Using intraoperative dynamic contrast-enhanced T1-weighted MRI to identify residual tumor in glioblastoma surgery

Technical note

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Object. The goal of surgery in high-grade gliomas is to maximize the resection of contrast-enhancing tumor without causing additional neurological deficits. Intraoperative MRI improves surgical results. However, when using contrast material intraoperatively, it may be difficult to differentiate between surgically induced enhancement and residual tumor. The purpose of this study was to assess the usefulness of intraoperative dynamic contrast-enhanced T1-weighted MRI to guide this differential diagnosis and test it against tissue histopathology.

Methods. Preoperative and intraoperative dynamic contrast-enhanced MRI was performed in 21 patients with histopathologically confirmed WHO Grade IV gliomas using intraoperative 3-T MRI. Standardized regions of interest (ROIs) were placed manually at 2 separate contrast-enhancing areas at the resection border for each patient. Time-intensity curves (TICs) were generated for each ROI. All ROIs were biopsied and the TIC types were compared with histopathological results. Pharmacokinetic modeling was performed in the last 10 patients to confirm nonparametric TIC analysis findings.

Results. Of the 42 manually selected ROIs in 21 patients, 25 (59.5%) contained solid tumor tissue and 17 (40.5%) retained the brain parenchymal architecture but contained infiltrating tumor cells. Time-intensity curves generated from residual contrast-enhancing tumor and their preoperative counterparts were comparable and showed a quick and persistently increasing slope (“climbing type”). All 17 TICs obtained from regions that did not contain solid tumor tissue were undulating and low in amplitude, compared with those obtained from residual tumors (“low-amplitude type”). Pharmacokinetic findings using the transfer constant, extravascular extracellular volume fraction, rate constant, and initial area under the curve parameters were significantly different for the tumor mass, nontumoral regions, and surgically induced contrast-enhancing areas.

Conclusions. Intraoperative dynamic contrast-enhanced MRI provides quick, reproducible, high-quality, and simply interpreted dynamic MR images in the intraoperative setting and can aid in differentiating surgically induced enhancement from residual tumor.

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Key Words • intraoperative magnetic resonance imaging • high-grade glioma • dynamic contrast imaging • glioblastoma • oncology

High-grade gliomas (HGGs) are widely infiltrative tumors. Although an oncological resection is not feasible, there is compelling evidence that patients benefit from resection of the tumor.19,22 The surgical target is the main tumor bulk, which is defined as the contrast-enhancing part of the tumor on preoperative MRI. Surgical treatment in HGGs is based on maximal safe resection of this mass2,18,31. Several new technologies have been devised to maximize the resection and intraoperative MRI is one of these new technologies. Intraoperative MRI has been shown by many studies to increase the extent of resection in glioma surgery.1,4,11,12,21,22,25,26,32,34,35 Intraoperative determination of the extent of resection, however, requires use of intravenous contrast administration, which has some technical limitations. Fundamental problems associated with the use of contrast material are the enhancement at the resection margin and contrast leakage into the...
Intraoperative dynamic contrast-enhanced MRI

resection cavity. Both problems can complicate the differential diagnosis between residual tumor and surgically induced changes. To overcome these problems we have adapted T1-weighted, dynamic contrast-enhanced MRI to intraoperative MRI for HGG resection. Our hypothesis was that intraoperative dynamic contrast-enhanced T1-weighted MRI can differentiate surgically induced enhancement from residual HGG tissue.

This is the first clinical study to show that dynamic contrast-enhancement analysis can be used to evaluate the extent of resection in HGG surgery. Intraoperative dynamic contrast-enhanced MRI is a fast and technically simple application that can be easily adapted to the routine intraoperative MRI paradigm for HGG.

Methods

Patient Selection

Patients who underwent resection for a supratentorial, hemispheric, unifocal HGG using intraoperative MRI were included in the study. Patients with tumors centered in the occipital and parietal lobes were not included due to technical limitations in patient positioning with their current hardware. Baseline, preoperative, dynamic contrast-enhanced MRI and intraoperative dynamic contrast-enhanced MRI were acquired in all patients, but only patients with contrast-enhancing regions at the resection border were included in the study (n = 21). Eighteen patients (86%) were male and 3 (14%) were female. The median age was 46 years (range 30–70 years). The tumor was localized in the frontal lobe in 10 patients (48%), in the temporal lobe in 8 (38%), and in the insula in 3 (14%). The tumor was localized on the right in 15 patients (71%) and on the left in 6 (29%). Pediatric patients, patients with multifocal tumors, and previously treated patients or those with tumor recurrence were not included in the cohort. The study was approved by the local ethics committee and informed consent was obtained from all patients.

MRI Procedure

All patients underwent imaging both preoperatively and intraoperatively with dynamic contrast-enhancing MRI using the same setup. Intraoperative MRI was performed in our intraoperative MRI facility with a dual-configuration 3-T magnet (Magnetom, Trio Tim; Siemens). The intraoperative MRI facility setup and workflow have been previously described.

Preoperative and intraoperative MRI examination protocols were identical. Axial, sagittal, and coronal T2-weighted turbo spin echo (TSE) sequences (TR 5800 msec/TE 103 msec) and an axial T1-weighted TSE sequence (TR 2700 msec/TE 102 msec) were standard in all examinations. For dynamic contrast-enhanced MRI, fast dynamic series using a TSE sequence were used in the first 11 patients. This was later converted to the syngo TWIST technique (Time-resolved angiography With Stochastic Trajectories; Siemens) in the last 10 patients because simple dynamic series with TSE were not sufficient for pharmacodynamic modeling. The syngo TWIST technique is based on special k-space sampling. In this setting, k-space is divided into 2 regions. The centrally located region of k-space provides information regarding image contrast, whereas the peripherally located aspect of k-space contributes principally to high spatial resolution. The main factor contributing to the acceleration of the sequence acquisition in this particular imaging approach is the fact that k-space lines in the center are more frequently sampled than are the k-space lines in the periphery during the passage of the contrast medium bolus through the covered 3D volume.

For simple dynamic series, 8 TSE T1-weighted dynamic series were initiated: just after acquiring the first series, a bolus of gadobenate dimeglumine (MultiHance, Bracco Diagnostics; 0.1 mmol/kg) followed by 35 ml of normal saline were injected intravenously at a rate of 4 ml/sec using a power injector (Spectris, Medrad) through an antecubital vein. Each dynamic series consisted of 10 slices (4-mm thickness, 0.4-mm interslice gap, voxel size 1 × 0.7 × 4 mm³, TR 476 msec, TE 13 msec, flip angle 150°, 1 acquisition, FOV 230 × 172.5 mm, 28 seconds per series), covering the whole tumor and/or resection cavity with neighboring tissues in an axial-oblique plane. Total acquisition time was 3 minutes 45 seconds for dynamic imaging.

The syngo TWIST technique consisted of 20 dynamic series covering the whole brain with a 1.71 × 1.2 × 5–mm spatial resolution and 3.1-second temporal resolution. After acquisition of the fifth series, the same amount of contrast material (also followed by saline) was injected using the same injection parameters and conditions as noted above. Parameters for the 3D gradient echo T1-weighted series were as follows: TR 4.64 msec, TE 1.83 msec, flip angle 12°, 20 axial slices in a slab, slice thickness 5 mm, FOV 230 mm, and matrix 134 × 192. The total acquisition time was 2 minutes 40 seconds for syngo TWIST imaging.

Nonparametric Analysis

For all patients (n = 21), immediately after acquisition of the dynamic images, 2 regions of interest (ROIs) were placed manually at contrast-enhancing areas at the resection border. Standardized ROIs (0.05 cm²) were used. A time-intensity curve (TIC) was calculated using the Mean Curve software (Siemens Healthcare). The newly calculated TICs were compared with those of corresponding ROIs from preoperative dynamic contrast-enhanced MR images of the same patient. Representative tissue biopsies were collected from the ROIs after completion of intraoperative imaging by the senior surgeon (M.N.P). The samples were clearly marked and examined by a single dedicated neuropathologist (A.S.), who was blinded to intraoperative MR spectroscopy findings.

Pharmacokinetic Modeling

In the last 10 patients quantitative measurements were made to confirm nonparametric analysis (TIC) findings. These quantitative measurements were the transfer constant (Ktrans); extravascular, extracellular volume fraction (Vₑ); rate constant (Kₑ); and initial area under the curve (IAUC). The data were processed immediately after acquisition using the Tissue4D software (Siemens Healthcare).
Additional ROIs were placed in areas of contrast enhancement and mirroring areas in the contralateral hemisphere. In contrast to the use of standardized ROIs in nonparametric analysis, ROIs for quantitative measurement incorporated the whole cross-sectional area of contrast-enhancing regions. Regions of interest for quantitative measurement were also selected manually. The number of ROIs was not predetermined. The dynamic data from each pixel was analyzed individually using the pharmacokinetic modeling described by Tofts et al.\textsuperscript{38} For each ROI the quantitative parameters $K_{\text{trans}}, K_{\text{ep}}, V_e,$ and $i\text{AUC}$ were calculated. The difference between tumoral and nontumoral areas, and surgically induced contrast-enhancing areas, were evaluated. Statistical analysis was performed using 1-way ANOVA. The quantitative data were also used to generate pixel-based maps for user-friendly visualization.

**Results**

Twenty-one adult patients underwent intraoperative dynamic contrast-enhanced MRI-guided resection for HGGs. The final pathological diagnosis was confirmed as glioblastoma (WHO Grade IV) in all patients. After resection of the main tumor bulk, linear or nodular contrast-enhancing areas were noted at the resection border in all patients ($n = 21$) at intraoperative dynamic contrast-enhancing MRI. Two standardized ROIs were studied intraoperatively for each patient to include these contrast-enhancing areas at the resection border (42 total ROIs) and all of these 42 areas were intraoperatively biopsied. Twenty-five biopsies (59.5%) contained solid tumor tissue and 17 (40.5%) were reported as normal brain parenchyma containing infiltrating tumor cells by a single neuropathologist (A.S.).

**Intraoperative Dynamic Contrast-Enhanced MRI Findings**

Contrast-enhancing areas on MRI exhibited 2 different patterns of TICs. A quickly climbing slope ("climbing type" TIC) was observed in 25 (59.5%) of the 42 ROIs. These were areas of nodular enhancement. In these 25 ROIs, the measured intensity increased continuously throughout the 3-minute 45-second intraoperative dynamic contrast-enhanced MRI period (Fig. 1). The corresponding biopsies from these areas yielded solid tumor tissue in all 25 (100%). A low-amplitude undulating curve ("low-amplitude type" TIC), which increased very slowly over time, was observed in 17 (40.5%) of the 42 ROIs. All of these areas were mild, linear enhancements at the cavity border. All of the biopsies (17 of 17) taken from these areas were histopathologically diagnosed as brain parenchyma with infiltrating tumor cells but not solid tumor tissue. When the 2 TIC types were compared, the "climbing type" reached higher intensities at the end of the measurement period of 3 minutes 45 seconds (Fig. 1). Hemorrhage or hemorrhagic fluid collections in the cavity were excluded using corresponding T2-weighted images, and when ROIs were placed in these collections, no characteristic curves were observed.

Pharmacokinetic modeling was performed in 10 patients and $K_{\text{trans}}, K_{\text{ep}}, V_e,$ and $i\text{AUC}$ values were calculated from preoperative and intraoperative measurements. Mean values are indicated in Fig. 2. The $K_{\text{trans}}, K_{\text{ep}}, V_e,$ and $i\text{AUC}$ measurements from tumor, normal brain, and nontumoral surgically induced enhancement were significantly different from each other ($p = 0.023$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively; ANOVA; Fig. 2).

**Discussion**

The goal of surgery in HGG treatment is to have a positive impact on patient outcome by performing an extensive resection of the main tumor bulk without creating novel neurological deficits.\textsuperscript{1,2,14} Intraoperative MRI is one of the tools used to increase the extent of resection and its efficiency for HGG has been demonstrated by independent studies.\textsuperscript{16,17,33}

The extent of resection in HGG is routinely judged by early postoperative contrast-enhanced MRI studies. The use of intraoperative MRI makes this evaluation possible while still in the operating room. A limitation of this technology is the surgically induced enhancement and the leakage of contrast material into the resection cavity.\textsuperscript{5,14,23,31,32,41} Nonspecific contrast enhancement is a very common phenomenon. Knauth et al.\textsuperscript{42} found linear enhancement at the resection margins or enhancement in the surrounding parenchyma in 90.2% of their patients. In our series, we observed surgically induced enhancement along the resection border in 13 (61.9%) of 21 patients. Surgically induced disruption of the blood-brain barrier and opening of blood vessels have been proposed as possible explanations for this problem, which worsens over time and with repeated examinations during surgery.\textsuperscript{14,31}

The exact mechanism underlying this problem is not known, but blood-brain barrier damage due to surgically induced damage (to the microcirculation at the tumor bed)\textsuperscript{31} and extravasation of the contrast-laden blood\textsuperscript{12} have been cited as possibilities. Different methods have been devised to overcome this problem, including alternative contrast agents,\textsuperscript{13,35} perfusion imaging,\textsuperscript{36,40} and irrigation suction devices to evacuate leaking contrast material.\textsuperscript{13}

To guide the differential diagnosis between residual tumor and nonspecific enhancement we used intraoperative dynamic contrast-enhanced MRI. Dynamic contrast-enhancement analysis is an established method for imaging gliomas that has been tested in both the clinical setting and animal models.\textsuperscript{3,8,19,29} The MR image is basically a snapshot representation of a structure at a given time, whereas dynamic contrast-enhanced MRI is a time-lapse evaluation through a series of temporally sequential images. To increase the information obtained from contrast-enhanced studies, a wide range of dynamic contrast-enhanced T1-weighted imaging sequences, protocols, image processing methods, and interpretation criteria have been developed and evaluated over the last 20 years.\textsuperscript{9,10,20,30} Dynamic contrast-enhanced MRI provides a measurement of tissue permeability to the paramagnetic contrast agent.\textsuperscript{3} A relatively low dose of Gd is administered (usually a single dose of 0.1 mmol/kg) and repeated acquisitions of a T1-weighted sequence covering the ROI are made at longer intervals before, during, and long after the injection of the paramagnetic contrast medium (typi-
Intraoperative dynamic contrast-enhanced MRI

cally every 15–30 seconds, for as long as 300 seconds). Such long acquisition durations allow the contrast agent to leak out into the extravascular space.

To analyze intraoperative dynamic contrast-enhanced MRI data, we used 2 techniques: nonparametric and parametric analyses. The nonparametric method is based on a standardized ROI–based analysis and was chosen for its simplicity and practicality in the intraoperative setting. Graphical representation of change in signal intensity in the ROI over a given time interval produces a so-called TIC. Every standard MRI machine can simply produce such TICs in minutes without the need for additional software. Alternatively, pharmacokinetic modeling was used to confirm the findings of the nonparametric analysis. Four parameters were used for this calculation. The $K_{\text{trans}}$ reflects the rate at which the contrast material passes from the intravascular compartment into the tumor interstitial space. The $V_e$ measures the fractional volume of extracellular contrast distribution. The $K_{\text{ep}}$ is a measure of back diffusion of contrast to the vascular compartment and is a function of the other 2 variables ($K_{\text{ep}} = K_{\text{trans}} / V_e$). The iAUC was also measured to provide a numeric representation of the curve. There was a consistent significant difference in $K_{\text{trans}}$, $V_e$, and iAUC measurements from the tumor remnant, normal tissue, and surgically induced contrast-enhancing areas. The curve characteristics, as quantified by iAUC, correlated well with the other pharmacokinetic parameters (correlation between $V_e$ and iAUC is demonstrated in Fig. 2D). The use of pharmacokinetic modeling made pixel-based spatial mapping possible, which can be used for intraoperative identification of tumor remnants (Fig. 3).

We chose to base our dynamic contrast analysis on the time-proven T1-weighted sequence, as it is practical

Fig. 1. Tumor remnants and surgically induced contrast enhancements have distinct TICs on intraoperative dynamic contrast-enhanced axial MR images. Four individual cases of glioblastoma surgically treated using intraoperative MRI are presented (A, F, K, and P). During the operation each case exhibited contrast enhancement at the resection border after initial resection (B, G, L, and Q) and T2-weighted images were not conclusive of tumor remnant (C, H, M, and R). Time-intensity curves from the tumor on preoperative dynamic contrast-enhanced MRI yielded rapidly increasing slopes that reached a high plateau (the “climbing type,” D, I, N, and S). On intraoperative MRI, 2 ROIs were manually biopsied. On intraoperative dynamic contrast-enhanced MRI, tumor remnants had “climbing type” TICs comparable to preoperative imaging (marked as “t” on E, J, O, and T). In contrast, surgically induced contrast-enhancing regions exhibited different “low-amplitude undulating” TICs (marked as “s” on E, J, O, and T).
in several respects: 1) the technique is familiar to every
neurosurgeon, eliminating a learning curve; 2) T1-weight-
ed images are comparable to corresponding preoperative
and postoperative images; and 3) T1-based intraoperative
dynamic contrast-enhanced MRI has high anatomical
resolution. Other researchers have attempted to use per-
fusion imaging (dynamic susceptibility contrast MRI) in-
traoperatively to evaluate residual glioblastoma tissue.39,40
Intraoperative dynamic contrast-enhanced MRI can yield
an up to 6-fold higher spatial resolution (1 × 0.7 × 4 mm³
for intraoperative dynamic contrast-enhanced MRI, vs 1.8
× 1.8 × 5 mm³ for dynamic susceptibility contrast MRI in
3-T scanners), which is important when analyzing small
areas at the resection border. Additionally, several factors,
including susceptibility artifacts and blood-brain bar-
rier leakage, can influence relative cerebral blood volume
maps created with dynamic susceptibility contrast MRI,
which may require validation and correction in each
case.28 A susceptibility artifact is commonly experienced
as a consequence of blood in the resection bed, air-fluid
tissue interface, or metallic head-fixation pins, and cre-
ates image distortion and registration difficulties. Intra-
operative dynamic contrast-enhanced MRI is less prone
to these artifacts. And lastly, the intraoperative dynamic
contrast-enhanced MRI is a basic sequence that can be
used even in very-low field intraoperative scanners.

Using intraoperative dynamic contrast-enhanced
MRI, we observed 2 distinct TICs at the resection border.
The current study has not addressed the underlying mech-
anism for these curve characteristics, but the nature of the
tissue targeted in the ROI was determined using histopa-
thology. A climbing type of TIC shape is characterized
by a rapid and marked rise in intensity followed by a pla-

tau, and this TIC shape is consistently observed at ROIs
with histologically confirmed solid tumor tissue.24,42
In contrast, the TIC observed at the
(mildly contrast enhancing) resection border that did not
contain solid tumor mass was of a “low-amplitude type.”
This TIC shape was characterized by larger fluctuations
in intensity by time and a slower and less marked rise in
intensity. Contrast accumulation or blood in the resection
cavity can also appear hyperintense on contrast-enhanced
T1-weighted MR images, but the differential diagnosis of
these are straightforward in comparison with noncontrast
T1-weighted and T2-weighted MR images.

This technical report shows that intraoperative dy-
namic contrast-enhanced MRI can be practically applied
to HGG surgery. Further refinements as well as clinical
testing are needed to assess sensitivity and specific-
ity more objectively. In its current state, the technology
is operator dependent and ROI based. An intraoperative
multi-ROI mapping would be desirable to evaluate for the
extent of resection in the walls of a 3D resection cavity.
Nevertheless, the technique, in its current state, can be
a practical and useful addition to routine intraoperative
MRI paradigms, and it can be used with intraoperative
MRI machines of all magnet strengths.

Fig. 2. To support the findings of the nonparametric analysis, pharmacokinetic modeling was also performed for areas of con-
trast enhancement at the tumor border. Measurements from tumor, nontumoral brain, and surgically induced contrast-enhancing
areas were significantly different from each other on measurements of contrast leakage (K trans, A) extravascular volume of con-
trast leakage (V e, B), and curve characteristics (iAUC, D). The same difference was not observed on back diffusion of contrast,
as measured by K ep (C). When the volume of contrast leakage (V e) was plotted against the curve characteristics (iAUC), measure-
ments from tumor, nontumoral brain, and surgically induced contrast-enhancement showed different distribution patterns (E). IN =
 intraoperative normal brain; IR = intraoperative remnant; IS = intraoperative surgically induced contrast enhancement; PN =
preoperative normal brain; PT = preoperative tumor. Error bars represent the standard error of the mean.
Intraoperative dynamic contrast-enhanced MRI provides technically simple, reproducible, high-quality, and simply interpreted dynamic MR images in the intraoperative setting, which can increase the reliability of intraoperative MRI in patients with HGG.

Disclosure

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: Özduman, Yıldız, Dinçer, Pamir. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Özduman, Yıldız, Dinçer, Pamir. 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: Özduman. Statistical analysis: Özduman. Study supervision: Özduman, Dinçer.

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