Journey of Intraoperative Magnetic Resonance Imaging into Daily Use: A Review

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European Association of NeuroOncology Magazine 2013; 3 (2)
61-67

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Introduction

Alongside adjuvant radio- and chemotherapy, surgery remains a mainstay in the treatment of patients with intracranial gliomas. Similar to recent advances in the field of neuro-oncology, resection techniques of intracranial gliomas have undergone many changes in the past decades. New technological developments range from microneurosurgery and multimodal neuro-navigation to routine implementation of high-field MRI scanners for intraoperative resection control in latest history. All these advances provide assistance to the operating surgeon, ensuring removal of as much tumour tissue as possible without causing any additional neurologic squalor.

The contribution of intraoperative MRI imaging (iMRI) to maximized tumour resection, patient safety, and outcome has been subject of many studies since the first appearance of this method in the late 1990s. Following a controversial debate, maximum extended safe tumour resection has been proven to harbour significant survival benefits for glioma patients. The role of iMRI is to guide such maximum extended safe tumour resection and its unprecedented precision in delineating tumour borders has become evident in recent research. Regardless of its clinical benefits, high costs and manpower requirements still pose heavy limitations to widespread availability of iMRI which makes this method subject to economical and ethical considerations.

This review outlines the significance of maximum extended safe tumour resection in present-day multidisciplinary glioma treatment, explains how iMRI can provide substantial decision guidance to the operating surgeon, and demonstrates how such a sophisticated method can be implemented into the daily routine of neurosurgical procedures.

Benefit of Extended Tumour Resections for Patient Prognosis

Diagnosed with an intracranial mass lesion, patients need confirmation of histological diagnosis in order to receive adequate and specific therapy. Treatment guidelines for intracranial tumours explicitly recommend that tissue specimens be obtained before commencement of radio- or chemotherapy. In case of intracranial gliomas, the least surgery can offer is to provide the histological diagnosis required for further adjuvant therapies. Beyond that, maximum extensive safe surgery is increasingly accepted as an independent, positive, prognostic factor [1].

In recent years, routine acquisition of early post-resection MRI scans within 48–72 hrs after surgery has provided the opportunity to evaluate the correlation between the extent of resection (EOR) and different outcome measures. Among the many studies dedicated to this matter, heterogeneity of data and patient samples is huge. Up-to-date, large, randomized, controlled trials evaluating the value of maximized resection vs partial resections are lacking and ethically debatable. Many conclusions are drawn from subgroup analyses based on patient data acquired in another context. Additionally, retrospectively designed and single-centre reports are unfortunately subject to a biased patient sample regarding age, overall performance, imaging modalities, or adjuvant therapy regimens. Nevertheless, there is a growing body of evidence supporting the pursuit of maximized safe resection in the treatment of intracranial gliomas.

In case of high-grade gliomas (HGG), besides yielding a histological diagnosis surgery is also performed to relieve symptoms caused by the rapidly growing tumour mass and brain oedema. Due to the inevitable tumour invasion into healthy brain parenchyma, it is obviously never possible to remove all tumour cells but rather important to achieve substantial relief from tumour burden in terms of gross total resection (GTR, ie no residual contrast enhancement [CE] on post-resection scan). As opposed to subtotal or partial resection of the tumour (STR or PR, nodular or solid CE residual, respectively), GTR has been shown in various studies to have significant impact on patient survival. Besides known prognostic factors
such as age and Karnofsky performance status (KPS), GTR has been shown to be another independent positive prognostic factor in HGG [1–8]. To our knowledge, evidence of the highest available quality can be derived from a German multicentre, randomized, controlled trial by Stummer et al that compares 5-aminolevulinic acid (5-ALA) fluorescence-guided with conventional white-light HGG resections [9]. In a balanced re-stratification for resection extent, all patients who underwent GTR experienced prolongation of overall survival compared to incompletely resected patients (16.7 vs 11.8 months, respectively; p < 0.0001) [1, 7]. In addition, another high-volume series of McGirt et al evaluated 1250 patients harbouring a high-grade glioma and found a survival benefit up to 5 months when comparing GTR to PR (13 vs 8 months, respectively) [8]. These results were adjusted for factors with known association to survival such as age, KPS, or adjuvant therapies. Sanai et al present a thorough analysis of the current literature with a focus on precise calculation of EOR and clear statistical measures. They report a statistically significant beneficial effect from maximized EOR in 16/28 HGG studies [6]. Although prognosis in HGG remains poor, these recent results should be valued as encouraging. We see the impact of extended safe resection upon overall survival in glioblastoma alongside with the beneficial effects of concomitant adjuvant radiochemotherapy as reported by Stupp et al in 2005, formerly offering a median 2.5-month longer survival compared to previous standard treatment [10]. Even though this study did not include mandatory postoperative imaging and EOR was partly assessed by means of inaccurate estimation of the operating surgeon, in a post-hoc data analysis by Gorlia et al EOR was shown to have a significant impact on patient survival. Building on this and remembering that 5-ALA data was acquired before the implementation of concomitant adjuvant radiochemotherapy, supplemental effects should be expected when both approaches are combined. Maximized safe resection followed by an individualized, targeted therapy is expected to further prolong overall survival for patients with HGG in the future [11].

Low-grade glioma (LGG) patients often show mild to nil clinical symptoms but eventual malignant tumour progression will aggravate symptoms and reduce life expectancy. As most of WHO I° and II° tumours are not easily amenable for radiochemotherapy due to their slow cell proliferation compared to their high-grade counterparts, watch-and-wait regimens are still applied after biopsy until a definite therapy is initiated [12]. To date, this approach should be questioned when surgery alternately can safely remove the tumour, diminishing the risk of malignant transformation or occurrence of neurologic symptoms or seizures. Besides, even small and deeply located lesions can be safely approached with today’s techniques so that factors complicating surgery such as growth, malignant transformation, and tumour infiltration can be anticipated instead. The literature provides support for radical surgery in supratentorial LGG amenable for safe resection as the treatment of choice [13, 14]. Even though formal quality of evidence is weak, a systematic review of Sanai et al quotes 9/10 selected LGG studies as being in favour of extensive resection of LGG lesions. In uni- and multivariate analyses, EOR was revealed to be a significant positive prognosticator in 7 of these studies [6]. Even in case of tumour recurrence, Ahmadi et al could show a clearly beneficial effect of more radical surgery in terms of time to malignant progression and overall survival [15].
iMRI for Intraoperative Resection Control

Accurate delineation of tumour and normal brain parenchyma remains one of the major challenges in glioma surgery. In recent years, many technical advancements have been developed to assist the surgeon in locating and precisely confining brain tumours. Alongside with multimodal neuronavigation, intraoperative ultrasound, and 5-ALA in glioblastomas, intraoperative MRI acquisition is used in a growing number of centres for tumour resection control. Initial evaluation following the introduction of this method quickly showed beneficial effects of iMRI in glioma surgery. Reports of increased EOR and improved patient prognosis have accumulated over recent years and other advantages such as compensation for brain-shift phenomena through intraoperative update of neuronavigation have been pointed out [16]. Moreover, surgeons have been exposed to commonly overestimate their own resection extent, which strengthens the call for routine intraoperative resection guidance based on the given correlation between resection radicality and patient prognosis [17].

In HGG, iMRI resection control is often compared to fluorescence-guided resection with 5-ALA, which has been shown to lead to more frequent GTR compared to white-light surgery. To corroborate the contribution of iMRI to a more radical EOR, a bundle of retrospective studies and cohort analyses have been published. Following the design of the 5-ALA study, Senft et al recently conducted a randomized controlled trial to further elucidate the use of iMRI. In their cohort of 49 HGG cases scheduled for total tumour resection, randomization assigned patients either to receive low-field iMRI-guided or conventional microneurosurgical extirpation of the tumour. In the iMRI resection group, this surgical goal was achieved in 96% of cases compared to only 68% in the conventional group (23 vs 17 of 49 patients, respectively) [18]. Adding up to other likeminded results, this study for the first time validated the gain of iMRI resection control in a randomized controlled fashion. For HGG resections, iMRI-guided surgery leads to a higher frequency of GTR at least comparable to results achieved using 5-ALA fluorescence.

In LGG, only intraoperative ultrasound (iUS) can help as an alternate imaging modality during surgery. High-field iMRI scanners are of special value in LGG surgery since they offer high anatomical resolution along with full-scale diagnostic capability. Sharp T2 and FLAIR sequences, MR-spectroscopy, and diffusion-weighted imaging (DWI) contribute greatly to a precise delineation of residual non-enhancing intracranial lesions. So far, there are only few retrospective studies available evaluating LGG outcomes after iMRI-guided resection. A group from the Brigham and Women’s Hospital in Boston compared long-term results derived from their iMRI-guided LGG resections to results from a national registry. Their central finding was a significant reduction of 1-2- and 5-year age- and histology-adjusted death rates compared to the national registry when iMRI was used for resection guidance (1.9% [95%-CI: 0.3–4.2%], 3.6% [95%-CI: 0.4–6.7%], and 17.6% [95%-CI: 5.9–29.3%], respectively). Stratifying for total and subtotal LGG tumour removal, a 1.4 times higher risk of recurrence (95-% CI: 0.7–3.1) and a 4.9 times higher risk of death (95-% CI: 0.61–40.0) was apparent when lesions were only removed subtotally [14]. These tendencies suggest a correlation between iMRI-guided extent of resection and longer patient survival also in low-grade tumours. But again formal evidence is weak, with the non-homogeneity of data and study groups impeding final conclusions until results are confirmed in larger, randomized, matched or other controlled populations.

Regarding EOR, volumetric analysis did also quantify the increased amount of tumour that could be removed by means of iMRI in some studies (Table 1). EOR could be increased from a median 76% to 96% in one series, and residual tumour fractions could be reduced from 21.4 ± 13.8 to 6.9 ± 10.3% in another series across all WHO grades [19, 20]. Accordingly, Kuhnt et al and Schneider et al showed an increase in EOR from 66.55% and 69.3% at the point where MRI was performed intraoperatively to a final EOR of approximately 85% on postoperative MRI scans [21, 23]. A preliminary analysis of our own prospective volumetric iMRI data has yielded similar results. In 101 analyzed patients operated under iMRI guidance in 2011, EOR was increased from 90.1 ± 15.6% on intraoperative images to a final EOR of 99.8 ± 0.8% (Scherer et al, unpublished data, 2012). In all of these studies, up to 20% of the overall tumour resection was not performed until after an iMRI scan confirmed tumour remnants.

To deduct an increased extent of resection solely from the intraoperative use of iMRI would be much of a hasty reaction. Since surgeons were aware of the feasibility of iMRI right from the beginning of surgery, this possibility biased the decision of when to do the first intraoperative scan and led to a more defensive resection strategy in those studies. Accordingly, the absolute values of EOR increase after iMRI partly represent the surgeon’s uncertainty in tumour delineation or the difficulty of surgery rather than the direct contribution of iMRI to more radical tumour surgery.

Rates of continued surgery after intraoperative resection control by means of iMRI are another interesting aspect when assessing the value of this intraoperative imaging modality. Among the iMRI studies presented here (Table 2), 21 out of 44 patients (47%) [19] and 17 out of 47 patients (36%) [20], respectively, underwent further tumour resection after iMRI resection control. Another report by Kuhnt et al states a 26%-incidence of additional resections after the first intraoperative scan. Referring to our own data analyzing the routine use of iMRI guidance for all glioma resections at our department, we observed high frequencies of ongoing resections beyond all WHO grades. In total, 71 of 101 (70.3%) cases received additional tumour resection after iMRI with even higher rates for WHO II and IIIA tumours (Scherer et al, unpublished data, 2012). In their randomized controlled cohort of WHO IV tumours, Senft et al reported additional tumour resection in 1/6 of cases of iMRI application, leading to successful accomplishment of GTR in all of these patients. In their conclusion, iMRI was accountable for the 30%-increase in complete resections and it was evident that without its use neither group would have differed significantly from the other [18, 23].
While these questions concern rather technical aspects of iMRI-guided surgery, it is important to focus on the true goal of surgery, which is to achieve maximized safe tumour resection in order to prolong patient survival. Among all iMRI studies that have documented their cases with respect to the preoperatively defined resection goal it becomes evident that this surgical goal can be attained in a vast majority of cases where iMRI was used (Table 2). While the predefined goal was already reached in 37–74% of cases when a first iMRI was performed, continued resections after iMRI led to eventual success in up to 100% of cases. This implicates that independently of other available modalities for resection control iMRI is a convincingly precise and efficient way to push resection boundaries and achieve the goal of surgery in an overwhelming majority of tumour resections across all WHO grades.

Most importantly, iMRI-guided extended resection radicality was not achieved at the cost of any increased morbidity. Neither did the randomized study of Senft et al show a significant accumulation of deficits when comparing the iMRI with the white-light group (3 vs 2 permanent deficits; 13% vs 8%, respectively), nor did Kuhnt et al observe any aggravation of motor or speech deficits when comparing their cohort of additionally resected tumours with those resections terminated after an iMRI resection control (7.7% vs 12.5% accumulated morbidity at discharge, respectively; Table 3).

As mentioned earlier, prolonged survival after extended glioma surgery has been reported many times in general. Some studies have also directly addressed the contribution of iMRI-guided extended tumour resection upon patient overall survival [18, 21, 22, 25–27]. Among the HGG series, Kuhnt et al present a series including 135 glioblastoma patients operated using 1.5 T high-field iMRI guidance. EOR > 98% and age < 65 were independent positive prognosticators leading to a 5-month longer overall survival when more radical surgery could be achieved (14 months [95%-CI: 11.7–16.2] vs 9 months [95%-CI: 7.4–10.5]) for EOR > 98% and < 98%, respectively (p < 0.0001) [22]. Results from other cohorts point in the same direction with a longer overall or progression-free survival after complete vs incomplete tumour resection (Table 4). Comparable to 5-ALA data, beneficial effects of extended surgical radicality have thus been observed independently of the technique used for resection guidance in HGG.

In their review, Kubben et al attempted not only to examine the benefit on survival but also to evaluate clinical performance and quality of life before and after iMRI-guided surgery. Focusing on precise EOR calculation, detailed reports of quality of life, and long-term documentation of patient survival, 12 non-randomized cohort studies out of 682 published studies from 1999 until 2010 were selected. Even though all included studies showed increased overall EORs, reliable data on the quality of life or prolonged survival was sparse. Only 3/12 studies included patient follow-up, each showing significantly longer median survival times. Another 3/12 studies evaluated clinical performance but failed to show a correlation to extended tumour resections. Data concerning quality of life after surgery was not provided by any study [28]. Performance scores are often documented before surgery in order to identify the calculated status as an outcome predictor; postoperative performance status, however, often remains elusive. Although a slight reduction in KPS within 2 weeks after surgery has been reported by Mehdorn et al, yet the value of this finding is unclear due to unbalanced and selected cohorts in this study [27]. So, apart from focal motor or speech deficits, the question of how patients are doing shortly after extended glioma surgery and during their assumedly longer survival has remained mostly unanswered.

Although not truly “online”, like intraoperative ultrasound (iUS) and 5-ALA, intraoperatively acquired MR imaging can reliably help the surgeon to delineate tumour tissue from healthy brain parenchyma. Especially in areas that are hard to explore with US or fluorescent light, iMRI might be superior in detecting residual tumour. Likewise, in LGG or anaplastic gliomas, where 5-ALA shows no or only weaker detection in detecting residual tumour. Likewise, in LGG or anaplastic gliomas, where 5-ALA shows no or only weaker detection rates, iMRI has full distinction power leading to a greater EOR across all tumour entities without adding any specific neurologic morbidity. Spatial precision of tumour delineation of iMRI combined with multimodal neuronavigation is unprecedented. This offers the chance not only to enhance complete tumour resections but also to guide partial resections with borders close to eloquent areas, limiting resection extent precisely to only harmless tumour parts. Compared to any other intraoperative imaging modality iMRI enables the sur-

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### Table 3. Postoperative neurological deficits (visual, motor, language) after iMRI-guided surgery, permanent deficits at > 4 months after surgery.

<table>
<thead>
<tr>
<th>Author, Year [Ref]</th>
<th>Postoperative Deficits</th>
<th>Further resections after iMRI (%)</th>
<th>No further resections after iMRI (%)</th>
<th>Permanent deficits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider et al, 2005 [21]</td>
<td>–</td>
<td>–</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Kuhnt et al, 2011 [22]</td>
<td>14</td>
<td>26</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Senft et al, 2011 [18]</td>
<td>0</td>
<td>13</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Outcome of patients operated under iMRI guidance with respect to the EOR. Data presented as difference in median survival times.

<table>
<thead>
<tr>
<th>Author, Year [Ref]</th>
<th>Survival</th>
<th>Resection ± (months)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wirtz et al, 2000 [25]</td>
<td>OS</td>
<td>GTR vs IR</td>
<td>+4.2</td>
</tr>
<tr>
<td>Schneider et al, 2005 [21]</td>
<td>OS</td>
<td>GTR vs IR</td>
<td>+10</td>
</tr>
<tr>
<td>Kuhnt et al, 2011 [22]</td>
<td>OS</td>
<td>GTR vs IR</td>
<td>+5</td>
</tr>
<tr>
<td>Senft et al, 2011 [18]</td>
<td>PFS</td>
<td>GTR vs IR</td>
<td>+4.3</td>
</tr>
</tbody>
</table>

GTR: gross total resection; IR: incomplete resection; OS: overall survival; PFS: progression-free survival.
geon to achieve the seemingly contradictory goal of extending radicality while improving safety.

In summary, the literature shows clear benefits from improved iMRI-guided resection radicality such as lower risk of recurrence, longer progression-free survival, lower 1–5-year death rates (LGG), and longer overall survival (HGG). However, formal evidence for this knowledge is still lacking. Due to inconsistency of data acquisition and presentation, mixed patient populations, and other technical limitations such as different measurements of EOR or MRI field strengths it has so far been virtually impossible to elaborate a clear meta-analysis of existing studies dealing with this topic. As further randomized controlled trials evaluating the extent of resection and its effect on survival are ethically debatable from our current state of knowledge, well-designed, prospective, observational studies might be the only way to underscore the importance and benefit from more radical surgery for the treatment of intracranial gliomas in the future. Precise and prospectively addressed definitions of surgical goals (GTR, no residual contrast enhancement, vs PR, residual contrast enhancement), routine postoperative imaging 48–72 hrs after surgery and volumetric documentation of resection extent should be the least common ground for future data collections. This well-defined baseline data will help to merge knowledge in the field and to present high-volume multicentre series providing age- and histology-adjusted estimates of survival rates with respect to the achieved EOR. Beyond technical aspects, future studies also have to focus on clinical performance and quality of life along with survival benefits in order to give sustainable answers to the questions evolving around the use of iMRI in glioma surgery.

Figure 1. 33-year-old male with seizures diagnosed with a WHO II astrocytoma by stereotactic biopsy. Complete tumour resection was scheduled. (A) Preoperative definition of target tumour volume of 31.72 cm³ on T2 FLAIR images. (B) On the first iMRI, a 1.92-cm³ residual tumour is detected at the ventral aspect of the resection cavity on sharp FLAIR images. (C) Postoperative MRI shows no signs of tumour remnants. iMRI guidance led to a fully successful procedure with no added neurologic morbidity.
Feasibility of Routine iMRI: Implementation into Daily Surgery

Since acquisition and maintenance costs are still a substantial drag to a greater prevalence of iMRI units in hospitals today, it is important to take into account all therapeutic indications and their benefits for patients to justify their establishment. High-field iMRI machines offer the full range of diagnostic sequences and high anatomical resolution. Accordingly, iMRI imaging can also assist in stereotactic biopsies, placement of catheters, or deep-brain stimulating electrodes and, lastly, transsphenoidal resections of pituitary tumours. From an economical point of view, frequent utilization of an iMRI promotes a faster return of initial investments while cutting maintenance costs at the same time. Hence, frequent and effective use of an iMRI unit will serve both medicine and management.

Routine implementation of an iMRI into daily surgical routine can only be accomplished under certain conditions. Patient safety has to be given top priority, which can easily be jeopardized by a strong magnetic field within an operating room (OR). Among different iMRI-suite set-ups, instead of placing the iMRI scanner in the OR itself, in our opinion a 2-room solution has obvious advantages for routine daily use. Our set-up in Heidelberg, where the patient is transported into the iMRI next door, allows us to perform regular surgery without any relevant limitations with regard to positioning or surgical instruments. Moreover, this set-up allows us to use the iMRI unit from 2 ORs, fostering efficient multiple daily use for various indications. Besides, separating the magnet from the OR is a relevant safety aspect, especially when the OR is used for cases where iMRI will not be used. Regardless of the iMRI set-up, dedicated standards of iMRI procedures and vigorous staff training are inevitable. On the one hand, standardized work-flows warrant patient safety while on the other hand, a straightforward iMRI procedure with reduced transfer times also contributes to efficient use of OR and labour time.

In Heidelberg, routine use of iMRI began when a new 1.5 T magnet was installed in June 2009. Since then, more than 670 surgical procedures have been performed using iMRI guidance. In our institution, all intracranial gliomas eligible for GTR are scheduled to undergo surgery with iMRI guidance. Whenever applicable, partial tumour resections are planned to be operated with iMRI resection control in order to safely increase radicality in these patients as well.

In 2011, we initiated a prospective collection of our iMRI-guided glioma resections in a volumetric database. Intended extent of tumour resection, iMRI residual tumour volumes, and postoperative tumour volumes are documented along with other patient parameters. An illustrative case demonstrating our routine procedures and volumetric documentation is shown in Figure 1 and some of our preliminary data, as mentioned above, is presented in Tables 1 and 2.

Implementing iMRI into routine glioma surgery certainly causes challenges and will most likely affect the strategic approach to a tumour as well as the manner of surgery itself. As a consequence of routine iMRI use in glioma surgery one might expect the frequency of post-iMRI resections to increase over time, together with residual tumour volumes seen in a first intraoperative scan. This would resemble a more defensive surgical strategy in the first place. A preliminary analysis of our data seems to confirm this hypothesis with continued tumour resections performed after iMRI scans in almost 2/3 of all patients. It might also be interesting to follow learning curves of young neurosurgeons over their time of training since iMRI provides immediate feedback on the resection progression. By means of this prospective single-institution database of unselected glioma cases, we hope to be able to address unanswered questions and confirm beneficial effects of iMRI surgery for glioma patients in the future. A newly formed German iMRI study group will further pursue this approach and try to derive a similar multi-centre database in order to merge data and produce solid evidence fostering the use and prevalence of iMRI in neurosurgery.

Conflict of Interest

The authors state that no conflict of interest exists.

References: