Surgically Induced Intracranial Contrast Enhancement: Potential Source of Diagnostic Error in Intraoperative MR Imaging

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BACKGROUND AND PURPOSE: Intraoperative MR imaging is being used increasingly during neurosurgical interventions. The aim of this study was to describe and classify different forms of surgically induced intracranial contrast enhancement observed during intraoperative MR examinations.

METHODS: A total of 51 intraoperative MR examinations were performed to assess the extent of brain tumor removal. The intraoperative MR results (T1-weighted images, unenhanced and obtained serially after the IV administration of paramagnetic contrast material) were compared with preoperative and early postoperative MR findings. Animal experiments were conducted to obtain further evidence of the mechanism of surgically induced contrast enhancement.

RESULTS: Four different types of surgically induced contrast enhancement were found: meningeal enhancement, increased enhancement of the choroid plexus, delayed enhancement at the resection margins, and immediate intraparenchymal contrast enhancement. The types of surgically induced contrast enhancement differ regarding their location, configuration, and time course. Their potential to be confused with contrast-enhancing, residual tumor also varies. Three of the four types of surgically induced contrast enhancement were reproducible in an animal model.

CONCLUSION: Surgically induced contrast enhancement is a potential source of error in intraoperative MR imaging. Careful analysis of the location, configuration, and time course of intraoperatively observed intracranial enhancement is critical to avoid confusing surgically induced contrast enhancement with contrast-enhancing, residual tumor.
paramagnetic contrast agent. Because we were examining anesthesized patients, the timing of the imaging was identical in all patients. A double dose of contrast agent was used, because at low-field imaging, it yielded the same lesion-to-white matter contrast as in high-field MR examinations after the administration of a standard dose (0.1 mmol/kg) (unpublished results), i.e., an enhancing tumor showed the same lesion-to-white matter contrast in the intraoperative (low-field) MR examinations as in the pre- and postoperative (high-field) MR examinations. The imaging parameters of the intraoperative MR imaging were 15/532/3 (TE/TR/excitations); section thickness, 6 mm; field of view, 230 x 230 mm; matrix, 192 x 256; and acquisition time, 5 minutes 10 seconds. In the cases of low-grade gliomas, an additional T2-weighted sequence was obtained before the IV administration of the contrast agent. The intraoperative unenhanced and postcontrast T1-weighted images were compared with preoperative and early postoperative T1-weighted images obtained with a high-field scanner (1.5 T) after the IV administration of a single dose (0.1 mmol/kg) of a paramagnetic contrast agent. Early postoperative MR examinations were performed on days 1 to 3 after surgery. The imaging parameters of the T1-weighted images of the high-field examinations were 20/674/2; section thickness, 6 mm; field of view, 230 mm; matrix, 192 x 256; and acquisition time, 3 minutes 14 seconds.

Surgically induced contrast enhancement was said to be present if the intraoperative postcontrast T1-weighted images showed contrast enhancement that had not been observed on MR images before the operation (maximum of 3 days). Surgically induced contrast enhancement was classified regarding its location, configuration, time course, and appearance on the early postoperative MR images.

The study was approved by our institution’s review board, and informed consent was obtained from all patients before the intraoperative examinations were performed.

Animal Experiments

Animal experiments were conducted in accordance with national animal protection laws. The aim of the animal experiments was to reproduce different types of surgically induced contrast enhancement to obtain information about their etiology. For this, 24 male Wistar rats were divided into three groups: in the control group, only a small craniotomy without dural opening was performed; in the second group, the cortex and underlying white matter were ablated by means of a sharp spoon; and in the third group, superficial electrocoagulation of the cortex was performed. The aim was to produce brain lesion types with and without vessel opening. Thirty minutes after inducing the different types of brain lesions (or after simple craniotomy), the animals were examined with a high-field MR scanner (1.5 T). A high-field scanner was used to obtain better signal-to-noise ratios in the small animal brains. The use of different field strengths (low-field in patients and high-field in rats) did not seem problematic because, in the animals, we focused on the configuration and time course of surgically induced contrast enhancement rather than the absolute amount of enhancement. The imaging protocol consisted of T1-weighted sequences obtained before and serially (5, 10, and 15 minutes) after the IV administration of a single dose (0.1 mmol/kg) of a paramagnetic contrast agent. The imaging parameters were 20/500/4; section thickness, 2 mm; field of view, 65 mm; matrix, 256 x 256; and acquisition time, 4 minutes 16 seconds.

Results

Patient Study

Surgically induced enhancement was observed in all patients. Four different types could be distinguished: meningeal enhancement, increased enhancement of the choroid plexus, linear enhancement at the resection margins, and immediate intraparenchymal contrast enhancement.

Meningeal enhancement was seen in all patients as linear enhancement of the leptomeninges or the dura or both. On the intraoperative MR image, enhancement was already visible on the first postcontrast study and remained stable during the observation period (20 minutes). On the early postoperative MR study, it was either the same as observed intraoperatively or had even increased (Fig 1).

Because the normal choroid plexus already shows contrast enhancement, enhancement of the choroid plexus is not surgically induced but surgically increased. It was observed in seven patients (13.7%) and simply consisted of increased enhancement of the choroid plexus on one side compared with the other (Fig 2). In each patient in
whom increased enhancement of the choroid plexus was observed, the ventricle had been opened surgically. In each of four other patients, however, a ventricle also had been opened but no increased enhancement of the choroid plexus was observed. It is likely that additional factors such as manipulation of the choroid plexus or exposure to air are necessary to produce this type of increased enhancement. On the early postoperative MR images, the degree of enhancement was either equal to that observed intraoperatively or had even increased.

In 41 patients (80.4%), a linear enhancement at the resection margins was visible that was more pronounced the more time elapsed from the injection of the paramagnetic contrast agent (Fig 3). In some cases, contrast agent diffused into the saline-filled resection cavity, leading to increasingly higher signal of the fluid (Fig 3). In early postoperative MR examinations, this kind of enhancement either was reduced markedly or absent (Fig 3). Because of its typical location, configuration, and time dependence, confident diagnostic separation from enhancing, residual tumor was the rule, although we did encounter some more difficult cases.

In five patients (9.8%), intraparenchymal enhancement was observed that was already fully developed in the first postcontrast study and showed practically no time dependence in the observed period thereafter (Fig 4). In contrast to the delayed enhancement at the resection margins, the immediate intraparenchymal enhancement had a "solid," sometimes almost nodular, appearance. Thus, immediate intraparenchymal enhancement has the same appearance and time course as enhancing residual tumor.

In all but one patient, in whom immediate intraparenchymal enhancement was observed, bleeding had necessitated repeated electrocoagulations in the region where the immediate intraparenchymal enhancement was later observed. In the other case, sonographic aspiration had been performed at the border between enhancing and nonenhancing tissue. In early postoperative MR examinations, the immediate intraparenchymal enhancement either was reduced markedly or absent (Fig 4).

**Animal Experiments**

Surgically induced enhancement was observed in all animals. Intraparenchymal enhancement was observed even in the control group (ie, in the animals in which only craniotomy had been performed). We take this as an indicator that our craniotomy technique was not as atraumatic to the brain as we intended it to be. In all animals in which electrocoagulation of the cortex had been performed, immediate intraparenchymal enhancement with practically no time dependence was observed (Fig 5), indicating a blood-brain barrier disruption. This type of enhancement, however, was also present in six of the eight animals in which an ablation of the cortex and the underlying white matter had been performed. In two of these animals, delayed, time-dependent enhancement was seen at the resection margin (Fig 6). In contrast, delayed enhancement at the resection margins was not seen in any of the animals of the control group or in any of the animals in which electrocoagulation of the cortex had been performed.

All rats showed some degree of dural enhancement regardless of the type of lesion inflicted on the brain. Thus, three of the four types of surgically induced contrast enhancement described above were reproduced in the animal model.

**Discussion**

The danger that surgically induced contrast enhancement represents for the interpretation of intraoperative MR findings is that it mistakenly can
be diagnosed as enhancing, residual tumor. The first two types of surgically induced contrast enhancement, meningeal enhancement and increased enhancement of the choroid plexus, do not present a problem because there is practically no potential of confusion with residual, enhancing tumor. Meningeal enhancement can be identified in early postoperative MR examinations (10), and our study found that meningeal enhancement is already visible very early (ie, during the course of surgery). The delayed enhancement at the resection margins is somewhat more difficult. Its time dependence, location, configuration, the observed diffusion of contrast agent into the fluid-filled resection cavity, and the fact that this type of enhancement is either reduced or absent on the early postoperative MR examination suggest that leakage of contrast media out of surgically opened vessels at the resection margin is the cause. This assumption also is supported by the results of animal experiments in which this type of enhancement was exclusively produced in animals in which a vessel-opening brain lesion had been created by ablation. Time dependence, location, and configuration are the key features for distinguishing this type of surgically induced contrast enhancement from residual enhancing tumor. Nonetheless, overlap exists and confident diagnostic separation is possible in most
but not all cases. Figure 7 shows a case that is problematic in this respect.

The most confounding surgically induced contrast enhancement is the immediate intraparenchymal enhancement, because residual, enhancing tumor has the same appearance and time course. In such cases, a comparison with the preoperative MR examination is essential. Whenever we observed immediate intraparenchymal enhancement intraoperatively, some additional surgical damage (mostly repeated electrocoagulation) had been done to the brain tissue. It likely represents surgically induced blood-brain barrier disruption, similar to that described after therapeutic brain lesions (16, 17). In these studies, however, the perilesional enhancement persisted during longer periods of time, whereas in our study, the enhancement already was reduced markedly or even absent on the early postoperative MR studies (ie, the blood-brain barrier disruption was transient). This difference may simply reflect the lesser amount of deposited energy and subsequent tissue damage in our patients as
compared with the patients of Kahn et al (16) and Anzai et al (17) who aimed at tissue necroses of considerable volume.

As noted above, immediate intraparenchymal enhancement necessitates careful comparison with preoperative MR examinations to avoid confusion with residual, enhancing tumor. Figure 8 shows one of the first cases in our study in which we did not adhere to that (then not yet established) rule.
Overview over the different types of surgically induced contrast enhancement

<table>
<thead>
<tr>
<th>Type of Surgically Induced Enhancement</th>
<th>Frequency (%)</th>
<th>Localization/Configuration</th>
<th>Time Dependence in Intraoperative MR</th>
<th>Early Postoperative MR</th>
<th>Hypothesized Pathomechanism</th>
<th>Potential for Misdiagnosis of Residual Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningeal</td>
<td>100</td>
<td>Leptomeningeal/dural</td>
<td>None</td>
<td>Equal or increased</td>
<td>Meningeal reaction/irritation</td>
<td>Practically none</td>
</tr>
<tr>
<td>Increased enhancement of choroid plexus</td>
<td>13.7</td>
<td>Choroid plexus</td>
<td>None</td>
<td>Equal or increased</td>
<td>Choroid plexus reaction/irritation</td>
<td>Practically none</td>
</tr>
<tr>
<td>Delayed enhancement at resection margin</td>
<td>81</td>
<td>Resection margin/linear</td>
<td>Marked</td>
<td>Reduced or absent</td>
<td>Leakage of contrast media out of surgically opened vessels</td>
<td>Moderate</td>
</tr>
<tr>
<td>Immediate intraparenchymal enhancement</td>
<td>9.8</td>
<td>Intraparenchymal “Solid”/Nodular</td>
<td>Little–none</td>
<td>Reduced or absent</td>
<td>Transient BBB disruption</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 1 summarizes the frequency, characteristic features, hypothesized pathomechanisms, and the confounding potential of the different forms of surgically induced contrast enhancement to be mistaken for residual, contrast-enhancing tumor. Using these findings, we were able to distinguish confidently surgically induced enhancement from residual, contrast-enhancing tumor in 90.2% of the cases.

Surgically induced contrast enhancement was the main source of trouble in the interpretation of intraoperative contrast-enhanced MR examinations. It is possible that new developments in MR contrast agents, such as iron oxide microparticles that are phagocytosed by high-grade gliomas (18, 19), will render the intraoperative administration of a paramagnetic contrast agent unnecessary and thus abolish the whole problem of surgically induced contrast enhancement.

MR imaging is being used increasingly as an interventional imaging technique, and it is foreseeable that many groups will use MR imaging to assess the radicality of brain tumor surgery. Nevertheless, one has to be aware of the different forms of surgically induced contrast enhancement that exist and that there is danger of confusing at least some of them with residual, enhancing tumor.

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References