological deficit postoperatively (Log Rank: p = 0.106, Breslow: p = 0.097), **g** progression free survival: surgery with 5-ALA versus surgery w/o 5-ALA (Log Rank: p = 0.154, Breslow: p = 0.425), **h** overall survival: surgery with 5-ALA versus surgery w/o 5-ALA (Log Rank: p = 0.038, Breslow: p = 0.153)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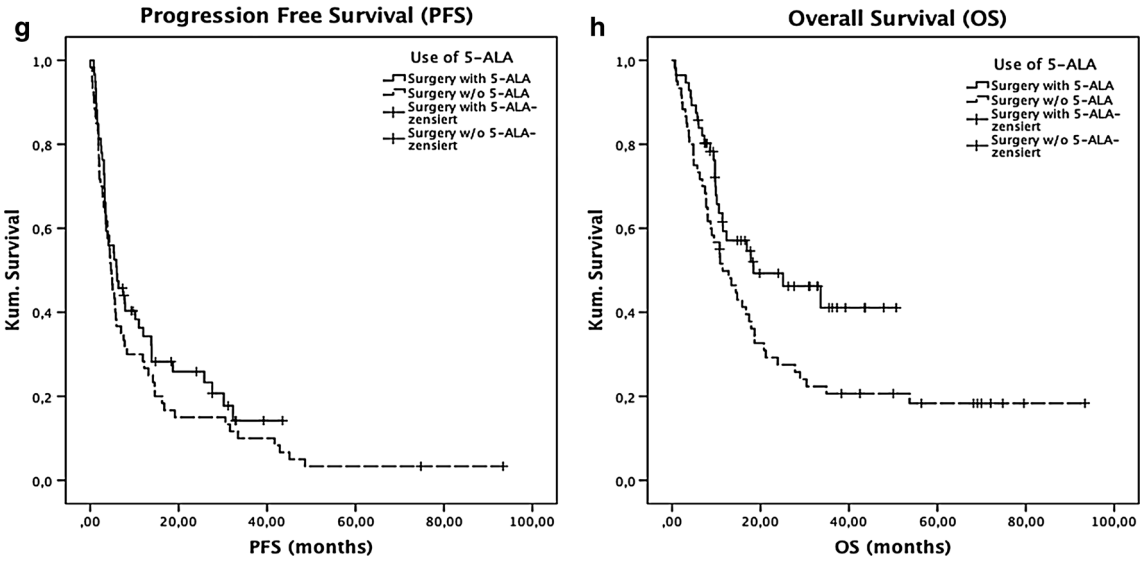

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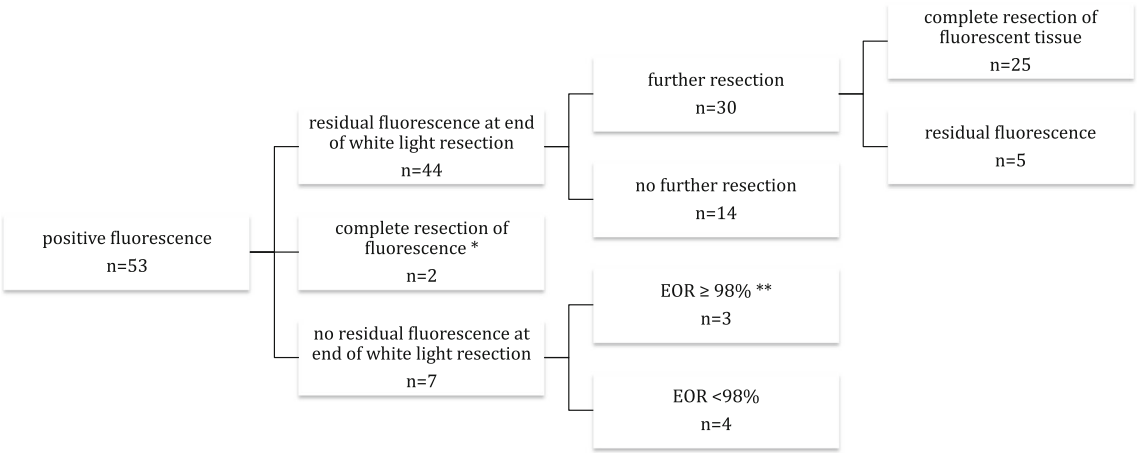

Fig. 2 Influence of Fluorescence on EOR. *Asterisk* No detailed information available comparing white light EOR and EOR based on fluorescence, according to surgeon 5-ALA of help during resection. *Double asterisk* 5-ALA of some help during surgery for more secure distinction of tumor and surrounding tissue

13.5 vs. 11.1 months) than patients with nFND underlining the statement by Hoover et al. that benefits of repeat surgery are lost if neurological complications occur [8]. Furthermore, quality of life is known to be better in patients with good physical and attention performances and should therefore be preserved as long as possible [12, 50]. Patients have to be carefully selected prior to offering repeat surgery based on tumor location and preoperative neurological status. Even partial resection may be beneficial to patients with a large tumor, edema and associated neurological deficits. In this series 3 patients showed neurological improvement due to reduction of tumor volume and decreasing edema.

Even though this is the largest series evaluating the impact of 5-ALA on outcome following surgeries for recurrent gliomas [28–30], the patient sample is probably still too small to allow for most of our results to be of statistical significance. Furthermore, the retrospective character of this study did not ensure standardized description of intraoperative fluorescence and separate histopathological evaluation of areas with inhomogeneous or residual fluorescence.

Conclusion

The use of 5-ALA in repeat glioma surgery is feasible despite adjuvant treatment (radiation, chemotherapy). It aids in achieving a greater EOR, which prolongs PFS and OS. It aids in differentiating tumor and surrounding tissue altered by adjuvant treatment.

It is safe even in eloquently located tumors if neurologic function is continuously monitored and respected during the resection.

Conflict of interest The authors declare no conflict of interest.

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