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General review

Optimization of high-grade glioma resection using 5-ALA fluorescence-guided surgery: A literature review and practical recommendations from the neuro-oncology club of the French society of neurosurgery

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ABSTRACT

Background. – When feasible, the surgical resection is the standard first step of the management of high-grade gliomas. 5-ALA fluorescence-guided-surgery (5-ALA-FGS) was developed to ease the intra-operative delineation of tumor borders in order to maximize the extent of resection.
Methods. – A Medline electronic database search was conducted. English language studies from January 1998 until July 2018 were included, following the PRISMA guidelines.
Results. – 5-ALA can be considered as a specific tool for the detection of tumor remnant but has a weaker sensibility (level 2). 5-ALA-FGS is associated with a significant increase in the rate of gross total resection reaching more than 90% in some series (level 1). Consistently, 5-ALAFGS improves progression-free survival (level 1). However, the gain in overall survival is more debated. The use of 5-ALA-FGS in eloquent areas is feasible but requires simultaneous intraoperative electrophysiologic functional brain monitoring to precisely locate and preserve eloquent areas (level 2). 5-ALA is usable during the first resection of a glioma but also at recurrence (level 2). From a practical standpoint, 5-ALA is orally administered 3 hours before the induction of anesthesia, the recommended dose being 20 mg/kg. Intra-operatively, the procedure is performed as usually with a central debulking and a peripheral dissection during which the surgeon switches from white to blue light. Provided that some precautions are observed, the technique does not expose the patient to particular complications.
Conclusion. – Although 5-ALA-FGS contributes to improve gliomas management, there are still some limitations. Future methods will be developed to improve the sensibility of 5-ALA-FGS.
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1. Introduction

High-grade glioma (HGG) is the most common and aggressive primary brain tumor in adults, with an incidence of more than 3,000 new cases per year in France [1,2]. When feasible, surgical resection is the standard first-line treatment [3]. It has been demonstrated that safe maximal tumor resection improves symptom management, quality of life, PFS (Progression-Free Survival), and OS (Overall Survival) in both DLGG (Diffuse Low-Grade Glioma) and HGG [4–8]. So-called "maximal cytoreduction" allows the most proliferative and therapy-resistant cancer cells to be removed and increases the effectiveness of adjuvant therapies [9–12]. Survival analyses clearly showed that prognosis in HGG directly depends

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on the quality of tumor removal [13–17]. A relatively recent analysis emphasized that increasing the GTR (Gross Total Resection) rate from 78% to 100% of the contrast-enhanced portion of HGG increases OS from 12.5 to 16 months [18]. Benefit in OS becomes significant for Extent Of Resection (EOR) greater than 98% or tumor remnant smaller than 2 cm^3 [2,19]. EOR also positively impacts PFS: 6-month PFS is 32% in case of incomplete resection versus 45% in case of GTR [20]. These results were validated in older patients in a retrospective analysis of 103 patients with a median age of 70.8 years [21]. Stratifying patients as above or below 60 years old showed that the survival advantage of total resection was significant in both subgroups [22]. Consequently, optimizing the quality of tumor resection is a major challenge in neuro-oncology [2,8,23,24].

Unfortunately, accurate intra-operative tumor delineation is challenging because diffuse gliomas, whatever the grade of malignancy, do not have clear boundaries: the tumor resembles the healthy parenchyma and visual assessment of resection quality is not reliable [25,26]. Various tools have therefore been developed to help neurosurgeons improve EOR, including intra-operative image-based technologies such as ultrasonography, MRI-based neuro-navigation or intra-operative MRI (iMRI) [27,28]. However, the main limitation of these techniques is that it is not possible to identify tumor infiltration extending beyond the contrast enhancement area [9,14]. FGS (Fluorescence-Guided Surgery) was first described in 1948 [29], and many fluorophores have since been tested [30]. Despite the promises of this technology, it has not been widely used over recent decades. 5-AminoLevulinic Acid-FGS (5-ALA-FGS), which was first introduced in Germany in 1998 [31], is now considered as a standard of care in many countries, including Switzerland, Australia, Canada, China, Japan [32–37] and, very recently, the USA [38]. In France, market authorization was obtained in 2007, but routine use of 5-ALA-FGS is limited to a small number of neurosurgical centers. In 2017, approximately 60 patients underwent 5-ALA-FGS according to the supplier (Medac, France). This may be explained by the absence of specific national health insurance reimbursement to cover the cost of the drug in French hospitals, and persisting doubts regarding efficacy [39] awaiting results from the French RESECT phase III trial (ClinicalTrials.gov Identifier: NCT01811121).

The present study on behalf of the Neuro-Oncology Club of the French Neurosurgery Society (SFNC) aimed to provide practical recommendations for routine surgical practice, founded on an evidence-based analysis of 5-ALA-FGS efficacy and safety.

2. Principle of tumor fluorescence induced by oral administration of 5-ALA

5-ALA is the endogenous precursor of protoporphyrin IX (PpIX), which is then converted into heme by ferro-chelatase in healthy cells [40]. Biodistribution after oral intake is particularly good in HGG cells, in which the blood–brain barrier, physiologically impermeable to 5-ALA, is broken [40]. Moreover, tumor cells overexpress membrane ABC-transporters that ease 5-ALA cell entry [41,42]. In HGG, tumor cells are able to transform 5-ALA into PpIX but are deficient in ferro-chelatase. Thus, the oral administration of 5-ALA in excess before surgery results in PpIX accumulation [31,41,43–46]. Moreover, exogenous administration bypasses the negative feedback control exerted by heme on the enzyme that synthesizes 5-ALA, enhancing the generation of PpIX [41]. Excitation of PpIX is then obtained by light radiation at a wavelength corresponding to its absorption spectrum (375–440 nm) [31,44,47]. When excited, PpIX returns to its equilibrium state, emitting a red fluorescence detectable between 635 and 704 nm (Fig. 1) [45,48]. To visualize the fluorescence, a combination of excitation and emission filters are positioned in the surgical microscope: a short-pass filter in the excitation light path filters out the PpIX excitation wavelength, which is shorter than the fluorescence emission wavelength; and a long-pass filter in the observer light path blocks out any excited light at wavelengths < 440 nm, allowing only red porphyrin-induced fluorescence to pass. The excitation and emission spectra have a small overlap, so that a small fraction of excited light is also re-emitted from tissue, giving the normal brain a blue color in contrast to the bright red porphyrin fluorescence of glioma [48]. During the procedure, when the surgeon switches from traditional white light (WL) to blue light, the fluorescence becomes easily and rapidly visible without interruption of surgery.

Consequently, 5-ALA acts as a “chemical neuronavigator” [49] and, unlike MRI-based technologies, theoretically highlights all tumor cells. However, the cellular and extracellular environment can also affect cell function and the formation of PpIX. For instance, hypoglycemia, hyperthermia or acidosis increase PpIX accumulation, while hypoxia slightly decreases it [48,50–52]. Moreover, Heme Oxygenase 1 protein expression was identified as a negative regulator of 5-ALA-induced fluorescence in HGG cells, and it was recently demonstrated that the co-expression of EGFR variant III influences the activity of this enzyme, interfering with cell fluorescence [53]. Furthermore, tumor remnants are more likely to be fluorescent in MGMT-methylated than MGMT-unmethylated tumors [54].

3. Literature search and review methodology

Following the PRISMA guidelines [55], we undertook a literature review to identify articles dealing with the clinical efficacy, safety and cost-effectiveness of 5-ALA-FGS.

We included all types of study design (including systematic reviews with meta-analysis) conducted on 5-ALA-FGS (used as stand-alone intervention or in combination with iMRI) in patients of any age undergoing surgery for HGG, low-grade glioma, meningioma, brain metastasis or lymphoma. Studies that assessed several fluorophores (i.e., not solely 5-ALA) and case reports were excluded.

Study endpoints comprised: diagnostic performance of 5-ALA, gross total resection compared with conventional WL surgery, survival, safety (3-month functional outcome in HGG located within or not within eloquent areas), and cost-effectiveness (expressed as incremental cost-effectiveness ratio).

English language studies were retrieved from the Medline database for the period January 1998 to July 2018. The keywords “5-ALA”, “5-Aminolevulinic acid” and “fluorescence-guided surgery” were used in combination with “high-grade glioma”, “glioblastoma”, “low-grade glioma”, “meningioma”, “metastasis” and “lymphoma”. One reviewer (T.P.) screened all titles and abstracts and then assessed potentially relevant full-text articles against eligibility criteria. The same reviewer undertook a quality assessment of each included article using the “Study Quality Assessment Tools” of the National Heart, Lung and Blood Institute, in relation to individual study design. Lastly, the levels of evidence of included studies were determined based on the French Health Authority (HAS) classification [56]. The reference lists of selected articles were also examined.

We summarized study, intervention, population and outcome characteristics narratively and in summary tables by indication type. Finally, we detailed the practical information necessary to integrate this technique in the armamentarium.

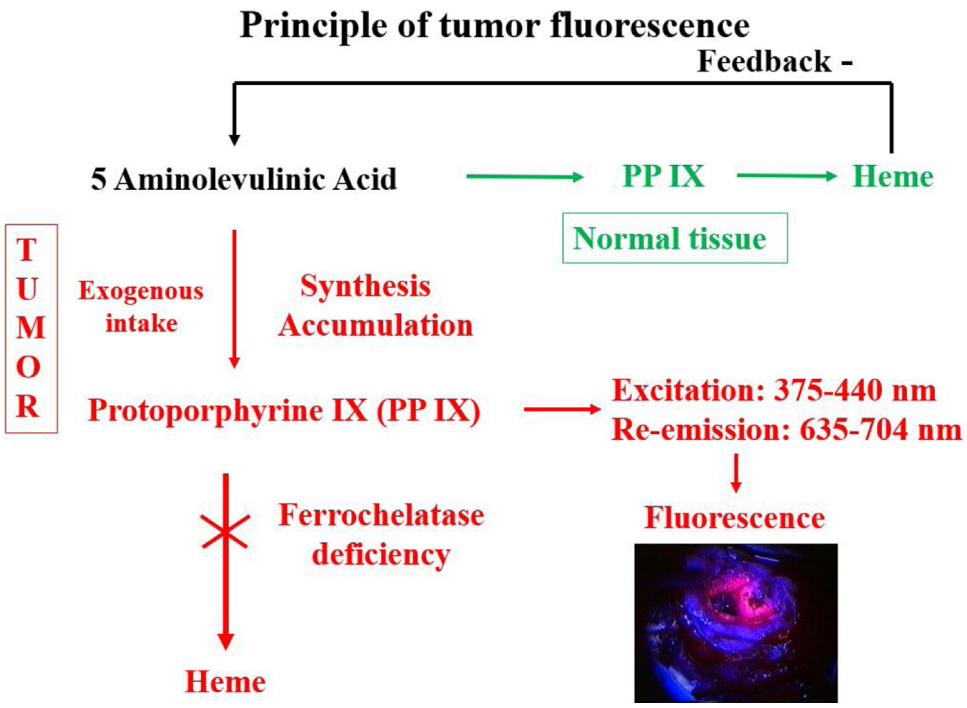

Fig. 1. Principle of tumor fluorescence by 5-ALA accumulation.

4. Evidence-based data for the contribution of 5-ALA to HGG resection

4.1. Diagnostic performance of 5-ALA fluorescence-guided surgery

The assessment of the diagnostic performances of 5-ALA-FGS for HGG requires histological confirmation of the presence or absence of tumor cells in fluorescent and non-fluorescent glioblastoma samples [57].

Three meta-analyses (level 2) published between 2012 and 2015 assessed the performance of 5-ALA-FGS in HGG resection [58–60] (Table 1). The meta-analysis conducted by Zhao et al. [58], based on 5 studies [36,44,61–63], estimated the pooled sensitivity and specificity of 5-ALA-FGS as 0.87 and 0.89, respectively, and pooled positive and negative likelihood ratios as 7.62 and 0.14, respectively. Although sensitivity and specificity vary according to fluorescence intensity [36,64], the pooled results did not take this problem into account. An older meta-analysis [59], partially overlapping with the previous one [58], included a total of 12 studies [36,44,45,61,63–70] and reported pooled sensitivity and specificity of 0.91 and 0.59, respectively, and of 0.77 and 0.92, respectively, in areas of strong fluorescence. The pooled positive and negative predictive values were 0.85 and 0.70, respectively, and 0.92 and 0.79 in areas of strong fluorescence. More recently, Eljamel et al. [60] concluded that the technique was highly sensitive (0.826) and specific (0.888), based on a systematic review that included 8 studies [61,62,65,71–75], yet with the same issue of partial overlap with previous meta-analyses.

Seven prospective studies (level 2), not included in the above meta-analyses, also assessed the performances of 5-ALA-FGS in HGG resection as main or secondary endpoint (Table 1). Six of them dealt with macroscopic detection of 5-ALA [49,54,57,76–78] while the other was based on spectrometric quantification of the fluorescence level [79]. Overall, the ranges of sensitivity and specificity were 0.75–0.86 and 0.43–1, respectively, and ranges of positive and the negative predictive values were 0.86–0.98 and 0.125–0.69, respectively. Thus, 5-ALA-FGS is highly specific in detection of HGG and has an excellent positive predictive value, but its performances in terms of sensitivity and negative predictive value are only moderate, especially in zones with low tumor infiltration [48,76,80]. However, spectroscopic detection of fluorescence can be more sensitive but less specific, depending on the selected threshold [79].

The major sources of false-positives negatively impacting specificity and positive predictive value are rare, mainly comprising reactive astrocytes, especially in recurrent previously irradiated tumors [26,34,62,68,79,81] (see below). Auto-fluorescence is also described in healthy brain parenchyma [26,62,82], especially from the choroid plexi [43] and from ependyma in more than 25% of ventricle walls free of tumor infiltration [83]. Several factors can lead to false negatives that impair sensitivity and negative predictive value. First, in peri-tumoral areas, where tumor cell density is decreased, fluorescence intensity is lower [26,34,36,48,49,62–64,71,84–86] and the technique is less reliable [26,49,57,76,79]. Proliferation index also correlates with fluorescence intensity [66,69,84,86–91]. Moreover, necrotic areas are usually non-fluorescent [26,57,70]. Thus, grade, fluorescence intensity [89,91] and the diagnostic performances of 5-ALA are strongly interdependent, which explains why performances are better in the core of the tumor than in the peri-tumoral area. Secondly, physical factors such as photobleaching, overhanging brain or blood covering can mask fluorescent areas [26,70]. Finally, pharmacokinetic parameters, and particularly 5-ALA intake timing, can interfere with fluorescence quality [26,45,70].

4.2. Improvement of surgical resection

Studies of mixed populations with either HGG or DLGG were excluded. Only one randomized controlled multi-center phase III trial (level 1), conducted by Stummer et al., was identified. Patients with HGG amenable to complete resection were assigned to conventional WL surgery or 5-ALA-FGS. Results based on interim analysis were released in 2006 [32], 5 years before publication of the final results [9]. The proportion of patients in whom CRET (Complete Resection of the contrast-Enhancing Tumor) was achieved was significantly higher with 5-ALA-FGS (interim analysis: 65%

Table 1
Evidence-based data of the performances of 5-ALA-FGS for the detection of HGG.

	Design	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Meta-analysis (Level 2)					
Colditz, 2012 [59]		0.91	0.59	0.85	0.71
Review of 12		(global)	(global)	(global)	(global)
studies		0.77	0.92	0.92	0.79
[36,44,45,61,63–70]		(strong	(strong	(strong	(strong
		fluorescence)	fluorescence)	fluorescence)	fluorescence)
Zhao, 2013 [58]		0.87	0.89	Positive likelihood	Negative likelihood
Review of 5 studies				ratio: 7.62	ratio: 0.14
[36,44,61–63]					
Eljamel, 2015		0.826	0.888		
[60]					
Review of 8 studies					
[61,62,65,71–75]					
Prospective studies of macroscopic fluorescence accuracy (Level 2)					
Gessler 2015 [77]	$n = 32$	0.75	1		
Lau 2015 [76]	$n = 59$	All tumors: 0.82	All tumors: 0.65	All tumors: 0.93	All tumors: 0.38
	211 samples	Grade IV: 0.84	Grade IV: 0.62	Grade IV: 0.92	Grade IV: 0.44
Yamada 2015	$n = 99$	Overall: 0.95	Overall: 0.53	Overall: 0.92	Overall: 0.69
[49]	286 samples	Tumor bulk: 0.99	Tumor bulk: NA	Tumor bulk: 1	Tumor bulk: 0
		Peritumoral brain:	Peritumoral brain:	Peritumoral brain:	Peritumoral brain:
		0.93	0.53	0.86	0.71
Hauser 2016 [78]	$n = 14$	0.81	0.43	0.96	0.125
	117 samples				
Coburger 2017	$n = 33$	0.84	1		
[54]	99 samples				
Kiesel 2017 [57]	$n = 77$	0.86	0.89	Overall: 0.98	Overall: 0.51
	267 samples			Strong	
				fluorescence:	
				1	
				Peritumoral brain:	
				0.94	
Prospective studies of spectroscopic fluorescence accuracy (Level 2)					
Stummer 2014	$n = 33$	Depending on	Depending on	Patient-based: 0.85	Overall: 0.40
[79]	Spectrometric	fluorescence	fluorescence	Strong	
	quantification of	detection	detection	fluorescence: 1	
	fluorescence	threshold	threshold	Vague	
				fluorescence: 0.95	

Table 2A
Evidence-based data on improvement in EOR with 5-ALA-FGS for HGG.

	Patients	EOR with 5-ALA-FGS	EOR with WL	*P*
Randomized trials (Level 1)				
Stummer, 2006	$n = 270$	65% CRET	36% CRET	$P < 0.0001$
[32]				
Phase III trial				
Stummer, 2011	$n = 349$	63.6% CRET	37.6% CRET	$P < 0.0001$
[9]				
Phase III trial				
Meta-analyses (Level 2)				
Eljamel, 2015	$n = 565$	75.4% GTR		
[60]				
Summary of 11				
studies				
[22,33,36,44,99–105]				
Prospective studies (Level 2)				
Schucht, 2012	$n = 53$ (eligible for	96% CRET		
[92]	CRET)	89% = 0 cm^3 residual		
		enhancement		
Idoate, 2013 [64]	$n = 30$	EOR > 98%		
		83.3% GTR		
Kim, 2014 [35]	$n = 80$	Mean EOR: 97.0%	Mean EOR: 84.7%	$P = 0.002$
		80% CRET	43% CRET	
Cordova, 2016	$n = 30$	Median EOR: 94.8%		
[93]		30% CRET		
Phase II trial				
Teixidor, 2016	$n = 85$	53.9% CR		
[94]				
Multicentric				
Retrospective studies (Level 3)				
Slotty, 2013 [95]	$n = 253$	48.5% CR	21.4%–27.2% CR	$P < 0.01$
Picart, 2017 [96]	$n = 51$	67.3% GTR	51.4% GTR	$P = 0.05$

EOR:Extent of Resection; GTR: Gross Total Resection corresponding to residual contrast-enhanced tissue volume < 1 cm^3; CRET: Complete Resection of Enhanced Tissue, corresponding to residual contrast-enhanced tissue volume < 0.175 cm^3; CR: Complete Resection; 5-ALA-FGS: 5-ALA fluorescence-guided-surgery; HGG: High Grade Glioma..

vs. 36%, $P < 0.0001$; final analysis: 63.6% vs. 37.6%, $P < 0.0001$) (Table 2A), independently of patient age or tumor location within eloquent areas [9,32].

A meta-analysis (level 2) that included 11 prospective or retrospective studies, for a total of 565 patients, reported a pooled complete resection rate of 75.4% (95% CI, 67.4–83.5%; $P < 0.001$) [60]. However, definitions of complete resection differed between studies, which may have led to slightly overestimated results.

Five prospective [35,64,92–94] (level 2) and 2 retrospective studies (level 3) [95,96] specifically assessed the EOR after 5-ALA-FGS (Table 2A). Although they did not systematically compare 5-ALA-FGS versus WL surgery, the results deserve to be analyzed. Again, heterogeneity in the definition of complete resection together with varying surgeon experience hampered comparison. However, rates of complete resection ranged from 30% to 96% and median EOR was consistently greater than 94%. In the 2 non-randomized studies that compared 5-ALA versus WL surgery, the EOR was significantly higher with 5-ALA-FGS [35,95]. Gain in EOR was constantly independent of tumor size [94], but some studies suggested that age [93] or location in eloquent areas [97] influence EOR. A study comparing the two techniques in HGG specifically located in eloquent areas [96] consistently reported higher GTR rates with 5-ALA-FGS, although the difference was not significant.

Interestingly, in a detailed remnologic study of 13 patients with CRET, Schucht et al. showed that mean resection volume under 5-ALA-FGS was significantly greater than the volume of the preoperative contrast-enhancing tumor (84 cm^3 vs. 39 cm^3; $P = 0.0087$) [98]. Moreover, in a series of 33 patients reported by Stummer et al. [79], 23 still had unresected fluorescing tissue at the end of the procedure. Residual MRI enhancement was detected in only 65% of them. These results suggest that 5-ALA also stains non-enhanced tumor tissue, and are consistent with the reported improvement in the EOR compared to conventional WL surgery, whether or not guided by MRI-based neuronavigation.

4.3. Improvement in surgical resection by combining 5-ALA-FGS and iMRI (intra-operative MRI)

Five prospective studies (4 level 2 [49,78,106,107] and 1 level 3 [20]) and 2 retrospective studies (level 3) [108,109] compared EOR on protocols combining 5-ALA and iMRI or not (Table 2B). Three additional prospective studies compared diagnostic performance between 5-ALA-FGS and iMRI [54,71,77].

A prospective study directly compared the EOR achieved by 5-ALA-FGS alone or iMRI alone [20]. The EOR was significantly greater with iMRI, but the results were biased by likely non-comparability between groups. Moreover, in another study combining iMRI and 5-ALA-FGS, the use of 5-ALA was a strong predictor of GTR on multivariate analysis (odds ratio = 3.19; 95% CI, 1.28–7.93; $P = 0.01$) [97].

Two studies [106,108], comparing 5-ALA alone and combined 5-ALA and iMRI, reported contradictory results. Eyüpoglu et al. found that the combination of the two methods significantly increased the EOR [106], whereas the difference was non-significant for Tsugu et al. [108], who nevertheless concluded that the combination of techniques had a synergistic effect. Conversely, a case-control study [109] compared iMRI only and combined iMRI and 5-ALA-FGS, and a prospective study [107] compared 5-ALA only, iMRI only, the combination of the two, or neither. Two prospective studies including patients in who 5-ALA-FGS and iMRI were combined [49,78,110] reported that each technique may leave some tumor tissue undetected and that the combination optimizes both the EOR and GTR rate. Likewise, in 30 consecutive patients, Eyüpoglu et al. achieved supra-total resection thanks to the combination of the two techniques [111].

Additionally, Coburger et al. concluded that 5-ALA was more sensitive but less specific than iMRI for the detection of HGG remnants [54,71] whereas Gessler et al. reported that iMRI was slightly more sensitive but equally specific in comparison with 5-ALA [77]. Although these findings are inconsistent, it seems to be generally agreed that combining 5-ALA and iMRI could increase the EOR.

4.4. Comparison with F18-FET PET (F18-fluoroethyl-tyrosine-positron emission tomography)

Although the gold-standard for glioblastoma EOR quantification is early post-operative MRI, 2 prospective studies (level 2) and 1 retrospective study (level 3) assessed the use of F18-fluoroethyl-tyrosine (FET)-positron emission tomography (PET) [67,75,112], with contradictory results.

In a series of 30 patients with grade II to IV glioma, in which 38 biopsies were taken [75], only 57% of these were fluorescent, although 86% of the HGG samples corresponded to areas of 18F-FET PET uptake. In low-grade glioma samples, there was 18F-FET uptake in 41% of cases, whereas only 5% were fluorescent. The authors concluded that 18F-FET PET is more sensitive than 5-ALA.

Conversely, Stockhammer et al. reported a series of 13 patients (12 HGGs) who underwent 5-ALA-FGS combined to pre- and post-operative 18F-FET PET [67]. The correlation between FET uptake and fluorescence was particularly good as the median FET SUV (Standardized Uptake Value) was significantly higher in fluorescent areas ($P < 0.0001$). Moreover, Roessler et al. retrospectively analyzed a series of 10 patients operated on by 5-ALA-FGS for resection of glioblastoma (11 surgeries) [112]. At the end of the procedure, there was a residual fluorescence corresponding to tumor infiltration according to the histological analysis. As there was no post-operative FET uptake in 3 cases, it appeared that 5-ALA was more sensitive than 18F-FET PET for detection of tumor remnant. Larger-scale prospective series are required for more definite conclusions.

5. Evidence-based data for gain in survival with 5-ALA-FGS

One phase III randomized controlled trial (level 1) conducted by a German group [9,22,32] compared survival (PFS and OS) between 5-ALA and conventional WL surgery. 5-ALA-FGS was associated with a significant gain in PFS but not in OS (Table 3) [9,32]. Conversely, adjustment for bias revealed that the achievement of GTR resulted in significantly higher OS (16.7 vs. 11.8 months; $P = 0.0001$) [22]. These survival gains were significant across all subgroups of patients, and revision surgery was performed marginally later in patients with GTR (6.7 vs. 9.5 months; $P = 0.0582$). On multivariate analysis, the other factors associated with improved prognosis were young age and high KPS (Karnofsky Performance Status) index [22,32].

A meta-analysis (level 2) [60] of pooled data from 4 prospective and retrospective studies [22,33,95,105] reported a mean PFS after 5-ALA-FGS of 8.146 months. The gain in OS was 6.167 months compared with WL surgery. After exclusion of 1 study [105] in which concomitant PDT (PhotoDynamic Therapy) was performed, results were more or less similar: PFS, 7.922 months; OS gain, 6.250 months.

Five prospective [35,44,93,94,113] and 5 retrospective [93,96,109,111,114] studies reported additional data on the outcome in HGG patients operated on with 5-ALA-FGS. In studies comparing the two techniques, 5-ALA-FGS provided better PFS [35,104] and OS [35,44,113,114] than WL surgery. An inverse correlation was noted between residual fluorescence intensity at end of resection and lower PFS [33] and OS ($P = 0.01$) [33,44]. On multivariate analysis, the independent predictors of better prognosis were young age [44,94], high KPS [93,113], extensive

Table 2B
Evidence-based data on improvement in EOR with 5-ALA-FGS, combined to iMRI or not.

	Patients	EOR with 5-ALA-FGS only or iMRI only or neither	EOR with 5-ALA + iMRI	*P*
Prospective studies (Level 2)				
Eyüpoglu, 2012 [106]	*n* = 37 All 5-ALA + iMRI	Mean EOR: Non-eloquent areas: 71.7% Eloquent areas: 57.6%	Mean EOR: Non-eloquent areas: 100% Eloquent areas: 71.2%	*P* < 0.002 *P* < 0.0003
Yamada, 2015 [49]	*n* = 97 All 5-ALA + iMRI		Mean EOR = 95% 52% GTR	
Hauser, 2016 [78]	*n* = 12 All 5-ALA + iMRI	9% CRET	82% CRET	
Nickel, 2018 [107]	*n* = 101 45 = no imaging 19 = 5-ALA only 10 = iMRI only 26 = 5-ALA + iMRI	73% GTR (no imaging) 74% GTR (5-ALA only) 94% GTR (iMRI only)	95% GTR	
Prospective non-randomized studies (Level 3)				
Roder, 2014 [20]	*n* = 54 19 = 5-ALA only 10 = iMRI only	46% CRET (5-ALA) 74% CRET (iMRI)		*P* = 0.049
Retrospective studies (Level 3)				
Tsugu, 2011 [108]	*n* = 21 11 = 5-ALA only 10 = 5-ALA + iMRI	Mean EOR = 91.8% 54.5% GTR	Mean EOR = 92.6% 40% GTR	*P* = 0.847
Coburger, 2015 [109]	*n* = 177 144 = iMRI only 33 = 5-ALA + iMRI	Mean EOR = $97.4% 82% GTR	Mean EOR = 99.7% 100% GTR	*P* < 0.004 *P* < 0.010
Case-control				

EOR: Extent of Resection; GTR: Gross Total Resection corresponding to residual contrast-enhanced tissue volume < 1 cm^3; CRET: Complete Resection of Enhanced Tissue, corresponding to residual contrast-enhanced tissue volume < 0.175 cm^3; CR: Complete Resection; 5-ALA-FGS: 5-ALA fluorescence-guided-surgery; HGG: High Grade Glioma; iMRI: intra-operative MRI..

resection [44,93,94], use of 5-ALA [114], and hypermethylation of MGMT promotor [93].

Compared to iMRI alone, combined iMRI and 5-ALA-FGS led to supra-total resection, associated with significantly better OS in one study [111], although this benefit was not found by Coburger et al. [109].

Finally, in a study dedicated to tumors located in the vicinity of eloquent areas, significantly better PFS was achieved with 5-ALA-FGS, although OS did not differ [96]. On another multivariate analysis, 5-ALA-FGS was also independently associated with PFS improvement [96].

6. 5-ALA fluorescence-guided surgery for recurrent HGG

Some of the above studies assessing performances and resection rates after 5-ALA-FGS included mixed populations of patients, with newly diagnosed or recurrent HGG [36,44,49,64,71,76,79,92,98,100]. Only 4 studies [81,115–117] and a recent review [118] specifically assessed the use of 5-ALA-FGS for recurrent HGG.

In terms of diagnostic performances, in a prospective non-controlled phase II study (level 2) including 36 patients [115], the predictive positive value was as high as 91.7% in strongly and 83.3% in weakly fluorescent areas in recurrent HGG. On the other hand, in a retrospective study (level 3) of 313 patients treated by 5-ALA-FGS for suspicion of HGG recurrence, reactive changes without active tumor cells were found in 13 cases and attributed to several factors: chemoradiotherapy, inflammation, etc. [68,81,118]. A strong or vague fluorescence was found in respectively 7 and 5 of these patients [81]. Thus, prior chemoradiotherapy may not dramatically impair the accuracy of 5-ALA-FGS in recurrent HGG, but 5-ALA-FGS is unable to discriminate between true progression and pseudo-progression.

In terms of outcome, Hickmann et al. reported a retrospective series (level 3) of 58 patients undergoing iterative surgical resection of HGG under 5-ALA. The overall mean EOR was 91.1%. Interestingly, 15.9% of tumors did not display any fluorescence intra-operatively. Compared to a control group operated on under WL, patients operated on with 5-ALA had longer PFS and OS, but not significantly (respectively, 10.7 vs. 10.6 months, *P* = 0.4; and 17.6 vs. 14.6 months, *P* = 0.26). However, the use of 5-ALA was an independent predictor of increased OS (*P* = 0.025). Moreover, the global rate of new permanent focal deficits was 6.3% [117].

As not all recurrent HGGs display fluorescence, a prospective study (level 2) assessed the combined use of 5-ALA-FGS and iMRI in 7 patients. GTR was achieved in all patients, and median survival after the second intervention was 7.6 months [116].

Finally, these results suggest that the benefit of 5-ALA-FGS is similar in recurrent and primary HGG.

7. Other indications for 5-ALA fluorescence-guided neurosurgery

It is important to note that there is theoretically no market authorization for 5-ALA in France in the following indications.

7.1. Glioma with non-significant contrast enhancement

The spectrophotometric profile is different from that of HGG as the main emission peak is at 620 nm, versus 634 nm for HGG [119]. Recently, it was demonstrated that the ratio between the emission peaks at 620 nm/634 nm is close to 0 in HGG and 1.5 in DLGG (unpublished data from Alston et al.).

As mentioned above, fluorescence intensity depends on tumor cells density [26,34,36,48,49,62–64,71,84–86] and proliferation index [57,66,69,84,86,88–91], which finally explains why

Table 3
Evidence-based data on improvement in Progression-Free and Overall Survival with 5-ALA-FGS for HGG.

	Patients	PFS	OS
Randomized trials (Level 1)			
Stummer, 2006 [32] Phase III trial	*n* = 270 (5-ALA vs. WL)	6-month PFS: 5-ALA: 41.0% WL: 21.1% *P* = 0.0003 Median PFS: 5-ALA: 5.1 mo WL: 3.6 mo	Median OS: 5-ALA: 15.2 M WL: 13.5 M *P* = 0.1
Stummer, 2008 [22]	*n* = 243 (5-ALA vs. WL) 122 GTR/121 Incomplete resections		Median OS: GTR: 16.7 M Non-GTR: 11.8 M *P* = 0.0001
Stummer, 2011 [9] Phase III trial	*n* = 349 (5-ALA vs. WL)	6-month PFS: 5-ALA: 35.2% WL: 21.8% *P* = 0.004	Median OS: 5-ALA: 14.3 M WL: 13.7 M *P* = 0.917
Meta-analyses (Level 2)			
Eljamel, 2015 [60] Review of 4 studies [22,33,95,105]	*n* = 565	Mean PFS: 8.146 mo 7.922 mo (excluding [105])	Gain in OS: 6.167 mo 6.250 mo (excluding [105])
Prospective studies (Level 2)			
Stummer, 2000 [44]			OS: Strong RF: 51 wks Vague RF: 79 wks No RF 101 wks *P* = 0.01
Kim, 2014 [35]	*n* = 80 (5-ALA vs. WL) 49 GTR	Median PFS: 5-ALA: 18.0 mo WL: 6.0 mo *P* = 0.001	Median OS: 5-ALA: 24.0 mo WL: 14.0 mo *P* = 0.045
Cordova, 2016 [93] Phase II trial	*n* = 30 with 5-ALA	6-month PFS: 45%	6-month OS: 81%
Teixidor, 2016 [94] Multicenter	*n* = 85 with 5-ALA	6-month PFS: 58% Median PFS: 6.9 M	6-month OS: 78.4% Median OS: 14.2 mo
Ng, 2017 [113]	*n* = 74 (5-ALA vs. WL)		Median OS: 5-ALA: 12.0 mo WL: 8.0 mo *P* < 0.020
Retrospective studies (Level 3)			
Aldave, 2013 [114]	*n* = 52 patients with 5-ALA, and GTR on post-operative MRI		Median OS: No RF: 27.0 mo RF: 17.5 mo *P* = 0.015
Diez-Valle, 2014 [104] VISIONA	*n* = 251 (5-ALA vs. WL)	6-month PFS: 5-ALA: 69% WL: 48% *P* = 0.002	
Coburger, 2015 [109] Case-control	*n* = 177 144 = iMRI only 33 = 5-ALA + iMRI	Median PFS: iMRI + 5-ALA: 6.0 mo iMRI: 6.0 mo *P* < 0.309	Median OS: iMRI + 5-ALA: 18.0 mo iMRI: 17.0 mo *P* < 0.708
Eyüpoglu, 2016 [111] Case-control	*n* = 105 75 = iMRI only 30 = 5-ALA + iMRI		Median OS: iMRI + 5-ALA: 18.5 mo iMRI: 14.0 M *P* < 0.0004
Picart, 2017 [96]	*n* = 51	6-month PFS: 5-ALA: 97% WL: 55% Median PFS: 5ALA: 13.21 mo WL: 7.24 mo *P* = 0.03	6-month OS: 5-ALA: 96% WL: 93% Median OS: 5ALA: 25 mo WL: 12 mo *P* = 0.080

GTR: Gross Total Resection; PFS: Progression-Free Survival; OS: Overall Survival; RF: Residual Fluorescence; WL: White Light; 5-ALA-FGS: 5-ALA fluorescence-guided-surgery; HGG: High Grade Glioma.

fluorescence intensity depends on tumor grade [89,91]. It was also recently demonstrated that tumors with IDH1-mutant or 1p/19 co-deletion are significantly less fluorescent that those without [90,91].

In 7 prospective (level 2) [65,69,86,90,91,120,121] and 1 retrospective (level 3) [108] study, the rate of WHO grade II glioma displaying fluorescence ranged from 0% to 50%. Intra-operative confocal microscopy could improve the intra-operative visibility of fluorescence [18,48,66,72,120,122]. Although it is less reliable than MRI, 5-ALA could facilitate intra-operative identification of anaplastic foci in gliomas with non-significant enhancement [65,69,121]. Very recently, it was established that fluorescence predicts malignant transformation and is independently correlated with OS [123].

7.2. Other tumors

A few studies were dedicated to the use of 5-ALA in other indications: brain metastasis [68,71,124,125], meningiomas [126–134], lymphomas [135,136], pediatric tumors [85], and intra-medullary and intra-dural extra-medullary tumors [137]. Eljamel et al. assessed 5-ALA FGS in a wide panel of 83 primary brain tumors: ependymomas, pituitary adenomas, glomus jugular tumors, chordomas and myelomas [138]. As the present review focuses on glial tumor and because the French market authorization does not concern these indications, we shall not detail these results here.

8. Evidence-based data on 5-ALA-FGS safety in terms of functional risk

Results from 2 randomized trials (level 1) [9,115], 4 prospective studies (level 2) [35,100,101,139] and 1 retrospective study (level 3) [96] are detailed in Table 4. They consistently suggest that 5-ALA-FGS in eloquent areas induces a higher rate of early neurological impairment than WL surgery. In eloquent areas, rates of neurological impairment ranged from 3% to 64%. Impairment is transient, and by 3 months the difference is no longer significant and general health status is even sometimes better in 5-ALA groups [35]. Moreover, in some cases, severe neurological impairment was related to iatrogenic cerebral infarction due to microvascular injury [77,85,99,139] and was thus not imputable to 5-ALA-FGS.

Finally, preoperative selection of the "right" candidates has to be particularly thorough. The risk of post-operative neurological deterioration is indeed higher in patients with pre-existing neurological deficits unresponsive to steroids, as these are more probably related to tumor infiltration than to the surrounding edema [32,35,44,92,100,101,106].

Aldave et al. reported that the rate of definitive functional impairment tends to be higher when all fluorescent areas are resected than when some fluorescent areas remain after resection [114]. As it offers no functional information, 5-ALA alone is obviously insufficient to determine the optimal onco-functional balance, and a multimodal approach is needed to decrease morbidity [48]. Preoperative neuroradiological examinations, including classical MRI, functional MRI (fMRI) and diffusion tensor imaging (DTI) sequences, are essential to visualize eloquent areas and fiber tracts [92,99–101]. In eloquent areas, it is also mandatory to associate intra-operative cortical and subcortical monitoring to 5-ALA-FGS [96,99,101,109,139–141]. According to Feigl et al.'s experience, based on 18 patients with primary malignant brain tumor located within eloquent areas, resection was stopped in 24% of cases because an eloquent area was identified while a fluorescent tumor remnant was still visible.

In a study comparing iMRI alone versus combined iMRI + 5-ALA-FGS in HGG located within eloquent areas, the latter did not lead to functional impairment as pre- and post-operative KPS index were comparable ($P = 0.394$) and there were no significant differences in terms of neurocognitive impairment between the two groups [111].

9. Cost-effectiveness of 5-ALA-FGS

Depending on patient body-weight, the use of one or two 5-ALA vials is required. Consequently, the cost of 5-ALA (Gliolan®, Medac Pharma, Wedel, Germany) per procedure is €1,000 (≤ 75 kg) or €2,000 (> 75 kg).

Three studies assessed the cost-effectiveness of 5-ALA-FGS [142–144]. In one, compared to conventional WL surgery, the incremental cost per additional complete resection was €4,550 [143]. In another, theincremental cost per life-year gained was €6,700 [144]. In the third,incremental cost per quality-adjusted life-year gained ranged from €9,021 to US$16,218 [142–144], which is 2-fold less than with iMRI [142].

On consensual thresholds, all studies concluded that 5-ALA-FGS was cost-effective for the resection of HGG [7,142–144].

10. Practical recommendations

Although 5-ALA-FGS is deemed to be easy, it is essential that neurosurgeons have a complete understanding of its technical specificities. Therefore, a training course sponsored by the manufacturer of 5-ALA, Medac Pharma (Wedel, Germany), is recommended before performing the operation for the first time. The learning curve is around 10 to 15 patients and is one of the limiting factors, as expertise varies between centers, inducing bias [22,32]. Few studies have detailed the practical aspects, and especially pitfalls that can potentially prevent macroscopically complete resection [45,145].

10.1. 5-ALA administration

In France, 5-ALA (Gliolan®) is marketed by Medac. It is a white powder contained in a glass vial (1.5 g/vial). It is administered orally, diluted in 50 mL drinking water. The solution is slightly sour but usually well tolerated by patients. It is not recommended to dissolve 5-ALA in fruit juice, as the increased acidity modifies absorption [145].

Two randomized phase I clinical trials (level 1) and a prospective study (level 2) were recently conducted to determine the most appropriate dose of 5-ALA [146,147]. Dose-escalation up to 50 mg/kg in 10 mg/kg increments was tested by Cozzens et al. in 19 patients. At 50 mg/kg, 33.3% of patients experienced grade I skin toxicity. However, patients with doses > 40 mg/kg tended to show stronger fluorescence, although no statistical analysis was performed [146]. Doses > 20 mg/kg decrease specificity and increase the risk of resecting non-tumor tissue and thus inducing neurological deficits and also systemic adverse effects [31,70]. Conversely, Stummer et al. tested dose-reduction in 21 patients (0.2 vs. 2 vs. 20 mg/kg) [147]. At 0.2 mg/kg, no fluorescence was elicited. Increasing doses did not elicit proportional increases in plasma PpIX level or tissue fluorescence, which would suggest that further increases would not enhance the tissue concentration of PpIX and thus the intensity of fluorescence [43,147]. Consequently, optimal dose-efficacy is 20 mg/kg [147,148].

The best time for ALA administration has been also studied [31,45,70,149,150]. For optimal fluorescence, 5-ALA has to be administered 3 hours before induction of anesthesia, to enable complete intestinal absorption (approximately 1 hour), followed by conversion into fluorescent PpIX in tumor cells. In humans, half-life varies between 0.85 and 3.05 hours [147]. Fluorescence peaks 6 hours after administration, and lasts more than16 hours [45].

Stummer et al. reported the importance of dexamethasone pre-treatment (3 × 4 mg for 2 days) to optimize 5-ALA uptake by reducing PpIX efflux and peritumoral fluorescence by tightening up the blood–brain barrier [44,145]. Pre-treatment with steroids also identifies patients at risk of neurological deficit after 5ALA-FGS. The persistence of preoperative deficit after dexamethasone indicates that the deficit is secondary to functional tumor infiltration and not due to edema, and represents a contraindication to 5ALA-FGS [32,48].

10.2. Adverse events and precautions for use

Adverse events inherent to 5-ALA administration *per se* are minor, transient and uncommon [32,36,61,62,76,79,115,149,150]

Table 4
Evidence-based data on safety of 5-ALA-FGS for HGG.

	Patients	Neurological status at 48 hours	Evolution
Randomized trial (Level 1)			
Nabavi, 2009 [115]	*n* = 36 recurrent HGG 22% in motor areas 19% in language areas	Median KPS = 75% Median NIH-SS: 3	Median KPS = 80% at 6 months Median NIH-SS: 1
Stummer, 2011 [9] Phase III trial	*n* = 349 (5-ALA vs. WL) 56.3% ALA = eloquent area 54.3% WL = eloquent area	Impaired NIH-SS: 5-ALA: 26.2% WL: 14.5% *P* = 0.020	No significant difference at 7 days, 6 weeks or 6 months
Prospective studies (Level 2)			
Della Puppa, 2013 [100]	*n* = 31 eloquent HGG (22 newly diagnosed, 9 recurrent)	64% neurological impairment KPS = 100 in 13/31	3% of persistent morbidity KPS = 100 in 25/3 at 3 months
Pastor, 2013 [101]	*n* = 34 HGG near eloquent areas (using combination of different neurophysiological techniques)	1/34 worsening	0/34 worsening 27.8% improvement compared to preoperative examination (3 months)
Kim, 2014 [35]	*n* = 80 (5ALA vs WL) 52.5% ALA = eloquent area 47.5% WL = eloquent area	Median KPS –5-ALA:82.7% –WL: 84.5%	Median KPS (3 months) –5-ALA:84.7% –WL: 77.7% p = 0.046 M Imp: 7.5% (5-ALA and WL) L Imp: 2.5% (5-ALA), 0% (WL)
Schucht, 2014 [139]	*n* = 72 HGG adjacent to cortico-spinal tract	30% deterioration at day 1 and 10% at discharge	4% permanent deficit (including 2 vascular injuries)
Retrospective studies (Level 3)			
Picart, 2017 [96]	*n* = 51 eloquent HGG (5-ALA vs. WL) 24 HGG = 5-ALA 27 HGG = WL	Motor deficit: 5-ALA: 66.7% WL: 59.3% Speech deficit: 5-ALA: 29.2% WL: 48.2%	Motor deficit: 5-ALA: 12.5% WL: 29.6% Speech deficit: 5-ALA: 12.5% WL: 14.8%

HGG: High Grade Glioma; KPS: Karnofsky Performance Status; NIH-SS: National Institutes of Health Stroke Scale; M Imp: Motor Impairment; L Imp: Language Impairment; WL: White Light.

provided that preventive measures are applied and contraindications are respected [48]. 5-ALA should not be given to patients with either inherited or acquired porphyria, hypersensitivity to porphyrins, or severe kidney or liver failure, or during pregnancy [48].

The most frequent adverse events are nausea, vomiting and gastroesophageal reflux [93], with frequency varying from 0% [94] to 3% [49]. They can be prevented by anti-emetic drugs. The only severe adverse effect potentially attributable to 5-ALA was a second gastrointestinal perforation 24 h after administration, in a patient with history of gastrointestinal perforation [93].

Another common adverse event is sunlight-induced erythema, with incidence ranging from 0% [94] to 1% [44,49]. It is prevented by avoiding direct sunlight or strong room light and by the eviction of other photosensitizers within 24 hours of 5-ALA intake [48,145].

The risk of normal brain photosensitization has also been raised but is only theoretical for two reasons. Firstly, in normal brain tissue, PpIX levels are very low. Secondly, current fluorescence microscopy equipment cannot create high enough energy levels to cause phototoxic damage in normal brain [31,45,48,70].

Biologically, the rate of transaminases and GGT (gamma-glutamyl-transpeptidase) elevation 24 hours after surgery was significantly higher in a 5-ALA group than in the WL group [32]. After 5-ALA intake, serum GGT and alanine aminotransferase levels corresponded to Grade 3 toxicity according to the criteria of the National Cancer Institute of Germany in 5.7% of cases [44]. Hypoalbuminemia and hyperbilirubinemia are sometimes reported [93]. They are asymptomatic and disappear within 1 to 6 weeks [85,93,94]. Patients with pre-existing asymptomatic hepatic enzymes elevation were at risk of further increase [94]. Pragmatically, hepatic enzymes concentration should be checked postoperatively.

To conclude, 5-ALA is well-tolerated and no severe general or biological adverse events have been linked to 5-ALA with certainty [80,85,132,146].

10.3. 5-ALA-FGS procedure

Technically, 5-ALA-FGS does not greatly differ from conventional HGG micro-neurosurgical resection. It is, however, more time-consuming than WL surgery, which partly explains its limited use. Anesthesia induction, patient positioning, draping and craniotomy are performed in the usual way.

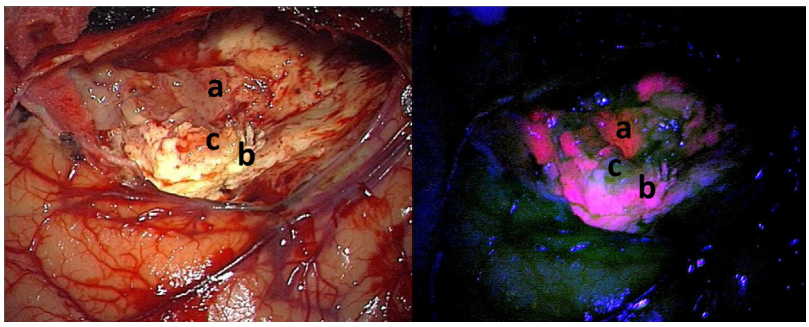

Fig. 2. Intraoperative fluorescence is not homogenous within a tumor. The same tumor is shown under white light (1) and blue light (2). It is possible to identify areas of strong fluorescence (a), areas of vague fluorescence (b) and non-fluorescent areas (c).

If the tumor is small, cortical and away from eloquent areas, it can be useful to begin by determining corticectomy boundaries by blue light excitation. The interface between fluorescent and non-fluorescent tissue represents the "pseudo-dissection plane". Debulking is performed centripetally, from periphery to tumor core, switching between WL and blue light during the procedure. More frequently, the tumor is large and/or close to an eloquent area. In this case, the surgeon may prefer to remove any easily distinguishable necrotic and solid tumor tissue predominantly under WL [48]. However, to remove infiltrating residual tumor not distinguishable under WL, fluorescence-guided resection is essential. Resection progresses centrifugally from core to periphery, switching between white and blue light until all signs of fluorescence have disappeared [48,145]. Alternatively, some neurosurgeons prefer beginning the resection using anatomical landmarks, performing subpial resection around the glioma core and using fluorescence in the deepest part of the resection, together with intra-operative brain mapping.

During resection, the surgeon usually identifies three areas: necrotic tissue, which is non-fluorescent, solid tumor, with strong red fluorescence (both of which are generally easily distinguishable under WL), and infiltration by isolated glioma cells, which gives a more or less distinctive pink fluorescence visualized only under blue light (Fig. 2). Red fluorescence corresponds to contrast-enhanced MRI, whereas pink fluorescence is the equivalent of non-contrast-enhanced MRI. Resection of the necrotic areas and red fluorescence, corresponding to the solid component of the HGG, are not at major risk. However, in eloquent areas, pink fluorescent areas have to be resected with caution and using permanent monitoring [64,96].

It is important to remember that blood can mask fluorescent areas, and it is consequently important to keep the surgical cavity as "clean" as possible [46]. Unlike other imaging methods, the surgeon never has to look up from the microscope, as switching between WL and blue light is done by finger touch on the microscope. Also, during resection, the neurosurgeon can see tumor tissue 'online' that is not visible to the naked eye [36,48,145].

Where possible, the microscope should be positioned so that the light is perpendicular to the resection surface. The light source should be close to the cavity, as the intensity of light excitation diminishes over distance.

With increasing surgical experience, longer phases of the operation can be performed under blue excitation light alone, although WL illumination may still be necessary to discern anatomical structures such as blood vessels, although they can also be identified on fluorescence by their blue-green color under blue light [48,145].

The problem of overhanging margins is recurrent in deep subcortical and cystic tumors [48,145]. During tumor resection, surgeons tend to undercut the cortex, leaving residual tumor hidden under the margins that remains visualizable under blue excitation light outside the surgeon's direct field of vision. This "shadow cone" phenomenon should be kept in mind. Likewise, cyst opening can lead to the collapse of tumor parts that, in some cases, may go unnoticed.

At the end of the procedure, it is important to wipe the resection cavity margins with cotton pads to remove blood and any superficial cell layers. Pink fluorescence may reappear, showing any residual tumor. This phenomenon of fluorescence refreshing is related to PpIX photobleaching, which is the chemical degradation of fluorophores as a result of exposure to light. The level of fluorescence decays to 36% in 87 minutes under WL and in 25 minutes under blue light [31,45,70]. Consequently, exposure to white or blue light has to be minimized.

11. Interpretation by the neuro-oncology club of the French neurosurgery society (SFN)

As argued above, 5-ALA shows good specificity for detection of a tumor remnant during resection of HGG but has weaker sensitivity (level 2).

The use of 5-ALA significantly increases the rate of GTR, which was higher than 90% in some series (level 1). Given the known relation between EOR and survival, 5-ALA-FGS can be expected to improve PFS (level 1). Gain in OS is more debatable according to the literature. Nevertheless, the combination of 5-ALA and iMRI could increase both EOR and survival (level 2).

Conversely, impaired neurological status is associated with poorer prognosis [10,14,18,22,151], which emphasizes the importance to find a tailored onco-functional balance in each patient [26,139]. In HGG located in an eloquent area, conserving and improving recovery of neurological function are thus prime objectives [2,8,14]. The use of 5-ALA-FGS in eloquent areas is totally feasible, but requires simultaneous monitoring to precisely locate and preserve eloquent areas (level 2). The general side effects of 5-ALA are rare and benign.

The use of 5-ALA is possible in both primary HGG resection and in recurrence, although reactive astrocytes can induce false-positive fluorescence. It could also be useful in other indications, and especially to help resection of high grade meningioma (level 2).

Finally, from an economic viewpoint, the few studies available suggest that 5-ALA is cost-effective.

12. Future perspectives

An ongoing prospective randomized multi-center trial (RESECT – ClinicalTrials.gov Identifier: NCT01811121) including 204 patients has been initiated in 20 French neurosurgical centers to assess the cost-effectiveness of 5-ALA-FGS for the resection of HGG, and may provide interesting data. Results will be available in 2019.

In the future, efforts should aim to strengthen the sensitivity of 5-ALA-FGS. Since fluorescence intensity directly correlates with proliferation index, 40% of non-fluorescent tumor biopsies have PpIX concentrations > 0.1 ng/mL, detectable on *ex-vivo* spectroscopy [79,89]. The development of this technique could subsequently contribute to optimizing resection of HGG [66,119].

Both an American study [120] and a recent study by our group [122] suggested that intra-operative in-vivo probe-based confocal laser endomicroscopy with 5-ALA could be used in DLGG, HGG and lymphoma, improving diagnostic performances by enhancing the rentability of biopsies and providing more precise analysis of resection margins [122].

Other projects are trying to develop PDT, which is based on the phototoxic properties of PpIX [133,46,152]. This strategy is currently applied in dermatology for actinic keratosis or basal cell carcinoma management [41]. The principle consists in producing cytotoxic molecules by light-activation of a photosensitizer [153]. Animal experimentation in rats with induced glioblastoma highlighted that interstitial PDT with fractionated light is able to induce intra-tumor necrosis and apoptosis but also peripheral neovascularization [153]. An ongoing phase I study (INDYGO trial) is assessing the feasibility of intraoperative PDT in human patients [152].

These strategies are promising and could improve or even transform the prognosis of HGG in the future.

Disclosure of interest

The authors declare that they have no competing interest.

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