PETITION

Petition for Intraoperative MRI in the Western Portion of State (HSAs I, II, and III)

PETITIONER

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d/b/a Carolinas HealthCare System
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STATEMENT OF THE PROPOSED CHANGE

The Charlotte-Mecklenburg Hospital Authority d/b/a Carolinas HealthCare System (CHS) respectfully petitions the State Health Coordinating Council (SHCC) to create a special allocation for one intraoperative magnetic resonance imaging (iMRI) unit in the western portion of the state (Health Service Areas I, II, and III) in the *2016 State Medical Facilities Plan (2016 SMFP)*.

An applicant shall demonstrate that the iMRI unit shall be located in or adjacent to an operating room. The proposed iMRI unit shall not be counted in the regular inventory of MRI scanners in the *SMFP*. Applicants shall not be required to meet the MRI equipment performance standards and shall be required to demonstrate that the iMRI will not result in an increase in charges to patients or payors. Finally, the applicant shall demonstrate that it is not able to apply for an iMRI through Policy AC-3.

BACKGROUND

MRI technology has advanced significantly over the past 16 years since the *1999 SMFP* first introduced a methodology for determining need for fixed MRI scanners. In addition to improvements in image quality, shorter scan times and wider bore designs for traditional scanners, specialty MRI scanners have been developed to focus on parts of the body (extremities, breasts, etc.), specific patient or clinical segments (pediatric, radiation oncology, cardiovascular) and other specialized needs, such as dynamic, or multi-position scanners. As the technology has developed, the SHCC has been responsive in allocating need for additional MRI scanners. For traditional MRI scanners, the standard methodology has increased the need from 81 fixed MRI scanners across the state in the *1999 SMFP* to 233 in the *2015 SMFP*. For specialized MRI

scanners, 11 scanners have been developed across the state, dedicated to a range of special needs, including one iMRI. CHS believes that the allocation of an iMRI to serve the western half of the state is warranted, as explained in detail below.

TECHNOLOGY OF iMRI

While many of the specialized MRIs that have been allocated in previous SMFPs perform special functions, iMRI is truly unique in the manner and location in which it operates. The technology used in iMRI allows a patient to receive a high quality MRI scan *during* a surgical procedure, that is, while a patient is under anesthesia, with an open cavity or skull. It is specially designed for and typically used in neurosurgery procedures and allows for the visualization of soft tissue in order to improve the surgical precision and clinical decision making, particularly for brain tumor resections (removal). Real-time imaging is vital as these tissues can shift from the position seen in pre-operative scans. The primary use of this technology to date has been in the removal of adult and pediatric tumors from the human central nervous system: the brain, the spinal cord and associated structures such as the spinal column or skull. When used with functional MRI technology, the surgeon can preserve essential tissue for brain function. It should be noted that the use of iMRI outside of neurosurgery is expanding into general surgery, for example, to assist in the visualization of the liver and kidneys. Surgeons perform iMRI scans during surgery to ensure complete resection of the tumor before the surgical opening is closed. The extent of tumor removal in the central nervous system is not always apparent at surgery, even when surgical adjuncts such as microscopes are used.

Without iMRI, patients are prepped for surgery, anesthetized, the surgery is performed, the skull (or other cavity) is closed, and the patient is sent to recovery and eventually to his or her room. Soon thereafter, based on availability of equipment, the patient is given a traditional MRI to confirm that the surgery has been effective (e.g. that the tumor has been successfully removed and that other abnormalities such as blood clots are not present). After the MRI results are interpreted and presented to the surgeon, if the surgery has not been effective and another attempt is warranted, either to remove more tumor or address complications, the surgeon must schedule a second surgery for the patient. Normally this occurs while the patient is still hospitalized, but the patient must still undergo a second surgery, including prep, anesthesia and reopening of the surgical site, and sometimes the second surgery does not occur until after the patient has been discharged, requiring a readmission. Clearly, a second surgery so temporally close to the first is not ideal, but currently that is the only choice for a potentially life-saving surgery. Such a scenario is difficult enough for adult patients, but for children with life-threatening disease, the challenges of a second surgery are difficult for both the patient and his or her caregivers as well. Moreover, for all patients, a second surgery adds unnecessary healthcare expenditures for patients and payors, increased

length of stay, and additional risks that could be improved through the use of iMRI in the surgical suite.

Equally important to resource considerations are the clinical benefits of this technology. Studies show that iMRI allows for improved accuracy of resections. As extent of resection is known to correlate with important metrics such as survival, iMRI promises to improve the outcomes of patients with central nervous system and other cancers. iMRI use has also been associated with decreased surgical morbidity and a reduction of repeat surgeries for adult and pediatric patients. The following is a sampling of the more than 50 abstracts from major scholarly peer-reviewed journals concerning the benefits of iMRI:

European Journal of Surgical Oncology (2014 Mar)
Maximizing the extent of resection and survival benefit of patients in glioblastoma surgery: high-field iMRI versus conventional and 5-ALA-assisted surgery.
Conclusions: Analysis of residual tumor volumes, total resections and neurological outcomes demonstrate that iMRI may be significantly superior to 5-ALA and white-light surgery for glioblastomas at comparable peri- and postoperative morbidities. Longer 6-month progression-free survival was observed in patients with total resections.

Journal of Neurosurgery (2014 Feb)
Determining the utility of intraoperative magnetic resonance imaging for transsphenoidal surgery: a retrospective study.
Conclusions: The use of high-field iMRI leads to a significantly higher rate of complete resection…after 2 years Kaplan-Meier analyses show a distinctly higher progression-free survival in the iMRI group. … The authors therefore recommend routine use of high-field iMRI for pituitary surgery.

Journal of Neurosurgery: Pediatric (2012 Mar)
Intraoperative magnetic resonance imaging to reduce the rate of early reoperation for lesion resection in pediatric neurosurgery.
Conclusions: Intraoperative MR imaging-guided resections resulted in a trend toward reduction in the need for repeat surgery in the immediate 2-week postoperative period compared with conventional pediatric neurosurgical resections for tumor or focal cortical dysplasia…the iMRI suite offers a comparable safety and efficacy profile while potentially reducing the per-case cost by diminishing the need for early reoperation.

Journal of Neuro Oncology (2011 Dec)
Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance.

Conclusions: Demonstration that navigation guidance and iMRI significantly contribute to optimal extent of resection (EOR) with low postoperative morbidity, where EOR ≥ 98% and patient age <65 years are associated with significant survival advantages. Thus, maximum EOR should be the surgical goal in GBM surgery while preserving neurological function.

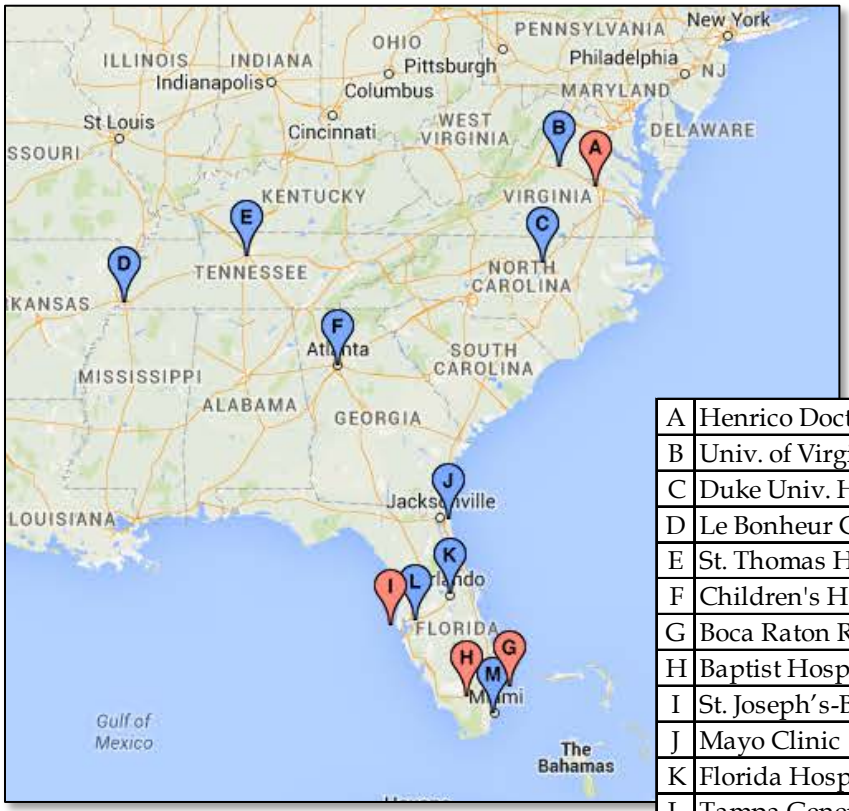
Please see Attachment 1 for the full articles.

As a result of these clinical benefits, iMRI is widely expected to become a standard of care for quaternary hospitals in three to five years.

ACCESS TO iMRI

Currently, there is one operational or approved iMRI in North Carolina. In 2008, Duke University Hospital received a Certificate of Need to construct a new bed tower, including the purchase of an iMRI unit. That project was completed and the iMRI became operational in July 2013. Approximately 60 hospitals nationwide have an iMRI unit. The table and map below shows the accessibility of iMRI scanners in North Carolina and neighboring states.

Location of iMRI Scanners



A	Henrico Doctor's Hospital
B	Univ. of Virginia
C	Duke Univ. Hospital
D	Le Bonheur Children's Medical
E	St. Thomas Hospital
F	Children's Hospital of Atlanta
G	Boca Raton Regional Hospital
H	Baptist Hospital of Miami
I	St. Joseph's-Baycare
J	Mayo Clinic
K	Florida Hospital
L	Tampa General Hospital
M	Miami Children's Hospital

Teaching? No Yes

Of the 13 hospitals on the map above, nine are major teaching hospitals including University of Virginia, Mayo Clinic-Jacksonville, and Miami Children's Hospital with excellent neurosurgery programs. Major teaching hospitals typically draw patients from a broad geographic area, thus increasing access to their specialized services, and provide training opportunities to new physicians on new technology such as iMRI.

The table below provides a comparison of the accessibility of iMRI scanners in North Carolina and neighboring states on a per population basis.

Accessibility of iMRI Scanners

State	*iMRI Units*	*2014 Population*	*iMRI per 1 Million Population*
South Carolina	0	4,832,482	0.00
Georgia	1	10,097,343	0.10
North Carolina	1	9,943,964	0.10
Virginia	2	8,326,289	0.24
Tennessee	2	6,549,352	0.31
Florida	7	19,893,297	0.35

Source: Monteris Medical (iMRI vendor); U.S. Census Bureau. Includes operational and pending installations of iMRI units.

As the table indicates, North Carolina has less access on a per population basis to iMRI scanners than Virginia, Florida, and Tennessee. Moreover, the lack of an iMRI provider in South Carolina also compounds access issues in North Carolina, particularly in the Charlotte region, where a significant number of South Carolina residents from bordering communities seek quaternary and other specialized care. If this petition is granted and ultimately another iMRI unit is developed in North Carolina, the state would have 0.20 units per 1 million population which would be comparable to but would not exceed access in Virginia and Florida. CHS realizes that a population to iMRI ratio, standing alone, may not be sufficient to show a need for another iMRI in North Carolina; however, it is helpful to show that the population of the state could support a second scanner. The data also show that the need for iMRI is currently not pervasive, and the state is not likely to need multiple scanners in addition to the one proposed in this petition, particularly outside of the setting of an academic medical center teaching hospital.

As noted above, the only existing iMRI unit in North Carolina is located at Duke University Hospital in Durham County which is in HSA IV. Specialized technology and unique services such as fixed multi-position MRI scanners and mobile PET have often been allocated between the eastern and western portions of the state to improve access to new technology. According to the most recent certified estimates from the North Carolina State Office of Budget and Management (NC OSBM), the population of the western portion of the state (HSAs I, II, and III) was nearly 350,000 people greater than the population of the eastern portion of the state (HSAs IV, V, and VI) in 2013.

Population by Eastern/Western Region

	2013 Certified Population
Eastern (HSAs IV, V, and VI)	4,757,737
Western (HSAs I, II, and III)	5,104,215
Total	**9,861,952**

Source: NC OSBM, 2013 Certified Estimates, last updated September 19, 2014.

As explained above, the primary population that benefits from iMRI is neurosurgery patients with certain specific conditions. To determine the number of patients in the state that could potentially benefit from iMRI, CHS reviewed surgical data from Truven for neurosurgery inpatient cases performed in the state and divided the total by the HSAs in which the cases were performed. As expected given the higher total population, the western portion of the state has a greater number of neurosurgery patients than the eastern portion, as shown below.

North Carolina Neurosurgery Inpatient Cases

Calendar Year	*Eastern NC*	*Western NC*	*Total Inpatient Cases*
2011	2,932	3,470	**6,402**
2012	3,050	3,551	**6,601**
2013	3,015	3,688	**6,703**
2014*	2,830	3,524	**6,354**

Source: Truven inpatient data for MS-DRGs 20-27, 31-33, 40-42, 614-615, and 955. *2014 data based on six months annualized.

Using this neurosurgery data for North Carolina, CHS estimated the number of neurosurgery inpatients that would benefit from iMRI services in North Carolina in total as well as in the western portion alone. Using available literature on the demonstrated clinical applications of iMRI technology as well as the considerable neurosurgical experience of CHS's neurosurgeons, CHS first estimated the number of neurosurgery patients by procedure type and then estimated the percentage of certain procedure types that are likely to benefit from iMRI scans during their procedure. Of note, CHS believes these assumptions are conservative as they only include a subset of procedures that have iMRI clinical applications.

Estimated iMRI Cases - North Carolina Total

	*Percent of Total Neurosurgery**	*2014 Neurosurgery (Annualized)*	*Potential Clinical Application of iMRI?*	*Percent of Neurosurgery Cases Assumed iMRI Appropriate**	*2014 iMRI Cases*
Functional Neurosurgery (DBS and Others)	5.1%	323	Yes	0%, conservatively	
Intracranial Tumor Surgery	26.9%	1,710	Yes	41%	701
Neurovascular Surgery	8.0%	508	Yes	0%, conservatively	
Pediatric Neurosurgery	12.0%	762	Yes	5%	38
Epilepsy Surgery	5.0%	318	Yes	0%, conservatively	
Peripheral Nerve Surgery	11.0%	699	Unknown	0%	
Neuro Trauma	11.6%	739	Unknown	0%	
Skull Base Neurosurgery	7.3%	462	Unknown	0%	
Other	13.1%	832	Unknown	0%	
TOTAL	**100.0%**	**6,354**	**57%**		**739**

Source: Truven data. *CHS/neurosurgeon estimates.

Estimated iMRI Cases – Western Portion of North Carolina

	*Percent of Total Neurosurgery**	*2014 Neurosurgery (Annualized)*	*Potential Clinical Application of iMRI?*	*Percent of 2014 Neurosurgery Cases Assumed iMRI Appropriate**	*2014 iMRI Cases*
Functional Neurosurgery (DBS and Others)	5.1%	179	Yes	0%, conservatively	
Intracranial Tumor Surgery	26.9%	948	Yes	41%	389
Neurovascular Surgery	8.0%	282	Yes	0%, conservatively	
Pediatric Neurosurgery	12.0%	423	Yes	5%	21
Epilepsy Surgery	5.0%	176	Yes	0%, conservatively	
Peripheral Nerve Surgery	11.0%	388	Unknown	0%	
Neuro Trauma	11.6%	410	Unknown	0%	
Skull Base Neurosurgery	7.3%	256	Unknown	0%	
Other	13.1%	461	Unknown	0%	
TOTAL	**100.0%**	**3,524**	**57%**		**410**

Source: Truven data. *CHS/neurosurgeon estimates.

Based on these calculations, CHS estimates that there were 739 iMRI appropriate neurosurgery cases in 2014, and that 55 percent of those, or 410 patients, originated in the western portion of the state. Of note, Duke University Hospital has historically served 26 to 32 percent of neurosurgery patients in the eastern portion of the state, but has only served five to seven percent of neurosurgery patients in the western portion.

Duke University Hospital – Neurosurgery Market Share Estimates

Calendar Year	*Eastern NC*	*Western NC*
2011	31.8%	6.7%
2012	31.6%	6.5%
2013	26.7%	5.5%
2014*	25.8%	4.8%

Source: Truven inpatient data for MS-DRGs 20-27, 31-33, 40-42, 614-615, and 955. *2014 data based on six months annualized.

Given its location in the eastern portion of the state and its clinical relationships and affiliation with other acute care providers in the eastern region, this market share difference for Duke is unsurprising. However, it underscores the geographic disparity that the eastern and western regions of North Carolina have to iMRI services. For comparison purposes, Carolinas Medical Center (CMC), CHS's academic medical center teaching hospital in Charlotte serves patients across the western portion of the state. According to 2014 Truven data, CMC treats 27 percent of neurosurgery patients in the western portion of the state. Should this petition be approved, CHS would apply for a Certificate of Need to develop an iMRI unit at CMC in order to expand access to iMRI services and provide training opportunities to its neurosurgical residency program. More broadly, given the access issues to iMRI technology compared to other states in the region and the absence of an iMRI unit in the western portion of the state (in comparison to the less populated eastern portion), CHS believes an iMRI unit in the western portion of the state is needed.

REASON FOR REQUEST

For numerous reasons, CHS believes that the most effective way to meet this need is to request the special allocation outlined in this petition. First, due to their unique and specialized nature, iMRIs are different from traditional diagnostic MRI units. As noted above, iMRI units are used during a surgical procedure. Thus, the unit must be located within an operating room or on a set of rails that allow it to be brought into the operating room quickly and easily. Case times for iMRI scans are related to the length of the neurosurgical procedure and are longer than traditional MRI scans (assumed to be two procedures per hour in *2015* SMFP). Currently, iMRI is designed for use in neurosurgery; thus, its applications are limited. Given these factors, an iMRI unit is not likely to be as highly utilized as traditional MRI scanners. Please note that CHS believes that the proposed iMRI unit should not be counted in the regular inventory of MRI

scanners in the *SMFP* because of its unique and specialized nature and should not be required to meet the MRI equipment performance standards. For these reasons, the standard methodology is not effective at determining need, and the need generated by the standard methodology should be addressed by MRI scanners that can more effectively meet the need of the population generating that need—only a small portion of whom are patients that would be served by an iMRI.

ALTERNATIVES CONSIDERED

Under the North Carolina Certificate of Need (CON) statute, CHS believes there are three ways to develop the needed iMRI, and only the last, through a special allocation in the 2016 *SMFP*, is a reasonable alternative. The rationale for not maintaining the status quo is discussed above regarding the need for an iMRI in the western half of the state. The other alternatives are as follows:

1. **Replace an existing MRI unit with an iMRI.** This option is unreasonable as a provider would add iMRI capacity at the expense of traditional MRI capacity. As noted above, iMRI units are not appropriate for use by traditional MRI patients given their location in or adjacent to an operating room. For providers, like Carolinas Medical Center which operates its MRI scanners at high utilization rates (79 percent utilization in 2013), the replacement of one traditional fixed MRI scanner with a iMRI scanner is not feasible as it would require a sacrifice of much-needed capacity for traditional MRI patients.

2. **File a CON to develop an iMRI in response to a need determination in the *SMFP*.** This option is unreasonable as an applicant seeking to develop an iMRI in response to a need determination would be disadvantaged in a competitive CON review due to specialized nature of iMRI services. An applicant seeking to develop an iMRI unit would not be able to effectively meet the need for additional MRI capacity identified by the need determination. Said another way, a need determination in the *SMFP* would be created by traditional MRI patient utilization and thus, the development of an iMRI unit would meet only a small portion of that need. Any competitive applicant seeking to develop a traditional MRI would be a more effective alternative to meeting the need in the *SMFP*. Historically, the SHCC has made adjustments to the *SMFP* so that specialized services could be developed without competing with the development of traditional services (e.g. *2009 SMFP* need determination for neonatal intensive care beds in Wake County; *2005 SMFP* need determination for pediatric MRI unit). This is the approach that is sought by the current petition. Additionally, an applicant seeking to develop an iMRI through a CON application would be forced to meet the performance standards for MRI services. As noted above, given its specialization, iMRI units are not likely to be as highly utilized as

traditional MRI scanners and thus would be unlikely to meet the MRI performance standards.

3. **Special allocation.** The currently proposed petition seeks a special allocation for one iMRI unit in the western portion of the state. Given the shortcomings of the previous three alternatives to meeting the need for iMRI services, CHS believes this approach is the only reasonable approach to developing greater access to this important new service.

The final alternative, a special allocation as proposed in the petition, is the only alternative that will ensure the development of iMRI services in the western portion of the state, where access is needed, without reducing access to traditional MRI services. As such, CHS believes the current petition is the most effective alternative for developing needed access to iMRI services. As discussed above, iMRI technology offers significant benefits for patient care as well as cost savings. The cost to payors for a repeat surgery is approximately $33,000 according to CHS estimates. It is difficult to estimate how many second surgeries could be avoided, however, it is believed that this technology could save millions of dollars in unnecessary expenses. North Carolina, and the western portion of the state in particular, do not yet have adequate access to this service. CHS estimates that there is adequate patient volume in the western portion of the state to support the need for a special allocation of an iMRI unit as requested in this petition. CHS believes that a special allocation in the *SMFP* is the only reasonable alternative to develop this service, given the deficiencies of other potential approaches.

Please note that CHS also considered filing a petition for an adjusted need determination for the *Proposed 2016 SMFP* during the summer petition cycle. However, given the regional impact of this proposal on HSAs I, II, and III, CHS believed its petition was more appropriately submitted at this time. Historically, the SHCC has reviewed petitions that have statewide or regional impacts during the spring petition cycle so that the *Proposed SMFP* can include the need for comment by interested parties.

Please note as well that CHS considered requesting that the iMRI be included as part of a demonstration project. CHS believes, however, that the utility of demonstration projects in the *SMFP* is limited and should be reserved for truly unique circumstances, particularly those in which the efficacy of the demonstration project could be used to deploy resources more broadly. In this instance, given the important, but currently narrow use of iMRI technology, and the limited utility outside of an academic medical center teaching hospital setting, CHS does not believe that the technology will need widespread adoption in the state in the near future.

ADVERSE EFFECTS IF PETITION IS NOT APPROVED

As discussed above, the proposed special allocation will enable increased access to iMRI services in the western portion of the state. iMRI technology offers significant benefits to patients and payors, as detailed above. By providing visualization of tumors during a neurosurgical procedure, iMRI improves surgical precision and helps ensure the complete resection of the tumor before the patient is closed up. Studies show that iMRI allows for improved accuracy of resections and a reduction of repeat surgeries for adult and pediatric patients.

Without the approval of this petition, patients in the western portion of the state will not have adequate access to iMRI services. As a result, patients will have an increased chance of repeat neurosurgery procedures and the associated delays in the healing process. These repeat procedures generate unnecessary healthcare expenses for patients, payors, and the system overall and often requires a readmission.

CHS believes that a special allocation in the *SMFP* is the only reasonable alternative to develop this service, given the deficiencies of other potential approaches.

NO UNNECESSARY DUPLICATION

As noted above, there is only one approved or operational iMRI unit in North Carolina. Based on a review of inpatient neurosurgery data, CHS believes that there is a demand for more than one unit and that patients in the western portion of the state do not have adequate access to this service. As a result, the proposed petition for a special allocation of one unit of iMRI equipment in the western portion of the state will not result in the unnecessary duplication of health resources in the area.

CONFORMITY WITH THE BASIC PRINCIPLES

The proposed petition is consistent with the basic principles of the *SMFP*: safety and quality, access, and value.

Safety and Quality

As discussed above, iMRI has demonstrated clinical benefits. Studies show that iMRI allows for improved accuracy of resections and a reduction of repeat surgeries for adult and pediatric patients. As a result, patients who have access to iMRI services receive higher quality and safer care. Patients who do not have access to iMRI technology receive a conventional MRI scan after their neurosurgery procedure to determine the effectiveness of the surgery. If the post-surgery MRI scan indicates a need for additional surgery, the patient undergoes a second, separate, neurosurgery procedure. Repeat

neurosurgery is a significant ordeal for patients, particularly children, and delays the healing process.

Access

As noted above, there is only one existing or approved iMRI unit in North Carolina and as a result the state, particularly the western portion, has inadequate access to this technology. Nearby states such as Virginia, Florida, and Tennessee have greater access to iMRI services on a per population basis.

Accessibility of iMRI Scanners

State	*iMRI Units*	*2014 Population*	*iMRI per 1 Million Population*
South Carolina	0	4,832,482	0.00
Georgia	1	10,097,343	0.10
North Carolina	1	9,943,964	0.10
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Tennessee	2	6,549,352	0.31

Source: Monteris Medical (iMRI vendor); U.S. Census Bureau.

The lack of an iMRI provider in South Carolina also compounds access issues in North Carolina. If this petition is granted and ultimately another iMRI unit was developed in North Carolina, the state would have 0.20 units per 1 million population which would be comparable to but would not exceed access in Virginia and Florida.

The only existing iMRI unit in North Carolina is located at Duke University Hospital in Durham County which is in HSA IV. Specialized technology and unique services such as fixed multi-position MRI scanners and mobile PET have often been allocated between the eastern and western portions of the state. According to the most recent certified estimates from the North Carolina State Office of Budget and Management (NC OSBM), the population of the western portion of the state (HSAs I, II, and III) was nearly 350,000 people greater than the population of the eastern portion of the state (HSAs IV, V, and VI) in 2013.

Value

The expansion of iMRI access will reduce repeat surgeries and readmissions. As noted above, CHS estimates that the cost to payers of a repeat surgery is approximately $33,000. It is very difficult to estimate how many second surgeries could be avoided, however, it is believed that this technology could save millions of dollars in unnecessary expenses. While these savings will be offset by the initial cost of the iMRI unit, the long-term financial savings and quality of care benefits will outweigh the

capital outlay. CHS estimates that there is adequate patient volume in the western portion of the state to support an iMRI unit. This broad geography will allow a future iMRI provider to draw sufficient volume to efficiently utilize this technology.

SUMMARY

In summary, CHS believes the proposed special allocation for one iMRI unit in the western portion of the state will provide the citizens of North Carolina with significant benefits in terms of safety/quality, access, and value and urges the SHCC to approve this petition.

Attachment 1

Evidence in the Literature

Over 50 abstracts from major journals documenting iMRI impact on* ***more complete resections****,* ***lower morbidity****, possibly* ***improved survival****,* ***less returns to the OR***

European Journal of Surgical Oncology (2014 Mar)

Maximizing the extent of resection and survival benefit of patients in glioblastoma surgery: high-field iMRI versus conventional and 5-ALA-assisted surgery.

CONCLUSIONS:

Analysis of **residual tumor volumes, total resections and neurological outcomes demonstrate that iMRI may be significantly superior** to 5-ALA and white-light surgery for glioblastomas at comparable peri- and postoperative morbidities. **Longer 6-month progression-free survival** was observed in patients with total resections.

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Intraoperative MR imaging-guided resections resulted in a **trend toward reduction in the need for repeat surgery in the immediate 2-week postoperative period** compared with conventional pediatric neurosurgical resections for tumor or focal cortical dysplasia…the iMRI suite offers a comparable safety and efficacy profile while potentially **reducing the per-case cost by diminishing the need for early reoperation.**

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Maximizing the extent of resection and survival benefit of patients in glioblastoma surgery: High-field iMRI versus conventional and 5-ALA-assisted surgery

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Abstract

Aims: A safe total resection followed by adjuvant chemoradiotherapy should be the primary goal in the treatment of glioblastomas (GBMs) to enable patients the longest survival possible. 5-aminolevulinic acid (5-ALA)- and intraoperative MRI (iMRI)-assisted surgery, have been shown in prospective randomized trials to significantly improve the extent of resection (EOR) and subsequently survival of patients with GBMs. No direct comparison of surgical results between both techniques has been published to date. We analyzed the additional value of iMRI in glioblastoma surgery compared to conventional surgery with and without 5-ALA.

Methods: Residual tumor volumes, clinical parameters and 6-month progression-free survival (6M-PFS) rates after GBM resection were analyzed retrospectively for 117 patients after conventional, 5-ALA and iMRI-assisted surgery.

Results: Mean residual tumor volume (range) after iMRI-assisted surgery [0.5 (0.0–4.7) cm^3] was significantly smaller compared to the residual tumor volume after 5-ALA-guided surgery [1.9 (0.0–13.2) cm^3; $p = .022$], which again was significantly smaller than in conventional white-light surgery [4.7 (0.0–30.6) cm^3; $p = .007$]. Total resections were significantly more common in iMRI- (74%) than in 5-ALA-assisted (46%, $p = .05$) or white-light surgery (13%, $p = .03$). Improvement of the EOR by using iMRI was safely achievable as peri- and postoperative morbidities were comparable between cohorts. Total resections increased 6M-PFS from 32% to 45%.

Conclusions: Analysis of residual tumor volumes, total resections and neurological outcomes demonstrate that iMRI may be significantly superior to 5-ALA and white-light surgery for glioblastomas at comparable peri- and postoperative morbidities. Longer 6M-PFS was observed in patients with total resections.

Keywords: Glioma; Intraoperative magnetic resonance imaging; Extent of resection; 5-ALA; Neuronavigation

Introduction

Intraoperative magnetic resonance imaging (iMRI) has been used for more than a decade aiming to achieve better results in the resection of gliomas. Literature shows that the extent of resection (EOR) of contrast enhancing lesions might be improved by iMRI.[1–10] A radical and safe tumor removal appears to be one of the most important prognostic factors in patients with glioblastomas (GBM).[8,11–15] Recent literature shows a benefit concerning the EOR in around 30–40% of all cases comparing the intraoperative and the postoperative MR scans.[6,7,13,16–18] While there are few studies comparing the intraoperative versus the postoperative residual tumor-volume, scarce evidence is available on the advantage of iMRI-guided versus conventional glioma resection.[8,9,19] Only three studies (two retrospective and one prospective randomized) comparing iMRI-guided and conventional resection were published to date showing a benefit for the iMRI-group in terms of

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the EOR and survival.[8,19,20] As of today's knowledge on state-of-the-art resection techniques for high-grade gliomas, 5-ALA fluorescence-guided resection appears to be the most radical method in terms of the EOR in conventional surgery. Due to the high expenses associated with iMRI (especially the high-field one) and the desire for continuous improvement of patient treatment and survival, there is a strong need to evaluate the use of iMRI-assisted surgery in comparison to cheaper and established supportive resection techniques such as 5-ALA. Therefore, we analyzed the EOR along with clinical, surgery-related chronological and 6M-PFS data comparing high-field iMRI-guided versus conventional surgery with and without 5-ALA in the resection of glioblastomas.

Methods

Patient cohort

This was a single-institution protocol driven, retrospective study approved by the local institutional review board. All patients provided informed consent for the analysis of clinical data. We reviewed the records of consecutive patients from the clinical database, who underwent resection of glioblastomas between June 2010 and November 2012. IMRI-guided surgery was available since July 2011. Eligibility criteria were as follows: histopathologically verified glioblastoma multiforme (WHO grade IV), intended total resection and availability of pre- and postoperative (within 72 h) MRI. Exclusion criteria were biopsies as well as incomplete resections due to worsening of intraoperative monitoring. In total, 117 patients met the inclusion criteria. 57 patients had surgery before the iMRI unit opening (further called "pre-iMRI period"), of these 5-ALA-fluorescence-guided tumor resection was performed in 27 individuals. Upon iMRI availability (further called "iMRI period"), a total of 60 patients had radical GBM surgery, 27 with iMRI guidance, 20 with 5-ALA-fluorescence and 13 conventionally with white light. Assignment of patients to iMRI, 5-ALA or conventional surgery was done independently of the present study design by choice of the surgeon. To ban possible selection bias of patients and different surgical strategies, the main analysis evaluates not only 5-ALA versus iMRI cases, but also patients from the pre-iMRI with the iMRI period, which are clearly chronologically separated.

Assessment of medical records

Assessment of medical records included gender, age, neurological deficits and Karnofsky performance scale (KPS) pre- and postoperatively, as well as after 6 months, histological report, surgery report, discharge note, duration of surgery, intensive care unit (ICU) as well as hospital stay, pre-, intra- and postoperative gadolinium-enhancing tumor volume, and 6M-PFS. If patients were lost for follow-up, the most recent clinical information was entered in the analysis. New postoperative neurological deficits were defined as "mild" if they were transient, as "severe" if they did not recover within days.

Operative setup

Intraoperative MR imaging was performed in an intraoperative MR suite (IMRIS Visius Surgical Theatre, IMRIS Inc., Winnipeg, Canada) with a modified ceiling-mounted 1.5 T moveable magnet (Espree; Siemens Medical Systems, Erlangen, Germany), described previously in the work of Chen et al.[6] Postoperative MR imaging was performed in a 1.5 T magnet (Aera, Siemens Medical Solutions, Erlangen, Germany). Electrophysiological monitoring (Nicolet Endeavor CR, Cardinal Health, Dublin, Ireland), 5-ALA (20 mg/kg bodyweight 4–6 h before surgery; Medac GmbH, Wedel, Germany), neuronavigation (CBYON (CBYON Inc, Mountain View, California) or BrainLab (BrainLab AG, Feldkirchen, Germany)) and ultrasound (Acuson Antares, SIEMENS AG, Erlangen, Germany) was used if indicated or requested by the surgeon. All surgeries were performed with an OPMI Pentero (Carl Zeiss, Oberkochen, Germany) or a Leica M720 OH5 (Leica Microsystems, Wetzlar, Germany) microscope.

Tumor volumetry

Based on free-hand drawn regions of interest (ROIs), tumor volumetry of pre-, (intra-) and postoperative imaging was performed in consensus by two experienced neuroradiologists who were blinded for the different groups. Residual tumor was defined as contrast-enhancing tissue on 3D-T1-weighted sequences. Tumor volumes were calculated by using commercially available software (AW Workstation, GE Medical Systems, Milwaukee, Ill., USA).

Statistical analysis

Statistical analysis was performed with GraphPad Prism software (GraphPad Software Inc., version 6.01 for Windows, La Jolla, CA, USA). The continuous values are given as mean values (range). Continuous, unpaired, non-parametric data was analyzed using the Mann-Whitney-U test. Continuous, parametric data was analyzed by *t*-test for unpaired samples. Categorical data was analyzed by Fisher's exact test. Multiple regression analyses using the enter method was conducted to analyze the relationship between postoperative tumor volume (dependent variable) and pre- and intraoperative independent variables (preoperative tumor volume, use of iMRI, 5-ALA, ultrasound, and neuronavigation). PFS was analyzed with the Kaplan–Meier method, curve comparison with the log-rank (Mantel–Cox) test. Statistical significance was declared at p-values < 0.05.

Results

Medical records of patients who underwent resection of glioblastoma multiforme were analyzed to evaluate the extent of resection, clinical parameters and 6M-PFS of iMRI-, 5-ALA- and conventional white-light-guided surgery. Inclusion criteria were met in 117 patients, 57 before and 60 after the iMRI unit was opened. MRI was not available or of insufficient quality for volumetry due to movement artifacts in 15% of the preoperative and 8% of the postoperative cases. 7% of the patients were lost during the follow-up. No complications correlating to the use of supportive surgical techniques (iMRI, 5-ALA, IOM, neuronavigation, ultrasound) were noticed.

Demographic and clinical data

Demographic and clinical data are listed in Table 1. No significant differences were noted between the sub-groups besides for the incision-suture time, which was significantly longer in the iMRI cases [354 vs. 213 (pre-iMRI period) or 187 (iMRI period) minutes in the conventional surgery cases]. 5-ALA was used less frequently during the pre-iMRI period (47% vs. 65% in the iMRI period); subgroup analyses for these patients are presented below. Neuronavigation was routinely used during iMRI surgery, which can be attributed to the workflow in the iMRI unit. Higher percentage of surgeries with IOM in the iMRI cohort (70% vs. 39% in conventional surgery within the iMRI period) can be seen as an indicator for more interventions in direct vicinity of eloquent sensorimotor regions in the iMRI unit. Distributions of tumor-localizations were comparable between the subgroups (Table 2).

New postoperative neurological deficits as well as KPS was analyzed pre- and postoperatively (status at discharge from the hospital), and after 6 months (KPS). No relevant differences were found between the groups, besides a significantly better KPS of patients in the iMRI period compared to the pre-iMRI period at the point of discharge ($p = .005$) (Table 3).

Table 2
Anatomical localization of tumors in the different cohorts.

Lobe	Pre-iMRI period	iMRI period		
	Entire cohort (57patients)	Entire cohort (60 patients)	iMRI only (27 patients, 45%)	Conventional surgery (33 patients, 55%)
Frontal	17 (30%)	16 (27%)	8 (30%)	8 (24%)
Temporal	28 (49%)	25 (42%)	13 (48%)	12 (37%)
Parietal	7 (12%)	12 (20%)	4 (15%)	8 (24%)
Occipital	5 (9%)	7 (12%)	2 (7%)	5 (15%)

Volumetry

Results of volumetric analysis can be found in Table 4. Mean preoperative tumor-volumes showed comparable tumor sizes with no significant differences between the groups.

Analysis of residual tumor volumes of iMRI surgery [0.5 (0–4.7) cm^3] compared to the entire pre-iMRI period cohort [3.3 (0–30) cm^3; $p < .001$] and the iMRI period conventional surgery cohort [1.46 (0–9) cm^3; $p = .006$], as well as to the pre-iMRI period 5-ALA-only cohort [1.9 (0–13.2); $p = .022$] and iMRI period 5-ALA-only cohort [1.3 (0–5.6) cm^3; $p = .022$] proved the superiority of iMRI guided surgery in terms of resection radicality. Analysis of total resections (defined as residual tumor of 0 cm^3) in the above mentioned subgroups also showed a significant beneficial effect of iMRI surgery. However, the comparison of total resections in the iMRI group compared to the iMRI period 5-ALA cohort slightly failed to reach the level of statistical significance (74% vs. 45%; $p = .069$). An overall comparison of the mean postoperative residual tumor-volumes between pre-iMRI and iMRI periods showed a significant beneficial effect on the entire cohort/department results since the launch of iMRI [3.3 (0–30) vs. 1.0 (0–9)

Table 1
Demographic and clinical parameters of the different cohorts. The values are given as mean or median (range). Annotation: KPS = Karnofsky performance scale; y = years of age; ICU = intensive care unit; IOM = intraoperative monitoring.

Test	Pre-iMRI period	iMRI period		
	Entire cohort (57patients)	Entire cohort (60 patients)	iMRI surgery (27 patients, 45%)	Conventional surgery (33 patients, 55%)
Female:male	22:35	28:32	14:13	14:19
Mean age (y)	58.8 (21–84)	56.3 (18–84)	52.7 (18–77)	59.2 (27–84)
Primary:relapse tumors	40:17	40:20	17:10	23:10
Median postop ICU stay (days)	1 (1–32)	1 (1–29)	1 (1–29)	1 (1–3)
Median postop hospital stay (days)	5 (5–53)	6 (4–47)	7 (5–47)	6 (4–17)
Mean incision-suture time (minutes)	213 (80–386)	262 (90–572)	354 (147–572)	187 (90–353)
5-ALA	27 (47%)	39 (65%)	19 (70%)	20 (60%)
Neuronavigation	13 (23%)	32 (53%)	24 (88%)	8 (24%)
IOM	27 (47%)	32 (53%)	19 (70%)	13 (39%)
Ultrasound	23 (40%)	16 (26%)	3 (11%)	13 (39%)

Table 3
Pre- and postoperative clinical condition of patients. Annotation: 6M-KPS = Karnofsky Performance Scale 6 months after surgery. *$p = .005$.

Test	Pre-iMRI period	iMRI period		
	Entire cohort (57patients)	Entire cohort (60 patients)	iMRI only (27 patients, 45%)	Conventional surgery (33 patients, 55%)
Median preop KPS	90 (50–100)	90 (60–100)	90 (80–100)	90 (60–100)
Postop no new neurological deficits	37 (65%)	45 (75%)	20 (74%)	25 (76%)
Postop mild new neurological deficits	13 (23%)	11 (18%)	5 (19%)	6 (18%)
Postop severe new neurological deficits	7 (12%)	4 (7%)	2 (7%)	2 (6%)
Median postop KPS at discharge*	80 (40–100)	90 (0–100)	90 (30–100)	90 (0–100)
Median 6M-KPS	80 (0–100)	90 (0–100)	90 (0–100)	90 (0–100)

cm^3; $p = .004$] increasing total resections from 28% to 53% ($p = .018$). As expected, conventional surgery with 5-ALA showed a significantly higher radicality than conventional white-light resections [1.9 (0–13.2) vs. 4.7 (0–30.6) cm^3; $p = .007$] with a significant increase in total resection ($p = .026$).

In the intraoperative MR scan the mean residual tumor volume was 2.4 (0–9.8) cm^3, resection was continued in all but three cases, when no residual contrast enhancing tissue was found. Of the remaining cases a total resection was achieved in 17 additional patients rising the percentage of total resections at the point of the intraoperative MR scan (11%) to 74% in the postoperative MRI.

Multiple regression analysis in the entire patient cohort demonstrated that only preoperative tumor volume ($p < .001$), iMRI ($p = .005$) and 5-ALA ($p = .01$) were significant independent predictors of the EOR. The significance level of the analysis of variance in this model reached $p < .001$. In the iMRI-surgery patient group only preoperative tumor volume was independent predictor ($p = .02$) but not 5-ALA ($p = .71$). The significance level of the analysis of variance in this multiple regression analysis reached $p < .05$. Further multiple regression analysis in the patient subgroup before opening of the iMRI unit showed that preoperative tumor volume ($p < .001$) and 5-ALA ($p = .05$) were constantly a significant predictor for surgical outcome (analysis of variance p-value < 0.001). Finally, multiple regression analysis in the patient subgroup of the iMRI period revealed again that only preoperative tumor volume ($p < .001$) and iMRI ($p = .04$) were significant independent variables for the extent of resection (analysis of variance p-value < 0.001).

Follow-up

Follow-up of patients was analyzed for 6 months. 6M-KPS did not show any significant differences between cohorts (Table 3). Kaplan–Meier curves for progression free survival showed a benefit for patients with no residual contrast enhancing tissue compared to patients with tumor remnants (45% vs. 32% 6M-PFS), yet statistical significance could not be reached ($p = .131$) (Fig. 1A). Separate analysis of the pre-iMRI and iMRI period, as well as comparison of the iMRI cohort with conventional surgery did not show significant differences, yet iMRI-guided surgery appeared to have a beneficial effect (Fig. 1B, C, D).

Discussion

The complete resection of glioblastomas with preservation of neurological function should be the primary therapeutic goal before starting adjuvant therapies to achieve the longest survival with good life quality possible to date.[14,15] To achieve this goal, 5-ALA and intraoperative MRI are the cutting-edge supportive techniques at this time.[8,9,21] While 5-ALA provides the possibility to identify fluorescent tumor tissue in the resection cavity through the microscope in a real-time manner, intraoperative MRI requires a time-consuming interruption of the surgery with acquisition of static images which, however, can show contrast-enhancing tumor on the surface of the resection cavity as well as underneath it. The use of 5-ALA has a reasonable extra cost and is possible without sophisticated technical equipment. On the other hand, iMRI (especially with a high-field system) has significantly higher acquisition and maintenance costs as well as extended OR times. For the first time, the present study compares consecutive patient cohorts operated with these technologies showing the additional value and superiority of iMRI-guided GBM surgery over conventional surgery with and also without 5-ALA.

Selection bias of patients

To detect any selection bias by the assignment of certain patients to iMRI-guided surgery in this retrospective study, additionally to the main analysis a direct comparison of surgical results between the chronologically separated groups before and after the iMRI system launch was performed. The results in 117 patients proved that, by adding iMRI as “extra tool”, a significant decrease of residual tumor volume and a significant increase of total resections could be achieved at comparable perioperative co-morbidities. At the same time subgroup analysis detected no selection bias between all other cohorts (5-ALA, white-light surgery), as pre- and postoperative tumor volumes after conventional surgery did not differ significantly.

Table 4
Pre- and postoperative tumor volumes [mean values (range)] and total versus subtotal resections. Total resection is defined as residual tumor volume equal to 0 cm^3. Subtotal resection defined as <1 cm^3. Statistically significant p-values are marked in bold letters. Annotation: MWU = Mann−Whitney-U-test; FE = Fisher's exact test.

Test	Pre-iMRI period (57 patients)			iMRI period (60 patients)				Results (p)
	Entire cohort (57patients)	5-ALA only (27 patients, 47%)	White-light surgery (30 patients, 53%)	Entire cohort (60 patients)	iMRI only (27 patients, 45%)	Conventional surgery (33 patients, 55%)	Conventional surgery with 5-ALA (20 of 33 patients, 60%)	
Mean preoperative tumor volume (cm^3)	47.5 (5−136)	43.9 (5−136)	52.6 (10−111)	41.2 (5−128)	46.2 (11−111)	38.6 (5−128)	37.95 (5−106)	
Mean residual tumor volume (cm^3)	3.3 (0−30)			1.0 (0−9)				**.004 (MWU)**
Mean residual tumor volume (cm^3)	3.3 (0−30)				0.5 (0−4.7)			**< .001 (MWU)**
Mean residual tumor volume (cm^3)	3.3 (0−30)					1.46 (0−9)		.227 (MWU)
Mean residual tumor volume (cm^3)					0.5 (0−4.7)	1.46 (0−9)		**.006 (MWU)**
Mean residual tumor volume (cm^3)		1.9 (0−13.2)					1.3 (0−5.6)	.869 (MWU)
Mean residual tumor volume (cm^3)		1.9 (0−13.2)			0.5 (0−4.7)			**.022 (MWU)**
Mean residual tumor volume (cm^3)					0.5 (0−4.7)		1.3 (0−5.6)	**.022 (MWU)**
Mean residual tumor volume (cm^3)		1.9 (0−13.2)	4.7 (0−30.6)					**.007 (MWU)**
Total resections (0 cm^3)	28%			53%				**.018 (FE)**
Total resections (0 cm^3)	28%					34%		.628 (FE)
Total resections (0 cm^3)		46%			74%			**.049 (FE)**
Total resections (0 cm^3)					74%		45%	.069 (FE)
Total resections (0 cm^3)		46%	13%					**.026 (FE)**

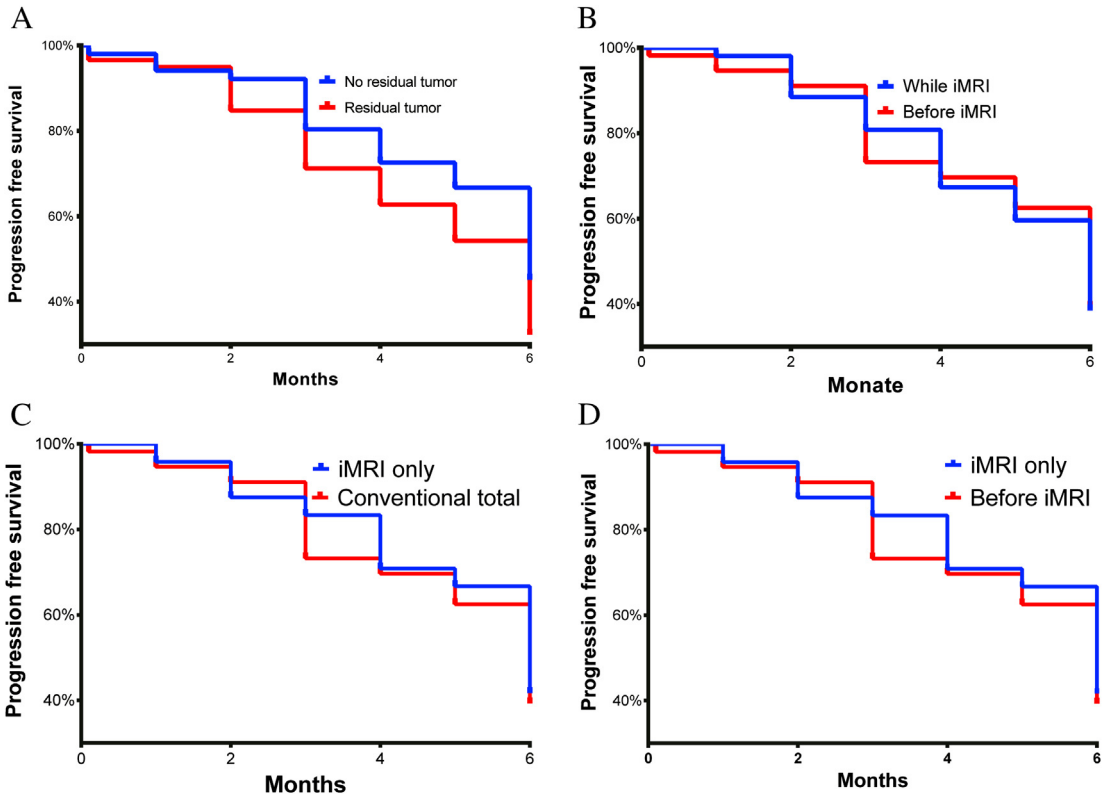

Figure 1. A: Kaplan–Meier curve of the entire cohort comparing 6M-PFS of patients with residual and no residual tumor. B: Kaplan–Meier curve comparing 6M-PFS of patients before and after the launch of iMRI. C: Kaplan–Meier curve comparing 6M-PFS after conventional versus after iMRI surgery. D: Kaplan–Meier curve comparing 6M-PFS of patients before the launch of iMRI and after iMRI surgery.

Comparability of cohorts

As to the beneficial results for iMRI surgery in terms of the EOR, comparability between both retrospectively analyzed cohorts needs to be questioned critically. Specifically, analysis of preoperative tumor volumes revealed no significant differences between the cohorts (Table 4). However, the frequency of tumors near eloquent sensorimotor areas in the iMRI group was higher, as IOM was used in 70% of these cases, compared to 47% in the conventional pre-iMRI period cohort ($p = .06$) (Table 1). This fact might influence the results in terms of the EOR unfavorable for iMRI-guided surgery as the resection might also be limited and guided by worsening of IOM, which is a very important additional tool for a safe resection. Nevertheless iMRI-guided surgery was still was shown to be better than conventional resection.

5-ALA was used less frequently in the pre-iMRI period (47%) than in the iMRI period (65%) (Table 1). However, 32% of patients in the iMRI period received 5-ALA combined with iMRI surgery. The contribution of 5-ALA fluorescence may be assumed to be confined to the initial resection phase, as after intraoperative image acquisition the resection of tumor remnants is mainly guided by the imaging findings and the updated neuronavigation. Also, subgroup analysis revealed that iMRI-guided surgery is superior to fluorescence-guided tumor resection in the pre-iMRI as well as in the iMRI period. These assumptions are underlined by Eyüpoglu et al.,[22] who were able to show that the extent of resection of high-grade gliomas according to 5-ALA criteria alone is less radical in comparison to the resection according to iMRI guidance. Also the use of 5-ALA in iMRI surgery was proven non-significant in the multiple regression analysis in our cohort, and thus, it should be further examined in future studies. Nevertheless, it is known that 5-ALA fluorescence might also be found behind contrast-enhancing areas in transitional areas of the tumor. Precise volumetric analysis including intraoperative update of imaging data to respect volume-changes caused by brain-shift are needed to finally answer this question.

Neuronavigation was used more frequently in iMRI-guided surgery (88%) than in the pre-IMRI (23%) and conventional surgery group within the iMRI period (24%). This is due to the added value of neuronavigation in iMRI-guided surgery owing to the identification of residual tumor after correction of brain shift using the iMRI data. The use of neuronavigation for conventional surgery was shown not to significantly improve the extent of resection in a prospective randomized trial, most likely due to the brain shift effect.[23] Therefore, we conclude that the less frequent use of neuronavigation in the

different subgroups does not bias our study results, as also seen in the multiple regression analysis. Nevertheless, use of neuronavigation in an iMRI setting, if updating of navigational data is possible, appears important and contributes to an improved EOR.[13]

Peri- and postoperative data

IMRI-assisted surgery is a time-consuming procedure. In our cohort, the mean incision suture time increased significantly from 213 (pre-iMRI period) to 262 (entire iMRI period) or 354 (iMRI surgery only) minutes. The additional time demand is due to longer general preparations, including iMRI scan preparation and the scanning time itself. The extended surgery and anesthesia time did not lead to any notable complications such as infection, thrombosis or relevant increase of pressure marks.

Progression free survival

We analyzed 6-month progression free survival (6M-PFS) of all patients and identified a strong benefit for patients with total resections compared to these with residual tumor tissue. However, subgroup analysis showed no significantly increased 6M-PFS in the iMRI cohort, which notably had the highest percentage of total resections. We were not able to identify any possible causal factor for these findings. Possible influences might be due to different adjuvant therapies (which have not been analyzed in detail for this study) or simply by chance caused by the limited number of patients in this study. Nevertheless, we assume that due to the significant higher numbers of total resections achieved by iMRI-guidance, longer PFS may be proven in larger scale studies in the future.

Total resections

Number of total resections in our cohort (white-light surgery 28%, 5-ALA surgery 46%, iMRI surgery 74%) appear low compared to the results in the literature (Senft et al.[8] 68% white-light vs. 96% iMRI surgery; Stummer et al.[11] 36% white-light vs. 65% 5-ALA surgery). Yet preoperative tumor volumes were smaller in the cited studies, as well the definition of total resections with a residual contrast enhancing volume below 0.175 cm^3, both likely explaining differences in the results compared to our analysis.

General considerations

The iMRI resection was continued after the intraoperative scan in all but three cases with initial total resections. Intraoperatively identified residual tumor volumes are often very small and can be removed totally resulting in a significant increase in total resections from 11% at the intraoperative MR scan time point to 74% after the end of iMRI-assisted surgery. Frequently such small tumor remnants are located in the entry zone of the resection cavity, where the microscope's field of view is restricted. This major strength of iMRI-assisted surgery, namely to detect and resect very small residual tumor remnants has crucial clinical impact, as these areas are known to be the starting point of relapse tumors in 80% of the cases.[12]

Limitations

Main shortcoming of this study is the retrospective design with limited number of patients. Yet the analysis of the two chronologically separated time periods before and after the opening of the iMRI unit, enabled to identify the extra value of a newly opened iMRI unit with free choice of other supportive surgical technologies as requested by the surgeon. The additional value of 5-ALA fluorescence in transitional areas of the tumor with no contrast enhancement was not analyzed in our study. This question should be addressed in precise volumetric studies in the future to identify a possible beneficial effect of a more radical resection with 5-ALA-guidance in these areas. Furthermore, any benefit of iMRI on patient survival should be assessed in the future by prospective multicenter studies with homogenous adjuvant therapy regimens, which was not possible in this study.

Conclusion

The present study is the first to provide evidence of the additional value of high-field iMRI in terms of extent of resection, perioperative clinical data and 6M-PFS compared to state-of-the-art conventional glioblastoma surgery with and without 5-ALA. Our analysis demonstrated that iMRI may be significantly superior to conventional surgery (with and without 5-ALA) for extended tumor resection and thus, higher number of total resections with comparable peri- and postoperative morbidities. The higher frequency of 6M-PFS among patients who underwent total resections in our study underlines the potential beneficial role of iMRI as "stand-alone" or adjunct technology to other intraoperative modalities for modern glioblastoma surgery.

Conflicts of interest

CR, SB and MT have received honoraria as speakers from IMRIS GmbH, Nürnberg, Germany. None of the other authors have any potential conflicts of interests to disclose.

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See the corresponding editorial in this issue, pp 342–345.

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Determining the utility of intraoperative magnetic resonance imaging for transsphenoidal surgery: a retrospective study

Clinical article

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Object. Intraoperative MRI (iMRI) provides updated information for neuronavigational purposes and assessments on the status of resection during transsphenoidal surgery (TSS). The high-field technique additionally provides information about vascular structures at risk and precise information about extrasellar residual tumor, making it readily available during the procedure. The imaging, however, extends the duration of surgery. To evaluate the benefit of this technique, the authors conducted a retrospective study to compare postoperative outcome and residual tumor in patients who underwent conventional microsurgical TSS with and without iMRI.

Methods. A total of 143 patients were assessed. A cohort of 67 patients who had undergone surgery before introduction of iMRI was compared with 76 patients who had undergone surgery since iMRI became routine in TSS at the authors' institution. Residual tumor, complications, hormone dependency, biochemical remission rates, and improvement of vision were assessed at 6-month follow-up. A volumetric evaluation of residual tumor was performed in cases of parasellar tumor extension.

Results. The majority of patients in both groups suffered from nonfunctioning pituitary adenomas. At the 6-month follow-up assessment, vision improved in 31% of patients who underwent iMRI-assisted surgery versus 23% in the conventional group. One instance of postoperative intrasellar bleeding was found in the conventional group. No major complications were found in the iMRI group. Minor complications were seen in 9% of patients in the iMRI group and in 5% of those in the conventional group. No differences between groups were found for hormone dependency and biochemical remission rates. Time of surgery was significantly lower in the conventional treatment group. Overall a residual tumor was found after surgery in 35% of the iMRI group, and 41% of the conventional surgery group harbored a residual tumor. Total resection was achieved as intended significantly more often in the iMRI group (91%) than in the conventional group (73%) ($p < 0.034$). Patients with a planned subtotal resection showed higher mean volumes of residual tumor in the conventional group. There was a significantly lower incidence of intrasellar tumor remnants in the iMRI group than in the conventional group. Progression-free survival after 30 months was higher according to Kaplan-Meier analysis with the use of iMRI, but a statistically significant difference could not be shown.

Conclusions. The use of high-field iMRI leads to a significantly higher rate of complete resection. In parasellar tumors a lower residual volume and a significantly lower rate of intrasellar tumor remnants were shown with the technique. So far, long-term follow-up is limited for iMRI. However, after 2 years Kaplan-Meier analyses show a distinctly higher progression-free survival in the iMRI group. No significant benefit of iMRI was found for biochemical remission rates and improvement of vision. Even though the surgical time was longer with the adjunct use of iMRI, it did not increase the complication rate significantly. The authors therefore recommend routine use of high-field iMRI for pituitary surgery, if this technique is available at the particular center.
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Key Words • **pituitary surgery** • **transsphenoidal approach** • **intraoperative magnetic resonance imaging** • **residual tumor** • **resection rate**

Pituitary surgery has come a long way from the first reported transsphenoidal surgeries (TSSs) performed by Schloffer (as discussed in Schmidt et al.[24]) and Cushing (see Cohen-Gadol et al.[5]) at the beginning of the 20th century. With improvement in operative techniques and defined postoperative follow-up, the goals of successful surgery extend beyond preserving vision to complete adenomectomy and preservation of pituitary function. Postoperative 1.5- or even 3-T MRI identifies even subtle tumor remnants. However, due to considerable early postoperative changes, reliable detection of residual tumor with MRI cannot be achieved earlier than 3 months after surgery.[17]

Despite the introduction of neuronavigation to facilitate precise intraoperative anatomical orientation, complete resection of adenomas is not always achieved. The application of intraoperative imaging methods such as CT

Abbreviations used in this paper: iMRI = intraoperative MRI; OR = operating room; TSS = transsphenoidal surgery.

(iCT) and MRI (iMRI)[30] seems to have improved resection rates, not only in gliomas but also in transsphenoidal pituitary surgery.[2,6,8] First introduced as a low-field technique[31] improving resection, especially in suprasellar tumors,[6] its sensitivity in detecting intra- and parasellar tumor remnants was significantly lower compared with postoperative 1.5-T MRI.[4,22] With application of high-field iMRI, the sensitivity in detecting tumor remnants in TSS was similar to a 3-month conventional follow-up MRI, and the rate of complete removal was higher in comparison with previously published literature.[4,13,21,22,25] The hitherto published data seem very favorable for the application of iMRI, yet the main drawback (beyond the considerable equipment cost) is a substantial increase in duration of surgery.[28] On the other hand, the increase of safety and resection rates would justify a prolonged operating room (OR) time for most surgeons.

At the time of this writing no study existed comparing microsurgical TSS with and without use of iMRI. We therefore conducted a retrospective comparative study with the aim of investigating the routine use of iMRI in TSS.

Methods

Our center has used a dedicated intraoperative 1.5-T MRI scanner (Espree, Siemens AG) as a one-room solution since October 2008. In the beginning we treated mostly complex pituitary cases with the aid of iMRI and prospectively analyzed its impact as a resection control tool and as a means of updating the neuronavigation route.[14] Encouraged by the results, we changed our surgical technique and now use iMRI for all TSSs. To evaluate the impact of the introduction of iMRI we compared the outcome of patients after conventional microsurgical transsphenoidal tumor resection between 2007 and 2008 in the "pre-iMRI era" with the outcome of patients treated between 2009 and 2011 with the aid of high-field iMRI.

Patient Population

A total of 143 patients who had undergone surgery via a transsphenoidal approach were assessed. A cohort of 67 patients who had surgery in 2007 and 2008 without the use of iMRI was compared with a cohort of 76 patients who had surgery between 2009 and 2011 with routine use of iMRI. Ninety percent of surgeries were performed by the senior authors (K.S., C.R.W.), who had at least 15 years of experience with TSS. Patient characteristics are summarized in Table 1.

Pituitary function was assessed before and 6 weeks after surgery. Ophthalmological assessment including visual fields was performed before admission and 6 months after surgery. Follow-up was performed 6 months after surgery. A clinical examination and a contrast-enhanced MRI study were conducted at this point.

Surgical Technique

A standard direct perinasal paraseptal transsphenoidal route was used in all cases. In the conventional group, fluoroscopic imaging was used for the approach and intrasellar orientation. The microsurgical technique was used for opening the sellar floor and for tumor dissection. A fibrin-coated sponge was used for reconstruction of the sellar opening. The nasal septum was repositioned and fixed with nasal packing. In cases of intraoperative CSF leakage, a lumbar drain was inserted for 3–5 days.

TABLE 1: Characteristics in 143 patients treated using TSS with or without iMRI

Characteristic	Conventional Op	Op w/ iMRI
no. of patients	67	76
age in yrs		
median	58	55
range	16–85	14–77
sex		
female	44%	38%
extent of tumor invasion		
intrasellar	15%	11%
suprasellar	60%	50%
parasellar	25%	38%
previous ops	13%	33%
intended complete resection	76%	62%

In patients in whom iMRI was used, the head was fixed in a dedicated head holder with integrated MRI coil (NORAS MRI Products GmbH). Registration of the navigation system (VectorVision Sky, BrainLab AG) was performed either by surface matching or automated registration after acquisition of T1-weighted MPRAGE (magnetization-prepared rapid acquisition with gradient echo) images by using an integrated registration matrix.

Intraoperative MRI

Intraoperative MRI was performed at the surgeon's discretion. For imaging, the nasal speculum was removed and the upper part of the MRI coil was reattached. The sterile operating field was covered with drapes and the patient was transferred into the MRI scanner as described by Hlavac et al.[13] Intraoperative imaging started with T2-weighted turbo spin echo sequences in the coronal and sagittal planes. When no obvious tumor remnant was identified, imaging continued with T1-weighted spin echo sequences with and without contrast enhancement in identical planes. In large tumors with parasellar extension, MR angiography was added to the imaging protocol. In cases of intraoperative tumor remnant, the navigation route was updated with the newly acquired intraoperative data set after segmentation of the remnant. Further resection was performed if the tumor was accessible at reinspection. In cases of extended resection after iMRI, repeat imaging was performed prior to closure. If a contrast agent had been applied in the previous imaging session, administration of contrast was not repeated.

Data Acquisition and Statistical Analysis

The data obtained in the 143 patients were analyzed retrospectively. As a first step, the 6-month follow-up records of all eligible patients were examined for hormone

substitution, requirement of hormone therapy, state of vision, and visual field in comparison with the preoperative findings. The MRI scans for the outpatient clinic at our center are performed by independent radiologists. The radiologist's judgment concerning residual tumor was used as the basis for a final decision by the senior neurosurgeon at the outpatient clinic. In our retrospective analysis we evaluated both interpretations. In case of conflicting assessments at the 6-month follow-up, the 12-month or the latest available follow-up was used to reassess the case. If 12-month follow-up was not available, residual tumor at 6-month follow-up was assumed. The assessment was done as a categorical judgment for all items in this step of the evaluation. Presence of residual tumor was only based on the first follow-up assessment after surgery. A later tumor recurrence, except for the above-mentioned situation, or a loss to follow-up did not affect the calculation. If no follow-up existed at 6 months, patients were not included in the calculation for residual tumor. Patient records were searched for peri- or postoperative complications. In cases in which there was an intradural extension of the lesion, opening of the CSF space and placement of a lumbar drain were planned as part of the surgical approach. These procedures were not classified as a complication.

The groups were split by date of surgery and use of iMRI into a conventional group and an iMRI group. Descriptive statistics tests were performed. The distribution of values of the above-mentioned items was analyzed using the Fisher exact test. A p value below 0.05 was considered statistically significant.

Concerning the assessment of residual tumor, we analyzed all surgeries in which gross-total resection was intended by using categorical judgment again. In all other patients with parasellar extension of tumor in whom a complete resection was not intended, a volumetric assessment of the residual tumor was performed. There were no patients in any cohort in whom the aim was a transsphenoidal biopsy only. For volumetric analysis, the MRI studies obtained at 6 months after surgery were imported into surgical planning software (Iplan 3.0, BrainLab AG) and residual tumor was segmented. In most cases treated before 2009, a volumetric assessment of the preoperative images was not possible because digital images were not available. Thus, statistical comparisons were only performed on the postoperative findings. The comparisons of mean values of tumor volume in the iMRI and conventional groups were conducted with the Student t-test. A positive finding of residual intrasellar tumor was analyzed using the Fisher exact test.

Kaplan-Meier plots were calculated to assess progression-free survival during the first 30 months after surgery for all primary lesions. Distribution of tumor recurrence was compared using the log-rank test. All statistical analyses were performed using SPSS 15.0 (Lead Technologies, Inc.).

Results

Patient Characteristics

Both groups showed a similar distribution of age. The iMRI group had a lower percentage of females (38% vs 44%) and a higher rate of parasellar tumors (38% vs 25%) than the conventional surgery group. Thus the rate of intended total resection was lower (62% vs 76%). We saw a higher percentage of patients with previous TSS in the iMRI group as well (33% vs 13%) (Table 1).

The majority of patients in both groups suffered from a nonfunctioning pituitary adenoma. The iMRI group included a higher share of functioning tumors, 22 (29%) versus 7 (10%). The distribution of diagnoses is summarized in Table 2.

At the 6-month follow-up assessment, 26 patients (35%) in the iMRI group and 27 in the conventional group (41%) harbored a residual tumor after surgery. The difference was not significant ($p < 0.729$). Hormone replacement was prescribed in 46 patients (61%) in the iMRI group and in 41 patients (63%) in the conventional surgery group. The difference was not significant ($p < 0.590$). Worsening of vision was seen in 2 patients (3%) in the conventional group and in 1 patient (1%) in the iMRI group. Vision improved in 23 patients (31%) of this group and in 15 patients in the conventional group (23%). No significant difference was seen based on the Fisher exact test ($p < 0.355$). Complications were found in 7 patients (9%) in the iMRI group and in 3 (5%) in the conventional surgery group. In the iMRI group 6 patients suffered from a rhinoliquorrhea, of whom 2 were treated with a lumbar drain and 4 had surgical repair. We used a multilayer technique including fascia lata in these cases. One patient in the iMRI group reported an impairment of olfaction. In the conventional surgery group, a single major complication was seen. The patient reported a decrease of vision after surgery. A CT scan revealed an intrasellar hematoma. Despite immediate surgical evacuation, the patient's vision did not recover to the preoperative level. One patient suffered from postoperative epistaxis, which was treated by nasal packing only. One patient presented at follow-up with a mucocele that has been treated conservatively so far. The Fisher exact test showed no significant difference in complication rates between the groups ($p < 0.216$). Duration of surgery was shorter in the conventional group, with a mean of 58 minutes, in contrast to the mean of 158 in the iMRI group. This difference was significant ($p < 0.025$) according to the Student t-test. In a subgroup analysis of intra-, supra-, and parasellar tumors a significant difference in surgery time was seen only for parasellar tumors ($p < 0.015$).

TABLE 2: Tumor characteristics in patients treated using TSS with or without iMRI

Diagnosis	Conventional Op (%)	Op w/ iMRI (%)
pituitary adenoma		
nonsecreting	52 (78)	52 (68)
hormone secreting	7 (10)	22 (29)
Rathke cleft cyst	6 (9)	0 (0)
prolactinoma	0 (0)	2 (3)
craniopharyngioma	1 (2)	1 (1)
miscellaneous	1 (2)	1 (1)

The overall results at the 6-month follow-up assessment are shown in Table 3. To exclude a learning curve during surgery after introduction of iMRI, the first 20 cases with iMRI were compared with the last 20 cases performed with iMRI. Even though a higher share of parasellar tumors was found in the first cluster of cases (10 vs 3), the mean OR time showed no significant difference (first 20 cases 154 minutes vs 140 minutes for the last 20 cases: $p < 0.335$). Rates of complications, biochemical remissions, and improvements of vision were not statistically different over time ($p < 0.967$, $p < 0.202$, and $p < 0.862$, respectively).

Resection Rate

Intrasellar and Suprasellar Tumors. Furthermore, we evaluated the rate of residual tumor in the first follow-up separately for surgeries with intended gross-total resection and those with planned subtotal resection, as was performed for most of the parasellar tumors.

In 51 patients in the conventional group and in 48 in the iMRI group a complete resection was intended. In 4 patients in the iMRI group no follow-up at 6 months was present; these cases were therefore excluded from the calculation. The goal was achieved in 37 of 51 patients (73%) in the conventional group and in 40 of 44 (91%) in the iMRI group. This difference was significant ($p < 0.034$) according to the Fisher exact test (Table 4, Fig. 1).

Parasellar Tumors. A volumetric assessment was performed in all other cases. Digital presurgical images were available in only 2 patients in the cases treated in 2007 and 2008. Therefore only postoperative residual volume was compared. Two patients were lost to follow-up in the conventional group and 1 was lost in the iMRI group. The mean volume of residual tumor was 1.2 cm^3 in the iMRI group in comparison with 2.1 cm^3 in the conventional group. This difference, however, is not statistically significant according to the Student t-test ($p < 0.216$). An intrasellar tumor remnant was found in 8 of 14 patients (57%) in the conventional group, whereas it was found in only 5 of 27 patients (18%) in the iMRI group.

TABLE 4: Tumor remnant on 6-month follow-up MRI in cases with intended total resection

Variable	Conventional Op (%)	Op w/ iMRI (%)
tumor remnant		
positive	14 (27)	4 (9)
negative	37 (73)	40 (91)
unknown (lost to follow-up)	0	4
total	51	48
2-sided Fisher exact test	p < 0.034*	

* Statistically significant difference.

The Fisher exact test confirmed this difference to be statistically significant ($p < 0.017$) (Table 5).

Progression-Free Survival

The mean follow-up was 28.9 months in the conventional group and 16.4 months in the iMRI group. Kaplan-Meier assessment showed 9 events in the conventional versus 1 event in the iMRI group. The progression-free survival chart is shown in Fig. 2. No statistically significant difference between groups was shown in the log-rank test ($p < 0.103$).

Functioning Adenomas

Additionally, we performed a subgroup analysis of biochemical remission rates in patients suffering from functioning adenomas. Patient characteristics were different between the iMRI and conventional groups. In the iMRI group (n = 20), patients had a higher share of supra- and parasellar tumors (66% vs 27%) and less completely resectable tumors (76% vs 91%) compared with the conventional group (n = 7). Moreover, the proportion of patients with previous TSS was higher in the iMRI group than in the conventional group (23% vs 9%). We retrospectively evaluated dependency on medication after surgery. Patients in both groups had a benefit from surgery in 80% (iMRI) versus 71% (conventional) of cases. In the subgroup analysis we found 5 patients in the conventional group (71%) versus

TABLE 3: Clinical and radiological findings at 6-month follow-up assessment in patients treated using TSS with or without iMRI*

Variable	Conventional Op (%)	Op w/ iMRI (%)	p Value
residual tumor	27 (41)	26 (35)	<0.729†
hormone replacement	41 (63)	46 (61)	<0.590†
vision			<0.355†
worse	2 (3)	1 (1)	
unchanged	48 (74)	47 (62)	
improved	15 (23)	23 (31)	
complications	3 (5)	7 (9)	<0.216†
mean duration of op in min, range	57.84, 25–200	157.58, 85–361	<0.025‡

* Two patients in the conventional group and 1 in the iMRI group were lost to follow-up; the denominators in this table are 65 and 75, respectively.

† No statistically significant difference (Fisher exact test).

‡ Statistically significant difference (Student t-test).

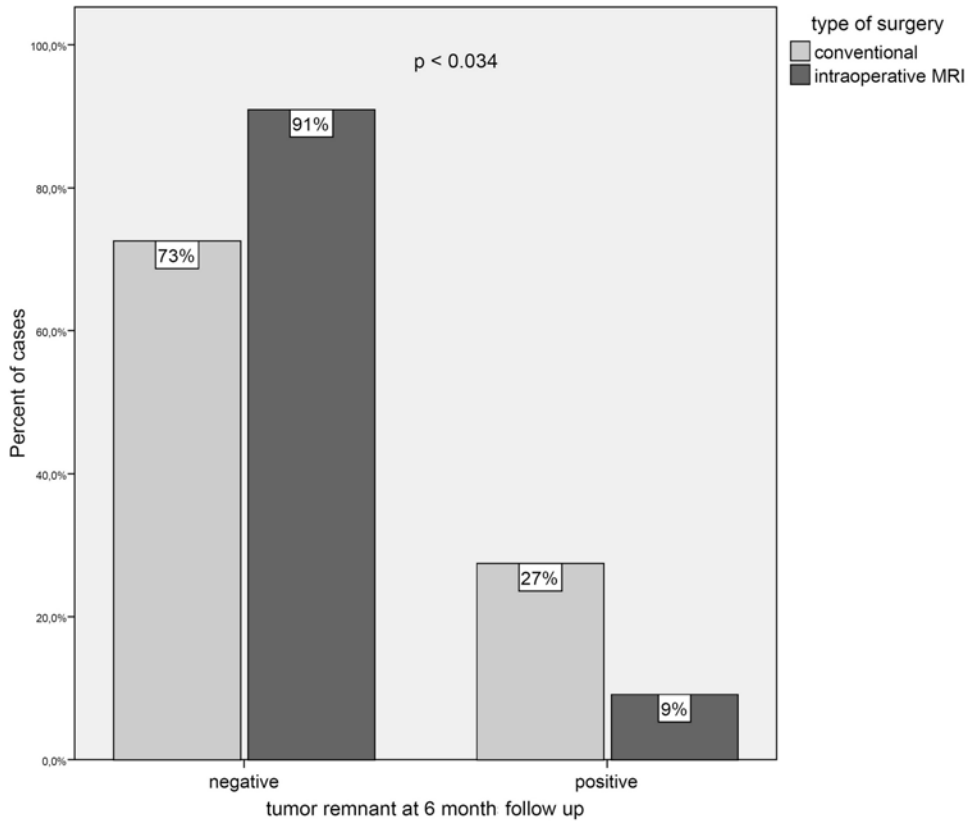

Fig. 1. Bar graph showing the share of tumor remnants at 6-month follow-up for lesions with intended total resection.

13 in the iMRI group (65%) to be independent from medication after surgery. Two patients in the conventional (29%) versus 4 patients in the iMRI (20%) group had no endocrinological benefit after surgery (Table 6). The difference between groups was not statistically significant according to the chi-square test ($p < 0.875$).

Illustrative Case

A clinical evaluation for chronic headache revealed the incidental finding of an intrasellar lesion in a 42-year-old woman. Endocrinological workup showed a nonfunctioning adenoma with a slightly elevated prolactin level. Results of the initial ophthalmological examination and visual fields were normal. After thorough counseling the patient decided against surgery; she was followed closely by an endocrinologist. No hypopituitarism was found. After 1.5 years a significant expansion into the suprasellar compartment was seen (Fig. 3). The ophthalmological examination was still without pathological findings; however, because of growth and proximity to the chiasm, we recommended microsurgical TSS performed with iMRI. Even though an intrasellar nonfunctioning adenoma with slight suprasellar extension is not a challenging case, we wanted to obtain the highest chance of a complete removal and the lowest risk of postoperative hypopituitarism for the as yet asymptomatic patient.

After positioning the patient in typical fashion in the

TABLE 5: Volumetric evaluation of parasellar tumors at 6-month follow-up in patients treated using TSS with or without iMRI*

Variable	Conventional Op		Op w/ iMRI
tumor vol in cm^3 ([% of preop] range)			
preop	NA		10.2 (1.9–36.4)
postop	2.1 ([NA] 0–8.3)		1.2 ([10%] 0–6.7)
t-test		$p < 0.216$†	
intrasellar tumor remnant	8 of 14 (57%)		5 of 27 (18%)
2-sided Fisher exact test		$p < 0.017$‡	

* NA = not available (no digitalized data of preoperative images before 2009).
† No statistical significance (Student t-test).
‡ Statistically significant difference (Fisher exact test).

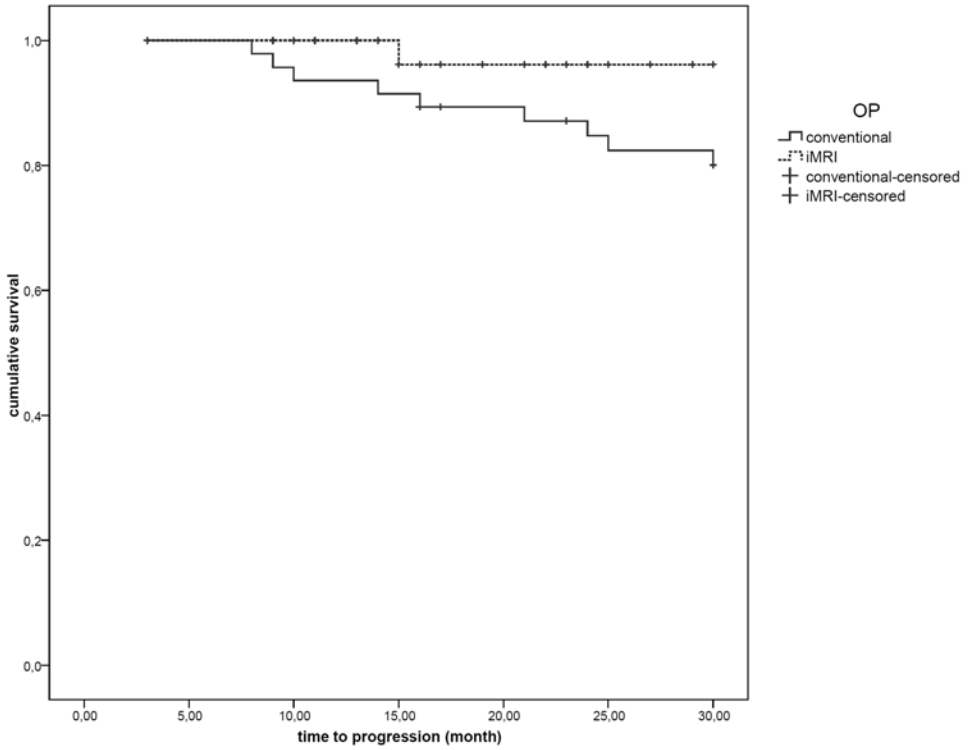

Fig. 2. Kaplan-Meier plot showing progression-free survival for the 30 months after primary surgery.

head coil, the first intraoperative imaging for neuronavigation was acquired. After that, T2-weighted turbo spin echo sequences in coronal and sagittal planes and T1-weighted spin echo sequences without contrast enhancement in identical planes were obtained. A preoperative contrast-enhanced coronal T1 image was fused to the above-mentioned sequences. The surgical approach was performed as described in the *Methods* section. Using neuronavigation despite several sphenoidal septae, orientation was unproblematic. The sellar floor was opened in typical fashion; however, no dissolved adenoma tissue was found. Tumor presented as a solid mass suggestive of a meningioma, but a fresh-frozen section nonetheless revealed an adenoma and microsurgical resection proceeded. Typical soft adenoma tissue was found in the dorsolateral parts of the tumor. After resection, a lowering of the diaphragm and the solid pituitary tissue attached to it could be visualized. After inspection of the cavity no residual tumor was found. Subsequently we performed iMRI. The sequence protocol was used as described above, including a T1-weighted image with contrast enhancement (Fig. 4). Imaging revealed lowering of the diaphragm and an adequate decompression of the suprasellar compartment. However, in the right sellar region with proximity to the carotid artery a contrast-enhancing remnant was found. After the patient was positioned for surgery, the residual lesion was curetted and sent to pathology as a separate specimen. A final iMRI was performed and showed complete removal of the tumor (Fig. 5). Typical closure as described in the *Methods* section was performed.

Postoperatively the patient recovered without neurological deficits. A transient diabetes insipidus was treated with 2 doses of desmopressin. The final histopathological diagnosis was a gonadotropic adenoma in all specimens. The patient was discharged with routine substitution of

TABLE 6: Results of 6-month follow-up of functioning tumors in patients treated using TSS with or without iMRI

Outcome	Conventional Op (%)	Op w/ iMRI (%)
no benefit from op	2 (29)	4 (20)
reduction of medication	0 (0)	3 (15)
independent from medication	5 (71)	13 (65)
total	7 (100)	20 (100)

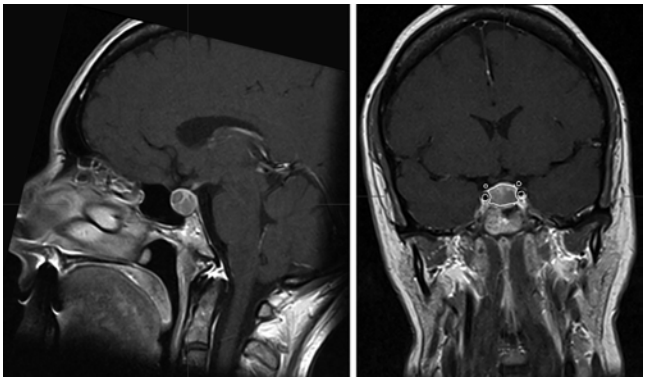

Fig. 3. Left: Preoperative MRI (sagittal contrast-enhanced T1 image) depicting an intrasellar pituitary adenoma with suprasellar extension. **Right:** Preoperative MRI (coronal contrast-enhanced T1 image) including the "objects" (see *outlined areas*) for adenoma and carotid artery created in the neuronavigation system.

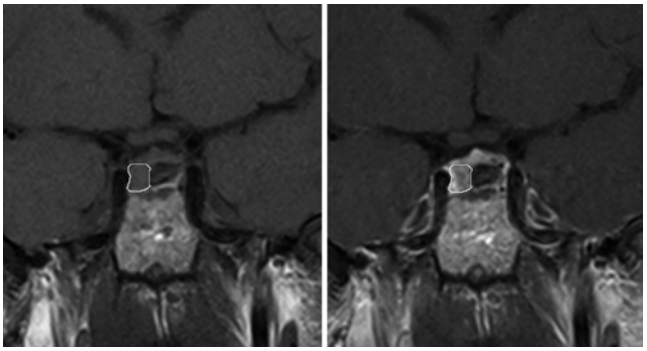

Fig. 4. **Left:** Intraoperative 1.5-T MRI (coronal T1 image without contrast) demonstrating residual tumor adjacent to the carotid artery below the pituitary gland, including a neuronavigation object *(outlined area)* of residual tumor. **Right:** Intraoperative 1.5-T MRI (coronal T1 image with contrast) demonstrating residual tumor adjacent to the carotid artery below the pituitary gland, including a neuronavigation object of residual tumor.

hydrocortisone until the first endocrinological evaluation after 3 to 4 weeks. No signs of hypopituitarism were found during evaluation. At the first follow-up visit after 6 months the patient presented without symptoms. Ophthalmological and endocrinological assessment showed no deficits. On the 6-month follow-up MRI a complete removal was confirmed. The last follow-up was done after 1 year, and showed no recurrent disease (Fig. 6).

Discussion

High-field MRI is a unique tool in the hands of a neurosurgeon. In pituitary surgery it enables the surgeon to reliably visualize tumor remnants in the OR that could previously be detected only after several months.[22] It helps us to display vascular structures at risk or demonstrates intraoperatively the level of decompression of the optic system.[3,14] Beneficial results have been shown for the challenging resections of craniopharyngiomas and the detection of tumor residua in acromegaly.[9,15] Many tertiary referral centers, meanwhile, have established iMRI mainly for routine use in glioma resection. This technique is therefore available to be applied in pituitary surgery too. This, however, raises the following question:

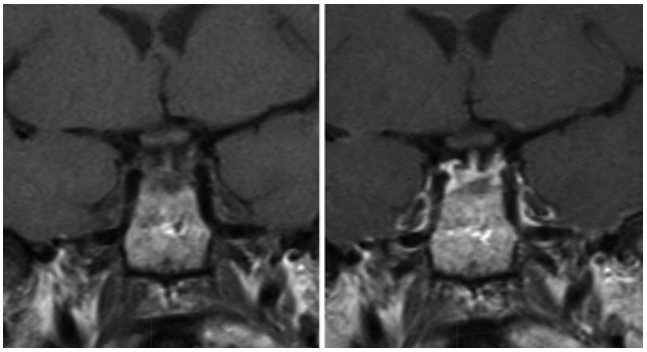

Fig. 5. **Left:** Intraoperative 1.5-T MRI (coronal T1 image without contrast) demonstrating complete tumor removal. **Right:** Intraoperative 1.5-T MRI (coronal T1 image with contrast) demonstrating complete tumor removal.

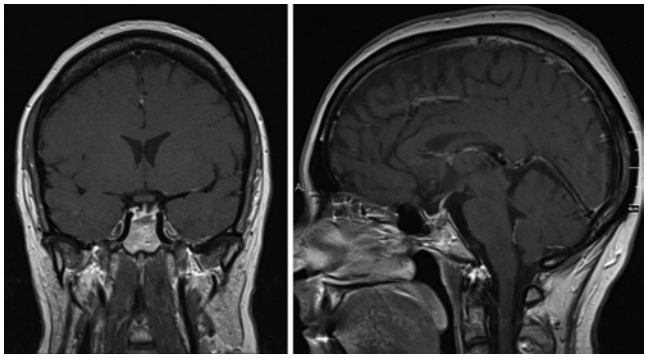

Fig. 6. Postoperative MRI studies obtained 12 months after surgery, depicting lowering of diaphragm and midline position of pituitary stalk. No residual or recurrent tumor is shown. **Left:** Coronal T1-weighted image with contrast. **Right:** Sagittal T1-weighted image with contrast.

can we justify the routine use of the technique for pituitary surgery, or shall we use it for selected cases only? We therefore conducted a retrospective assessment of all conventional TSSs performed at our center in 2007 and 2008, and compared the results with those from the cases treated between 2009 and 2011 (after introduction of iMRI) to address the above-mentioned questions. Our report is the first comparative study between high-field iMRI–assisted and conventional TSS. We include the highest number of cases (143) in comparison with all previously published reports. A statistically significant benefit for extent of resection when using iMRI in comparison with a control cohort has not been shown before.

Patient Characteristics

Due to the sequential design of the study there is a selection bias between the cohorts. Results for age and sex distribution are balanced between both groups. However, the iMRI group had a higher share of parasellar tumors and hence a lower share of completely resectable lesions. The rate of previous TSS was higher in the iMRI group as well. We can conclude from these data that we have a negative selection bias in the iMRI group, which promotes more favorable results for all assessed items in the conventional group. This negative selection bias might be due to the fact that after introduction of iMRI at our center, primarily complex cases were treated with the help of the new technology. Not until the second half of 2011 were all TSSs performed routinely with iMRI. Introduction of iMRI made intraoperative neuronavigation readily available for all surgically treated cases. Surgical technique and postoperative management of disease were otherwise identical in both groups. In the conventional group, neuronavigation was only performed in selected cases (n = 4) with parasellar extension and recurrent disease. As Thomale et al.[29] pointed out, many surgeons see the impact of neuronavigation without intraoperative updating of imaging findings only in a small number of patients. Thus the possible bias in our study due to the few cases in which intraoperative neuronavigation was used might be minute and rather reflects the typical application of the technique. Additionally, the opportunity to have an "updated" neuronavigation route readily available during

surgery is part of the concept of intraoperative imaging and might add to its benefits.

Even though a larger share of complex cases was found in the iMRI group, we see lower rates of residual tumor and higher rates of patients with improved vision after surgery. The proportion of patients requiring hormone replacement for hypopituitarism is slightly lower in the conventional surgery group. This finding as well as the higher rate of complications in the iMRI group might be due to the above-mentioned selection bias. In a detailed assessment of the complications described here, we see CSF leaks as the most common complication with iMRI. It is debatable if this is a side effect of the increased share of previous surgeries, the increased extent of resection, or the higher rates of parasellar tumors in this group. The major complication reported in the conventional group demonstrates a typical case of early bleeding that could have been detected with the use of iMRI before closure. Statistically no significant differences were found for postoperative hypopituitarism and peri- and postoperative complications in our study. For low-field iMRI, Berkmann et al.[2] demonstrated no increase in postoperative hypopituitarism or complications, which was similar to our data. No publication exists so far comparing complication rates between high-field iMRI and conventional surgery.[4]

Surgical Time

We have found a significant difference in OR time between the groups; the mean values were more than doubled in the iMRI group. Previously published data do not provide a direct comparison between conventional and iMRI OR times. Nimsky et al.[22] report an interruption of surgical workflow for approximately 15 minutes per scan, but the mean OR times were not provided. Szerlip et al.[28] published a mean duration of procedure of 166 minutes when using iMRI. These authors reported a similar share of parasellar tumors as that found in our series. Gerlach et al.[11] compared conventional surgery versus low-field iMRI–guided surgery and found a significant increase of duration of surgery and anesthesia. The mean surgery time was 116 minutes, versus 78 minutes for conventional surgery. The rate of parasellar tumors was considerably lower in this series, which might explain the shorter OR times. The mean duration of conventional surgery without iMRI in our series is lower than the average time of 78–170 minutes published in the literature. This fact might influence the results as well as the high incidence of "complex" cases in the iMRI group. If the cases with parasellar tumor extension are excluded, no statistical significance for OR time can be found between the iMRI and conventional groups.

A comparison of the first 20 with the last 20 cases in the iMRI cohort excluded a significant difference of surgical time as well as complications, biochemical remission rates, and improvement of vision. This finding might be due to the fact that iMRI was mainly used for glioma surgery in the beginning. Thus, our surgical team might have completed the usual learning curve at the time of inception of iMRI-supported pituitary surgery.

Rate of Resection

Intrasellar and Suprasellar Tumors. The main goal of any type of intraoperative imaging in neurosurgery is to increase the rate of tumor resection. In our study we saw a higher proportion of total resections in the iMRI group. The results were not statistically significant because a total resection was intended in only 62% of cases. When we assessed only cases with intended total resection, we saw significantly higher resection rates in the iMRI group. To our knowledge, we provide the first report demonstrating a statistical benefit for resection rates in operations in which high-field iMRI is used. In our study resection rates were as high as 91% with the use of iMRI, in comparison with 73% in the conventional group. The report by Berkmann et al.[2] demonstrated a benefit in resection rates when low-field iMRI was used; however, that study was limited by a small retrospective control cohort of only 30 patients. The published resection rates were 85% for low-field iMRI and 68% for the conventional group. Similar results were provided by Wu et al.,[32] with a gross-total removal rate of 83% with the low-field technique. The resection rate in our study, which was determined using a 1.5-T MRI unit, is comparable to the results in 91.8% of cases in the Prague group, in which a 3-T device was used.[20] Nimsky et al.[22] published a resection rate of 82% in operations performed with the aid of intraoperative high-field (1.5-T) MRI.

Our report is the only high-field MRI study providing a control cohort; thus, comparability might be limited. Our actual data demonstrate a significant advantage of high-field iMRI in comparison with a conventional procedure, especially for "straightforward," completely resectable tumors. Furthermore, compared with the literature, the results suggest higher resection rates with application of the high-field technique. No additional benefit to resection rates has been shown so far with the 3-T technique. However, more data are needed to evaluate this technique in greater detail. Similar resection rates of 91% for endocrine-inactive tumors were recently published by McLaughlin et al.[18] after performing an endoscope-assisted transsphenoidal approach. An improved intrasellar visualization attained using an endoscopic technique might improve resection rates to a comparable extent as with high-field iMRI. To our knowledge, so far no study exists comparing microsurgical versus endoscopic or endoscope-assisted surgery directly. Schwartz et al.[27] describe the combined use of a low-field iMRI and endoscope-assisted surgery, reporting complementary information from each imaging modality.

Parasellar Tumors. When we were establishing iMRI at our center, the patient group we thought would benefit most from intraoperative imaging did not comprise the above-mentioned "straightforward" cases, but the more complex giant adenomas with parasellar extension. The iMRI technique provides updates of navigation routes and crucial information about vascular structures at risk.[14] To evaluate the impact of iMRI on the extent of resection in lesions with intended subtotal resection, we used a volumetric measurement and assessed the presence of intrasel-

lar tumor remnants. Our study is the only report at time of publication providing this type of detailed assessment of parasellar tumors. However, the data are limited by the relatively small number of cases in the subgroup, which might lead to a Type I error. Even a 50% smaller mean volume after surgery in the iMRI group showed no statistically significant difference on the Student t-test. Yet, intrasellar tumor remnants were found significantly less often in the iMRI group. In our opinion this finding best demonstrates the goal of a successful subtotal TSS.

Although intrasellar tumor remnants are not an issue for compression of the optic system, these residua represent resectable parts of the adenoma that might require repeated surgery. A limitation of the comparison is that preoperative imaging was available for volumetric measurements in only 2 patients in the conventional group. Thus, no information about individual extent of resection is provided in this group. The results might be biased by the presence of differing preoperative tumor sizes. As of this writing, there are no data provided in the literature concerning volumetric assessment of extent of resection in parasellar tumors. Our data suggest a benefit regarding extent of resection with iMRI in parasellar tumors and demonstrate significantly lower rates of intrasellar tumor remnants. To our knowledge no study exists providing comparable information about resection of parasellar tumors in operations in which iMRI was used. A limitation of assessing resection rates is that the observer was not blinded to type of surgery when determining residual or recurrent tumor.

Progression-Free Survival

Evaluation of progression-free survival is the most important factor in ultimately assessing the value of a new technique that provides higher resection rates. Unfortunately, due to the novelty of the technique no published data exist so far in this regard.

We assessed our patients' data concerning recurrence rates. Follow-up for the patients treated with the aid of iMRI is shorter, given the fact that we compared a cohort from 2007 and 2008 with a cohort from 2009 to 2011. We therefore calculated Kaplan-Meier plots for the first 30 months after surgery to make the cohorts comparable. The difference we found looks very beneficial for the use of iMRI, especially because a higher share of parasellar tumors is included in the iMRI cohort. The evaluation is limited by the relatively short follow-up. Even though a meta-analysis by Roelfsema et al.[23] describes the peak for tumor recurrence as occurring between the 1st and 5th years after surgery, further follow-up for iMRI is needed to draw a final conclusion.

Functioning Adenomas

Functioning adenomas are a unique challenge in the field of pituitary surgery. Small tumor remnants can lead to persisting hormone excesses, making patients still dependent on medication after surgery. So far no distinctive visualization of microadenomas has been achieved with low-field iMRI; in particular, adenomas invading the cavernous sinus could not be detected.[26] In our study population a higher share of functioning adenomas in the iMRI than in the conventional surgery group was present. The data suggest a slightly higher rate of biochemical remission in the conventional group in comparison with the iMRI group. The limitation of the comparison is the low number of cases in the conventional group and the heterogeneity of both groups. Size of adenoma and tumor extension as well as the pattern of hormone secretion considerably influence the prognosis of a complete biochemical remission. Remission rates of 74% have been published for microadenomas, whereas macroadenomas invading the cavernous sinus have cure rates as low as 39%–43%.[7,10,16] Although the report of Fahlbusch et al.[9] concerning the impact of high-field iMRI in acromegaly is very promising, no final conclusion concerning the benefit of biochemical cure rates with the use of iMRI can be drawn. Because our data are limited by the small subgroup of functioning adenomas in our cohorts, further studies are needed.[9,15]

Our data support the routine use of high-field iMRI for pituitary surgery. Especially for the "straightforward" intra- and suprasellar nonfunctioning adenomas, we were able to demonstrate a significant benefit regarding total resection rates. The study is limited by its retrospective design and the absence of randomization. However, even with the negative selection bias of more complicated cases in the iMRI group, which favors positive results for the conventional group, preservation and improvement of vision was higher and no significant increase in complications or hypopituitarism was found. A possible bias in a retrospective control cohort might be the progress in surgical technique or medical treatment over time, which might lead to an improvement in patient outcome independently from iMRI usage. In our study we hope to have minimized this effect because all evaluated surgeons in our study were far beyond their learning curve and did not change their surgical technique after or during the introduction of iMRI at our center.

A disadvantage of the intraoperative resection control might be the increased OR time. Part of the data for iMRI cases was acquired right after introduction of the technique at our center; therefore, a learning curve might bias the results. Nevertheless, an experienced transsphenoidal surgeon might have his or her OR time almost doubled with iMRI. This is indeed an important issue to discuss, especially with regard to OR cost and hospital efficiency. In our opinion the benefit of a complete resection in more than 90% of cases without the need for a repeat surgery outweighs this argument significantly. In our series we have seen 11 cases of patients who had to have surgery for a recurrent tumor. All patients underwent conventional operations without the help of intraoperative imaging.

Additionally, during the first 30 months, 9 patients in the conventional group and only 1 patient in the iMRI group had recurrent disease. In particular, we demonstrated that huge parasellar tumors have a significantly lower rate of intrasellar tumor remnant, which is the major goal in tumors that are only subtotally resectable. This was achieved with similar rates of hypopituitarism. No data exist to date in this regard. Based on our experi-

ence since 2009, we advocate the routine use of iMRI for pituitary surgery if available at the institution. Detailed studies are needed to evaluate the impact of iMRI for surgery in functioning adenomas. Our data as well as the few published papers addressing this topic suggest a benefit in regard to biochemical remission rates with use of iMRI. The data in our study support the benefit of high-field iMRI in comparison with the conventional microsurgical approach.

No endoscopic device was used in our series. Further studies are needed to evaluate resection rates and outcome in patients undergoing iMRI-assisted versus endoscopic TSS. Because many centers have established iMRI for resection control in glioma surgery, often as two-or-more–room solutions, increased costs of iMRI in comparison with the endoscopy equipment, at least at these institutions, would not be such a big issue anymore. Both techniques seem to be beneficial for adenomas with supra- and parasellar extension. It would be interesting to compare the techniques with regard to small intrasellar lesions. No benefit was shown for using endoscopically guided in comparison with microsurgical resection for this entity.[19] Systematic reviews and meta-analyses so far have shown no significant benefit for resection rates by using endoscopic surgery. Results for complication rates are heterogeneous. However, Ammirati et al.[1] described a significantly higher rate of vascular complications when using the endoscopic technique in comparison with the conventional microsurgical approach.[12] Intraoperative updates of neuronavigation routes and depiction of vascular structures are important advantages of high-field iMRI. However, to our knowledge at the time of this writing, no meta-analysis exists for the use of iMRI in TSS.

Most likely the combined use of endoscopy-assisted surgery and intraoperative resection control attained using iMRI could be the most favorable solution. Intraoperative MRI provides the possibility to "look behind" structures and not only "around the corner," whereas an endoscope provides improved visualization during surgery and thus might prevent multiple iMRI scans in case of a residual tumor. We are in need of a large prospective randomized study to elucidate this issue.

Conclusions

The use of high-field iMRI leads to a significantly higher rate of complete resection in comparison with the conventional microsurgical transsphenoidal approach. In parasellar tumors a lower residual volume and a significantly lower rate of intrasellar lesion remnants were shown with the technique. Follow-up concerning recurrence rates so far is limited for iMRI; however, after 2 years Kaplan-Meier analyses show a distinctly lower rate in the iMRI group. No significant benefit of iMRI was found for biochemical remission rates and improvement of vision. Even though surgical time was longer with the addition of iMRI, it did not increase the complication rate significantly. We therefore recommend the routine use of high-field iMRI for pituitary surgery if this technology is available at a particular center.

Disclosure

Dr. König is a consultant for BrainLab. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Coburger, Wirtz, Seitz, Hlavac. Acquisition of data: Coburger, Seitz, Hlavac. Analysis and interpretation of data: Coburger, König, Wirtz, Hlavac. Drafting the article: Coburger, König, Bäzner, Hlavac. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Coburger. Statistical analysis: Coburger. Administrative/technical/material support: Wirtz. Study supervision: Wirtz.

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Intraoperative magnetic resonance imaging to reduce the rate of early reoperation for lesion resection in pediatric neurosurgery

Clinical article

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Object. This study describes the pediatric experience with a dual-multifunction-room IMRIS 1.5-T intraoperative magnetic resonance imaging (iMRI) suite and analyzes its impact on clinical variables associated with neurosurgical resection of intracranial lesions, including safety and efficacy.

Methods. Since the inception of the iMRI–guided resection program in April 2008 at both Barnes-Jewish and St. Louis Children's Hospital, a prospective database recorded the clinical variables associated with demographics and outcome with institutional review board approval. A similarly approved retrospective database was constructed from February 2006 to March 2010 for non–iMRI resections. These databases were retrospectively reviewed for clinical variables associated with resection of pediatric (age 20 months–21 years) intracranial lesions including brain tumors and focal cortical dysplasia. Patient demographics, operative time, estimated blood loss, additional resection, length of stay, pathology, and complications were analyzed.

Results. The authors found that 42 iMRI–guided resections were performed, whereas 103 conventional resections had been performed without the iMRI. The mean patient age was 10.5 years (range 20 months–20 years) in the iMRI group and 9.8 years (range 2–21 years) in the conventional group ($p = 0.41$). The mean duration of surgery was 350 minutes in the iMRI group and 243 minutes in the conventional group ($p < 0.0001$). The mean hospital stay was 8.2 days in the iMRI group, and 6.6 days in the conventional group, and this trended toward significance ($p = 0.05$). In the first 2 weeks postoperatively, there were 8 reoperations (7.77%) in the conventional group compared with none in the iMRI group, which was not significant in a 2-tailed test ($p = 0.11$) but trended toward significance in a 1-tailed test ($p = 0.06$). The significant complications included reoperation for hydrocephalus or infection: 6.8% (conventional) versus 4.8% (iMRI).

Conclusions. Intraoperative MR imaging–guided resections resulted in a trend toward reduction in the need for repeat surgery in the immediate 2-week postoperative period compared with conventional pediatric neurosurgical resections for tumor or focal cortical dysplasia. Although there is an increased operative time, the iMRI suite offers a comparable safety and efficacy profile while potentially reducing the per-case cost by diminishing the need for early reoperation.

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Key Words • **intraoperative magnetic resonance imaging** • **pediatric** • **tumor** • **glioma** • **reoperation**

Although there are few randomized controlled trials, it is generally accepted that maximizing the extent of resection increases survival for patients with many CNS tumors.[1,10,16,17,22–24,27] Recent advances in MR imaging technology have permitted the application of high-field intraoperative imaging modalities as an adjunct to neurosurgical procedures.[3,6,9,14,15,21] In adult patients, iMRI has been linked to enhanced glioma resection and longer survival.[2,7,12,18] Several series also have shown the benefit of iMRI–guided resection, including using advanced techniques such as diffusion tensor imaging–tractography to improve the safety of resections in regions of eloquent motor and language function.[19,20]

While the safety and feasibility of iMRI in children

Abbreviations used in this paper: BJH = Barnes-Jewish Hospital; EBL = estimated blood loss; iMRI = intraoperative magnetic resonance imaging; LOS = length of stay; PNET = primitive neuroectodermal tumor; SLCH = St. Louis Children's Hospital; WHO = World Health Organization.

undergoing neurosurgical resection has been described previously,[14] its application and utility remain unclear. The question of whether iMRI is truly beneficial in pediatric brain tumors or lesional epilepsy resections remains; previously cited concerns include the high initial capital cost, the added operative time, and the notion that the aggressiveness of resection may be moderated by the knowledge that the imaging adjunct is available.[8,13,25] In the present study we compare the clinical variables associated with resection of tumors and focal cortical dysplasia in children with and without the iMRI at SLCH. Herein, we report the benefits and risks of iMRI–guided resections relative to conventional resections in the pediatric population.

Methods

Study Methods

After institutional review board approval, clinical data collection began in a prospective iMRI database from the inception of the iMRI–guided program at our institution on April 1, 2008. Data accrual for this project continues. The current study includes all pediatric resections for brain tumors or epilepsy performed using iMRI through March 31, 2010. Similarly, data for the conventional resections performed without iMRI were collected, with an independent institutional review board approval, from February 1, 2006, to March 31, 2010. Children younger than 18 months of age were excluded from the conventional group to avoid confounding due to age (children younger than 18 months are unable to undergo iMRI due to limitations in head fixation). These data were retrospectively reviewed for clinical variables including demographics, use of iMRI, operative duration, surgical objective, EBL, further resection, hospital LOS, pathological diagnosis, overall survival, complications, and financial costs for additional resections. Preoperative and postoperative imaging studies were reviewed by attending neuroradiologists and surgeons at the time of surgery for further management decisions. These reports and notes were reviewed for the current study. The demographic and clinical characteristics were summarized and presented as the mean ± SD. Statistical analyses were performed using a Student t-test or Wilcoxon rank-sum test, as appropriate for continuous variables, and a Fisher exact-test for categorical variables. The analyses were performed using standard statistical packages (SAS Institute; Graphpad Prism, Graphpad Software, Inc.). All the tests were 2 sided unless otherwise specified, and a p value < 0.05 was used to indicate a significant effect.

Conventional (Non–iMRI) Craniotomies for Resection for Tumor and Epilepsy

All children underwent high-field (1.5- or 3-T) preoperative MR imaging with volumetric sequences for image-guided resection using the Stealth System (Medtronic Inc.). The goal of surgery, gross-total resection versus biopsy/subtotal resection, was decided a priori and documented in the clinical and operative notes. The conventional craniotomies were performed at SLCH by 1 of 4 pediatric neurosurgeons (J.R.L., M.D.S., D.D.L., and T.S.P.), and the patients were admitted to the pediatric intensive care unit postoperatively until stable enough for transfer to the floor. During the early postoperative period, within 48 hours, the children underwent high-field postoperative MR imaging to evaluate for residual tumor, at which point the decision for further operation was made. Depending on the pathological diagnosis and functional outcome, further adjunctive therapy and rehabilitation were determined. In cases in which surgery was performed in the conventional group after installation of the iMRI suite (April 2008), the procedures were performed without iMRI depending on the availability of the device and the neurosurgeon's discretion and preference.

Intraoperative MR Imaging Treatment

Chicoine and colleagues[6] have previously described the dual operating room suites at BJH with a ceiling-mounted 1.5-T high-field wide-bore iMRI unit (IMRIS, Inc.). All pediatric iMRI–guided resections were performed in the iMRI suite at BJH by 1 of 3 pediatric neurosurgeons (J.R.L., M.D.S., and D.D.L.). The iMRI suite is located approximately 1 city block from SLCH, and patients were transported directly to and from the suite via climate-controlled bridges. Anesthesia staffing and operating room personnel were provided by SLCH and are the same individuals who staff the neurosurgery operating rooms at SLCH. Children younger than 18 months of age did not undergo resection in the iMRI suite because of the required rigid head fixation. The time for the intraoperative imaging was approximately 30–45 minutes depending on the sequences obtained, which were at the discretion of the surgeon. The decision to perform additional resection after the iMRI was decided by the surgeon after review and discussion of the findings with an attending neuroradiologist. Postoperatively after extubation, the children were transported to SLCH, where routine postoperative imaging and care paradigm were continued, as described above, for the conventional non–iMRI group. One child started in the iMRI suite for resection, but his head proved too small to fix in the headholder. He was then taken, while anesthetized, to the conventional suite at SLCH for resection. He remained intubated for MR images obtained during the procedure at SLCH, with the operating room prepared for further resection, which was not needed. He, thus, remains in the iMRI group for analysis.

Results

Between April 2008 and March 2010, there were 42 consecutive iMRI–guided neurosurgical resections performed in pediatric patients. Between February 2006 and March 2010, there were 103 consecutive conventional non–iMRI pediatric neurosurgical resections performed. The patient demographics and clinical variables are summarized in Table 1. The male/female ratio was equivalent with 24:18 in the iMRI group and 55:48 in the conventional group ($p = 0.72$). The mean age was 10.5 years (range 1.7–20 years) in the iMRI group and 9.8 years (range 2–21 years) in the conventional group, which was equivalent. The mean EBL was not significantly different at 208 and 212 ml in the iMRI and conventional groups, respectively.

The mean operative duration was significantly different ($p < 0.0001$) at 350 minutes (range 82–562 minutes, median 344.5 minutes) for the iMRI group and 243 minutes (range 64–566 minutes, median 240 minutes) for the conventional group. The mean LOS trended toward a difference at 8.2 days (range 3–58 days) for the iMRI group and 6.6 days (range 2–50 days) for the conventional group ($p = 0.05$).

The distribution of the pathology results is summarized in Table 2. The majority of surgically treated tumors in both the iMRI group (28 [67% of the total]) and conventional group (59 [57% of the total]) were low grade (Grades I and II) according to the WHO pathological grading scale.[11] As shown in Table 2, a low-grade glioma (WHO Grades I and II) was the most common histopathological classification for both the iMRI and conventional surgery groups, with 17 in the former and 34 in the latter. Of those low-grade gliomas, 11 in the iMRI group and 19 in the conventional group were pilocytic astrocytomas (WHO Grade I). In the higher WHO grade tumor subset, the majority of the tumors in both groups were PNETs, with 3 in the iMRI group and 12 in the conventional group. There were also epilepsy resections for focal cortical dysplasia in 6 of the iMRI cases and 16 of the conventional cases.

There were 42 intraoperative MR images obtained, 26 of which demonstrated the presence of residual lesion. In 18 iMRI cases (42.9%), additional resection was undertaken during the same operation based on the iMRI findings. While the surgical objective of either gross-total resection or biopsy/subtotal resection was achieved equally in both groups (33 iMRI cases [79%] and 76 [80%] of 95 conventional cases; $p = 0.67$), the rate of reoperation within 2 weeks based on postoperative imaging was higher in the conventional group (8 reoperations [7.77%] vs no reoperations in the iMRI group [$p = 0.11$, 2-tailed test, or $p = 0.06$, 1-tailed test). Of the 8 cases requiring reoperation, 2 were for low-grade lesions—pituitary adenoma and focal cortical dysplasia—necessitating total resection for potential cure. Two reoperations were to further debulk medulloblastomas to put the patient in a lower-risk group with a tumor residual of less than 1.5 cm^3. One case was a biopsy that was nondiagnostic that required repeat imaging and a "redo" biopsy to determine the final pathology of a ganglioglioma. The other 3 reoperations were for WHO Grade IV lesions—an ATRT, PNET, and high-grade glial neoplasm with ependymal features—in which gross-total resection was sought in reoperation. The significant complications included reoperation for hydrocephalus or infection in 7 conventional cases (6.8%) compared with 2 iMRI cases (4.76%), which was not significantly different ($p > 0.99$). There were no deaths as a result of the operations.

TABLE 1: Summary of demographics and procedure-related data for patients who underwent a conventional resection or a resection guided by iMRI*

Variable	Resection Group		p Value
	w/ iMRI	Conventional	
mean age at op (yrs)	10.5 ± 5.1	9.8 ± 5.1	0.41
age range (yrs)	1.7–20	2–21	NA
mean weight (kg)	47.8 ± 30.7	39.8 ± 24.4	0.12
mean height (cm)	134.4 ± 31.9	130.0 ± 32.8	0.42
mean EBL (ml)	208 ± 235.3	212 ± 189.4	0.45
mean op time (mins)	350 ± 117.5	243 ± 87.6	<0.0001
mean LOS (days)	8.2 ± 9.6	6.6 ± 6.9	0.05

* Mean values are presented ± the SD. Abbreviation: NA = not applicable.

Discussion

Compared with conventional craniotomy, we found the use of the intraoperative MR imaging suite for pediatric craniotomies for both tumor and epilepsy appeared to reduce the number of immediate reoperations in the first 2 postoperative weeks. The 2 groups represented comparable pathological entities and had a similar complication rate. This study suggests that using iMRI as a pediatric neurosurgical adjunct may be beneficial in preventing immediate reoperations compared with conventional treatment without an iMRI–guided craniotomy.

The demographic features of the tumor cases in both the iMRI and conventional surgery groups were comparable with regard to age, sex, and pathology. Most lesions in both groups were low-grade gliomas, although the conventional craniotomy group had more patients overall (103) than the iMRI group (42). Both groups had a similar complication rate in the immediate postoperative period: 6.8% in the conventional group and 4.8% in the iMRI group. The fundamental difference between the groups was the necessity of "take-backs" in the first 2 weeks postoperatively in the conventional group. The reoperation rate in the first 2 weeks after surgery was 0% in

TABLE 2: Distribution of pathology*

Pathology	Resection Group	
	w/ iMRI	Conventional
Grade I/II	28	59
ganglioglioma	4	9
pituitary adenoma	3	2
craniopharyngioma	0	2
DNET	0	3
low-grade glioma	17	34
choroid plexus papilloma	1	2
ependymoma	1	6
neurocytoma	2	1
Grade III/IV	6	17
high-grade glioma	2	3
PNET	3	12
choroid plexus carcinoma	1	1
ATRT	0	1
focal cortical dysplasia/epilepsy	6	16
other	2	11
total	42	103

* ATRT = atypical teratoid rhabdoid tumor; DNET = dysembryoplastic neuroepithelial tumor.

the iMRI group compared with 7.77% in the non–iMRI group. The 8 conventional cases requiring reoperation represented a variety of pathological entities, reflecting the necessity of complete resection in low-grade pathology, as well as the survival benefit afforded by maximal debulking and gross-total resection in high-grade lesions like medulloblastoma and high-grade glial neoplasms. Although this result was not significant using the a priori chosen 2-tailed Fisher exact test, it is important to note that the iMRI group would not be more likely than the conventional group to need immediate reoperation. For this reason, a 1-tailed test may be more informative, and this test gives a result of $p = 0.06$, which trends toward significance. This result represents an important advantage for the iMRI–guided resection, because avoiding reoperation in the immediate postoperative period has many benefits.

The primary and obvious beneficiary of preventing reoperation is the patient. Although not seen in this series, there is a substantially increased risk from wound infection and hematoma formation from immediate reoperation.[5,28] Once the wound heals appropriately, some of these patients with higher-grade tumors need to undergo further evaluation for chemotherapy and radiotherapy, which a second operation inevitably delays. The emotional and psychological toll on the patient and family is often neglected in such cases but is very important to consider: the amplification of such anxiety is well documented with each imaging session.[26]

We illustrate 2 cases from the overall series in Fig. 1 to demonstrate the utility of intraoperative MR imaging. The first case is a 6-year-old girl who underwent conventional resection of a medulloblastoma (Fig. 1A). The postoperative Day 1 image (Fig. 1B) demonstrates a residual nodule that measures more than 1.5 cm^2, which would have put her in the "high-risk" group of medulloblastoma, affecting her prognosis and plans for adjunctive treatments. She thus underwent another craniotomy on postoperative Day 3 to remove the residual lesion, and the second postoperative image demonstrates total removal (Fig. 1C). The first patient required 2 craniotomies to achieve an optimal resection and be in the "standard risk" group. In contrast, the second patient is a 15-year-old boy with intractable seizures who presented for iMRI–guided resection of a small right frontal ganglioglioma (Fig. 1D). In the first intraoperative image, there is a small amount of residual tumor (Fig. 1E), which was subsequently resected and is no longer present on the second intraoperative image (Fig. 1F). An optimal resection was achieved with a single craniotomy, and the patient remains seizure-free at 1 year after surgery with no residual lesion.

By preventing reoperation, there is a potential cost-savings benefit to intraoperative MR imaging. A single intraoperative MR image adds to operating room time (about $6000) and a floor day ($951), but the primary additional cost is that of the contrast-enhanced brain MR imaging, which is a $3992 patient charge at our institution. This is compared with the cost of another craniotomy ($26,333)

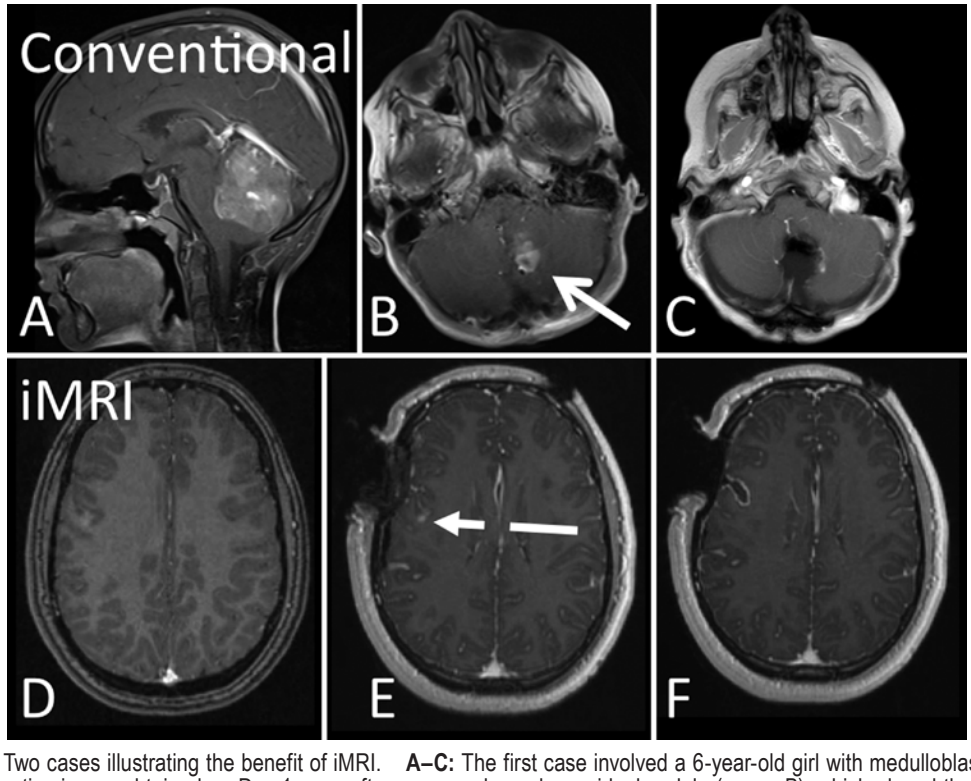

Fig. 1. Two cases illustrating the benefit of iMRI. **A–C:** The first case involved a 6-year-old girl with medulloblastoma (A). A postoperative image obtained on Day 1 scan after surgery showed a residual nodule (*arrow,* B), which placed the patient in the high-risk group. She underwent further resection in an early reoperation, after which she was in the standard-risk group (C). **D–F:** In contrast, the second case involved a 15-year-old boy with a small right frontal ganglioglioma (D) who underwent iMRI–guided resection. The first intraoperative image (E) showed some residual tumor *(arrow)* that was completely resected and confirmed with a second image (F) within the same craniotomy.

and an additional intensive care unit day ($2494) and 2 floor days ($1902) postoperatively for a second operation in addition to a second postoperative MR imaging session to examine for residual tumor, which is approximately $34,721 total. This equates to a remarkable cost savings of $23,778 per case or $190,224 for the 8 conventional cases in our series that required reoperation, and that amount is substantial. Also, there is the potential additional $3992 per case cost savings if the iMRI has diffusion sequences and is sufficient to serve as postoperative imaging.

The initial capital investment in an iMRI suite is between 5 and 10 million dollars; the IMRIS iMRI suites at BJH in St. Louis were constructed to be highly versatile operating rooms. Because the movable ceiling mounted iMRI unit is stored in a separate room between the surgical suites, a wide variety of adult and pediatric neurosurgical procedures can be performed in these rooms, thereby maximizing efficiency and resource utilization. Since installation in April of 2008 the IMRIS iMRI operating room suites at BJH have been used for more than 400 iMRI–guided neurosurgical procedures (including the 42 pediatric cases reported in this current study), as well as for more than 400 non–iMRI adult neurosurgical procedures. Other centers have integrated combined diagnostic/surgical MR imaging suite designs as an alternative to the dedicated iMRI surgical suites. With the alternative combined suites, when the iMRI device is not being used for surgery, the unit can be used for diagnostic imaging to provide another revenue source to offset the initial installation costs.[3,21] Creative arrangements among hospital administrators, engineers, architects, physicians, nurses, and other staff are needed to optimize integration of high-field iMRI into the complex environments of neurosurgical operating rooms.

The primary limitation inherent in this study is its retrospective, unmatched design. There is also some confounding influence from the inclusion of multiple surgeons, because one surgeon was added midway through the study period, whereas another surgeon primarily used the conventional modality. This made it impossible to have a matched case-control series, and the findings of the study are thereby tempered; there is not a perfect match between the histopathological entities of the groups, and surgical experience with resection in both modalities improved over time. To address the latter point, some groups suggest that surgeons are less aggressive with the initial resection when iMRI is available, but our current study and a previous study[4] suggest that this is not true. In fact, our study specifically suggests there is a substantial difference in the reoperation rate between the 2 groups, favoring the iMRI cohort. Overall, one must weigh risks and benefits of iMRI–guided resection, specifically for WHO Grade I and II tumors. Although the operative time and initial capital cost are higher with iMRI, the reduced need for additional surgeries in the immediate postoperative period offers considerable advantages. A randomized prospective trial comparing pediatric neurosurgical resections with or without iMRI including cost analysis is needed to prove the benefit of iMRI, but the current study provides strong evidence that using iMRI substantially reduces the need for additional resection in the immediate 2-week postoperative period. Furthermore, the financial, logistical, and ethical issues surrounding a randomized trial of this kind are likely prohibitive. In the absence of a randomized trial, it would be informative to have a multicenter registry for pediatric neurosurgical procedures to assess the benefit of iMRI–guided resection in a large patient population, and we are currently adapting our database so that it might be used in such a multicenter format.

Conclusions

Compared with conventional pediatric neurosurgical resections for tumor and focal cortical dysplasia, resections guided by a movable high-field-strength iMRI unit showed a trend toward reducing the need for repeat surgery in the immediate 2-week postoperative period. Pediatric neurosurgical procedures performed with iMRI are associated with an increased operative time but without an increased risk of surgical complications. An iMRI suite has additional implementation and construction costs over conventional surgical suites, but creative utilization strategies and decreased reoperation rates can lead to decreased costs on a case by case basis.

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Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance

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Extent of resection (EOR) still remains controversial in therapy of glioblastoma multiforme (GBM). However, an increasing number of studies favor maximum EOR as being associated with longer patient survival. One hundred thirty-five GBM patients underwent tumor resection aided by 1.5T intraoperative MRI (iMRI) and integrated multimodal navigation. Tumor volume was quantified by manual segmentation. The influences of EOR, patient age, recurrent tumor, tumor localization, and gender on survival time were examined. Intraoperative MRI detected residual tumor volume in 88 patients. In 19 patients surgery was continued; further resection resulted in final gross total resection (GTR) for 9 patients (GTR increased from 47 [34.80%] to 56 [41.49%] patients). Tumor volumes were significantly reduced from 34.25 ± 23.68% (first iMRI) to 1.22 ± 16.24% (final iMRI). According to Kaplan–Meier estimates, median survival was 14 months (95% confidence interval [CI]: 11.7–16.2) for EOR ≥98% and 9 months (95% CI: 7.4–10.5) for EOR <98% ($P < .0001$); it was 9 months (95% CI: 7.3–10.7) for patients ≥65 years and 12 months (95% CI: 8.4–15.6) for patients <65 years ($P < .05$). Multivariate analysis showed a hazard ratio of 0.39 (95% CI: 0.24–0.63; $P = .001$) for EOR ≥98% and 0.61 (95% CI: 0.38–0.97; $P < .05$) for patient age <65 years. To our knowledge, this is the largest study including correlation of iMRI, tumor volumetry, and survival time. We demonstrate that navigation guidance and iMRI significantly contribute to optimal EOR with low postoperative morbidity, where EOR ≥98% and patient age <65 years are associated with significant survival advantages. Thus, maximum EOR should be the surgical goal in GBM surgery while preserving neurological function.

Keywords: extent of resection (EOR), glioblastoma multiforme (GBM), intraoperative MRI (iMRI), patient survival, tumor volumetry.

With a frequency of approximately 38%, gliomas are the most common primary brain tumors,[1] most of them being glioblastoma multiforme (GBM) grade IV, as classified by the World Health Organization (WHO). GBM is one of the most malignant human neoplasms, with a mean patient survival of still only ~14 months,[2] despite recent advances in surgery and radiochemotherapy.[2] The mean life expectancy for patients with anaplastic astrocytoma (WHO grade III) is slightly longer, at 41 months.[3] A complete surgical excision of high-grade gliomas (WHO grades III and IV) without tumor recurrence is impossible, due to their biological behavior. Thus, the interdisciplinary therapeutic concept today combines microsurgery followed by fractionated external beam radiation and chemotherapy. Despite better life expectancy and 5-year survival rates of 42%–92%,[4] astrocytomas (WHO grade II) tend to develop into high-grade gliomas.

In the current literature there is no general consensus regarding the role of surgical extent of resection (EOR) as a predictive parameter for longer patient survival.[3,5] Up to now, patient age, tumor histopathology, and Karnofsky Performance Scale (KPS) have proven to be dependable predictors of patient outcome. Although there remains a lack of supporting class I evidence, to date most authors favor a maximum safe EOR as being

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associated with a better patient outcome in low- and high-grade gliomas. To optimize EOR, intraoperative imaging methods such as CT, ultrasound,[6] 5-aminolevulinic acid (5-ALA),[7] and MRI have been established in neurosurgical operating theaters, serving as immediate resection control. Of these, high-field intraoperative MRI (iMRI) scanners, with the major drawback of high cost, provide highest resolution for detection of even small tumor remnants and have thus proven to be a sufficient tool providing extended tumor volume resections and higher percentages of gross total resections (GTRs) in glioma surgery.[8–12] As a major addition to iMRI, integrated navigation delivers anatomical image data and information on the localization of eloquent cortical sites (functional MRI),[13] fiber bundles (diffusion tensor imaging [DTI]),[14–16] and metabolic function (single photon emission CT, positron emission tomography [PET], MR spectroscopy [MRS]).[17] Registration of iMRI to update navigation compensates for intraoperative brain deformations known as brain shift, caused by tumor mass resection itself, loss of cerebrospinal fluid, brain swelling, or the use of retractors.[18–21] The combination of multimodal navigation and iMRI contributes to higher percentages of EOR in glioma surgery with minimum postoperative morbidity.

In the present study, we evaluated the prospectively collected data of 135 GBM patients, who were operated on with high-field (1.5T) iMRI and multimodal navigation guidance (functional MRI, DTI-tractography, MRS, PET). EOR data were calculated after manual tumor segmentation of the tumor outlines in the intraoperative scans before and after tumor resection according to iMRI results. The interdependence of EOR, patient age, recurrent tumor, tumor localization, and gender for patient survival was examined in univariate and multivariate analyses.

To our knowledge, this study is the largest to assess the correlation of EOR and patient survival, involving high-field iMRI guidance and volumetric assessment of tumor volume by manual segmentation.

Patients and Methods

Patients

A cohort of 135 patients with supratentorial GBM underwent elective surgery with high-field iMRI resection control in the Department of Neurosurgery at the University of Erlangen-Nuremberg from April 2002 to October 2008. The group consisted of 78 men and 57 women, with a mean age of 59.3 years (SD: 13.3; range: 11–81 y). The cohort included 27 recurrent lesions.

The patients' postoperative survival times (in months) were retrospectively obtained according to the Erlangen tumor register database. Of the 135 patients in the study, 117 were included in the follow-up; 18 have been unavailable for follow-up.

Ethics committee approval and written informed consent of all patients or adequate family members were obtained preoperatively. Collected prospectively was the postoperative course, including complications and morbidity, histopathological analysis, operative and discharge reports, and imaging data. Adjuvant therapy was either fractionated external beam radiation with a maximum of 54 Gy or combined radiochemotherapy with one or a combination of the following chemotherapeutics: temozolomide; procarbazine/lomustine (CCNU)/vincristine; and/or nimustine (ACNU)/teniposide (VM-26), depending on the patient's KPS or previous therapy.

Multimodal Navigation

Microscope-based neuronavigation (BrainLAB) was performed in all cases with an NC4 or Pentero multivision navigation microscope (Carl Zeiss) combined with a VectorVisionSky navigation system (BrainLAB).

Functional data sets, which were acquired 1 to 2 days prior to surgical intervention, were rigidly registered to a 1.0-mm isotropic 3D data set in magnetization prepared rapid acquisition gradient echo (MPRAGE), with the following sequence parameters: field of view (FOV), 250 mm; repetition time (TR), 2020 ms; echo time (TE), 4.38 ms; matrix, 256 × 256; voxel size, 1.0 × 1.0 × 1.0 mm). Functional MRI was obtained in 20 cases, magnetoencephalography in 1 case, DTI in 14 cases, MRS in 4 cases, and PET in 1 case. These data sets were used either separately or in combination. The 3D data set with the integrated functional data was finally registered to the navigational data set used for automatic patient registration (obtained after induction of anesthesia and head fixation and prior to skin incision, with an MPRAGE sequence with identical scanning parameters as described above) with Image Fusion Software (VectorVision Planning 1.3, BrainLAB) by a semiautomatic rigid registration algorithm.

Intraoperative Imaging Protocol

The imaging protocol on the 1.5T MR scanner (Siemens Sonata, Siemens AG) included T2-weighted turbo spin echo (slice thickness, 4 mm; FOV, 230 mm; TR, 6490 ms; TE, 98 ms), fluid attenuated inversion recovery (slice thickness, 4 mm; FOV, 230 mm; TR, 10 000 ms; TE, 103 ms), T1-weighted spin echo (slice thickness, 4 mm; FOV, 230 mm; TR, 525 ms; TE, 17 ms), echo planar imaging dark fluid (slice thickness, 5 mm; FOV, 230 mm; TR, 9000 ms; TE, 85 ms), and 1.0-mm isotropic 3D MPRAGE (described above).

An MRI after induction of anesthesia was obtained directly prior to skin incision for automatic patient registration. The first iMRI for resection control was obtained after the surgeon's estimation of best possible tumor resection. To avoid misinterpretation between residual tumor and small bleeding or contusion by accumulation of gadolinium, the pre–skin incision scan was performed without contrast agent. Application of 0.2 mL/kg gadolinium–

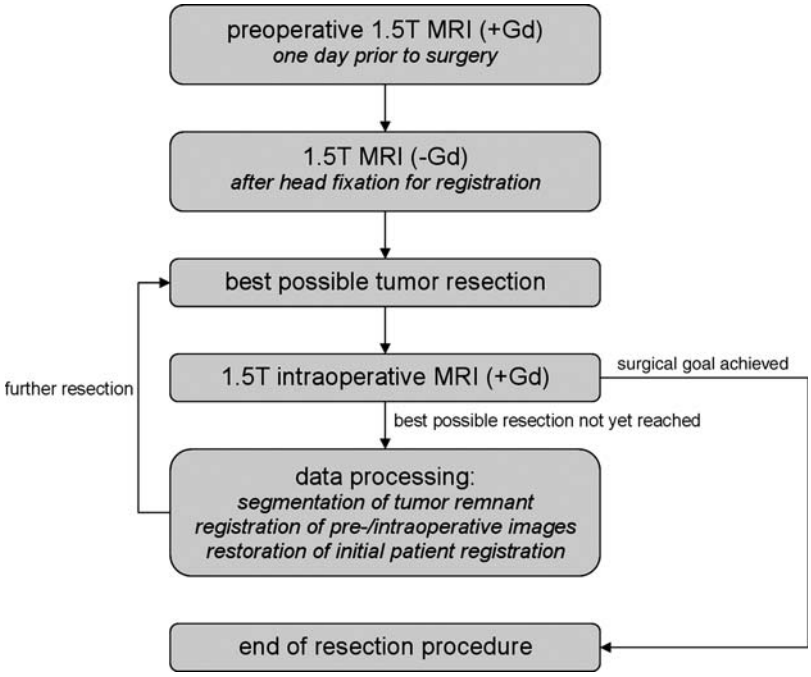

Fig. 1. Workflow figure illustrating the surgical procedure in the setting of iMRI. (Gd: gadolinium).

diethylenetriamine pentaacetic acid was used for the intraoperative scans after the intraoperative T1-weighted spin echo sequence before the 3D MPRAGE sequence. The first iMRI resection scan was performed after best possible tumor resection. For facilitating image interpretation, identical pre- and intraoperative sequences (with identical slice positions) were displayed in a side-by-side display fashion. For further detailed analysis, the images were also rigidly registered in the navigation planning software. Tumor segmentation was performed on MRI scans (obtained at least 1 day prior to surgery, contrast enhanced) on the identical scanner. Figure 1 illustrates the surgical workflow in the iMRI setting.

If iMRI revealed residual tumor, it was followed by data processing: segmentation of tumor remnant, registration of pre- and intraoperative image data sets (with the Image Fusion Software), and restoration of the initial patient registration.[22]

Tumor Volumetry

Tumor segmentation and postoperative volumetric analysis were performed with the VectorVision planning software on an offline workstation, and 1.0-mm isotropic 3D MPRAGE and T1-weighted images ($\pm$ gadolinium) were transferred with the help of PatXfer data transfer software (BrainLAB). The tumor was segmented manually across all slices, lasting approximately 5–30 min. Contrast enhancement on T1-weighted images displayed the outline of segmentation. All tumors showed a defined border with annular contrast enhancement. Metabolically active areas displayed by PET or MRS images were not taken into account due to their low resolution. T2-weighted enhancement was considered tumor-infiltrated edema but not chosen to outline the resection boundaries. After completing the segmentation, the volume was calculated in milliliters or cubic centimeters.

Statistics

All results are presented as mean $\pm$ SD.

The Wilcoxon–Mann–Whitney (Mann–Whitney U) test and Student's t-test were used for statistical analysis in Predictive Analytics SoftWare Statistics 18 for Mac (SPSS) to obtain the EOR values. For comparison of postoperative morbidity in several groups, a chi-squared test was used. Univariate analysis was performed using Kaplan–Meier estimates[23] (comparing the subgroups with the log-rank test), and a multivariate analysis was performed using a Cox proportional hazards model.[24] Hazard ratios (HRs) and their adjusted 95% confidence intervals (CIs) were calculated. Significance was at $P < .05$.

Results

Tumor Volumetry and Postoperative Morbidity

The patient cohort consisted of 135 GBM patients who were operated on with iMRI-guidance. There were no ferromagnetic accidents or difficulties during the intraoperative imaging or update procedure. The mean target registration error, documenting the localization of a separate skin fiducial placed on the patient's forehead,

Table 1. Tumor volumes for different patient cohorts

No. of Patients	Initial Tumor Volume (cm^3)	Residual Tumor Volume in First iMRI		Final Tumor Volume after iMRI Once or Twice		No. (%) of Patients with Final Gross Total Resection
		(cm^3)	(%)	(cm^3)	(%)	
Patients with intended subtotal tumor resection						
79	49.10 ± 46.41	31.20 ± 21.27	36.84 ± 19.56	10.70 ± 24.27	23.16 ± 24.67	0
Patients with intended gross total resection						
56	27.82 ± 25.65	2.32 ± 13.93	15.92 ± 27.64	0	0	56 (100%)
Patients without further removal after iMRI						
116	33.94 ± 39.67	2.29 ± 21.70	8.19 ± 25.40	2.29 ± 21.70	8.19 ± 25.40	47 (40.51%)
Patients with further tumor removal after iMRI						
19	52.65 ± 49.72	9.92 ± 20.90	34.25 ± 23.68	0.3 ± 15.88	1.22 ± 16.24	9 (47.37%)

which was not used for registration, was 2.0 mm (± 1.2 mm).

Residual tumor was seen in 88 patients in the first iMRI resection control. In 19 cases, resection was enlarged after iMRI, resulting in a significant increase of EOR from a mean tumor volume of 34.25 ± 23.68 cm^3 in the first intraoperative scans to finally 1.22 ± 16.24 cm^3 ($P < .01$). Furthermore, GTR rate was increased from 47 (34.80%) to 56 patients (41.49%). Surgery was terminated after the first iMRI in 116 cases (85.9%). Of these, in addition to the initial GTR tumors, there was subtotal resection (STR) in 51.1% of patients, further resection being impossible due to the residual tumor's close relation to eloquent areas. In these 116 patients, the initial tumor volume was 33.94 ± 39.67 cm^3. Mean final tumor volume counted 8.19 ± 25.4 cm^3.

GTR was intended in 56 cases, so that this goal was initially achieved in 83.9%, and finally in all cases. Of these 56 patients, the initial tumor volume was 27.82 ± 25.65 cm^3. STR was considered as the goal in 79 patients prior to surgery (Table 1).

For the recurrent lesions, initial tumor volume was 34.35 ± 31.02 cm^3, tumor volume in the first iMRI resection control was 10.23 ± 22.33 cm^3, and final tumor volume was 9.02 ± 15.74 cm^3.

For all cases in which the surgical procedure was supported by iMRI, subgroups were evaluated for percentage of resected tumor volume: 99.9%–98.0% = 0 patients; 97.9%–95.0% = 3 patients; 94.9%–90.0% = 1 patient, and <90% =15 patients. Further resection led to GTR in 9 patients, with resected tumor volumes of 99.9%–98.0% in 1 patient, 97.9%–95.0% in 0 patients, 94.9%–90% in 1 patient, and <90% in 8 patients. Thus, as opposed to 0 patients in the cohort of ≥98% EOR in the first intraoperative scans, after continued surgery the cohort contained 10 patients (Table 2).

Table 2. Influence of iMRI on EOR

Resected Tumor Volume (%)	First iMRI, No. of Patients	Final iMRI, No. of Patients
100%	0	9
99.9%–98.0%	0	1
97.9%–95.0%	3	0
94.9%–90.0%	1	1
<90.0%	15	8

Illustrative Case

A 60-year-old male patient presented with intermittent aphasia. A left parieto-occipital lesion had had GTR performed. Histopathological analysis revealed GBM, so that the patient underwent adjuvant radiochemotherapy (54 Gy, temozolomide). A routine MRI after 6 months revealed a recurrent left parietal tumor. The clinical examination showed a slight right-sided hemiparesis and a sensomotor aphasia. Surgery of the recurrent lesion (initial tumor volume: 57.3 mL) was performed under high-field MRI guidance. The first iMRI revealed a residual tumor (2.32 mL) that was completely removed, as confirmed in a second iMRI (Fig. 2). Postoperatively the patient's neurological status remained at baseline function and the patient was discharged for chemotherapy with ACNU-VM26.

Further tumor volume reduction was not associated with a higher long-term morbidity evaluated for language deficits and motor deficits, the overall long-term neurological worsening among patients being 1/19 (5.26%) and 6/116 (5.17%, $P > .05$), respectively. For those 19 patients with further tumor volume resection after iMRI, there were no motor deficits. Language deterioration occurred in 2 patients (10.5%) 3 days postoperation. At discharge there was a residual aphasia in only 1 case (5.3%). This is in contrast to the group of 116 patients who did not undergo further tumor resection after iMRI. Three days postsurgery, deficits in motor and in language capacity were found in 12 and 5 patients (10.3% and 4.3%), respectively, compared with 10 and 4 patients (8.6% and 3.4%) at discharge. Long-term follow-up examination was performed after 4 months. Six patients (4.4%) had residual motor deficits, all of them included in the *no further resection* cohort. Language deficits were still apparent in only 1 patient (0.7%). This particular patient underwent further tumor resection after iMRI (Table 3).

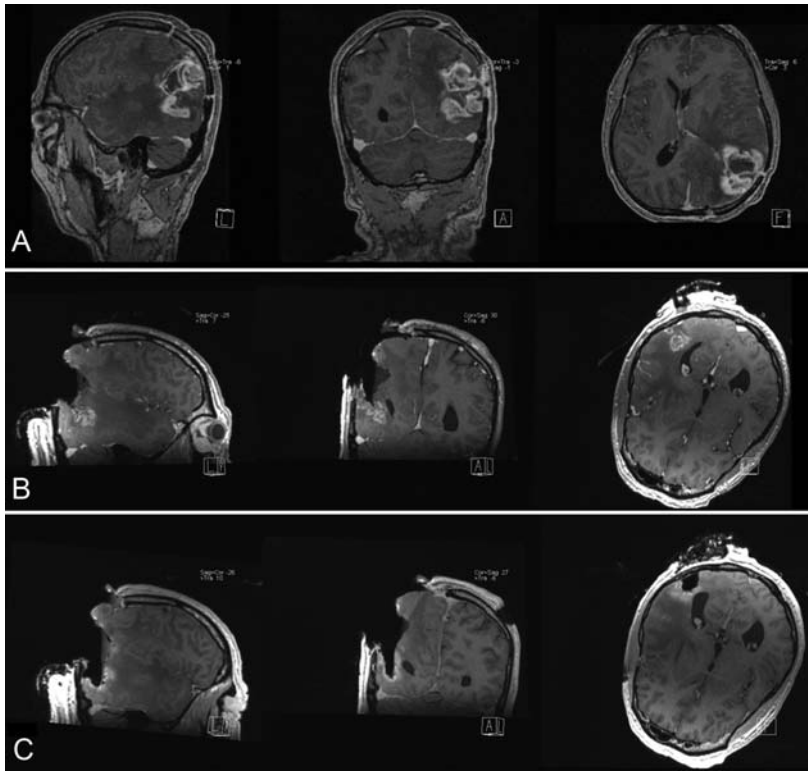

Fig. 2. Illustrative Case: MRI scans of a 60-year-old male patient with recurrent left parietal GBM during the surgical procedure. (A) Preoperative MRI, head already fixed, immediately before surgery (tumor volume: 57.3 mL). (B) First iMRI after estimated best possible tumor resection with a residual tumor mass of 2.32 mL. (C) Second iMRI after further tumor resection due to the first intraoperative scans, now showing gross total resection.

Table 3. Postoperative morbidity

Postop		At Discharge		After 4 Months	
fr	*nfr*	*fr*	*nfr*	*fr*	*nfr*
Motor deficits					
0 (0.0%)	12 (10.3%)	0 (0.0%)	10 (8.6%)	0 (0.0%)	6 (5.2%)
total: 12 (8.9%)		total: 10 (7.4%)		total: 6 (4.4%)	
Language deficits					
2 (10.5%)	5 (4.3%)	1 (5.3%)	4 (3.4%)	1 (5.3%)	0 (0.0%)
total: 7 (5.2%)		total: 5 (3.7%)		total: 1 (0.7%)	

Abbreviations: fr, further tumor removal after iMRI; nfr, no further tumor removal after iMRI.

For the recurrent tumors, morbidity was assessed separately. Postoperatively, we found new or aggravated motor deficits in 1 case (3.7%) and language deficits in 2 cases (7.4%). Long-term motor deficits were still apparent in 1 patient. Language deficits had completely resolved. Furthermore, morbidity at time of discharge (for motor and language) was evaluated for the EOR $\geq$98% group versus the EOR $<$98% group. Motor deficits were found in 4 patients in the former and in 6 patients in the latter ($P = .76$). Language deficits were still apparent in 2 patients in the EOR $\geq$98% group and in 3 patients in the EOR $<$98% group ($P = .421$). Comparing the STR and GTR groups at discharge, we found that 4/56 (7.14%) and 6/79 (7.59%), respectively, had motor deficits, while 2/56 (3.57%) and 3/79 (3.8%) had language deficits.

Length of Survival and Predictors of Survival

For 117 patients, median survival times (in months) were obtained. The remaining 18 patients were classified as censored cases in the statistical analysis, as they had been unavailable for follow-up examinations. The following variables were examined: EOR, age ($<$65 y and $\geq$65 y), gender, and recurrent tumor and its localization (frontal, temporal, parietal, or occipital).

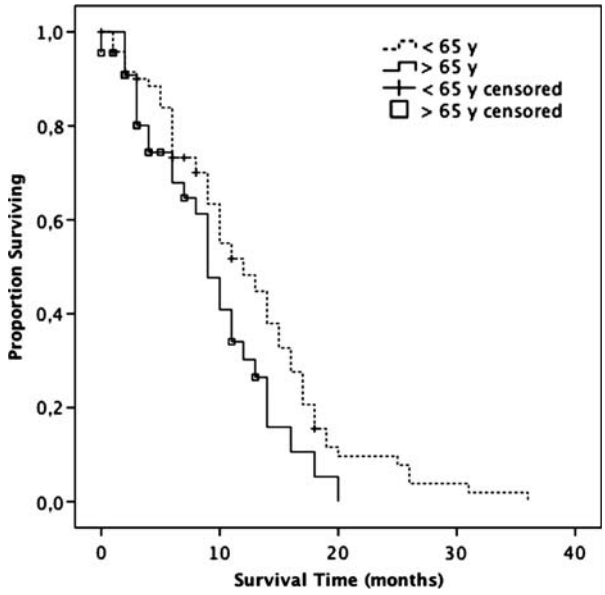

Fig. 3. Kaplan–Meier estimates of survival in univariate analysis with respect to patient age (≥65 years/<65 years). Median survival: 9 months (95% CI: 7.3–10.7) for patients ≥65 years, 12 months (95% CI: 8.4–15.6) for patients <65 years ($P < .04$).

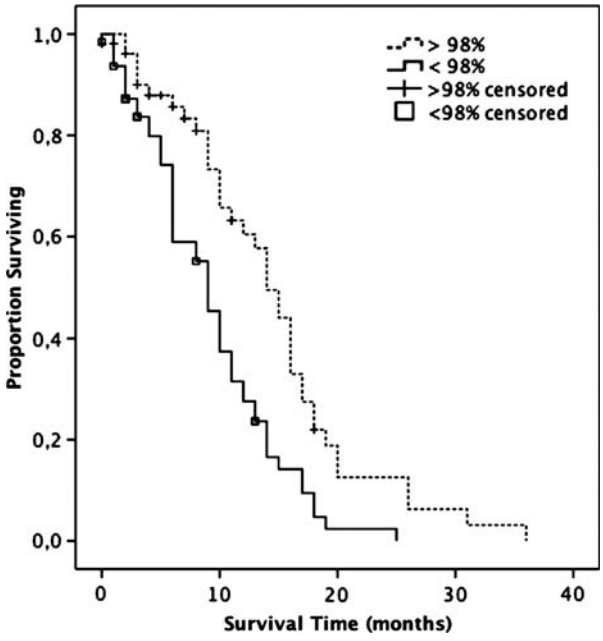

Fig. 4. Kaplan–Meier estimates of survival in univariate analysis with respect to EOR (≥98%/<98%). Median survival: 14 months (95% CI: 11.7–16.2) for EOR ≥98%, 9 months (95% CI: 7.4–10.5) for EOR <98% ($P < .001$).

Univariate Analysis Using Kaplan–Meier Estimates

A univariate analysis was performed for each of the variables mentioned above.

Median survival in male patients was 12 months (95% CI: 9.3–14.7); in female patients, 9 months (95% CI: 7.9–10.1; $P = .323$). Median survival for primary GBM was 12 months (95% CI: 9.7–14.2) versus 10 months (95% CI: 8.0–12.0) for recurrent lesions ($P = .165$). As for the parameters gender and recurrent lesion: the different tumor localizations were not associated with a statistically significant survival advantage (each $P > .05$).

Regarding patient age, median survival was 9 months (95% CI: 7.3–10.7) for patients ≥65 years and 12 months (95% CI: 8.4–15.6) for patients <65 years ($P < .04$) (Fig. 3).

Examining the influence of EOR on the patient cohort ≥98%, median survival was 14 months (95% CI: 11.7–16.2), as opposed to 9 months (95% CI: 7.4–10.5) in the cohort of EOR <98% ($P < .001$) (Fig. 4). Identical analyses were performed for the following EOR groups: 97.9%–96.0%, 95.9%–94.0%, 93.9%–92.0%, and so on to 85.9%–84.0% (comparing ≥96% EOR with <96% EOR, ≥94% EOR with <94% EOR, etc.; each $P > .05$).

Multivariate Analysis Using a Cox Proportional Hazards Model

A Cox proportional hazards assessment was performed to estimate the relative risk for death considering the influence of our variables. For EOR ≥98%, an HR of 0.39 (95% CI: 0.24–0.63; $P = .001$) was found. For patient age <65 years, the HR was 0.61 (95% CI: 0.38–0.97; $P < .05$). The HR of 0.39 corresponds to a reduced hazard for death of 61% if EOR is ≥98% (Fig. 5). For patient age <65 years, it is close to 39%. Also at the multivariate level, there was no significant influence on relative risk for death found for the variables of recurrent tumor, tumor localization, and gender (Table 4).

Discussion

We demonstrate that high-field iMRI and multimodal navigation contribute to a significantly improved EOR (34.25 ± 23.68 cm^3 to 1.22 ± 16.24 cm^3; $P < .001$) in GBM surgery with a preservation of neurological-function (long-term morbidity for motor and language deficits counting only 4.4% and 0.7%, respectively). An EOR ≥98% and a patient age <65 years are associated with a significant survival advantage in GBM surgery at both the univariate and multivariate levels, whereby further tumor resection after iMRI or tumor volume of EOR ≥98% are not associated with higher postoperative morbidity ($P > .05$). The variables of tumor localization and gender are not suitable as statistically significant prognostic factors on extended survival in our univariate and multivariate analyses. Surprisingly, we also found no significant influence on postoperative survival time for the variable of primary versus recurrent lesion. However, this might be due to bias, with a low number of recurrent tumor cases in the cohort ($n = 27$). Furthermore, it has to be noted that the further resection due to iMRI led to a significantly higher EOR in the total collective (34.25 ± 23.68 cm^3 to 1.22 ± 16.24 cm^3), but only from 10.23 ± 22.33 cm^3 to 9.02 ± 15.74 cm^3 for recurrent lesions.

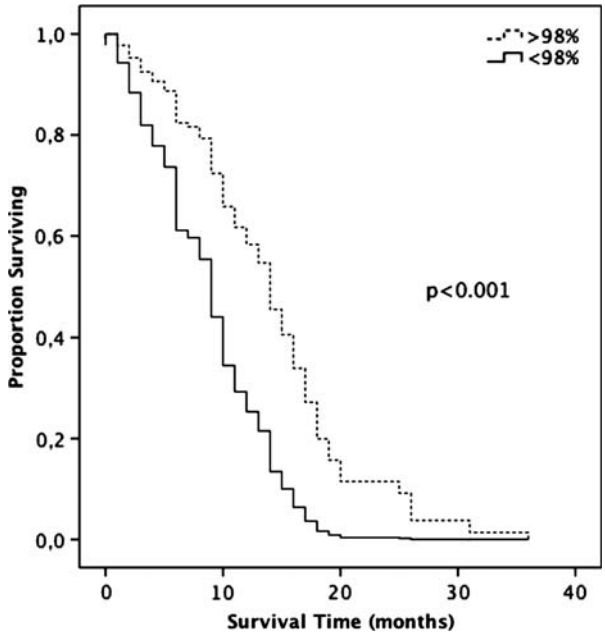

Fig. 5. Cox proportional hazards model with respect to EOR (≥98%/<98%), ($P < .0001$).

Table 4. Predictors of survival in multivariate analysis

Variable	HR	95% CI	*P*-value
EOR ≥98%	0.39	0.24–0.63	.000
Age <65 y	0.61	0.38–0.97	<.03
Localization			
Frontal	0.74	0.41–1.34	.32
Temporal	0.60	0.34–1.09	.94
Parietal	1.07	0.49–2.37	.86
Occipital	1.26	0.41–3.84	.69
Gender	0.74	0.47–1.18	.21
Recurrent	0.80	0.48–1.32	.37

Abbreviations: HR, hazard ratio; CI, confidence interval.

In this respect, our study supports iMRI as an essential tool in the surgical management of GBM. An EOR of ≥98%, which practically means tumor GTR combined with a preservation of neurological function, should be considered the surgical goal. This finding is in conjunction with the results of other large cohort studies involving quantification of tumor volumes supporting maximum EOR in glioma surgery.

Comparison with other Studies Evaluating the Postoperative Volumetric Assessment of GBM Tumor Volume and Associated Outcomes

In the current literature, there is still no general consensus regarding the role of surgical EOR as a predictive parameter for longer patient survival.[3,5] For low-grade gliomas, *all* studies published in the literature support maximum EOR.[25–27] For high-grade gliomas, *the majority* of studies using volumetric assessment consider extensive surgical resection to be associated with longer survival rates.[28,29] An overview of the common literature by Sanai and Berger (2008) reviewing studies with and without assessment of tumor volume (high- and low-grade gliomas) found 25 studies supporting maximum EOR, as opposed to 13 studies in which statistics did not favor any resection group.[30]

In agreement with a large study reporting on volumetric tumor assessment of 416 GBM patients by Lacroix et al. at MD Anderson Cancer Center in 2001,[29] we found that an EOR of ≥98% is associated with a significantly improved outcome regarding patient survival. Keles et al.[28] studied a group of 92 GBM patients and the effect of EOR on survival. They analyzed 5 "percent of resection" subgroups: 100% EOR was associated with a mean survival of 93 weeks, whereas in the 75%–99% EOR group, the mean survival was 88.5 weeks. A mean survival of only 62.9 weeks was calculated for an EOR of 50%–74%. McGirt et al.[31] published a retrospective study on a large patient cohort of 1215 malignant glioma patients. In this study, resection was classified according to the early postoperative MRIs in near-total resection (NTR), STR, and GTR. They found that GTR versus NTR as well as NTR versus STR were independently associated with improved survival after resection of GBM (mean survival = 11 mo for GTR, 9 mo for NTR, and 5 mo for STR for primary tumors).

Comparison with other Studies Evaluating the Prognostic Factor of Glioma EOR on Survival in Association with Intraoperative Imaging Methods

5-ALA–guided resection. The largest prospective, controlled, randomized study combining patient survival with intraoperative visualization is by Stummer et al.[7] In this study, surgery guided by 5-ALA was compared with surgery without 5-ALA resection control. A significantly smaller tumor volume appeared in the 5-ALA group compared with the "white-light" control group ($P < .0001$). Furthermore, the median progression-free survival was 5.1 months (95% CI: 3.4–6.0) in the 5-ALA "fluorescence" group and 3.6 months (95% CI: 3.2–4.4) in the white-light group. Another recent study by Stummer et al.[32] compared the groups "residual tumor on postoperative MRI" and "no residual tumor on postoperative MRI" per the protocol of the earlier 5-ALA study, in 2006.[7] Complete resection was here identified as an independent and prognostic factor of survival ($P < .0004$), now providing level 2b evidence that survival depends on complete resection of contrast-enhancing tumor in GBM. Median survival was 11.8 months for patients with residual tumors and 16.9 months for patients without tumor remnant ($P < .0001$). Tumor volume was approximated by fitting a rotational ellipsoid defined by the maximum tumor diameters in the three dimensions.

Intraoperative MRI–guided resection. To date, there are few studies assessing glioma EOR in iMRI-guided surgery and the associated patient outcome.

Wirtz et al.[33] compared GTR and STR cases and their association with survival in a retrospective study of 62 patients. Surgery was continued due to 0.2T iMRI in 67%. The authors found that GTR was a statistically significant prognostic factor for extended survival compared with STR (13.3 mo vs 9.2 mo, $P = .0035$). Schneider et al.[12] found a significantly prolonged median survival comparing GTR and STR in their study of 31 GBM patients. In 2010, Senft et al.[34] published a study examining iMRI resection control by applying a 0.15T MR scanner compared with a control group operated on with conventional neuronavigation in a collective of 41 GBM patients. GTR was achieved in 100% of the iMRI group and 9/31 in the neuronavigation group. Median survival was 74 weeks in the GTR group and 46 weeks in the STR group ($P < .001$). Median survival in the iMRI group showed no statistically significant survival advantage compared with the neuronavigation group ($P = .07$).

Hirschberg et al.[35] found no statistically significant difference for survival time comparing an iMRI group and a control group (14.5 vs 12.1 mo, $P = .14$) in a retrospective study of 32 GBM patients.

Maximizing EOR in GBM Surgery due to iMRI and Associated Postoperative Morbidity—Comparison with Previous Studies

A few studies have shown to date that iMRI contributes to maximize EOR in glioma surgery. Among these studies, that by Hatiboglu et al.[10] evaluated prospectively 27 GBM patients who were operated on with 1.5T iMRI guidance and found after iMRI that 48% required extended tumor resection. The final GTR rate was increased from 44% to 89%. Schneider et al.[12] reported a larger GTR rate from 2 to 11 patients in a cohort of 31 GBM patients due to 0.5T iMRI. Tumor volume was reduced from 21% to 12% after iMRI and continued surgery. In a study by Bohinski et al.[9] applying 0.3T iMRI for surgery on 30 high-grade glioma patients, surgery was continued after iMRI in 60% of patients. Busse et al.[8] reported GTR in 17% of participants due to 0.5T iMRI in a study of 24 GBM patients. Our study evaluated a cohort of 22 GBM patients operated on with 1.5T iMRI guidance in 2004.[11] We showed a final GTR rate of 31.8%, whereby complete resection in the first iMRI was 13.7%. Furthermore, EOR was significantly improved by the use of iMRI (21.3% $\pm$ 13.1% [tumor volume in first iMRI] vs 5.1% $\pm$ 11.9% [tumor volume in final iMRI]). In the present study, we show a significantly enlarged EOR, with tumor volumes dropping from 34.25 $\pm$ 23.68 cm^3 to 1.22 $\pm$ 16.24 cm^3, thus the final tumor volume is extremely low compared with those in the other studies we have mentioned. The GTR rate remained slightly lower than in previous studies but was increased from 34.8% to 41.49%. We assume that this is due to the preservation of neurological function. Long-term morbidity of 0.9% and 4.4% regarding language and motor deficits after GBM surgery are comparatively low percentages. Hatiboglu et al.[10] found a long-term morbidity of 9% for his whole cohort of 46 glioma patients. Bohinski et al.[9] and Schneider et al.[12] reported a perioperative morbidity of 12.5% and 12.9%, respectively, in their studies regarding the whole patient cohort. Compared with studies omitting iMRI guidance (ie, by using alternative methods for resection control), the morbidity also remains low.[7,36–38]

Limitations of this Study

As limitations of the study we consider that tumor volume data were obtained and analyzed retrospectively, so a control group with patients operated on without iMRI guidance was not available. Furthermore, there was no standardized protocol for adjuvant therapy, so that patients were treated with different combinations of chemotherapeutics. Patients with a low KPS did not receive radiotherapy or chemotherapy.

So far, to our knowledge, the literature does not provide a prospective, controlled, randomized study including volumetric assessment of EOR and patient outcome in the setting of high-field iMRI. Although a control group could not be obtained in our study, we consider iMRI as a feasible method for extended tumor volume resection. The surgeon tried to achieve best possible tumor resection before the first iMRI resection control was performed. Of course, he might have been influenced by the certainty that iMRI would be obtained. However, his estimation was correct in the high majority (85.9%) of cases, in which surgery was terminated after iMRI (initial GTR was 34.8% of cases, and STR was terminated after iMRI in 51.1% of cases). Only in 19 cases was the surgeon mistaken. In this way, we can see that the surgeon was not really tempted toward earlier termination of surgery.

KPS was not obtained. However, we evaluated the neurological deficits for motor and language quantitatively and qualitatively pre- and postoperatively, estimating the patients' general conditions. Here, our results show no significant difference of neurological deficits, comparing the *further tumor resection after iMRI* group versus *no further tumor resection after iMRI* and $EOR \geq 98\%$ versus $EOR < 98\%$.

All lesions were included in the study, including those in the vicinity of eloquent brain areas. A separate statistical analysis for lesions in non-eloquent areas versus lesions near eloquent areas could not be performed, as the distance considered to be close to an eloquent area was not explicitly defined preoperatively. However, final STR in iMRI was the case only if further resection was not to be performed. Therefore, the 79 STR lesions can be assumed to be located close to eloquent regions, while all 56 GTR lesions are located in non-eloquent areas. Percentages were comparatively low for both groups. We can therefore hypothesize that our results for the influence of EOR on outcome can also be applied to lesions near eloquent brain areas.

Conclusions

GTR with a focus on preservation of neurological function should be the major goal in surgical treatment of GBM, as an EOR $\geq$98% was shown to significantly improve patient survival. This goal can be achieved with iMRI and an intraoperative update of navigation data, thus compensating for the general problem of brain deformations during surgery, known as brain-shift. In addition to EOR $\geq$98%, patient age $<$65 years significantly improves survival, whereas parameters such as gender, localization, and whether primary or recurring lesion cannot be considered as prognostic factors for a significant survival advantage.

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Conflict of interest statement. Christopher Nimsky, MD is scientific consultant for intraoperative imaging for BrainLab (Feldkirchen, Germany). The corresponding author declares that all authors contributed to the work in a way that justifies their co-authorship.

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