Accuracy of High-Field Intraoperative MRI in the Detectability of Residual Tumor in Glioma Grade IV Resections

Treffsicherheit der Intraoperativen MR-Bildgebung (ioMRI) in der Nachweisbarkeit von Resttumorgewebe zur Resektion hochgradiger (Grad IV) Gliome

Authors
Volker Heßelmann¹, Ann-Kathrin Mager¹, Claudia Goetz², Oliver Detsch³, Hannah-Katharina Theisgen⁴, Michael Friese⁵, Wolfram Schwindt⁶, Joachim Gottschalk⁵, Paul Kremer²

Affiliations
1 Radiology/Neurologie, Asklepios-Klinik Hamburg-Nord, Hamburg, Germany
2 Department of Neurosurgery, Asklepios Klinik Nord, Hamburg, Germany
3 Department of Anaestesiology and Intensive Care Medicine, Asklepios Klinik Nord, Hamburg, Germany
4 Department of Neurosurgery, Universitatsklinikum Schleswig-Holstein Campus Kiel, Germany
5 Department of Pathology and Neuropathology, Asklepios Klinik Nord, Hamburg, Germany
6 Department of Clinical Radiology, University Hospital Münster, Münster, Germany

Key words
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Correspondence
Dr. Volker Heßelmann
Radiology/Neurologie, Asklepios-Klinik Hamburg-Nord
Tangstedter Landstraße 400
22417 Hamburg
Germany
Tel.: ++ 40/18 18/87 33 32
Fax: ++ 40/18 18/87 36 88
v.hesselmann@asklepios.com

ZUSAMMENFASSUNG

Einleitung Ziel der Studie ist die Untersuchung der Sensitivi-
tät und Spezifität der intraoperativen MRT (iOMRI) zum Nach-
weis von Resttumorgewebe auf der Basis der T1-Wichtung
nach GD-DPTA im Vergleich zur Histopathologie (Goldstan-
dard) bei neurochirurgischen Operationen von WHO Grad IV
Gliomen.

Material und Methoden 68 Patienten (Durchschnittsalter
59 Jahre, 26 weiblich, 42 männlich mit primären oder rezidi-
vierenden WHO Grad IV Gliomen erhielten gleichzeitig eine
fluoreszenz-, eine neuronavigations- und ein ioMRI-gestützte
Resektion. Bei Nachweis von KM-Anreicherungen in T1-Wich-
tung in der ioMRI erfolgte eine Nachresektion, deren histopa-
thologischen Proben (Goldstandard) von einem Neuropatho-
logen bewertet wurde. Nach kompletter Entfernung des
fluoreszierenden oder MR-tomografisch nachweisbaren Rest-
tumorgewebes wurde die OP beendet. Zusätzlich wurde die
postoperative MRT zum Nachweis residueller KM-Anreiche-
run gen mit der ioMRI verglichen und als in die Auswertung
mit einbezogen.

Ergebnisse Bei 43 Patienten wurde in der ioMRI Resttumor-
gewebe nachgewiesen und histopathologisch bestätigt. In 16
Fällen war die zweite ioMRI ohne histopathologischen Nach-
weis von Resttumor richtig negativ (4 Rezidive, 12 Primärtu-
more). In 7 Fällen (3 Rezidive, 4 Primärtumore) war der ioMRT
Befund falsch positiv, in zwei Patienten (1 Rezidiv, 1 Primärtu-
more) falsch negativ. Für alle Patienten betrug die Sensitivität
95 %, die Spezifität 69,5 %, für die Rezidive 94 % und 57 % und
für die Primärtumore 96 % und 75 %. Der positive Vorhersage-
wert war 86 %, der negative Vorhersagewert 88 % für alle
Patienten, 84 % und 80 % für die Rezidive und 87 und 92 % für
die Primärtumore.

Schlussfolgerung Die ioMRI ist sensitiv im Nachweis von
kontrastmittelanreicherndem Resttumorgewebe nach
Gliomresektion. Narbengewebe und Kontrastmitteldecken
durch Blutaustritt führen zu Fehlinterpretationen und reduzie-
die Spezifität.
Kernaussagen
• Die ioMRI ist hochsensitiv im Nachweis residueller, kontrastmittelanreichernder Resttumorteile in der Glioma-sektion
• Artefakte durch blutungsbedingte Kontrastmittelausritte und reaktive Kontrastmittelaustritte sind gerin- begeweben limitieren die Spezifität der ioMRI
• Eine suffiziente Blutungsstiluung ist entscheidend für eine hohe Aussagekraft der ioMRI

ABSTRACT
Objective To assess the sensitivity/specificity of tumor detection by T1 contrast enhancement in intraoperative MRI (ioMRI) in comparison to histopathological assessment as the gold standard in patients receiving surgical resection of grade IV glioblastoma.

Materials and Methods 68 patients with a primary or a recurrent glioblastoma scheduled for surgery including fluorescence guidance and neuronavigation were included (mean age: 59 years, 26 female, 42 male patients). The ioMRI after the first resection included transverse FLAIR, DWI, T2-FFE and T1 – 3 d FFE +/- GD-DPTA. The second resection was performed whenever residual contrast-enhancing tissue was detected on ioMRI. Resected tissue samples were histopathologically evaluated (gold standard). Additionally, we evaluated the early postoperative MRI scan acquired within 48 h post-OP for remaining enhancing tissue and compared them with the ioMRI scan.

Results In 43 patients ioMRI indicated residual tumorous tissue, which could be confirmed in the histological specimens of the second resection. In 16 (4 with recurrent, 12 with primary glioblastoma) cases, ioMRI revealed truly negative results without residual tumor and follow-up MRI confirmed complete resection. In 7 cases (3 with recurrent, 4 with primary glioblastoma) ioMRI revealed a suspicious result without tumorous tissue in the histopathological workup. In 2 (1 for each group) patients, residual tumorous tissue was detected in spite of negative ioMRI. IoMRI had a sensitivity of 95 % (94 % recurrent and 96 % for primary glioblastoma) and a specificity of 69.5 % (57 % and 75 %, respectively). The positive predictive value was 86 % (84 % for recurrent and 87 % for primary glioblastoma), and the negative predictive value was 88 % (80 % and 92 %, respectively).

Conclusion IoMRI is effective for detecting remaining tumorous tissue after glioma resection. However, scars and leakage of contrast agent can be misleading and limit specificity.

Key points
• Intraoperative MRI (ioMRI) presents with a high sensitivity for residual contrast-enhancing tumorous tissue during glioma resection.
• Contrast leakage due to bleeding and scars with reactive contrast enhancement can cause possible misleading artifacts in ioMRI, leading to a limited specificity of ioMRI.
• Bleeding control in glioma resection is crucial for successful usage of ioMRO for glioma resection.

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Introduction
Evolution of imaging technologies and procedural techniques like operation microscope, intraoperative ultrasound, neuronavigation, fluorescence-guided resection, and intraoperative MRI continuously improved the surgical resection of high-grade gliomas. Improved resection grade of contrast-enhancing tissue [1 – 7] prolongs the patient survival rate and preserves eloquent brain function and life quality [1 – 9]. Studies dealing with the accuracy of fluorescence-guided resection detected a sensitivity of about 90 % and a negative predictive value of 76 – 91 % [1, 10, 11]. However, a negative predictive value of 0.26 in the study of Roberts et al. also showed that there are deficits in fluorescence-guided resection with respect to the detection of residual tumorous tissue in normal appearing resection borders [11] so that there is a need for additional intraoperative resection control. Intraoperative CT and MRI have been integrated since the last decade into the operating room [12]. Starting with low-field systems between 0.02 – 0.5 Tesla [13] and open MRI scanners [14], high-field systems were introduced starting in 2000 [15]. In a controlled randomized study with a low-field system, Senft et al. [16] detected 96 % gross tumor resection in the patient group who were investigated by ioMRI, versus 68 % gross total resection in the control group. Combining the concept of fluorescence-guided tissue resection and ioMRI, Coburger et al. found a higher extent of resection with fluorescence-guided resection and ioMRI (100 %) in comparison to ioMRI alone (82 %) [2]. Gessler et al. found that ioMRI and fluorescence guidance were inconsistent in 47 % of patients being resected under surveillance with ioMRI in the first line and fluorescence-guided resection after ALA administration in the second line [17]. A direct comparison between the sensitivity and specificity of linear intraoperative ultrasound and intraoperative MRI was provided by Coburger et al. [18], who found a sensitivity of 76 % for linear intraoperative ultrasound and 55 % for intraoperative MRI. The specificity was 58 % for linear ultrasound and 74 % for intraoperative MRI [18]. Linag and Shoulder stated in their review that ioMRI is a useful tool in conjunction with other techniques like neuronavigation with fMRI and DTI-based planning and fluorescence-guided resection [19], but others continue to criticize the still insufficient number of controlled prospective studies and regard fluorescence-guided resection of high-grade gliomas as equal according to the extent of tumor resection [12]. A recent randomized controlled study of these authors including a rather
small sample size of 14 showed no benefit of ultra-low-field ioMRI compared to standard resection therapy [20].

The aim of this study was to define the rate of true positive detection of residual tumor by T1 contrast enhancement in intraoperative MRI on the basis of sensitivity/specificity assessment and histological specimens received by repeated post-ioMRI resection of suspected tissue and to describe the imaging appearance of false-positive MRI lesions to help assess the validity of this new method in glioma resection control.

**Materials and Methods**

**Patients**

All 68 of 220 patients with a grade IV glioma diagnosed by MRI and receiving an ioMRI and 5ALA guide resection of primary and recurrent glioblastoma from July 2011 to February were prospectively collected and included in this investigation (mean age: 59 years, 26 female, 42 male patients) in a consecutive manner. Data were prospectively and retrospectively assessed for scientific investigation. Eligibility criteria for patient selection were defined as follows according to the STARD criteria. Inclusion criteria were: patients with newly diagnosed or recurrent glioblastoma between 18 and 75 years, a preoperative MRI scan with a contrast-enhancing tumor and additional intraoperative fluorescence-guided resection and written informed consent to the application of 5ALA and intraoperative MRI. Written informed consent was obtained prior to the operation procedure and the scientific evaluation of data. The exclusion criteria were: radiation therapy 6 months prior to the operation procedure and the scientific evaluation of data. The exclusion criteria were: radiation therapy 6 months before surgery or resurgery, security concerns or contraindication for ioMRI or preexisting neurological disease or deterioration.

**Technique**

For intraoperative MRI we used a 1.5 Tesla MRI scanner (Philips Achieva 1.5T, Philips Best, The Netherlands) which is integrated into the neurosurgical operating room but is separated by an automatic door when not in use so that it is accessible for outpatient procedures.

The bottom part of the coil is placed under the head prior to operation. After complete sterile draping, the upper part of the coil is positioned on top of the patient and connected to the lower part and to the scanner (Heidberg Coil system, NORAS, Höchberg, Germany). After positioning of the patient in the scanner and acquisition of a scout, the following scans were performed: FLAIR tra (TR 6000 ms, TI 2000 ms, TE 120 ms, slice thickness 6 mm), T1 SE sag (TR 510 ms, TE 10 ms, slice thickness 5 mm) and T1–3 D FFE (TR 10.1 ms, TE 4.6 ms, slice thickness 1 mm) before and after administration of Gd-DPTA with a dosage of 0.2 mg/kg b.w.HU. Tissue was regarded as suspicious for tumorous rest if there was a defined area of contrast enhancement close to the resection margin or area of contrast enhancement in areas distant from the resection.

The reports, documentation of the detection of residual tumor and the documented PACS information were used as the radiological definition of residual tumor. It was correlated with the final neuropathological report that was regarded as the gold standard. All false-positive MRI cases were reevaluated, and the histopathological diagnoses were collected and described in the results section.

Data were investigated for sensitivity, specificity, positive and negative predictive value for all patients, primary and recurrent glioblastomas. Statistical workup of patient characteristics, imaging and histopathological results were evaluated using the PSPP software package (www.gnu.org/software/pspp) (Fig. 1).
Results

68 patients with grade IV glioma were included in this investigation, as they received intraoperative MRI and immediate postoperative MRI and data were completed for further evaluation (▶Table 1). 45 patients presented with primary glioblastoma, and 23 patients presented with recurrent glioblastoma. Patient characteristics are summarized in ▶Table 1. 43 of these 45 patients with residual tumor tissue being detected in the specimens of the repeated resection were counted with a true-positive ioMRI evaluation. In 16 cases ioMRI revealed truly negative results without enhancing residual tumor and enhancing tissue in postoperative follow-up MRI, 4 in the recurrent glioblastoma group and 12 in the primary glioblastoma group. A second resection was not performed in these cases. Postoperative control MRI confirmed complete removal of contrast-enhancing tissue in the histopathological workup, so that they were regarded as false-positive results of ioMRI. In two (1 for each group) patients, residual tumorous tissue was found in spite of negative ioMRI as defined by the radiologist, after repeated resection initiated by the neurosurgeon due to suspicious intraoperative aspects of resection margins that were not concordant with the ioMRI appearance. In the false-positive cases, MRI was reevaluated for the appearance of contrast-enhancing tissue. In 4 cases the contrast enhancement showed a rather weak appearance, and in 2 cases a signal increase on the T1-weighted native scan was detected. In one case T2-weighted suspected residual tumorous tissue was diagnosed in addition to residual contrast enhancement, but no residual tumorous tissue was found.

The sensitivity was 95 %, the specificity was 69.5 %, the positive predictive value was 86 % and the negative predictive value was 88 % for the whole group. For the recurrent glioblastoma group the values were 94 %, 57 % and 84 % and 80 %, respectively. For the primary glioblastoma group the values were 96 % and 75 % for sensitivity and specificity and 87 % and 92 % for the positive and negative predictive value, respectively (▶Table 2, ▶Fig. 2, 3).

Discussion

Optimization of the resection rate of diseased tissue in glioblastoma is crucial for patient survival [21]. Patients with almost com-
The sensitivity for all tumors was calculated as 95 % and the specificity as 69.5 %. The negative predictive value was 88 %, and the positive predictive value was 86 %. For recurrent glioblastoma the sensitivity was 94 %, the specificity was 57 %, the negative predictive value was 88 % and the positive predictive value was 84 %. For primary glioblastoma the sensitivity was 96 %, the specificity was 75 %, the positive predictive value was 87 % and the negative predictive value was 92 %. Showing equal sensitivity ioMRI appears more specific in primary than in recurrent glioblastoma.

<table>
<thead>
<tr>
<th>no rest (MRI) n</th>
<th>rest (MRI) n</th>
<th>sensitivity %</th>
<th>specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
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Table 2 Tabellarische Darstellung der ioMRI-Diagnosen nach der ersten Resektion und der histopathologischen Befunde der Gewebsproben. Die Sensitivität konnte mit 95 % bestimmt werden und die Spezifität mit 86 %. Für Rezidivglioblastome beträgt die Sensitivität 94 %, die Spezifität 57 %, der negative Vorhersagewert 88 % und der positive Vorhersagewert 84 %. Für primäre Glioblastome betrug die Sensitivität 96 %, die Spezifität 75 %, der positive Vorhersagewert 87 % und der negative Vorhersagewert 92 %. Bei gleicher Sensitivität erscheint die ioMRI bei primären Glioblastoma spezifischer für Resttumorgewebe.

Complete resection of diseased tissue showed a better overall survival rate [8, 22]. As Albert et al. showed already in 1994, the extent of tumor resection influences the survival rate of glioblastoma resection [23]. However, the rate of complete resection at that time point was only 20 % using neuronavigation and white light microscope technology. A crucial improvement in glioma resection technique was achieved with fluorescence-guided glioma resection [8]. Since this decade, intraoperative MRI has become an additional technical procedure for intraoperative resection control in glioma surgery [2, 15, 16]. Eyüpoglu et al. used high-field (1.5 T) ioMRI and ALA-guided resection and could show that the extent of resection increases from 84 % to 99 % with the additional usage of ioMRI. The combination with 5-ALA-guided resection was also advantageous in the vicinity of eloquent brain regions, facilitating more radical resection compared to 5-ALA alone [5].

Showing 97 % resectability of contrast-enhancing tissue after intraoperative MRI [24], high-field ioMRI in our study showed a sensitivity of 95 % but a rather low specificity of 69.5 %, which was related to scars, bleeding, artifacts and a personal factor of a higher affinity to decide for a second resection if contrast enhancement was seen, to avoid misinterpretations leading to remaining contrast-enhancing tumor tissue. After dividing glioblastomas into subgroups of recurrent and primary glioblastomas, the specificity was markedly reduced to 57 % in the recurrence glioblastoma group, showing the role of reactive changes in misinterpreting ioMRI.

The sensitivity in our evaluation exceeds the sensitivity of 55 % in the study of Coburger et al. [18], while their specificity of 74 % is comparable with our findings. They stated that the accuracy of ioMRI might be underestimated due to this limitation, and that ioMRI shows an underdetection of solid tumor masses. This goes along with the findings of Eyüpoglu and Gessler [5, 17], who both revealed inconsistent findings between ioMRI and fluorescence guidance. Gessler described that ioMRI was the only indicator for residual tumor in only 26.3 % of cases and fluorescence guidance in 21.1 % of cases. Gessler et al. agree with Eyüpoglu that 5-ALA may by misleading if tumorous tissue is hidden by healthy tissue, spatula or blood [25], and complementary use of ioMRI may help to avoid these pitfalls [5]. In this study the sensitivity was 75 % and the specificity was 100 % for ioMRI, while the sensitivity was 70 % and the specificity was 100 % for fluorescence guidance. As in our study, Knauth et al. found cases with inconclusive MRI findings (9.7 %). As stated by the authors, uncertain MRI findings were mainly surgery-induced (electrocoagulation, tissue ablation) and were not residual tumor.

In summary, complementary use of fluorescence guidance, intraoperative ultrasound and/or ioMRI may optimize resection rates and can be regarded as a contemporary operative setting in glioma surgery, although it is not proven so far that ioMRI is crucial to increase resection rates of tumorous tissue [5, 17]. So far, the gold standard to define the extent of resection and to detect tumor borders in MRI is GD-DPTA enhancement [26]. However, leakage of contrast agent and enhancement of reactive tissue might be misleading in T1 imaging with contrast enhancement [21]. More advanced techniques like T1-weighted dynamic contrast-enhanced MRI or 3D-spectroscopic imaging were recently applied to identify residual tumor in glioblastoma surgery under assistance of intraoperative MRI [27].

In accordance with Coburger et al. and Akbari et al., [1, 28, 29] we believe that a multimodality approach including T2, FLAIR, DTI and spectroscopic imaging as well as dynamic T1-weighted imaging will further improve the sensitivity and specificity of ioMRI and might lead to an improved detection rate and that advanced imaging like dynamic T1-weighted imaging might increase the accura-
Dynamic contrast enhancement may provide better differentiation between contrast-enhancing tissue and leakage and DTI may reveal additional information about tumor margins [28]. Moreover, operation techniques can be adapted to ioMRI to avoid or reduce leakage of contrast agent [30].

Conclusion

Intraoperative MRI can sensitively detect residual tumors and can provide optimized control in the resection of high-grade gliomas. Intraoperative MRI can accurately diagnose tumorous contrast-enhancing residual tissue using contrast-enhanced T1-weighted imaging after the administration of GD-DPTA. However, false-positive contrast enhancement may occur due to tissue scars and contrast agent leakage in the tumor margin, which may lead to spotted or linear enhancement at the tumor border in T1-weighted imaging after contrast administration. To avoid false-positive
results, we recommend exact control of bleeding of the resection margins and application of contrast agent immediately before starting T1-weighted imaging and complementary use of ioMRI and fluorescence guidance.

GLOSSARY

<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>EOR</td>
<td>extent of resection</td>
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<td>GTR</td>
<td>gross total resection</td>
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<td>ioMRI</td>
<td>intraoperative MRI</td>
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<td>FFE</td>
<td>fast field echo</td>
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<td>FLAIR</td>
<td>fluid attenuated inversion recovery</td>
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<td>HE-staining</td>
<td>hematoxylin eosin staining</td>
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<td>IDH-1</td>
<td>isocitrate dehydrogenase 1</td>
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<tr>
<td>CD31</td>
<td>endothelial cell adhesion molecule</td>
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<td>EMA</td>
<td>epithelial membrane antigen</td>
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<tr>
<td>GFAP</td>
<td>glial filament acid protein</td>
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<td>aminolaevulinic acid</td>
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Conflict of Interest

The authors declare that they have no conflict of interest.

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