Intraoperative MRI-guided Resection in Pediatric Brain Tumor Surgery: A Meta-analysis of Extent of Resection and Safety Outcomes

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J Neurol Surg A

Abstract

Background The objective of this meta-analysis was to analyze the impact of intraoperative magnetic resonance imaging (iMRI) on pediatric brain tumor surgery with regard to the frequency of histopathologic entities, additional resections secondary to iMRI, rate of gross total resections (GTR) in glioma surgery, extent of resection (EoR) in supra- and infratentorial compartment, surgical site infections (SSIs), and neurologic outcome after surgery.

Methods MEDLINE/PubMed Service was searched for the terms "intraoperative MRI," "pediatric," "brain," "tumor," "glioma," and "surgery." The review produced 126 potential publications; 11 fulfilled the inclusion criteria, including 584 patients treated with iMRI-guided resections. Studies reporting about patients <18 years, setup of iMRI, surgical workflow, and extent of resection of iMRI-guided glioma resections were included.

Results IMRI-guided surgery is mainly used for pediatric low-grade gliomas. The mean rate of GTR in low- and high-grade gliomas was 78.5% (207/254; 95% confidence interval [CI]: 64.6–89.7, $p < 0.001$). The mean rate of GTR in iMRI-assisted low-grade glioma surgery was 74.3% (35/47; 95% CI: 61.1–85.5, $p = 0.759$). The rate of SSI in surgery assisted by iMRI was 1.6% (6/482; 95% CI: 0.7–2.9). New onset of transient postoperative neurologic deficits were observed in 37 (33.0%) of 112 patients.

Conclusion IMRI-guided surgery seems to improve the EoR in pediatric glioma surgery. The rate of SSI and the frequency of new neurologic deficits after IMRI-guided surgery are within the normal range of pediatric neuro-oncologic surgery.

Keywords
- pediatric brain tumor
- extent of resection
- glioma
- intraoperative MRI
- surgical site infection

Introduction

Pediatric brain tumors are the most common solid tumors and the second leading cause of cancer death in patients between the age of 0 and 19 years in the United States and Canada.[1,2]

There is a vast variety of histopathologic entities such as astrocytomas, medulloblastomas, and ependymomas, especially in the infratentorial compartment.[3] The extent of resection (EoR) plays a major role in the treatment of pediatric brain tumors. In particular, in benign histopathologic entities such as pilocytic astrocytoma, complete removal can be curative.[4]

Established tools to achieve high rates of gross total resection (GTR) in glioma surgery are intraoperative ultrasound,[5] intraoperative magnetic resonance imaging (iMRI),[6–8] and 5-aminolevulinic acid (5-ALA).[9]

received
January 7, 2020
accepted
April 7, 2020

DOI https://doi.org/10.1055/s-0040-1714413.
ISSN 2193-6315.

In the typical pediatric histopathologic entities, poorer results of 5-ALA are reported. Useful fluorescent reactivity was found in only 40% of primitive neuroectodermal tumors (PNET), in 25% of medulloblastomas, and in 15% of pilocytic astrocytomas.[9]

Since the first surgeries guided by iMRI at Brigham and Women's Hospital in 1994, iMRI has spread widely, especially in adult neurosurgery for the treatment of high- and low-grade gliomas.[10] Cerebral neoplasms such as pilocytic astrocytoma can be difficult to distinguish from normal brain tissue.[11] Consequently, intraoperative imaging, like the iMRI, seems to be plausible. Furthermore, iMRI enables the neurosurgeon to control whether the preoperative surgical goal was reached, to detect residual tumor tissue, to update neuronavigation, to compensate for brain shift, and to avoid early reoperation.[12,13] In particular, in low-grade glioma surgery in an eloquent location, it can prevent the neurosurgeon from removing too much tumor tissue and protect essential neurologic functions.[14] In the past decade, many departments have brought high-field MRI into the surgical theater. Generally, there are two major concepts in high-field iMRI. Either the iMRI is transported to the patient based on a ceiling-mounted system with rails or the patient is transported to the magnet.[15–17] In pediatric neurosurgery, there are, so far, various fields that report the use of iMRI. For instance, use of iMRI in tumor surgery, epilepsy surgery, and ventricular catheter placement has been reported.[18–20]

Although there is a lack of useful fluorescent dyes in pediatric neurosurgery and iMRI is an established tool in adult high-grade glioma surgery,[6–8] data rated as level I evidence to promote the use of iMRI in pediatric neurosurgery are lacking. Thus, we did a meta-analysis to evaluate histopathologic entities that were operated on, the number of iMRI scans and additional resections secondary to iMRI, the improvement of the rate of complete resections in gliomas, and the rate of surgical site infections (SSIs) after brain tumor surgery with iMRI guidance in pediatric patients.

Material and Methods

The medical literature was searched extensively by two independent reviewers, beginning with basic searches of the MEDLINE/PubMed service of the U.S. National Library of Medicine, using the MeSH (medical subject heading) terms "intraoperative MRI," "pediatric," "brain," "tumor," "glioma," and "surgery" in various combinations. Furthermore, the Web of Knowledge database, Cochrane library, BIOSIS Previews, and Web of Science were searched. Full-text versions were obtained from all studies that were considered potentially relevant by both reviewers. Each article was screened and its reference list was checked to make sure that no essential article was missed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was respected, and analysis was conducted according to its guidelines.

The relevant clinical studies were selected on the basis of one of the following selection criteria:

- Patients were $<$ 18 years.
- The setup of iMRI and surgical workflow were reported.
- The EoR of iMRI-guided brain tumor resection was reported.

Overlapping articles, letters, comments, and reviews; articles not concerning the subject or not written in English; or articles without detailed report on histopathology, EoR, age of patients, or kind of iMRI system were excluded.

Eventually, 126 potential articles were accumulated for review (►**Fig. 1**). Only 11 of 13 potential articles met the inclusion criteria and were included in the final meta-analysis. The meta-analyses were conducted according to statistical heterogeneity between the studies, using OpenMetaAnalyst software (Brown University, Providence, Rhode Island, United States) for Mac. If there was no heterogeneity, fixed-effects models were applied for meta-analyses. If not applicable, the random-effects model was used. Furthermore, an arcsine of square root proportion was done. Statistical heterogeneity was explored by χ^2 and inconsistency (I^2) statistics; an I^2 value of 50% or more represented substantial heterogeneity. Weight to the size of the two or more independent studies was involved with regard to the estimation of treatment effects.

Analysis was performed to determine the frequency of histopathologic entities resected by iMRI guidance, number of scans per procedure, number of extended resections secondary to iMRI, rate of GTR in glioma surgery, and the rate of SSI in iMRI-guided pediatric brain tumor resection. The inclusion criteria, exclusion criteria, primary endpoints, measurements of primary endpoints, and iMRI systems of the included studies are summarized in ►**Table 1**. Results of eight high-field (1.5- or 3-T) and three low-field (0.12-, 0.15-, and 0.2-T) iMRI suites were included. Two iMRI suites were operated as a two-room solution setup in dual use for intraoperative and diagnostic imaging in two studies.[21,22]

Results

Number of iMRI Scans per Brain Tumor Resections

Five hundred and eighty-four intracranial procedures were identified in the included studies. Among those patients, 673 iMRI scans were reported. The mean number of scans per procedure was 1.15 (range: 1–4).[19,21–30] The highest average number of scans per procedure (1.73) was observed in a series of 11 optic or hypothalamic gliomas treated by iMRI-assisted surgeries.[21]

Histopathologic Entities Resected by iMRI-guidance

Frequency of histopathologic entities treated by iMRI-guided resections was determined in 346 patients.[19,21–30] The most common brain tumors, in descending order, were pilocytic astrocytoma (98/346, 28.3%), low-grade astrocytoma (70/346, 20.2%), and ganglioglioma (28/346, 8.1%).

WHO grade III or IV tumors, such as high-grade gliomas (22/346, 6.4%) or medulloblastomas (8/346, 2.3%) were observed less frequently.

Sellar lesions, including craniopharyngioma (27/346, 7.8%), pituitary adenoma (5/346,1.4%), and Rathke's cleft cyst (4/346, 1.2%) were seen in 10.4% (►**Table 2**).

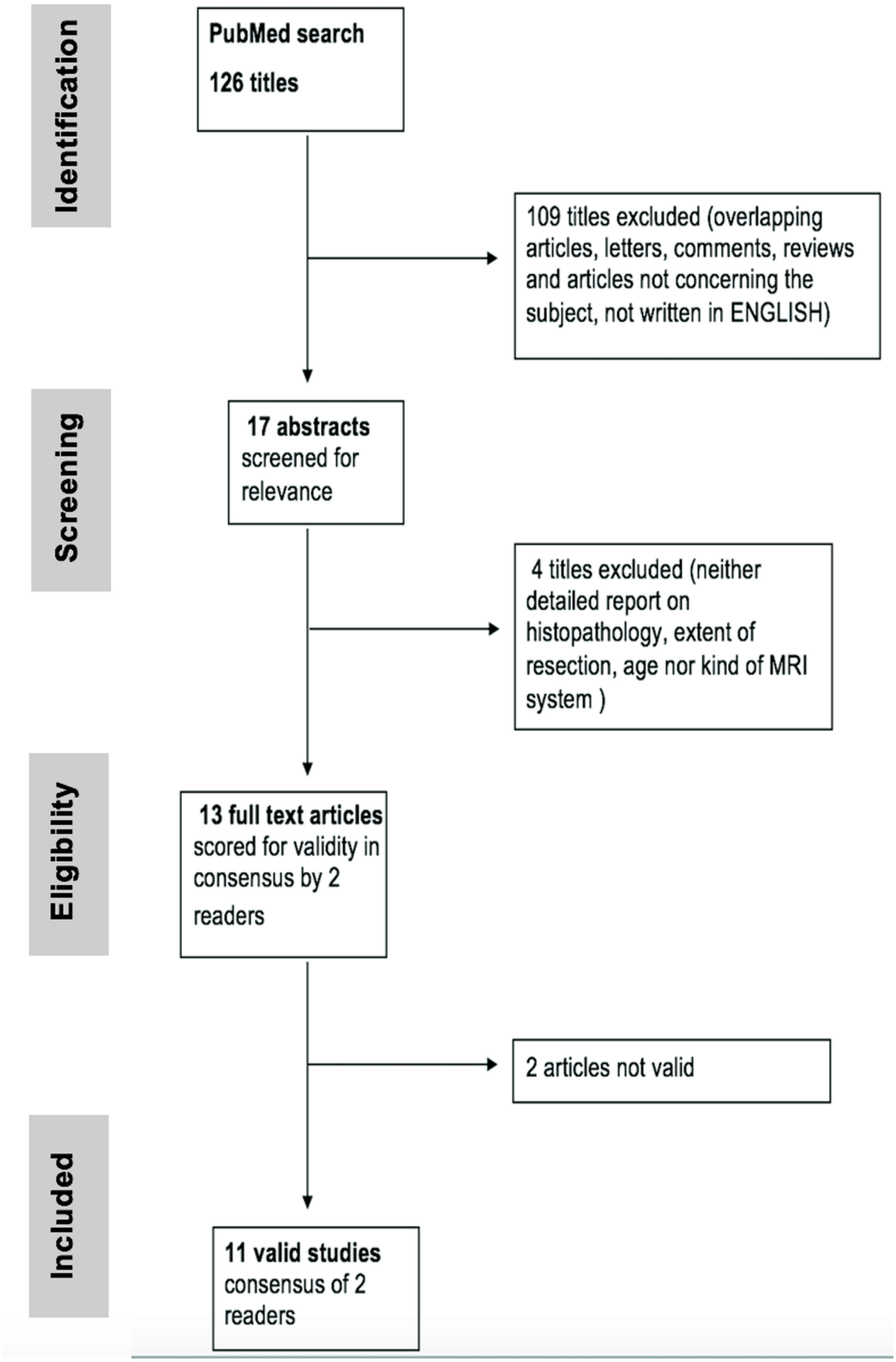

Fig. 1 Flowchart showing search strategy.

Rate of Additional Resections after iMRI

The rate of additional resections after iMRI was analyzed in all reported intracranial (supra- or infratentorial) pediatric brain tumor cases in which GTR was the primary aim.[19,22–30] The study by Millward et al, which investigated the benefit of iMRI in the subtotal resection of optic/hypothalamic gliomas, was excluded for this analysis.[21] The overall rate of additional resections after iMRI was 35.1% (159/530) in these studies (95% confidence interval [CI]: 24.8–46.2, $p < 0.001$; ►**Fig. 2**).

Table 1 Study designs and parameters of included studies

Study	Type	Tesla	Agent (dose)	Sequences	Inclusion criteria	Exclusion criteria	Time frame	Primary endpoint	Measurement of primary endpoint
Giordano et al[23]	R	1.5	Gd-dimeg (0.2 mL/kg)	T1, T2, FLAIR, DTI	Age < 16 y, brain tumor resections	NS	May 2007–November 2014	EoR	Volumetric analysis based on segmentation
Roder et al[24]	R	1.5	Gadobutrol (0.1 mL/kg)	T1, T2, FLAIR	Age < 18 y, low-grade glioma	Emergency indications (surgery within 48 h after diagnosis)	2007–2014	EoR	Volumetric analysis (Brainlab iplan.net)
Millward et al[21]	R	3.0	Gd (NS)	T1, T2, FLAIR, DWI, DSC perfusion imaging	Optic pathway/hypothalamic gliomas, intended STR	Intended GTR	2010–2013	EoR	Semiautomatic volumetric segmentation (MRIcron)
Choudhri et al[25]	R	3.0	Gd-dimeg (0.1 mL/kg)	T1, T2, DWI	Age ≤ 18 y, brain tumor resections	NS	February 2011–February 2013	EoR	Volumetric analysis based on segmentation
Yousaf et al[22]	R	3.0	Gd-dimeg (0.2 mL/kg)	T1, T2, FLAIR, DWI, DTI	Brain tumor resection	NS	October 2009–January 2012	EoR	Consensus of neurosurgeon and neuroradiologist
Kubben et al[26]	R	0.15	Gd-dimeg (0.1 mL/kg)	T1, T2, FLAIR	Age ≤ 17 y, brain tumor resections	NS	2005–2010	EoR	Interpretation of neurosurgeon and neuroradiologist (both blinded)
Shah et al[27]	R	1.5	NS	NS	Pediatric brain tumor resections	Age <18 mo	April 2008–March 2010	NS	NS
Levy et al[28]	R	1.5	Gd (NS)	NS	Age ≤ 18 y, brain tumor resections, epilepsy surgery, vascular lesions, spinal procedures, electrodes, and catheter placement	NS	March 1998–April 2008	NS	NS
Kremer et al[19]	R	0.2	NS	T1 (enhancing lesions), T2, FLAIR (low-grade gliomas, nonenhancing)	Age < 16 y, brain tumor resections, biopsies, epilepsy surgery, catheter placement	NS	1996–2004	EoR	Consensus of neurosurgeon and neuroradiologist
Roth et al[30]	R	0.12	NS	T1, T2, FLAIR	Age < 17 y, brain tumor resections, biopsies, epilepsy surgery, shunt placement	NS	June 2001–June 2004	NS	NS
Lam et al[29]	R	1.5	Gd (NS)	T1, T2, FLAIR	Posterior fossa tumors	NS	1997–2000	NS	NS

Abbreviations: DSC, dynamic susceptibility contrast; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EoR, extent of resection; FLAIR, fluid-attenuated inversion recovery; GTR, gross total resection; NS, not specified; R, retrospective; STR, subtotal resection.

Table 2 Frequency of histopathologic entities treated by iMRI-guided surgery

Histopathology	*n* (total = 346)	%
Pilocytic astrocytoma (WHO grade I)	98	28.32%
Low-grade astrocytoma (WHO grade II)	70	20.23%
Ganglioglioma (WHO grade I)	28	8.09%
Craniopharyngioma (WHO grade I)	27	7.80%
PNET (WHO grade IV)	23	6.65%
High-grade glioma (WHO grade IV)	22	6.36%
Ependymoma (WHO grade II)	20	5.78%
Medulloblastoma (WHO grade IV)	8	2.31%
DNET (WHO grade I)	8	2.31%
Oligodendroglioma (WHO grade II)	5	1.45%
Pituitary adenoma	5	1.45%
Rathke's cleft cyst	4	1.16%
Central neurocytoma (WHO grade II)	4	1.16%
Cystic hamartoma	3	0.87%
Choroid plexus carcinoma (WHO grade III)	3	0.87%
Nasopharyngeal angiofibroma	2	0.58%
Germinoma	2	0.58%
Anaplastic astrocytoma (WHO grade III)	2	0.58%
Ependymoma (WHO grade I)	2	0.58%
Choroid plexus papilloma (WHO grade I)	1	0.29%
Pilomyxoid astrocytoma (WHO grade II)	1	0.29%
Glioneuronal tumor of infancy (WHO grade I)	1	0.29%
Anaplastic oligodendroglioma (WHO grade III)	1	0.29%
Anaplastic ependymoma (WHO grade III)	1	0.29%
Glioblastoma multiforme (WHO grade IV)	1	0.29%
ATRT (WHO grade IV)	1	0.29%
Meningioma (WHO grade I)	1	0.29%
pineal tumor	1	0.29%
olfactory nerve schwannoma	1	0.29%

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; DNET, dysembryoplastic neuroepithelial tumor; iMRI, intraoperative magnetic resonance imaging; PNET, primitive neuroectodermal tumor.

iMRI-guided Rate of GTR in Pediatric Brain Tumor Surgery

Rates of GTR Stratified by Anatomical Location: Supratentorial and Infratentorial Compartment

Rates of GTR in all pediatric gliomas were investigated according to their locations in supratentorial or infratentorial compartments of the brain. Data regarding EoR, additional resections after iMRI, histopathology, and the precise description of the anatomical location of the tumors were the inclusion criteria and were given in the studies by Giordano et al,[23] Kubben et al,[26] and Lam et al[29] as far as the infratentorial region is concerned. Data with regard to supratentorial tumors and the above-mentioned inclusion criteria were only given in the studies by Giordano et al[23] and Kubben et al.[26] In the infratentorial compartment, 10 tumors were identified in which a GTR was the preoperative determined surgical aim. IMRI revealed a GTR in only 5 of 10 (50.0%) cases intraoperatively. Additional resections secondary to these iMRI scans were performed and revealed a final rate of GTR of 100% (10/10 cases). Meta-analysis with a comparison of the rates of GTR before iMRI-guided additional resections and afterward revealed the following results: odds ratio (OR): 7.33 (95% CI: 0.94–57.10, $I^2 = 0\%$, $p = 0.77$).

As far as the supratentorial compartment is concerned, 18 tumors were eligible according to the inclusion criteria. Intraoperatively, in 11 (61.1%) cases a GTR was observed according to the iMRI scans. Afterward, additional resections secondary to these iMRI scans were performed and complete resections were achieved in another 6 cases, revealing a final rate of GTR of 94.4% (17/18 cases). Meta-analysis with a comparison of the rates of GTR before iMRI guided additional resections and afterward revealed the following results: OR: 2.27 (95% CI: 0.22–4.31, $I^2 = 0\%$, $p = 0.97$).

Rate of GTR in Gliomas (WHO Grades I–IV)

The rate of GTR was evaluated in all gliomas (WHO grades I–IV).[19,22–26] Brainstem, optic, thalamic, hypothalamic gliomas and biopsies were excluded. The studies by Levy et al[28] and Roth et al[30] were excluded due to the lack of detailed reports about histopathology or EoR. Millward et al[21] and Shah et al[27] were excluded due to the intent to achieve a subtotal resection and sellar pathologies within the reported rate of GTR. At least also the study by Lam et al was excluded due to tumor location in eloquent areas (infratentorial gliomas with brain stem involvement).[29] Single-arm meta-analysis of all gliomas (WHO grades I–IV) showed GTR in 207/254 (78.5%) of these studies (95% CI: 64.6–89.7, $p < 0.001$; ►**Fig. 3**).

Rate of GTR in Low-Grade Gliomas (WHO Grades I and II)

Analysis of the rate of GTR of iMRI-guided resections of low-grade gliomas (WHO grades I and II) was performed.[19,24,26,29]

The iMRI-guided rate of GTR in low-grade glioma surgery (WHO grades I and II) was 74.3% (35/47) in the included studies (95% CI: 61.1–85.5, $p = 0.76$; ►**Fig. 4**).

STUDIES	ESTIMATE (95% CI)	ADDITIONAL RESECTION/ TOTAL	WEIGHT (%)
GIORDANO ET AL. 2017	0.21 (0.13-0.30)	17/82	11.8
RODER ET AL. 2016	0.52 (0.34-0.69)	16/31	10.0
CHOUDHRI ET AL. 2014	0.21 (0.15-0.27)	35/168	12.5
SHAH ET AL. 2012	0.43 (0.28-0.58)	18/42	10.7
YOUSAF ET AL. 2012	0.15 (0.08-0.24)	12/79	11.7
KUBBEN ET AL. 2012	0.46 (0.19-0.74)	5/11	7.0
LEVY ET AL. 2009	0.49 (0.36-0.62)	27/55	11.2
KREMER ET AL. 2006	0.60 (0.44-0.75)	21/35	10.3
ROTH ET AL. 2006	0.28 (0.100.0)	5/18	8.5
LAM ET AL. 2001	0.33(0.08-0.65)	3/9	6.2
OVERALL (I^2=83.09 %, P<0.001)	**0.35 (0.25-0.46)**	**159/530**	**100**

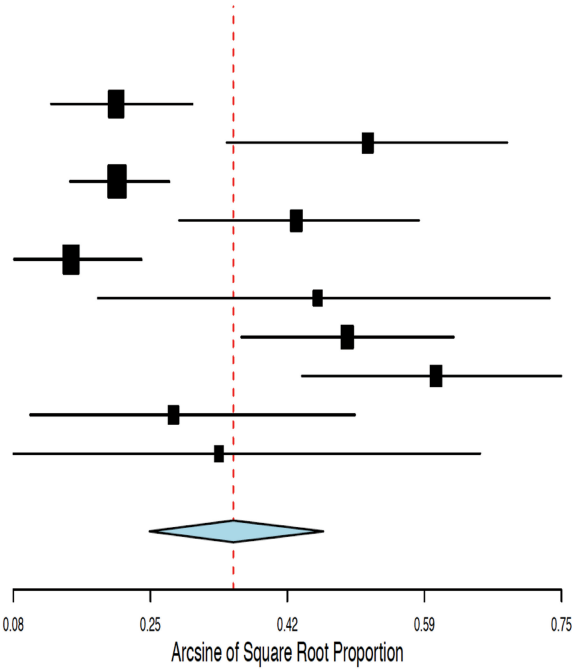

Fig. 2 Frequency of additional resections secondary to intraoperative MRI (iMRI). Meta-analysis of the rate of additional resections secondary to iMRI in pediatric brain tumor surgery. Mean rate of additional resections: 35.1% (95% confidence interval [CI]: 24.8–46.2). *Squares* represent the mean; the bigger the square, the greater the weight given because of the narrower 95% CI. D*iamond* represents the mean in the combined data in the meta-analyses. Heterogeneity was significant ($I^2 > 50\%$).

STUDIES	ESTIMATE (95% CI)	GTR/TOTAL	WEIGHT (%)
GIORDANO ET AL. 2017	0.556 (0.369-0.735)	15/27	16.5
RODER ET AL. 2016	0.708 (0.515-0.869)	17/24	16.0
CHOUDHRI ET AL. 2014	0.929 (0.874-0.969)	104/112	20.3
YOUSAF ET AL. 2012	0.723 (0.588-0.840)	34/47	18.5
KUBBEN ET AL. 2012	0.889 (0.618-1.000)	8/9	11.1
KREMER ET AL. 2006	0.829 (0.688-0.933)	29/35	17.5
OVERALL (I^2=80.86%, P<0.001)	**0.785 (0.646-0.897)**	**207/254**	**100**

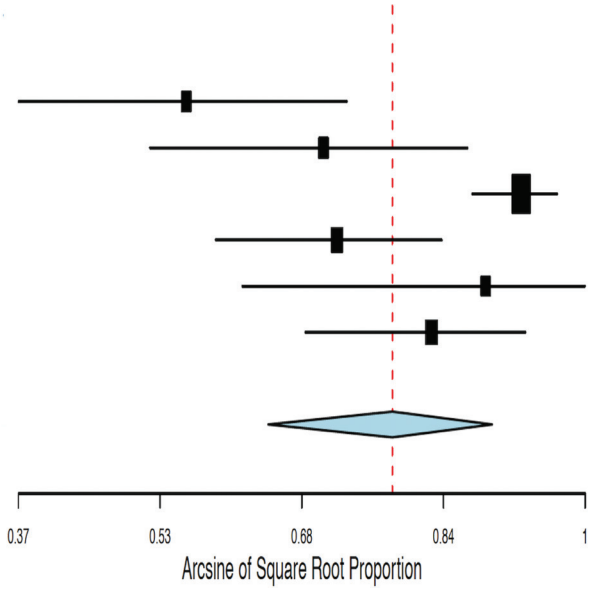

Fig. 3 Intraoperative MRI (iMRI) guided rate of gross total resection (GTR) in low- and high-grade glioma surgery (WHO grades I–IV). Meta-analysis of the rate of GTR in pediatric glioma (WHO grades I–IV) surgery. Mean rate of GTR: 78.5% (95% confidence interval [CI]: 64.6–89.7). *Squares* represent the mean; the bigger the square, the greater the weight given because of the narrower 95% CI. *Diamond* represents the mean in the combined data in the meta-analyses. Heterogeneity was significant ($I^2 > 50\%$).

Safety

Rate of Surgical Site Infections

All superficial (cutis and subcutis) and deep (abscess, subdural empyema, meningitis) wound infections after intracranial procedures were analyzed.[19,23–30] All intracranial tumor resections as well as epilepsy and neurovascular surgery by craniotomy were analyzed with regard to SSI. The overall rate of SSI was 1.6% (6/482) of the analyzed studies (95% CI: 0.7–2.9; ►**Fig. 5**).

Postoperative Neurologic Deficits

New transient or permanent neurologic deficits were investigated. Data were reported in the studies by Giordano et al,[23]

STUDIES	ESTIMATE (95% CI)	GTR/TOTAL	WEIGHT (%)
RODER ET AL. 2016	0.708 (0.52-0.87)	17/24	50.0
KUBBEN ET AL. 2012	0.800 (0.39-1.0)	4/5	10.4
KREMER ET AL. 2006	0.714 (0.46-0.91)	10/14	29.1
LAM ET AL. 2001	0.900 (0.53-1.0)	4/4	10.4
OVERALL (I^2=0%, P=0.759)	0.743 (0.61-0.86)	35/47	100

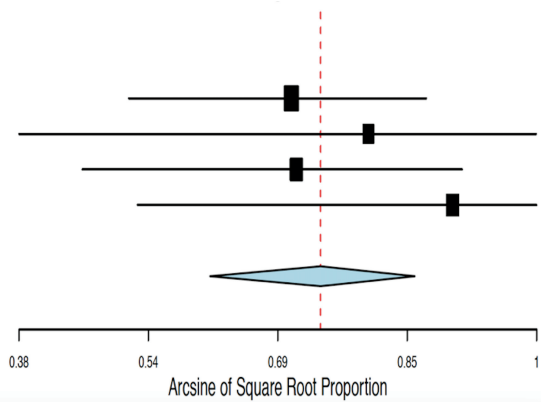

Fig. 4 Intraoperative MRI (iMRI) guided rate of gross total resection (GTR) in low-grade glioma surgery (WHO grades I and II). Meta-analysis of the rate of GTR in pediatric low-grade glioma (WHO grades I and II) surgery. Mean rate of GTR: 74.3% (95% confidence interval [CI]: 61.1–85.5). *Squares* represent the mean; the bigger the square, the greater the weight given because of the narrower 95% CI. *Diamond* represents the mean in the combined data in the meta-analyses. Heterogeneity was not significant ($I^2 < 50\%$).

STUDIES	ESTIMATE (95% CI)	SSI/TOTAL	WEIGHT (%)
GIORDANO ET AL. 2017	0.006 (0.000-0.034)	0/82	17.0
RODER ET AL. 2016	0.016 (0.000-0.087)	0/31	6.6
CHOUDHRI ET AL. 2014	0.018 (0.003-0.043)	3/168	34.4
KUBBEN ET AL. 2012	0.050 (0.000-0.260)	0/9	2.0
SHAH ET AL. 2012	0.048 (0.005-0.132)	2/42	8.6
LEVY ET AL. 2009	0.006 (0.000-0.032)	0/86	17.8
KREMER ET AL. 2006	0.029 (0.000-0.108)	1/35	7.2
ROTH ET AL. 2006	0.024 (0.000-0.130)	0/20	4.3
LAM ET AL. 2001	0.050 (0.000-0.260)	0/9	2.0
OVERALL (I^2=0%, P=0.829)	**0.016 (0.007-0.029)**	**6/482**	**100**

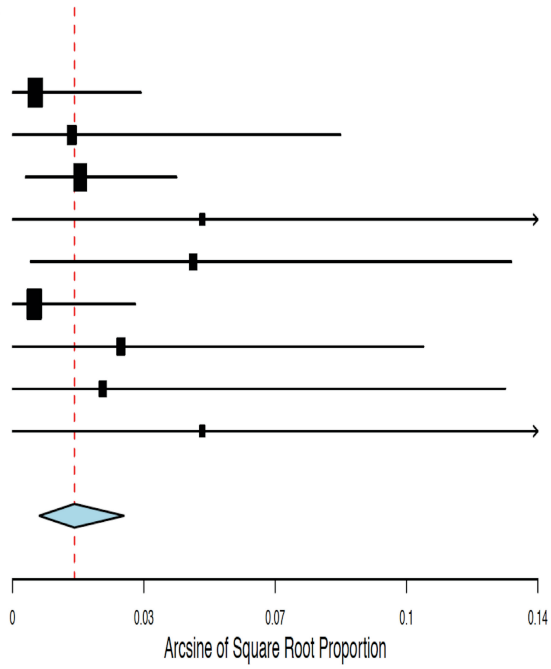

Fig. 5 Intraoperative MRI (iMRI) guided brain tumor resections and the rate of surgical site infections. Superficial (cutis, subcutis) and deep (brain abscess, subdural empyema, meningitis) wound infections were included. Overall rate of surgical site infections: 1.6% (95% confidence interval [CI]: 0.7–2.9). *Squares* represent the mean; the bigger the square, the greater the weight given because of the narrower 95% CI. *Diamond* represents the mean in the combined data in the meta-analyses. Heterogeneity was not significant ($I^2 < 50\%$).

Kremer et al,[19] Kubben et al,[26] Millward et al,[21] and Roder et al[24] in which a control group of patients without iMRI-guided brain tumor surgery was also given. In 37 (33.0%) of 112 patients in whom iMRI-guided resections were performed, new transient neurologic deficits were observed postoperatively.

Discussion

Number of Scans and Extended Resections Secondary to iMRI

The average number of scans per procedure was 1.15. In anatomically complex brain tumor locations such as for optic or hypothalamic gliomas, repeated scans can be useful to achieve maximal cytoreductive surgery and preservation of neurologic function. In the series by Millward et al, it was necessary to perform an average number of 1.73 scans per procedure. The study included 11 procedures in which a subtotal resection of hypothalamic or optic gliomas was intented.[21]

IMRI led to extended tumor resections in 35.1% of the analyzed pediatric brain tumors. In an analysis of 804 iMRI-guided procedures in adult neurosurgery, a rate of extended resections at 37.3% was reported, ranging from 13.3 to 54.8%.[31] Consequently, our analysis seems to be concurrent with the literature concerning glioma surgery in adult patients. The relevance of extended resections secondary to iMRI regarding long-term complications, mortality, and quality of life is unknown so far.

Frequency of Histopathologic Entities

Pilocytic astrocytomas account for up to 25% of all pediatric brain tumors. GTR seems to be an independent prognostic factor for prolonged survival rates of patients. Complete resection can be curative, and survival rates of 96% at 10 years are reported.[32] The most common histopathologic entities operated on in iMRI suites were WHO grade I and II gliomas. Fifty-six percent of the reported histopathologic entities were pilocytic astrocytomas, low-grade astrocytomas, or gangliogliomas. These entities can be cured by complete surgical resection.[11,32,33] High-grade lesions such as medulloblastoma, brainstem glioma, or atypical teratoid rhabdoid tumor (ATRT) were not much as common as low-grade lesions among the tumors resected by iMRI guidance, presumably because of their location in the posterior fossa and the technical limitations of iMRI in semi-sitting positioning.[34]

Rate of iMRI-Guided Gross Total Resection

Rates of GTR Stratified by Anatomical Location: Supratentorial and Infratentorial Compartment

Rates of GTR after the iMRI-guided secondary resections were significantly higher compared with the rates of GTR before the additional resections. These findings were observed in the supratentorial and infratentorial compartments. Consequently, iMRI seems to be a useful tool in various regions of the brain. Furthermore, neurosurgeons should not hesitate to use it in the infratentorial compartment despite the known pitfalls as far as positioning and the use of head-clamp systems are concerned.[29,34]

Rate of GTR in Gliomas (WHO Grades I–IV)

The current meta-analysis included seven studies that clearly reported the EoR in all intracranial gliomas (WHO grades I–IV) and revealed the following mean rate of GTR: 78.5% (95% CI: 64.6–89.7, $p < 0.001$). There are no stringent cutoff values for the definition of the term *GTR* in pediatric gliomas, such as the resection of 98% tumor volume in glioblastoma surgery.[35] In adult glioblastoma surgery, prospective randomized data showed a statistically significant superiority of iMRI-guided rates of GTR to conventional neuronavigation-guided surgery.[7] IMRI-assisted surgery improves the EoR significantly, which is a positive predictor for long-term survival in glioblastoma surgery.[6] So far, there is only one study that reported on the results of iMRI-guided resections in high-grade gliomas and compared their results to a group of patients operated on without iMRI in a pediatric population. However, this study includes heterogenous histopathologic entities, MRI field strengths, and uneven sample sizes in the iMRI-assisted and conventional surgery groups.[27]

Rate of GTR in Low-Grade Gliomas (WHO Grades I and II)

The iMRI-guided rate of GTR in pediatric low-grade glioma surgery was 74.3% in our meta-analysis. Prospective data with regard to the role of EoR in pediatric low-grade glioma surgery are so far predominantly limited to series reporting surgeries guided without the use of iMRI. A large prospective database on EoR and survival in pediatric low-grade gliomas operated without iMRI assistance by Wisoff et al[11] showed, in the multivariate analysis of 726 patients, that GTR without residual tumor tissue was the predominant predictor of progression-free survival. The rate of GTR in this prospective, multicentric trial was 64.1% among 518 patients who were amenable to cytoreductive surgery and treated by surgery without iMRI guidance. Tumor locations (cerebral hemispheres, cerebellar hemispheres, cerebellar vermis, midline tumors) were homogeneously distributed in this prospective series.[11] Limitation of this study is the investigated time period from 1991 to 1996 in which today's follow-up imaging techniques using high-field (1.5- or 3.0-T) MRI to assess EoR or tumor progression were not available. Furthermore, a more recent retrospective volumetric study by Margol et al[36] analyzed the progression-free survival and the overall survival in 468 children (age 0–14 years) and 50 early adolescents (15–21 years) after low-grade glioma surgery without iMRI assistance. Rate of GTR in this series investigating low-grade glioma surgery without iMRI guidance was 63.9% in the children group, whereas 66.0% of the early adolescent group had a GTR of the tumor in the postoperative MRI. Multivariate Cox analysis revealed that patients with a residual tumor volume of $\geq 1.5\ cm^3$ had a hazard ratio for progression of 8.38 and residual tumor volume was independently associated with progression.

In pediatric neuro-oncologic surgery, there is, so far, no prospective randomized trial that can confirm a significantly better EoR when surgical resection is guided by iMRI. At least one retrospective single-center study by Roder et al[24] analyzed iMRI-assisted and conventional surgery without the use of iMRI in pediatric low-grade gliomas. In this study, the rate of GTR after iMRI-guided surgery was 71 %, whereas in the group of patients who underwent surgeries without iMRI assistance the rate of GTR was 41%. The rate of GTR differed significantly between the patients operated on with or without iMRI assistance in their study and the volumetric analysis also revealed significant lower residual tumor volumes at the 3-month follow-up MRI examination in the iMRI group. Hence, iMRI seems to be a useful tool for maximizing EoR and might result in prolonged progression-free survival in pediatric low-grade gliomas. However, stronger evidence of the benefit of an iMRI is assumed to be given in adult low-grade glioma surgery.[8]

Overall, iMRI seems to be a plausible tool to achieve a maximal resection of pediatric low-grade gliomas while preserving the patient's functional integrity. Further data regarding histopathologic assessment of iMRI-guided pediatric low-grade glioma surgeries/biopsies and prospective, randomized trials with and without iMRI assistance investigating the EoR in low-grade glioma surgery are needed.

Safety

Rate of Surgical Site Infections

There are concerns that an iMRI of an open wound can be a relevant risk factor for SSIs. Osteomyelitis in the bone flap and other deep infections are complications that often

require reoperation. In pediatric neurosurgery and craniotomies for neoplasms, SSI was reported to be 2.5% in a collective of 2,434 procedures.[37] Postoperative pneumonia, immune disease/immunosuppressant use, cerebral palsy, emergency operations, acquired central nervous system (CNS) abnormalities, and female sex are claimed to independently increase the risk of an SSI after craniotomies in pediatric patients.[37] SSIs were observed in only 6 (1.6%) of 482 patients treated by iMRI-guided resections following craniotomies in this meta-analysis. Thus, it seemed to be a safe procedure in pediatric neurosurgery. Roder et al[24] found no differences with regard to perioperative infections in their retrospective single-center experience in which pediatric low-grade glioma surgery with and without iMRI assistance was compared. However, operation length was significantly longer in the iMRI group compared with the non-iMRI group. Contrary to their finding of no significant increase of SSIs by using iMRI, which resulted in prolonged operative duration, Hardy et al[38] showed that each additional hour of time in surgery for adult brain tumors resulted in a 43% increase in the OR for developing an SSI in a retrospective series of 2,485 patients. However, this study included predominantly adult patients with comorbidities.

Another point to be considered as a potential risk factor for SSIs is the operating room design. Several studies reported that procedures in one-room iMRI suites have SSI rates as low as conventional operations in adult glioma surgery.[39,40] Even in a shared-resource iMRI for diagnostic and intraoperative imaging, the rate of SSI was analyzed to be 5.06% in an adult glioblastoma population and the rate SSI was not significantly increased.[41]

Postoperative Neurologic Deficits

In 37 (33.0%) of 112 patients in whom iMRI-guided resections were performed, new transient neurologic deficits were observed postoperatively. Roder et al[24] observed new transient neurologic deficits in 32% of patients operated on without the assistance of iMRI, whereas in patients who underwent surgery guided by iMRI new transient neurologic deficits were found in 42% of these cases. New persistent neurologic deficits were present in 9% of the patients in the non-iMRI group and in 3% of the patients operated on with iMRI guidance. They have observed no statistically significant association between the use of iMRI and new postoperative neurologic deficits. However, the assessment of neurologic function is also dependent on the anatomical location of the CNS tumor. Das et al[42] analyzed 65 children who underwent surgery for pediatric glioblastoma in their retrospective study. In this study, 95.4% of the tumors were located in the supratentorial compartment and new persistent postoperative neurologic deficits were found in 4.6% of the investigated patient collective. As far as the infratentorial compartment is concerned, Di Rocco et al[43] investigated neuroradiological findings and histopathology as potential risk factors for the persistence of postoperative neurologic deficits in a prospective series of 41 patients with medulloblastomas or pilocytic astrocytomas in the posterior fossa. They showed that hydrocephalus, brainstem infiltration, and the histopathology of a medulloblastoma were statistically significantly associated with the persistence of postoperative deficits such as the impairment of the intelligence quotient, procedural memory deficits, imagery disorders, and linguistic processing deficits. Surgical excision of the tumor entity did not cause a worsening of preexisting functional deficits in their series and tumor removal was followed by an improvement in the defective performances. The EoR, which was analyzed for total and subtotal removal of the tumor, was not significantly associated with a worsening of the neurologic functions in this study.

Frequently, concerns are raised that an increase of the EoR can neglect the functional preservation. Our findings assume that the use of an iMRI does not lead to more new postoperative neurologic deficits despite higher rates of GTR. Limitation of the observations in literature is that the control group by Roder et al[24] included only 34 children and the degrees of these neurologic deficits in our analysis of the literature are not objectively described in scores or indices in any of these included studies.

Limitations

The present meta-analysis has several limitations. Acquisition of data in all included studies was retrospective. No prospective randomized studies are available to address the issues of our analysis. Furthermore, there is heterogeneity in our meta-analysis of the literature due to varieties in population sizes, definitions, and measurements of the rate of GTR by different field strengths of the iMRI systems and operation theater designs. However, to minimize heterogeneity, we applied highly selective inclusion criteria, which is reflected in the low number of included studies. Additionally, no data with regard to the sensitivity and specificity of iMRI-guided resections to detect histopathologic confirmed tumor tissue exist so far. However, this meta-analysis shows the multiple limitations that result in the need for a prospective randomized trial in pediatric glioma surgery guided by iMRI such as the study by Senft et al,[7] which investigated the role of iMRI in adult glioblastoma patients in a prospective randomized design.

Conclusion

IMRI is predominantly used for low-grade glioma surgery. The current data support the hypothesis that iMRI-guided surgery improves the rate of GTR in pediatric gliomas, located in the infra- and the supratentorial compartment. The rate of SSI and the amount of new postoperative neurologic deficits are within the normal range, which makes iMRI a safe tool to assist in pediatric neuro-oncologic surgery.

Conflicts of Interest

None declared.

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