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REVIEW ARTICLE - PEDIATRIC NEUROSURGERY

# 5-ALA fluorescence–guided surgery in pediatric brain tumors—a systematic review

Michael Schwake[1] · Stephanie Schipmann[1] · Michael Müther[1] · Michaela Köchling[1] · Angela Brentrup[1] · Walter Stummer[1]

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## Abstract

**Background** 5-Aminolevulinic acid (5-ALA)-guided resection of gliomas in adults enables better differentiation between tumor and normal brain tissue, allowing a higher degree of resection, and improves patient outcomes. In recent years, several reports have emerged regarding the use of 5-ALA in other brain tumor entities, including pediatric brains tumors. Since gross total resection (GTR) of many brain tumors in children is crucial and the role of 5-ALA-guided resection of these tumors is not clear, we sought to perform a comprehensive literature review on this topic.

**Methods** A systematic literature review of EMBASE and MEDLINE/PubMed databases revealed 19 eligible publications encompassing 175 5-ALA-guided operations on pediatric brain tumors. To prevent bias, publications were revised independently by two authors.

**Results** We found that 5-ALA-guided resection enabled the surgeons to identify the tumor more easily and was considered helpful mainly in cases of glioblastoma (GBM, 21/27, 78%), anaplastic ependymoma WHO grade III (10/14, 71%), and anaplastic astrocytoma (4/6, 67%). In contrast, cases of pilocytic astrocytomas (PAs) and medulloblastomas 5-ALA-guided surgery did not show consistent fluorescent signals and 5-ALA was considered helpful only in 12% and 22% of cases, respectively. Accumulation of fluorescent porphyrins seems to depend on WHO tumor grading. One important finding is that when 5-ALA-guided resections were considered helpful, the degree of resection was higher than is cases where it was not helpful. The rate of adverse events related to 5-ALA was negligible, especially new postoperative sequelae.

**Conclusion** 5-ALA could play a role in resection of pediatric brain tumors. However, further prospective clinical trials are needed.

**Keywords** 5-ALA · Pediatric brain tumors · Tumor resection

## Introduction

At the end of the last millennium, 5-aminolevulinic acid (5-ALA)-guided surgery was first introduced into neurosurgery and has since evolved into a widespread tool, helping surgeons to perform maximal resection of gliomas in the adult population and thus leading to a higher rate of gross total resection (GTR), progression-free survival (PFS), and prolonged overall survival (OS) without causing a higher rate of neurological sequelae [15, 20, 50, 60, 63, 71–73, 75, 82]. Moreover, the intracellular accumulation of protoporphyrin IX (PPIX) caused by the administration of 5-ALA enables a very good distinction between tumor tissue and the surrounding brain tissue [24, 26, 39, 49, 77, 84, 85].

Neoplasms of the central nervous system (CNS) are the most frequent solid tumors in children [54]. In many subtypes, resection is crucial and an important part of treatment. The main goals of surgery are to reduce tumor volumes as far as possible without causing neurological damage [3–5, 16, 23, 25, 35, 48, 54, 88].

To maximize resection, several techniques were developed in the last years apart from the surgeon's knowledge of brain anatomy and microsurgical technique, for example, intraoperative magnetic resonance imaging (ioMRI) [1, 21, 22, 31, 80],

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✉ Michael Schwake
schwakem@uni-muenster.de

[1] Department of Neurosurgery, University Hospital Münster, Germany
Albert-Schweitzer-Campus 1, Building A1,
48149 Munster, Germany

intraoperative ultrasound (ioUS) [38, 56, 68, 79], or neuronavigation [33, 44, 55, 64]. Although used in an off-label setting, several cases have previously been published regarding 5-ALA-guided resection of these tumors, showing potential benefit. However, the biology of pediatric brain tumors differs from adults [9] and malignant gliomas are rare in comparison to adults. Furthermore, common tumors in children such as pilocytic astrocytoma (PA), medulloblastoma, and ependymoma can be distinguished due to different tumor consistency, appearance, and color [57] and the added value of fluorescence-guided resection is unknown. Furthermore, a higher grade of resection could potentially cause neurological deficits.

The aim of this systematic review is to evaluate the usage of 5-ALA fluorescent–guided surgery in pediatric neurosurgery to determine which tumors types are possibly amenable for 5-ALA-guided resection and whether this technique helps in maximizing tumor resection, thus enabling prolonged PFS and OS. Additionally, we aimed to determine whether possible side effects from the administration of 5-ALA, mainly development of new neurological sequelae, and to discuss in vitro experiments on 5-ALA and pediatric CNS tumors.

## Methods

This study was conducted and reported according to the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) statement as reported previously [36, 37, 61, 62].

### Search strategy and article selection

A computed search on MEDLINE and Embase databases was conducted to identify publications on 5-ALA-guided surgery in pediatric brain tumors. The search included only articles published in English published before December 2018, with no lower date limit. We used combined keywords and medical subject headings as search terms for abstract and full text. The following terms were used: "aminolevulinic acid AND pediatric AND tumor," "aminolevulinic acid AND medulloblastoma," "aminolevulinic acid AND ependymoma," "aminolevulinic acid AND pilocytic," "aminolevulinic acid AND childhood," "aminolevulinic acid AND PNET," "aminolevulinic acid AND rhabdoid tumor," "ALA AND pediatric AND tumor," "ALA AND medulloblastoma," "ALA AND ependymoma," "ALA AND pilocytic," "ALA AND childhood," "ALA AND PNET," and "ALA AND rhabdoid tumor." All articles were screened regarding their titles and abstracts. Only articles describing clinical the usage of 5-ALA in pediatric patients with brain tumors or laboratory investigation on the usage of 5-ALA on pediatric brains tumors were selected. Subsequently, relevant articles were then retrieved and evaluated independently by two authors (M.S. and S.S.) using EndNote (Version X8.2, Thompson Reuters, Carlsbad, CA, USA). A cross-reference check of the citations of each relevant literature review included was performed to ensure that no relevant studies were missed by the computed database search.

### Data extraction

Two authors (MS and SS) independently extracted the following characteristics from the included studies: type of tumor, tumor grade according the WHO classification, localization, patients' age, sex, preoperative and postoperative neurological status, imaging, reported fluorescence signal intensities, resection rates, and laboratory findings. In addition, all papers were interrogated for accustomed outcome parameters that might have indicated clinical benefit from using 5-ALA, for example, resection rates or survival. 5-ALA-guided surgery was considered helpful in case it aided the surgeon in taking decision regarding tumor resection or when it assisted in achieving a higher grade of resection.

### Statistics

Statistical analyses were performed using the software IBM SPSS Statistics 24.0 (IBM, Armonk, NY, USA). Data were described by standard descriptive statistics. Due to the heterogeneity of the data, we relinquished statistical tests and did not set a level of statistical significance.

## Results

Our search identified 557 potential citations. After duplicates were excluded, 402 studies were retrieved for abstract evaluation. Screening of abstracts identified 17 articles suitable for further full-text evaluation and additional 2 conference papers. One abstract was omitted because the age of the patient was not mentioned (Fig. 1). Other reasons for exclusion were studies on adult patients, non-CNS disorders in pediatric cases, and reports without 5-ALA. The selected studies comprised five case reports, nine case series, and five experimental studies. Studies and cohort analyses were performed, respectively, compiled in Croatia, Denmark, Germany, Ireland, Italy, Israel, Japan, Spain, Switzerland, Russia, the United Kingdom (UK), and the United States of America (USA).

In sum, we found reports on 175 cases of 5-ALA fluorescence–guided resection of CNS tumors on patients between 1 and 19 years (Table 1). The most frequent tumor type was PA ($n = 33$), followed by glioblastoma (GBM, $n = 27$), medulloblastoma ($n = 23$), anaplastic ependymoma ($n = 14$), germinoma ($n = 11$), ganglioglioma ($n = 10$), and primitive

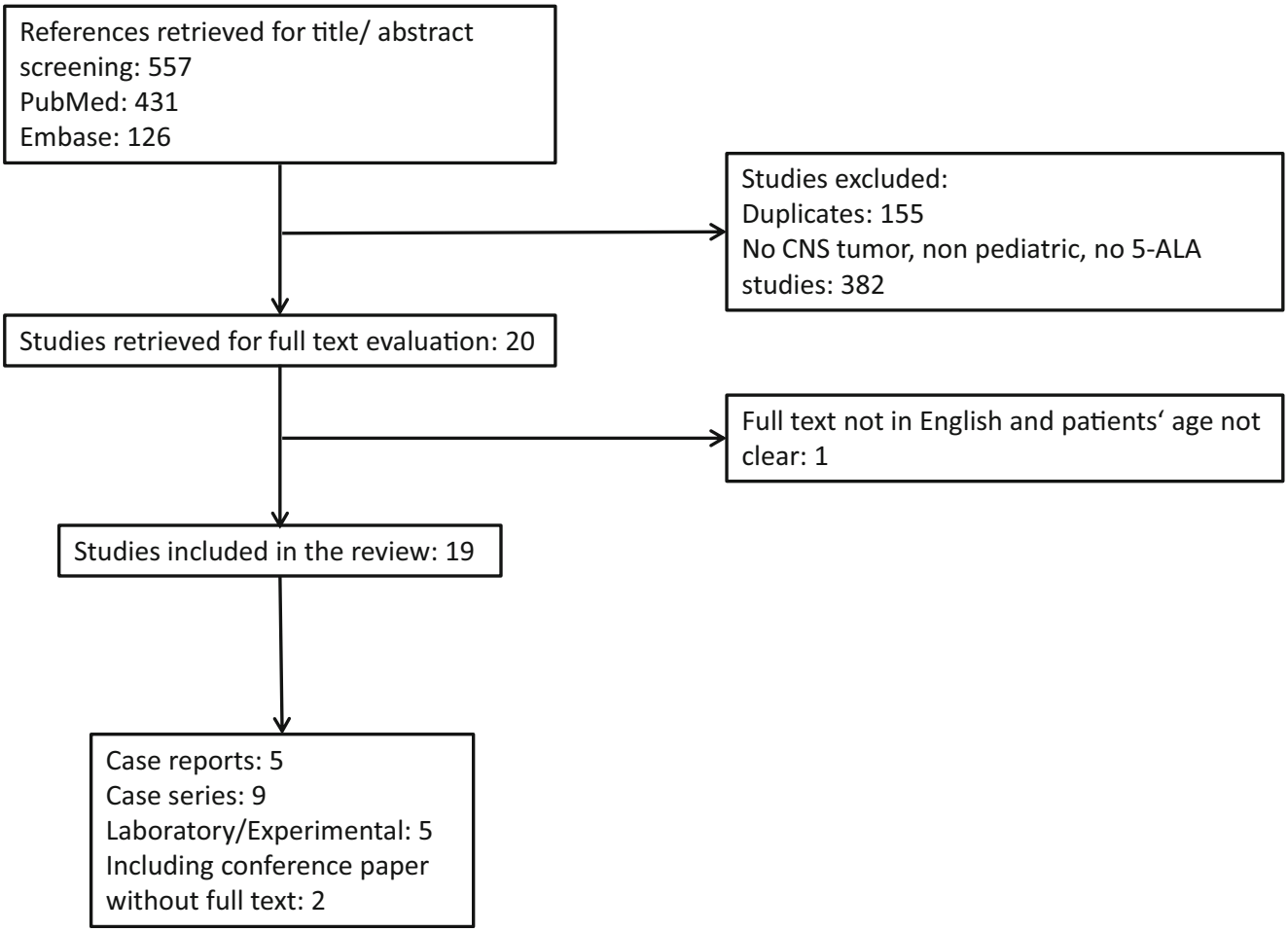


**Fig. 1** Flowchart of the study screening and selection process

**Table 1** Summary of the 14 cases series and reports reporting the usage of 5-ALA-guided surgery on CNS tumors in children and adolescents, in summary 175 cases. *One case with unclear histology

| Study | Year | Origin | Design | Number of patients | Age (years) |
|---|---|---|---|---|---|
| Agawa et al. | 2018 | Japan | Case report | 1 | 13 |
| Barbagallo et al. | 2014 | Italy | Case series | 3 | 12, 8, 18<br>*12.67 (± 5.03)* |
| Beez et al. | 2014 | Germany | Case series | 16 | *Median 8.5 (range 1–16)* |
| Bernal Garcia et al. | 2015 | Spain | Case report | 1 | 7 |
| Burford et al. | 2017 | UK | Case series | 6 | Median 6.5 (range 1–15) |
| Kim et al. | 2017 | Russia | Case series | 13 | Median 8 (range 3–17) |
| Preuß et al. | 2013 | Germany | Case series | 18 | 10.94 (4.67)<br>12 (range 3–18) |
| Roth et al. | 2017 | Israel | Case series | 14 | Median 11 (4–19) |
| Ruge et al. | 2009 | USA | Case report | 1 | 9 |
| Skjøth-Rasmussen et al. | 2015 | Denmark | Case report | 1 | 9 |
| Stummer et al. | 2014 | Germany, Spain, Denmark, Ireland, Italy, Switzerland | Case series | 78 | Median 13 (range 1–17) |
| Suzuki et al. | 2012 | Japan | Case series | 11 | NA |
| Eicker et al. | 2011 | Germany | Case report | 1 | 15 |
| Watanaya et al. | 2017 | Japan | Case series | 11* | Range 1–18 |

**Table 2** Summary 174 cases with known tumor type

| Histology | Number | Percent | First surgery | Recurrence | Supratentorial | Infratentorial | Strong fl | Weak/ patchy | No fl | Helpful fl | Percent |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pilocytic astrocytoma | 33 | 19 | 24 | 9 | 9 | 24** | 4 | 3 | 26 | 4 | 12 |
| Glioblastoma | 27 | 15 | 13 | 14 | 24 | 3 | 21 | 3 | 3 | 21 | 78 |
| Medulloblastoma | 23 | 13 | 19 | 4 | 0 | 23 | 5 | 13 | 5 | 5 | 22 |
| Ependymoma grade III | 14 | 8 | 5 | 9 | 9 | 5 | 8 | 3 | 3 | 10 | 71 |
| Germinoma | 11 | 6 | 11 | 0 | 11 | 0 | 10 | 0 | 0 | 10 | 91 |
| Ganglioglioma | 10 | 6 | 8 | 2 | 10 | 0 | 2 | 2 | 6 | 2 | 20 |
| PNET | 9 | 5 | 2 | 7 | 9 | 0 | 2 | 2 | 5 | 4 | 44 |
| Anaplastic astrocytoma | 6 | 3 | 6 | 0 | 6 | 0 | 3 | 2 | 1 | 4 | 67 |
| Ependymoma grade II | 5 | 3 | 2 | 3 | 2 | 3 | 3 | 1 | 1 | 4 | 80 |
| DNET | 4 | 2 | 3 | 1 | 4 | 0 | 1 | 0 | 3 | 1 | 25 |
| Pilomyxoid astrocytoma | 4 | 2 | 1 | 3 | 0 | 4 | 1 | 0 | 3 | 1 | 25 |
| Oligodentroglioma III | 3 | 2 | 2 | 1 | 3 | 0 | 1 | 1 | 1 | 2 | 67 |
| Oligodentroglioma II | 3 | 2 | 3 | 0 | 3 | 0 | 1 | 1 | 1 | 1 | 33 |
| Pleomorphic xantoastrocytoma | 3 | 2 | 2 | 1 | 3 | 0 | 1 | 0 | 2 | 1 | 33 |
| Astroblastoma | 2 | 1 | 2 | 0 | 2 | 0 | 2 | 0 | 0 | 2 | 100 |
| Meningeal sarcoma | 2 | 1 | 2 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 50 |
| Diffuse astrocytoma grade II | 2 | 1 | 2 | 0 | 1 | 1 | 0 | 0 | 2 | 0 | 0 |
| Glioneural tumor | 2 | 1 | 2 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Neuroblastoma | 2 | 1 | 2 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 0 |
| Papillary meningeoma | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 100 |
| Choroid plexus carcinoma | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Ganglio-neuroblastoma | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Gliotic tissue | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Hemangioblastoma | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Hemangiopericytoma | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Lipoma | 1 | 1 | 1 | 0 | 0 | 1* | 0 | 0 | 1 | 0 | 0 |
| Plexus papilloma II | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Sarcoma | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| SUM | 174 | 100 | 117 | 57 | 106 | 69 | 67 | 33 | 71 | 74 | 43 |

Summary including histology finding, localization, the intensity of fluorescence signal, and whether 5-ALA (5-aminolevulinic acid)-guided surgery was helpful for decision making during resection of the tumor

*PNET* primitive neuroectodermal tumor, *DNET* dysembryoplastic neuroepithelial tumor, *fl* fluorescence

*Spinal cord

**Two in the spinal cord

neuroectodermal tumors (PNET, according the 2007 WHO Classification, $n = 9$) (Table 2). In one case, histology was unclear [86].

5-ALA-guided surgery was described as helpful in astroblastomas (2/2, 100%), papillary meningiomas (1/1, 100%), spinal ependymomas (1/1, 100%), germinomas (10/11, 91%), ependymomas WHO grade II (4/5, 80%), GBMs (21/27, 78%), anaplastic ependymomas WHO grade III (10/14, 71%), anaplastic astrocytomas (4/6, 67%), and oligodendrogliomas WHO grade III (2/3, 67%). The higher the tumor grade was according to the WHO classification, the higher the probability was that 5-ALA-guided surgery was considered helpful (Fig. 2a, b). Moreover, we found that supratentorial tumors accumulated more fluorescent porphyrins and that the usage of 5-ALA was described as helpful for resection in these cases (Fig. 2c). When 5-ALA was considered helpful, the degree of resection was higher (gross or near total resection GTR/NTR in 58% in comparison to 22% of cases, Fig. 2d).

## Side effects

Most postoperative complications were related to tumor resection, for example, posterior fossa syndromes and neurological deterioration. These complications appeared independent of the

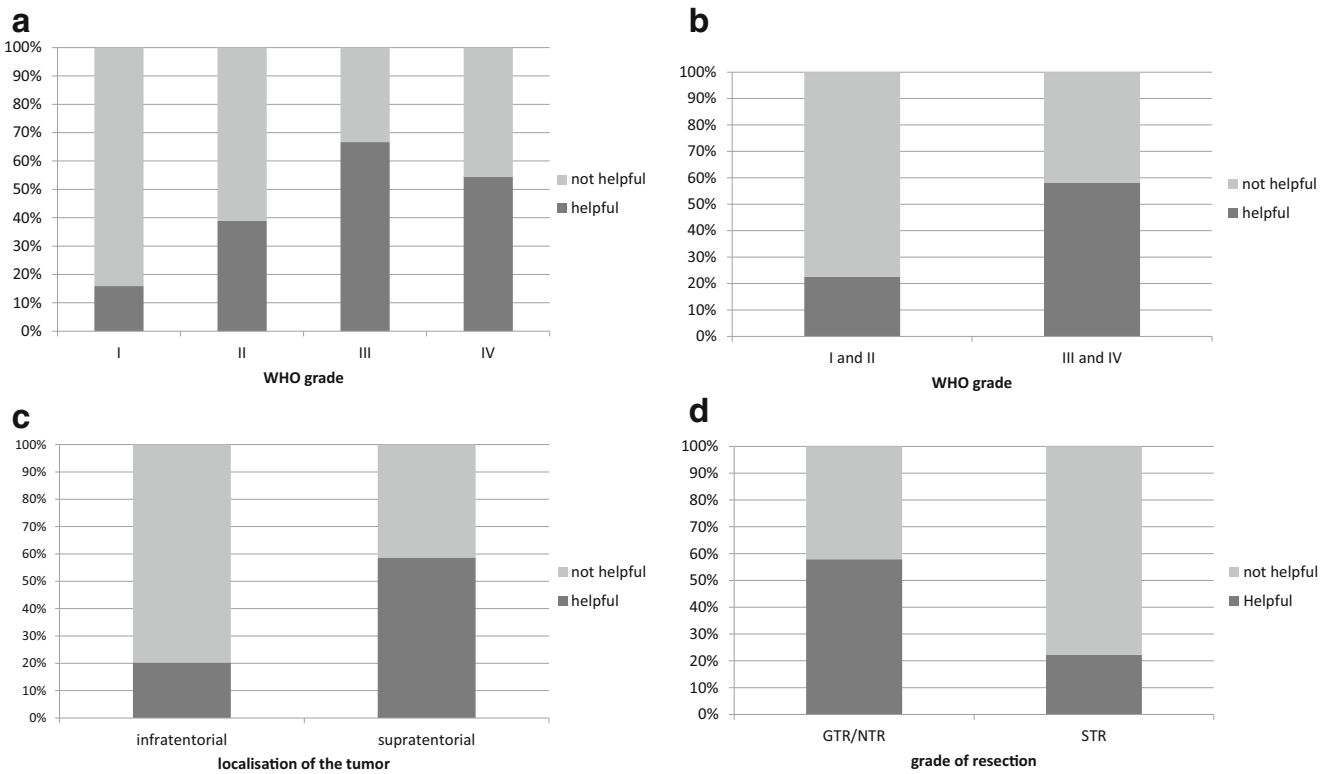


**Fig. 2** **a** The association between tumor grade according the WHO classification and usefulness of 5-ALA-guided resection; see text for further information. **b** Dichotomic association between low-grade pediatric brain tumor (grades I and II according WHO classification) and high-grade tumors (grades III and IV according WHO classification). 5-ALA was considered more helpful in high-grade tumor rather in low-grade ones. **c** The association between the localezation of the tumor in the brain and 5-ALA-guided surgery. It was consodered more helpful in supratentrial tumors. **d** In the case 5-ALA-guided surgery was considered helpful, the rate of gross total resection (GTR) or near total resection (NTR) was higher than the rate of subtotal resection (STR)

amount of tumor fluorescence. As in the adult population, reversible slight elevation of liver transaminases was determined after the administration of 5-ALA during the first days. Beez et al. indicated that lower age was associated with higher enzyme levels [7]. However, the mean level stayed below normal values and no long-term liver morbidity was found [7]. One case of a massive rash was identified a week after 5-ALA application in case of a 12-year-old girl with medulloblastoma. However, the fact that the rash appeared 1 week after 5-ALA application, much longer than expected from physiological 5-ALA metabolism, made a causal relationship between 5-ALA and the adverse event unlikely [57]. The youngest child to be dosed with 5-ALA was 1 year old [7] without side effects being observed.

### Experimental studies

In addition to the clinical studies, we found five experimental studies regarding 5-ALA-guided surgery and 5-ALA-derived photodynamic therapy (PDT) of pediatric CNS tumors. All in vitro experiments demonstrated porphyrin accumulation in tumor cells after exposure to 5-ALA to a certain extent. One study analyzed pharmacokinetics of the fluorescent porphyrins in different cell lines, showing maximal fluorescence signal intensity about 3 to 6 h after the application of 5-ALA [65]. However, the maximum intensity of fluorescence signal differed in various cell lines; especially, two medulloblastoma cell lines had different latencies of maximum intensity. Furthermore, the level of fluorescence intensity was variable in the different tumor types. Further studies showed the efficacy of 5-ALA derived photodynamic therapy (PDT) on different pediatric CNS tumors [10, 14, 53, 66].

## Discussion

5-ALA-guided surgery was considered useful in tumor types such as malignant astrocytoma, anaplastic astrocytoma, grade III oligodendrogliomas and ependymomas, improving grade of resection, and thus potentially PFS and OS (Fig. 2d). On the other hand, the data from available publications were from patient-based case series; as such, they do not yet justify the uncritical use of 5-ALA in the pediatric population. However, in two of the most frequent tumor types in this patient group, medulloblastoma and PA, 5-ALA-guided surgery was not considered helpful in making decisions regarding tumor resection in most cases.

Stummer et al. compiled the largest series of pediatric patients operated with 5-ALA and found that—from the ex-ante

view with unknown histology—mainly contrast enhancing, supratentorial tumors were amenable for 5-ALA-guided resection. This was due to the fact that medulloblastomas and PAs, the most frequent tumor types in the posterior fossa, did not accumulate sufficient fluorescent porphyrins to show a fluoresce signal using the operation microscope under blue light in many cases [74]. These findings were confirmed as 5-ALA-guided surgery was considered more helpful in supratentorial tumors (Fig. 2c).

## Glioblastoma and anaplastic astrocytoma

GBM is the most frequent CNS tumor in adults, but it is not as frequent in children with an incidence of only 10% of all primary pediatric CNS tumors [46, 54, 57]. In our literature analysis, GBM was the second most frequent tumor with 27 cases (15%) subjected to fluorescence-guided resections. In 21 out of the 27 (78%) case tumors, a strong fluorescent signal was reported, and 5-ALA was considered helpful for resection. In patients for whom the degree of resection was reported, GTR was achieved in 8 of 12 cases (67%) of the cases (Fig. 2d) [6, 7, 28, 52, 74, 86].

The rate at which useful fluorescence was reported in anaplastic astrocytoma (WHO grade III) was similarly high (4/6, 67%) [7, 74]. Thus, 5-ALA-guided resection of pediatric high-grade glioma appeared to be of similar utility as in the adult population [15, 20, 50, 60, 63, 71–73, 76, 82]. In suspected high-grade glioma in the pediatric population, or in cases with known histology, e.g., after biopsy or in recurrences, fluorescence-guided resections might therefore aid in enhancing resection and possibly outcomes. However, there are no clinical trials analyzing the effects on survival after 5-ALA-guided resection in pediatrics so far.

## Ependymoma

The cases identified in this review revealed a high rate of strong fluorescence in ependymomas, both of grades II and III [7, 11, 28, 52, 74, 86]. Though ependymomas can be identified quite well under white light only [57], additional fluorescence guidance could be helpful in allowing a higher grade of surgical resection, the most consistent prognostic factor for progression-free survival (PFS) and overall survival (OS) [23, 30, 34, 35, 48]. Clinical reports on 5-ALA-guided resection of ependymomas in adults support these results, including those located in the spinal cord [17, 27]. Especially in cases of non-cystic intramedullary ependymomas, fluorescence helps the surgeon to identify residual tumor tissue [27].

## Medulloblastoma and pilocytic astrocytoma

Conversely, 5-ALA-guided surgery did not seem to be very helpful in the most frequent CNS tumor types in pediatric patients, medulloblastoma and PA. Both tumor types usually differ from surrounding brain tissue, and thus, high degrees of resection can be achieved using the standard white light operating microscope. PAs are considered cured after GTR, and too large remnants of medulloblastoma are considered as risk factor [4, 30, 47, 88]. Therefore, 5-ALA-guided surgery, though considered helpful only in about one of five cases [6, 7, 11, 18, 52, 57, 74, 86], could be an option for a second look resection [69]. Notably, reported cases of medulloblastoma so far have not been stratified by the new molecular classification of these tumors—with differences in clinical presentation, prognosis, and treatment options [29, 41–43, 58, 67, 81]. In comparison to clinical results, in vitro incubation of medulloblastoma cell lines with 5-ALA leads to the accumulation of fluorescent porphyrins in all cases, albeit with different signal intensities and pharmacokinetics, in order to identify the fluorescence signal using the operating microscope a specific threshold of PPIX concentration has to be exceeded [77]. One reason could again be different molecular types of medulloblastoma cell lines, which were not reported in available studies [10, 12–14, 40, 41, 53, 58, 66]. Our hypothesis regarding the lack of PPIX accumulation in PA is the benign nature of this tumor type, as we noticed that tumor grading plays some role in PPIX accumulation.

## Germinomas

In cases of suspected germinoma tumor, resection is not the treatment of choice; however, tissue samples are usually required for diagnosis in addition to MRI scans and additional markers in serum and cerebrospinal fluid (CSF) [45]. One case series from Japan showed very good efficacy of 5-ALA-guided endoscopic biopsy of intraventricular germinomas ($n = 10/11$, 91%). Indeed, in the only tumor without fluorescence signal, it had a spontaneous regression [78].

## Other entities

In cases of PNET, according the former 2007 WHO classification, fluorescence-guided surgery was considered helpful in about half of the cases (4/9, 44%) [28, 52, 74, 86]; such in the case of medulloblastomas, it would be interesting to further investigate the PPIX accumulation in embryonal tumors according the novel classification [32, 51]. The frequency of other tumor types was too low for determining the role of 5-ALA-guided surgery [2, 8, 11, 28, 52, 57, 59, 74, 86].

## Side effects

Overall, reports of complications related to 5-ALA appeared very low. Beez et al. (2014) found an age-dependent elevation of liver transaminases [7], a reaction reported for adult patients [72]; however, mean values did not exceed upper limits of

normal range. An interesting finding was the reverse association between patients' age and post-operative elevation of alanine aminotransferase (ALT) [7], indicating age-related pharmacodynamics. No further 5-ALA-related adverse events were reported. One problematical issue was the oral administration of 5-ALA to infants, which could be overcome by using nasogastric tubes. In one case, vomiting was reported after oral administration [74]. A major concern regarding 5-ALA-guided surgery is the potential development of new neurological deficits due to a too aggressive resection. This concern could not be confirmed in the reviewed publications. Studies on adults found neither major side effect nor higher rate of neurological deficits after 5-ALA-guided resection of malignant gliomas despite higher rate of GTR [15, 63, 72, 73, 82].

### Comparison to alternative methods

As mentioned above many typical pediatric CNS tumors such as ependymomas, PAs and medulloblastoma can be differentiated easily from normal brain tissue, thus allowing safe complete resection in most cases with the help of white light operation microscope alone [57, 89]. So far, the most widespread technique used for tumor location is neuronavigation [55, 87, 89], which enables planning of surgical approaches, finding the tumor and defining tumor margins. However, the high probability of brain shift has to be kept in mind. In addition, in infants, the use of a Mayfield clamp, which is required for most neuronavigation systems, is contraindicated.

Another alternative method to identify and to prove extent of resection of CNS tumors is intraoperative ultrasound (ioUS) [56], with the ioUS findings usually correlating with postoperative MRI [38, 68, 70, 79]. However, ioUS has technical limitations and its interpretation requires sufficient experience. In recent years, the use of intraoperative MRI (ioMRI) has become more common [1, 21, 22, 31, 80]. ioMRI allows obtaining scans during the operative procedure and helps the surgeon to identify residual tumor tissue, thus reducing the need of a second look operations. However, ioMRI devices, especial high-field ioMRI, are quite expensive and their use is time consuming, as surgery must be paused in order to perform the scan. Furthermore, ioMRI requires additional experience and expertise for interpreting the images. Centers that have both ioMRI and 5-ALA consider the methods to be synergetic rather than competitive [19, 83].

### Legal issues

At present, the use of 5-ALA in neurosurgery in Europe is only approved for adults with malignant gliomas. This fact makes every usage of 5-ALA in children and adolescents off-label. However, in clinical practice, especially in the pediatric population, many medications are used off-label due to lack of trials supporting use in this population subset.

In the German setting, the use of a medication on an off-label basis in children pre-requires clinical necessity, informed consent by guardians as, well as data obtained from trials in the adult population, indicating a favorable risk–benefit ratio. On the other hand, off-label use of a drug is not permitted when approved drugs are available for the same indication, which is not the case for 5-ALA.

### Limitations

This review is based on various reports from different neurosurgical departments around the world. Assessments of the tumor fluorescence signal reflected in these reports are subjective and depend on the surgeon's perception, the operating microscope used, and light conditions in the operating room. The quality of some publications was low as many reports lacked pertinent data regarding tumor subtype, imaging, neurological status, and degree of resection. Furthermore, no data regarding the accuracy of the association of 5-ALA fluorescence signal and histopathology were available. Nevertheless, the classification of 5-ALA in helpful and not helpful is not the most scientific way to describe an operative method; however, alternative descriptions were not applicable due to the lack of data. However, this is the first systematic review of literature conducted to prove the role of 5-ALA-guided resection of pediatric brain tumors; moreover, we addressed clinical topics such as grade of resection, side effects, and complications.

## Conclusion

We conclude that 5-ALA-guided surgery might play a role in resection of CNS tumors in children and adolescents, especially in cases of suspected malignant glioma or ependymoma, enabling a greater extent of tumor resection and thus improving patients' outcome. However, further studies, both experimentally and clinically, should be performed to increase the overall level of evidence concerning the usage of 5-ALA in the pediatric population. In addition, the steadily increasing number of patient-based publications regarding the use of 5-ALA to guide the resection of brain tumors in children and adolescents makes the general use of 5-ALA in the pediatric population more likely, despite the lack of information regarding safety. Therefore, prospective trials are urgently required. Such trials should have an emphasis on drug safety but should also attempt to correlate the fluorescence signal closely with histopathological findings.

## Compliance with ethical standards

**Conflict of interest** Walter Stummer has received consultant fees from Medac, Wedel, Germany. All other authors declare that they have no conflict of interest.

**Ethical approval** For this type of study, formal consent is not required.

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