Beneficial impact of high-field intraoperative magnetic resonance imaging on the efficacy of pediatric low-grade glioma surgery

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OBJECTIVE Intraoperative MRI (iMRI) is assumed to safely improve the extent of resection (EOR) in patients with gliomas. This study focuses on advantages of this imaging technology in elective low-grade glioma (LGG) surgery in pediatric patients.

METHODS The surgical results of conventional and 1.5-T iMRI-guided elective LGG surgery in pediatric patients were retrospectively compared. Tumor volumes, general clinical data, EOR according to reference radiology assessment, and progression-free survival (PFS) were analyzed.

RESULTS Sixty-five patients were included in the study, of whom 34 had undergone conventional surgery before the iMRI unit opened (pre-iMRI period) and 31 had undergone surgery with iMRI guidance (iMRI period). Perioperative data were comparable between the 2 cohorts, apart from larger preoperative tumor volumes in the pre-iMRI period, a difference without statistical significance, and (as expected) significantly longer surgeries in the iMRI group. According to 3-month postoperative MRI studies, an intended complete resection (CR) was achieved in 41% (12 of 29) of the patients in the pre-iMRI period and in 71% (17 of 24) of those in the iMRI period ($p = 0.05$). Of those cases in which the surgeon was postoperatively convinced that he had successfully achieved CR, this proved to be true in only 50% of cases in the pre-iMRI period but in 81% of cases in the iMRI period ($p = 0.055$). Residual tumor volumes on 3-month postoperative MRI were significantly smaller in the iMRI cohort ($p < 0.03$). By continuing the resection of residual tumor after the intraoperative scan (when the surgeon assumed that he had achieved CR), the rate of CR was increased from 30% at the time of the scan to 85% at the 3-month postoperative MRI.

The mean follow-up for the entire study cohort was 36.9 months (3–79 months). Progression-free survival after surgery was noticeably better for the entire iMRI cohort and in iMRI patients with postoperatively assumed CR, but did not quite reach statistical significance. Moreover, PFS was highly significantly better in patients with CRs than in those with incomplete resections ($p < 0.001$).

CONCLUSIONS Significantly better surgical results (CR) and PFS were achieved after using iMRI in patients in whom total resections were intended. Therefore, the use of high-field iMRI is strongly recommended for electively planned LGG resections in pediatric patients.

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KEY WORDS pediatrics; intraoperative MRI; neurosurgery; low-grade glioma; extent of resection

IT is well known that in pediatric low-grade glioma (LGG) surgery, total resection has the potential to cure patients. However, since these patients have a high overall survival rate, the cost of total resection must not include an increased risk of iatrogenic neurological defi-

cits.^{8,10} One of the most important neurosurgical tools in achieving the goal of safe, complete resection (CR) of an intraaxial lesions is, together with intraoperative electrophysiological monitoring (IOM), surgical guidance via intraoperative MRI (iMRI), which has become more widely

ABBREVIATIONS CR = complete resection; DNET = dysembryoplastic neuroepithelial tumor; EOR = extent of resection; ICU = intensive care unit; iMRI = intraoperative MRI; IOM = intraoperative electrophysiological monitoring; IR = incomplete resection; LGG = low-grade glioma; PFS = progression-free survival; PR = partial (or subtotal) resection.

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available through several new installations throughout the past years.^{5,11,14} The use of iMRI in pediatric neurosurgery has been described and evaluated in a few retrospective studies with low-^{4,9,12,13} and high-field^{2,3,6,7,15,16} magnets for various pathologies including glioma, vascular, and epilepsy surgery. A common conclusion in these studies is that iMRI is a safe technology for increasing the extent of resection (EOR) in pediatric patients. A direct comparison with conventional resection without iMRI guidance was conducted in the study by Shah et al.,¹⁵ who were able to show that the surgical goal of either gross-total resection or biopsy/subtotal resection was achieved equally in both groups (79% vs 80%) but with a significantly higher rate of reoperation within 14 days in the conventional group (0% with iMRI vs 7.77% in the conventional group).

To our knowledge, no study has specifically focused on the use of iMRI in pediatric LGG surgery. Yet electively planned LGG surgery in pediatric patients is the group in which the best surgical results, including cure, are often expected by patients and their families, as well as by the surgeons themselves. Therefore, we evaluated the role of iMRI in elective pediatric LGG surgery and its effect on EOR according to the 3-month follow-up MRI with an independent reference radiology evaluation, in comparison with conventional resections without iMRI. We also analyzed perioperative and follow-up data, including tumor volumetry, intention-to-treat, and supportive surgical tools, as well as the patients' clinical condition and progression-free survival (PFS).

The aim of this study was to offer a comprehensive referral on the use of iMRI in elective pediatric LGG surgery based on our single-center experience.

Methods

Patient Cohort

The local institutional ethics review committee approved this retrospective single-institution study of prospectively collected data. We analyzed the pediatric clinical database records of consecutive patients who had undergone LGG resection between 2007 and 2014. Intraoperative MRI-guided surgery has been possible since July 2011. All pediatric patients (age < 18 years) with electively planned surgery (intended complete, subtotal, and partial resections) for suspected LGG were eligible for analysis. All patients with an emergency indication for surgery within 48 hours after an initial diagnosis were excluded from analysis because surgery in these patients could not often be planned under "perfect" conditions. Since opening the iMRI unit, all elective pediatric LGG patients have had surgery in the iMRI suite.

Assessment of Medical Records

Medical records were assessed for patient sex; age; height; weight; neurological status pre- and postoperatively; histological report; surgery report; discharge note; duration of surgery; intensive care unit (ICU) and hospital stay; pre-, intra-, and postoperative MRI; results of 3-month postoperative MRI reference radiology report; general clinical and imaging follow-up; and PFS. If patients were lost to follow-up, the most recent clinical in-

formation was entered in the analysis. New relevant postoperative neurological deficits were defined as none (0), mild (1) if they were transient, or severe (2) if they did not resolve by 3 months postoperatively.

Operative Setup

Intraoperative MRI was performed in an iMRI suite (IMRIS Visius Surgical Theater, IMRIS Inc.) with a modified, ceiling-mounted, 1.5-T movable magnet (Espree, Siemens Medical Systems), as described in the work by Chen et al.¹ Electrophysiological monitoring (Nicolet Endeavor CR, Cardinal Health) using platinum needles, which can stay in place during scanning, and careful avoidance of cable-to-skin contact; BrainLab neuronavigation (VectorVision compact system and Curve); and high-resolution ultrasound (Acuson Antares, Siemens AG) were used in almost all cases. All surgeries were performed with an OPMI Pentero (Carl Zeiss) or a Leica M720 OH5 (Leica Microsystems) microscope.

Magnetic Resonance Imaging Analysis

Preoperative, postoperative, and follow-up MRI in all patients was discussed and evaluated in our interdisciplinary neuropediatric tumor board. Since all LGG patients at our center were routinely included in the SIOPP-LGG 2004 study and, after its closure, in the national interim registry, all 3-month postoperative MRI scans in the present study were routinely and independently assessed and reported by the German pediatric neuroradiology reference center. This report was used to classify the postoperative outcome regarding the EOR. Tumor volumetry was performed on preoperative, intraoperative, and 3-month postoperative MRI using Brainlab iplan.net (BrainLab AG; by R.D.S.F. and supervised by M.U.S.). Volumes were measured in each case in the most relevant imaging sequence (FLAIR, T2, T1 with or without contrast medium).

Statistical Analysis

Statistical analysis was performed with GraphPad Prism (version 6.01 for Windows, GraphPad Software Inc.). Continuous values are given as mean values (range). Continuous, unpaired nonparametric data were analyzed using the Mann-Whitney U-test. Continuous parametric data were analyzed using the t-test for unpaired samples. Categorical data were analyzed using Fisher's exact test. Progression-free survival was analyzed using the Kaplan-Meier method, and curve comparisons were made with the log-rank (Gehan-Breslow-Wilcoxon) test. Statistical significance was defined at p values ≤ 0.05 .

Results

General and Perioperative Patient Data

Sixty-five patients met the inclusion criteria. Thirty-four patients had elective LGG surgery before the iMRI unit was opened (henceforth called "pre-iMRI period"). After iMRI became available (henceforth called "iMRI period"), 31 patients had elective LGG surgery. Clinical and perioperative data are given in Table 1. In short, despite seeing small differences between the groups from these 2 periods, no significantly relevant differences were

TABLE 1. Clinical patient data for the pre-iMRI and iMRI period*

Parameter	Pre-iMRI	iMRI
No. of patients	34	31
Mean age in yrs (range)	9.3 (1.75–17)	10.9 (2–17)
Mean height in cm (range)	135 (74–176)	145 (89–181)
Mean weight in kg (range)	37 (7.5–76)	45 (12–84)
F/M ratio	19:15	12:19
Newly diagnosed tumors (%)	28 (82)	23 (74)
Recurrent tumors (%)	6 (18)	8 (26)
OR time in min (range)	271 (52–528)	383 (201–610)
Mean ICU stay in days (range)	1.5 (1–7)	1.2 (1–4)
Mean postop hospital stay in days (range)	8.8 (5–20)	7.0 (5–20)
Supratentorial tumors (%)	25 (74)	23 (74)
Infratentorial tumors (%)	9 (26)	8 (26)
Pilocytic astrocytoma WHO Grade I (%)	19 (56)	12 (39)
Astrocytoma WHO Grade II (%)	5 (15)	4 (13)
DNET WHO Grade I (%)	6 (18)	6 (19)
Ganglioglioma WHO Grade I (%)	3 (9)	7 (22)
Oligodendroglioma WHO Grade II (%)	1 (3)	2 (6)
Intraop MRI scans/case	0	1.1
Use of IOM (%)	18 (53)	20 (64)
Mean FU time in mos (range)	53.9 (13–89)	22.5 (8–45)

FU = follow-up; OR = operating room.

* The only relevant statistically significant difference was found in the longer operating room times ($p < 0.05$) for the iMRI group.

noted except for the duration of surgery, which was significantly longer in the iMRI period (mean 383 vs 271 minutes, $p < 0.05$), and larger preoperative tumor volumes in the pre-iMRI period (did not reach statistical significance). Other than that, both groups were absolutely comparable. No relevant iMRI-related or infectious complications were noted.

New transient postoperative neurological deficits were found in 11 patients (32%) in the pre-iMRI period and in 13 patients (42%) in the iMRI period, whereas persistent neurological deficits (those lasting longer than 3 months) were found in 3 patients (9%) versus 1 patient (3%), respectively. No new postoperative deficits were found in 20 patients (59%) in the pre-iMRI cohort and 17 patients (55%) in the iMRI cohort. No statistically significant difference in neurological deficits was seen between these 2 groups.

Intention to Treat and Achievement of Surgical Goals

Among the 34 patients in the pre-iMRI period, complete tumor resection was intended in 29 (85%) and partial (or subtotal) resection (PR) in 5 (15%). Among the 31 patients in the iMRI period, CR was intended in 24 (77%) and PR in 7 (23%). Among the 29 children in whom CR was intended in the pre-iMRI period, 12 (41%) had no residual tumor at the 3-month MRI follow-up, whereas 17 (59%) showed residual disease. In comparison, among the

24 patients in whom CR was intended in the iMRI period, 17 (71%) were free of tumor and 7 (29%) had residual tumor at the 3-month follow-up. These numbers reveal a statistically significantly ($p = 0.05$) higher rate of achieving the goal of CR in the iMRI group (Fig. 1).

Independent of the preoperative intention to treat, surgeons sometimes have to change their strategies and goals intraoperatively because of, for example, unexpected anatomical findings or worsening of IOM. Therefore, we also analyzed the consistency between the surgeon's postoperative impression of the EOR and the final evaluation at the 3-month postoperative MRI. Of 29 intended CRs in the pre-iMRI period, only 22 were achieved according to the surgeon's postoperative impression. The reasons for leaving tumor behind were infiltration in relevant anatomical areas in 5 cases, limited field of view in 1 case, and significant decrease in IOM in 1 case. However, of 22 postoperatively assumed CRs in patients in the pre-iMRI period, only 11 (50%) were free of tumor at the 3-month follow-up MRI.

In the iMRI period, the surgeon was postoperatively convinced that he had achieved CR in 21 of the 24 patients in whom CR was intended. The reasons for changing the surgical strategy from an intended CR to PR was based on infiltration of relevant anatomical structures in 2 cases and on worsening of IOM in 1 case. Of the 21 postoperatively assumed CRs, the goal was actually achieved in 17 patients (81%) at the 3-month postoperative MRI. A comparison of these 2 groups strongly suggested a significant higher rate of achieved CRs at the 3-month postoperative MRI in the iMRI period than in the pre-iMRI period ($p = 0.055$; Fig. 2).

Influence of iMRI on the Intraoperative Course of LGG Resection

Thirty-one children underwent surgery with iMRI guidance. In 20 of these patients, resection control with iMRI was performed at a point in the surgery when the surgeon assumed that he had achieved CR; the surgeon also used intraoperative high-resolution ultrasound for resection control before scanning, if applicable. However, the goal of CR was achieved in only 6 (30%) of these 20 cases. In the other 14 cases (70%), residual tumor was found and the resection was therefore continued with the updated information. Complete resection was subsequently achieved in 11 of these 14 cases according to the 3-month follow-up MRI. Thus, iMRI increased the rate of CR from 30% (6 of 20 cases) to 85% (17 of 20 cases).

All 6 cases with CR when the iMRI was performed—and thus with no continued tumor resection—had confirmed CR at the 3-month postoperative MRI.

In 11 of the 31 iMRI cases, the intraoperative scan was obtained and the surgery was paused so the surgeon could orient himself to the current status of the resection; this was done in 4 of the 24 patients in whom CR was planned and all 7 cases in which PR was intended. In 2 (29%) of the 7 children in whom PR was planned, the resection was continued after obtaining the intraoperative scan, whereas in 5 (71%) the resection goal had been achieved and the surgery was discontinued. In none of the 4 cases in which CR was intended, in which an intraoperative scan was

FIG. 1. Plot of the distributions of the intent of resection in the pre-iMRI and iMRI periods with the respective 3-month follow-up MRI results. Differences in achieved CRs were statistically significant, with $p = 0.05$.

obtained for orientation because of surgery in highly eloquent areas such as the basal ganglia, could a CR finally be achieved.

Volumetric Aspects of Preoperative, Intraoperative, and 3-Month Postoperative MRI

Tumor volumetry was performed on preoperative, in-

traoperative, and 3-month postoperative MRI for all patients in the iMRI period and on preoperative and 3-month postoperative MRI in all patients in the pre-iMRI period. Volumes and p values for cohort comparisons are given in Table 2. Statistically significant smaller tumor volumes were found on the 3-month follow-up scans in the iMRI period than those in the pre-iMRI period for the entire

FIG. 2. Plot of the distributions of the postoperatively assumed EOR in the pre-iMRI and iMRI periods with the respective 3-month follow-up MRI results. Differences in achieved CR showed a strong trend toward significance, with $p = 0.055$.

TABLE 2. Overview of pre-, intra-, and postoperative tumor volumes*

Group	Pre-iMRI Period		iMRI Period			p Value
	Preop	3-Mos Postop	Preop	Intraop	3-Mos Postop	
Entire cohort	19.1 (1.1–62.3)		11.3 (0.3–61.3)			>0.05
		2.7 (0–27.5)			0.8 (0–7.8)	0.03
		2.7 (0–27.5)		2.2 (0–30.7)		>0.05
Intended CR	19.5 (1.1–62.3)		10.9 (0.3–61.3)			>0.05
		3.0 (0–27.5)			0.5 (0–7.8)	0.01
		3.0 (0–27.5)		2.1 (0–30.7)		>0.05
				2.1 (0–30.7)	0.5 (0–7.8)	NA
Postoperatively assumed CR		1.2 (0–7.0)			0.4 (0–7.8)	0.005
				0.8 (0–3.9)†	0.4 (0–7.8)†	NA

NA = not applicable.

* Values expressed as the means (range) in cm³. Boldface type indicates statistically significant differences.† One patient showed only small amount of residual disease (3.8 cm³) on iMRI but a larger volume at the 3-month MRI (7.8 cm³). For further explanations, see the *Discussion*.

cohort ($p = 0.03$), the cohort with intended CR ($p = 0.01$), as well as the cohort with postoperatively assumed CR ($p = 0.005$).

In the 7 cases with intended CR and residual tumor despite the use of iMRI, the detected mean residual tumor volume at the 3-month postoperative MRI was 0.5 cm³ and thus minimal.

Tumor volumes at iMRI were similar to the 3-month postoperative tumor volumes in the pre-iMRI period, suggesting a comparable intraoperative radicality despite

knowing that subsequent MRI would be performed for the control of resection margins.

Patient Follow-Up and Influence of the EOR on PFS

The mean follow-up was 36.9 months (3–79 months) in the entire cohort, 50.4 months (3–79 months) in the pre-iMRI period, and 22.5 months (8–45 months) in the iMRI period. Kaplan-Meier PFS curves can be found in Fig. 3.

Analysis of PFS in the entire pre-iMRI and iMRI co-

FIG. 3. **A:** Kaplan-Meier curves of PFS for the entire cohort separated into the pre-iMRI and iMRI groups. No statistically significant difference was observed between the 2 groups; however, a trend for a higher percentage of patients with PFS is visible using iMRI. **B:** Kaplan-Meier curves of PFS for patients in whom the surgeon assumed that CR had been achieved at the end of surgery. A strong trend in favor of iMRI can be seen, yet statistical significance was not quite achieved because of 1 patient with recurrent tumor after 37 months. **C:** Kaplan-Meier curves of PFS for patients with CR and those with IR at the 3-month MRI control. Statistically highly significant differences ($p < 0.001$) favored CR as the primary goal of any LGG surgery in children.

hort, as well as differences between the 2 groups of patients with intended CR or PR (data not shown) did not show statistically significant results, although there was a minor trend for a PFS advantage in the iMRI group (Fig. 3A).

In analyzing the pre-iMRI and the iMRI cohorts with postoperatively assumed CR, a clear difference in favor of the iMRI group was seen, yet statistical significance was not reached ($p = 0.14$), since 1 patient had tumor recurrence at 37 months and had had the longest recurrence-free tumor control until this point, causing the curve to drop to 0% (Fig. 3B).

Finally, analysis between patients with a 3-month postoperative MRI-confirmed CR and those with incomplete resections (IRs) showed a statistically highly significantly longer PFS in the former group ($p < 0.001$). In the group of patients with CR, only 1 patient with a ganglioglioma WHO Grade I had a tumor recurrence after 37 months. Since the rate of CR was statistically higher in the iMRI period, there was a strongly assumable advantage for patients after the introduction of iMRI, even if statistics failed to show this with the current numbers and follow-up (Fig. 3C).

Discussion

In this study we analyzed the surgical results in 65 pediatric patients with LGGs, of whom 34 had undergone conventional surgery before an iMRI unit was available at our center and 31 had undergone surgery with the support of iMRI. To our knowledge, this is the first study of pediatric LGGs with a direct comparison of the surgical and clinical results between conventional and iMRI-guided surgery.

As seen in other studies, the use of high-field iMRI is a safe technology even for very small children,^{2,3,6,7,15,16} and we have defined a body weight of 10 kg as the minimum for iMRI-guided surgery in our department because of longer ventilation tubes for in-scanner ventilation and thus critical dead space in small tidal volumes. Therefore, any concerns due to extended anesthesia when using iMRI can be overcome as long as specialized anesthesiologists and pediatric intensive care teams supervise the patients both intra- and postoperatively. The most relevant risks are related to pressure and heat-related skin damage due to increased operating times and possible heating of the patient in the scanner. To ensure safe positioning, we specifically focus on all exposed body parts at risk from continuous pressure such as the heels, knees, and elbows, among others. Besides the standard padding of the operating room table, we also use various foam paddings to ensure soft positioning of all areas at risk. To avoid loops and subsequent heating of the cables of the MR-compatible platinum/iridium needles, which can remain on the patient during scanning, we use tape to straighten the cables. Direct skin-skin or plastic-skin contact as a possible source of heating due to condensed water is avoided by the interposition of large, soft cotton pads. These additional safety issues require only a few extra minutes of preparation time. The significantly extended operating room times (383 in the iMRI period vs 271 minutes in the pre-iMRI period) due to longer preparation times preoperatively and pres-

canning plus the scanning time can be perceived as a disadvantage of this technology. In our experience, however, this extra time has no impact on perioperative complication rates. The higher costs of the longer procedures and the iMRI-specific equipment are justified by the substantially improved results in terms of surgical radicality and better PFS rates.

To show advantages of iMRI-guided surgery, we added a case example with pre-, intra-, and postoperative MRI (Fig. 4).

Importance of CR

Extra efforts seem to pay off in terms of a significantly improved surgical result with comparable neurological outcomes. A significantly higher number of CRs at the 3-month follow-up MRI (41% in the pre-iMRI period vs 71% in the iMRI period) in patients with preoperatively intended CRs could be achieved using iMRI. However, sometimes surgeons must change their strategy intraoperatively when critical anatomical structures are infiltrated or IOM is worsening. Therefore, the most interesting cases are those with postoperatively assumed CRs that were truly tumor free at the 3-month postoperative MRI: only 50% of all cases in the pre-iMRI period versus 81% in the iMRI period. Thus, PFS was better in the iMRI cohort of patients with assumed CR. The importance of CR can also be seen in Fig. 3C, as PFS was significantly better in these patients and can almost be seen as a cure for the disease. In our series, with its total of 30 CRs according to 3-month postoperative MRI, only 1 patient had a recurrence after 37 months. Therefore, decreasing the number of secondary interventions to remove residual disease is of great benefit not only for the patients, but also for the health system.

Aspects of Using iMRI

One might ask why residual tumor was found in 4 children at the 3-month MRI follow-up despite the fact that the surgeon had postoperatively assumed that CR had been achieved after using iMRI. In none of the 4 patients did we perform additional intraoperative scanning after the end of the secondary resection (as was not done in almost all other cases). In 1 of these cases, the residual tumor tissue was very close to an eloquent area where a functional limitation existed according to IOM. In 1 case, the reference radiologist was not 100% sure if the assumed residual tumor corresponded to glial scar tissue or to vital tumor. So far, the “residue” has not grown during the follow-up in this case. Therefore, in the 2 remaining cases, IR may have been prevented by obtaining another intraoperative scan after the secondary resection of residual tumor. Nevertheless, efforts toward advantages of an additional scan at the end of surgery, which we do not routinely perform in our department, must be critically balanced in every case.

One case with an extensive and diffusely infiltrating pilocytic astrocytoma of the cerebellar hemisphere (preoperative tumor volume 35.7 cm³) showed rather small residual disease (2.7 cm³) on the second iMRI scan but a much larger tumor volume at the 3-month postoperative MRI (7.8 cm³). This is the only case of an intraoperative false-negative or falsely low tumor volume determination. In retrospect, we believe we were misled by blood

FIG. 4. Axial and coronal MR images obtained in a 10-year-old boy with epilepsy caused by a left temporooccipital DNET (A) close to the visual tract, as also shown by high-resolution fiber tracking (B). Intraoperative MR images (C) show residual tumor (asterisk) anterior and posterior to the resection cavity; the tumor remnant was removed after the intraoperative scan. Three-month postoperative MR images (D) show tumor-free resection margins, yet a tiny FLAIR change (arrow) near the visual tract that will require further control, as reference radiology was not 100% sure whether these changes were glial scar tissue or residual disease. Postoperatively, no more epileptic seizures were reported, and the visual field was tested and showed no deficits.

artifacts in the resection cavity at the time of the second iMRI, which prevented correct identification of FLAIR-hyperintense residual tumor tissue. This case emphasizes the importance of having an absolutely blood-free resection cavity filled with clear fluid at the time of iMRI to have the best image quality possible.

In those cases in which tumor did not take up contrast medium preoperatively, the intraoperative scan, if it showed no or minimal residual tumor, could substitute for the usual postoperative scan, which is mandatory in the SIOPP-LGG study protocol.

In contrast-enhancing tumors there is a small likelihood of false-positive intraoperative scans, since surgical manipulation-induced blood-brain barrier leakage of gadolinium could be incorrectly interpreted as residual tumor. Consequently, continuing surgery for minimal contrast-enhancing spots may be unnecessary, or if no further surgery is undertaken, the reading of the intraoperative scan may be false-positive for minimum residual tumor, as compared with an otherwise negative postoperative scan within 24–72 hours after surgery.

However, since observation in any low-grade tumor case is mandatory for at least 3 months and since the 3-month postoperative MRI is usually considered as baseline for any further assessment, we are convinced that iMRI that shows no or little residual tumor (with subsequent surgery) can substitute for the usual postoperative scan 24–72 hours later. This is important in small children, who need to have sedation for MRI and would thus either be subjected to a second anesthesia or would be continued on sedation for 24 hours until the postoperative scan was obtained.

Planned PRs on iMRI

When iMRI was used for planned PR, in only 2 of the 7

cases was the resection continued after scanning. In both of these cases, the resection was initially limited because of worsening IOM. Larger-than-expected residual tumor was identified in both cases on iMRI, with a good chance of further resection without causing neurological deficits. Whether these further resections have had a beneficial impact on the further clinical course of these patients remains unanswered. So we must critically question whether the additional effort of iMRI-guided surgery is generally beneficial for patients with incompletely resectable LGGs, since the prevention of function will always limit the resection. Furthermore, there is a high likelihood that a residual tumor mass of a certain size (for example, 5 vs 4 cm³; as a result of not using iMRI) in a low-grade tumor case will not make a difference in the overall survival of the patient, although of course CR versus IR is important.

Specific Volumetric Aspects and Comparability of Cohorts

In addition to our analysis of CR, we performed volumetric analyses of preoperative, intraoperative, and 3-month postoperative MRI studies to gain a broader understanding of changes identified in this study. Surprisingly, we found a large, though not statistically significant, difference in mean preoperative tumor volumes between the pre-iMRI period (19.1 cm³) and the iMRI period (11.3 cm³). Even after looking at the volumes more intensively, we did not find any relevant selecting factors and would assume that this difference was most likely caused by chance and by the fact that some tumors in the iMRI period were very small. Furthermore, the volume of the preoperative tumor mass per se is not the limiting factor in terms of the radically of resection. What is always limiting is the border zone and the eloquence of bordering tissue. The 2 cohorts had a comparable amount of patients with

tumors in eloquent localizations requiring IOM (18 of 34 patients in the pre-iMRI period vs 20 of 31 patients in the iMRI period).

In the subgroup analysis of patients with postoperatively assumed CR, it was clearly shown that iMRI adds significant additional value by pinpointing small residual disease, independently of the surgeon's impression of the respective EOR and preoperative tumor volumes. In analyzing the 3-month postoperative tumor volumes, we showed that the use of iMRI did not only significantly increase the number of total resections, but was also capable of significantly decreasing the volume of residual disease in the entire cohort ($p = 0.03$), the subcohort with intended CR ($p = 0.01$), and the subcohort with assumed CR ($p = 0.005$).

In specifically looking at the 3-month postoperative residual tumor volumes of patients with a postoperatively assumed CR in the iMRI period, we clearly saw that all residual tumor volumes were very small (0.2, 0.1, 0.07 cm³), except in 1 case with misleading iMRI results (as described above).

To the best of our knowledge, these numbers constitute the best results in pediatric LGG surgery in the reported literature.

Intraoperative MRI-Guided Brain Tumor Surgery in Children

We have reviewed the literature on iMRI-guided surgery in pediatric patients for comparison with the results of our study. Four low-field^{4,9,12,13} and 6 high-field^{2,3,6,7,15,16} iMRI studies exist and generally report that it is safe to use iMRI in pediatric patients. No serious ferromagnetic accidents were reported, nor were more wound infections or anesthesia complications due to extended surgery times, which mirrors our experience. Most of the above-mentioned studies retrospectively stress the value added by iMRI, in particular because of the significant number of continued resections after the intraoperative scan. Direct comparison of our results with the findings in these studies is difficult because of the different study designs. Yet the percentage of continued resections after iMRI in mixed pathologies was between 21% and 49%, as opposed to the 60% in our patients with intended CR and 65% in our entire cohort. The higher rates in our study may be attributable to the fact that we only included LGGs and no other pathologies such as epilepsy surgery, pituitary tumors, or high-grade gliomas. In the larger studies (> 30 patients) with high-field magnets, the initial intention to treat was achieved in 70%–90% of all patients.^{2,15,16} These numbers go along with our results concerning patients with a preoperatively intended CR and an intraoperatively confirmed and assumed CR, with achievement of this goal in 71% and 81% of patients, respectively. Although direct comparison is difficult because of the mixed pathologies in all of the other studies and only low-grade tumors in our analysis, our data appear comparable and therefore suggest that they are representative for pediatric iMRI surgery in general.

Study Limitations

The main limitations of this study are its retrospective

nature and limited number of patients. However, planning a future randomized prospective study comparing iMRI and conventional surgery appears impossible from an ethical point of view considering the results of this study.

A possible bias in each surgical series can be introduced by the surgical abilities of different surgeons. In this study all surgeons had extensive neurosurgical experience (> 15 years), and most interventions (51 of 65) were performed by the senior author (M.U.S.). Analysis did not reveal any relevant differences in the results between the senior author and the other 2 surgeons involved. Despite the experience of the neurosurgeons, however, a learning curve over the years may have existed and may constitute a bias on the surgical results in favor of the iMRI cohort.

Furthermore, the volumetric analysis may have been biased by the fact that it was not totally blinded. It was primarily performed by a neurosurgeon (R.d.S.F.) not involved in any of the cases, but was supervised by the senior author. On the other hand, it appears advantageous to have the input of a very experienced surgeon, since the identification of residual tumor on the intraoperative and 3-month postoperative scans can be tricky and needs experienced eyes. Another limitation may be the fact that tumors in the pre-iMRI period were substantially larger than those in the iMRI period. In our understanding, however, the border zone to eloquent tissue is the main limiting factor to CR, not the tumor mass itself, which can be easily debulked in most cases and may only have an impact on the operating time and factors such as blood loss.

Lastly, there was an imbalance between the 2 cohorts regarding the PFS analysis because of the different follow-up time frames (50.4 months in the pre-iMRI period vs 22.5 months in the iMRI period). Yet the Kaplan-Meier curves and the Gehan-Breslow-Wilcoxon test may accommodate these differences, which did not reach statistical significance in these analyses, although curves appeared to be rather distant from each other.

Conclusions

In this series of 65 pediatric LGG patients, we showed that in cases in which total resection was assumed postoperatively, significantly more CRs at the 3-month postoperative MRI were achieved when using iMRI guidance (81%). In the 19% of cases in which tumor remained, the residual tumor volume was significantly lower and was clearly below 0.5 cm³. These numbers are the best surgical results reported in pediatric LGG surgery, since radicality was not accompanied by increased surgical morbidity, with a 3% rate of permanent new deficits. The higher rate of CRs resulted in longer PFS. Despite the limitations of this study, we suggest the routine use of iMRI for any pediatric LGGs. However, the use of iMRI in planned PRs of pediatric LGGs remains questionable.

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Disclosures

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Author Contributions

Conception and design: Roder, Schuhmann. Acquisition of data: Roder, Breitkopf, Bisdas, Freitas, Dimostheni, Ebinger, Wolff, Schuhmann. Analysis and interpretation of data: Roder, Breitkopf, Bisdas, Freitas, Schuhmann. Drafting the article: Roder. Critically revising the article: Bisdas, Tatagiba, Schuhmann. Approved the final version of the manuscript on behalf of all authors: Roder. Statistical analysis: Roder, Breitkopf, Schuhmann. Administrative/technical/material support: Roder, Bisdas, Dimostheni, Ebinger, Wolff, Tatagiba, Schuhmann. Study supervision: Roder, Schuhmann.

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