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Intraoperative MR Imaging Increases the Extent of Tumor Resection in Patients with High-Grade Gliomas

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BACKGROUND AND PURPOSE: **MR is being used increasingly as an intraoperative imaging technique. The purpose of this study was to test the hypothesis that intraoperative MR imaging increases the extent of tumor resection, thus improving surgical results in patients with high-grade gliomas.**

METHODS: **Thirty-eight patients with intracranial high-grade gliomas underwent 41 operations. Using a neuronavigation system, tumors were resected in all patients to the point at which the neurosurgeon would have terminated the operation because he thought that all enhancing tumor had been removed. Intraoperative MR imaging (0.2 T) was performed, and surgery, if necessary and feasible, was continued. All patients underwent early postoperative MR imaging (1.5 T). By comparing the proportions of patients in whom complete resection of all enhancing tumor was shown by intraoperative and early postoperative MR imaging, respectively, the impact of intraoperative MR imaging on surgery was determined.**

RESULTS: **Intraoperative MR imaging showed residual enhancing tumor in 22 cases (53.7%). In 15 patients (36.6%), no residual tumor was seen, whereas the results of the remaining four intraoperative MR examinations (9.7%) were inconclusive. In 17 of the 22 cases in which residual tumor was seen, surgery was continued. Early postoperative MR imaging showed residual tumor in eight patients (19.5%) and no residual tumor in 31 cases (75.6%); findings were uncertain in two patients (4.9%). The difference in the proportion of ''complete removals'' was statistically highly significant ($P = .0004$).**

CONCLUSION: **Intraoperative MR imaging significantly increases the rate of complete tumor removal. The rate of complete removal of all enhancing tumor parts was only 36.6% when neuronavigation alone was used, which suggests the benefits of intraoperative imaging.**

Even for experienced neurosurgeons, it is very difficult to define the margins of a tumor during surgery. Early postoperative MR imaging has shown residual enhancing tumor much more often than the neurosurgeon expected (1, 2). For this reason, neuronavigation systems were developed that enable neurosurgeons to use the detailed information provided by modern imaging methods intraoperatively. Neuronavigation systems have one fundamental shortcoming: during the operation, the patients' pathologic anatomy changes. Because of CSF loss, brain swelling, and tumor resection, brain shifts occur. This leads to inaccuracies of the navigation system, which tend to be the more pronounced the longer an operation lasts. The consequence of this is that the navigation systems cannot provide reliable information at the end of an operation (ie, when the neurosurgeon wants to evaluate the tumor resection). This is a problem inherent to all kinds of navigational systems. Reliable information regarding the extent of tumor resection can be obtained only by intraoperative imaging that depicts the changes in pathologic anatomy. CT and sonography already have been used during neurosurgical operations (3–5). With the advent of the so-called open scanners, MR, the imaging method with the highest soft-tissue resolution, now can be used intraoperatively to guide the neurosurgeon and to assess the extent of tumor resection. The aim of this study was to investigate whether intraoperative MR imaging, in combination with neuronavigation, improves the results of brain tumor surgery as compared with neuronavigation alone.

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Methods

A total of 38 patients who underwent 41 operations were included in the study. Two patients had grade 3 oligodendrogli-

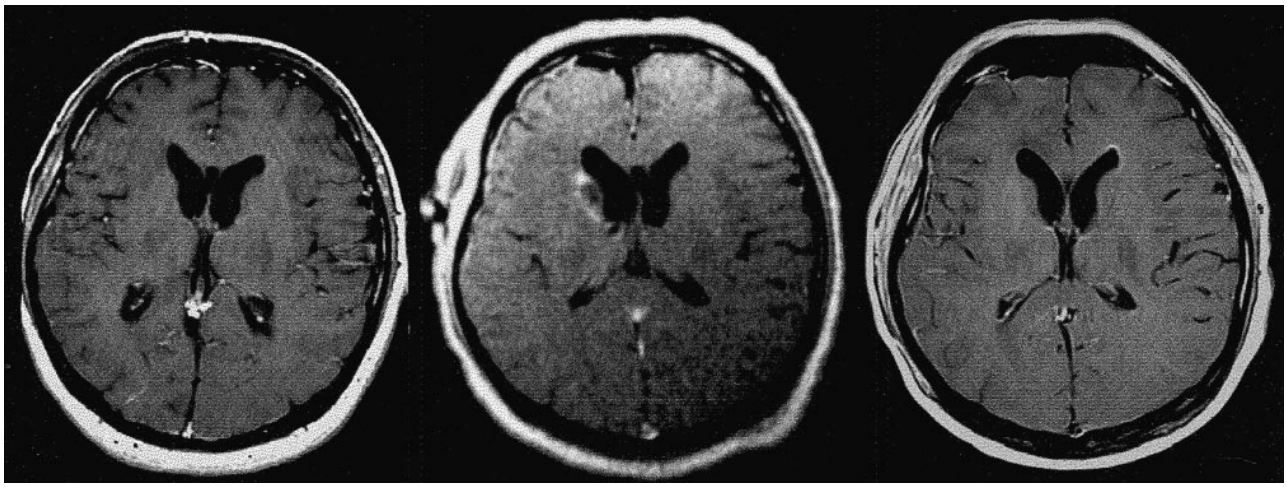

FIG 1. Surgically induced enhancement in the ''uncertain'' case of a 45-year-old man with a glioblastoma multiforme. The tumor is above the level of these T1-weighted images.

Left, Preoperative MR image (674/20/2) does not show enhancement in the head of the right caudate nucleus. Problems with hemostasis necessitated repeated electrocoagulations in this region.

Middle, Intraoperative MR image (532/15/3) shows partially solid-appearing contrast enhancement of the head of the caudate nucleus. A small biopsy was obtained from this region and did not show residual tumor histologically. Surgery was terminated.

Right, Early postoperative MR image (674/20/2) does not show persistent enhancement of the head of the caudate nucleus. The intraoperative enhancement probably represented transient blood-brain barrier disruption.

omas, one patient had a grade 3 astrocytoma, and the rest of the patients were treated surgically for glioblastomas multiforme. In all patients, the neurosurgeon preoperatively considered the removal of all contrast-enhancing tumor tissue to be possible. Using a neuronavigation system (MKM; Zeiss, Leibinger, Germany), the operation was performed in all patients to the point at which the neurosurgeon would have terminated the operation because he thought that all enhancing tumor had been removed. A contrast-enhanced (0.1 mmol of gadolinium diethylenetriamine penta-acetic acid/kg of body weight) T1-weighted 3D gradient-echo dataset obtained with a high-field scanner (1.5 T) was used for the neuronavigation.

A total of 41 intraoperative MR examinations were performed in 38 patients to assess the extent of brain tumor resection. The setup of the intraoperative MR unit was identical to that previously described (6–8). The field strength was 0.2 T. Intraoperative imaging consisted of T1-weighted spin-echo sequences that were obtained before and serially after (5, 10, and 20 minutes) the IV administration of a double dose (0.2 mmol/kg of body weight) of a paramagnetic contrast agent (gadolinium diethylenetriamine penta-acetic acid). A double dose of contrast agent was used, because we have found that 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 of body weight). The imaging parameters were 532/15/3 (TR/TE/excitations); section thickness, 6 mm; field of view, 230 × 230 mm; and matrix size, 192 × 256. For the continuation of the operation, an additional T1-weighted 3D gradient-echo sequence was acquired (3D fast low-angle shot; 39/17/1; flip angle, 40°; section thickness, 1.4 mm; field of view, 250 × 250; and matrix size, 192 × 256). This 3D MR dataset was used to ''update'' the neuronavigation system if surgery was to be continued. The total duration of the intraoperative MR examination was approximately 1 hour, consisting of 25 to 30 minutes of imaging time and approximately 30 to 35 minutes of set-up time.

Each patient underwent an early (day 1 to day 3 after surgery) postoperative MR examination using a high-field scanner (1.5 T). The examination protocol included T1-weighted sequences obtained before and after the IV administration of a single dose (0.1 mmol/kg of body weight) of a paramagnetic contrast agent (gadolinium diethylenetriamine penta-acetic acid). The imaging parameters of the T1-weighted images of the early postoperative MR examinations were 674/20/2; section thickness, 6 mm; field of view, 230 mm; and matrix size, 192 × 256.

The study was approved by the local ethics committee. Informed consent was obtained from all patients before the intraoperative examinations were performed.

Statistical Evaluation

With our approach, the impact of intraoperative MR imaging on the extent of tumor resection in patients with high-grade gliomas can be assessed. Using a neuronavigation system, the surgeon operated to the point at which he would otherwise have terminated surgery. Therefore, the results of the intraoperative MR examination represent the surgical outcome achievable using neuronavigation alone. If necessary and feasible, surgery was continued after the intraoperative MR examination. By comparing the proportions of patients in whom a complete resection of all enhancing tumor was shown by intraoperative and early postoperative MR imaging, respectively, the impact of intraoperative MR imaging on the extent of tumor resection can be determined. Fisher exact tests were used for this purpose.

Results

The intraoperative MR examinations showed residual enhancing tumor in 22 cases (53.7%). In 15 patients (36.6%), no residual tumor was seen, whereas the results of the remaining four intraoperative MR examinations (9.7 %) were inconclusive (ie, it was not possible to confidently diagnose or exclude residual enhancing tumor tissue). Uncertain findings were due to ''surgically induced enhancement;'' ie, contrast enhancement that was caused by the surgical manipulation itself (eg, electrocoagulation, tissue ablation) and not residual tumor (9, 10). In one of the four uncertain cases, a small biopsy was obtained that did not show residual tumor (Fig 1).

Summary of the findings of intraoperative MR and early postoperative MR

	Residual Enhancing Tumor no. of Patients (%)	No Residual Enhancing Tumor no. of Patients (%)	Uncertain Findings no. of Patients (%)
Intraoperative MR	22 (53.7)	15 (36.6)	4 (9.7)
Early postoperative MR	8 (19.5)	31 (75.6)	2 (4.9)

Note.—By comparing the proportions of patients in whom a complete resection of all enhancing tumor was seen at intraoperative MR and early postoperative MR, respectively, the impact of intraoperative MR on the radicality of surgery can be determined. The difference in the proportion of ''complete removals'' was statistically significant (Fisher exact test; $P = .0004$).

In 17 of the 22 cases in which residual enhancing tumor was shown by intraoperative MR imaging, surgery was continued using a neuronavigation device. No further intraoperative MR examination was performed. The tissue removed during the second surgical pass was sent separately for neuropathologic analysis and proved to be tumor tissue in all cases.

Early postoperative MR imaging showed residual enhancing tumor in eight patients (19.5%), and no residual enhancing tumor in 31 patients (75.6%); findings were uncertain in two patients (4.9%). In all eight patients in whom early postoperative MR imaging showed residual enhancing tumor, intraoperative MR imaging also had shown residual tumor. The results are summarized in Table 1. Figures 2 through 4 show examples of residual tumor seen at the intraoperative MR examination.

The proportion of patients in whom complete removal of all enhancing tumor tissue was diagnosed by the intraoperative MR examinations (36.6%) was compared with the rate of complete removals seen on early postoperative MR images (75.6 %). This difference in the proportion of ''complete removals'' was statistically highly significant (Fisher exact test, $P = .0004$) and reflects the impact of the intraoperative MR examinations on the extent of tumor resection in patients with high-grade gliomas (see above).

This analysis compares the proportions of patients in whom the goal of surgery, which is the removal of all enhancing tumor, has been achieved. By doing so, ''uncertain'' cases are counted implicitly as failures. If the analysis is conducted from the opposite perspective (ie, if the proportions of patients in whom residual enhancing tumor was definitely seen are compared), only the definite failures are compared. Intraoperative and postoperative MR imaging definitely showed residual enhancing tumor in 22 of 41 cases and eight of 41 cases, respectively. This difference was also statistically significant (Fisher exact test, $P = .0026$).

Discussion

Intraoperative MR imaging is being used increasingly during neurosurgical interventions (6, 11–14); however, it has not yet been proved that its use leads to better surgical results. Our data show a highly significant increase in the proportion of patients in whom complete removal of all enhancing tumor tissue can be achieved when intraoperative MR examinations are performed. To the best of our knowledge, this is the first proof of the effectiveness of intraoperative MR examinations during neurosurgical operations. The total duration of the intraoperative MR examination of approximately 1 hour is quite long, but with increasing experience in the interpretation of intraoperative MR images, the examination protocol probably can be shortened. Other intraoperative MR groups work with an MR scanner with a different configuration

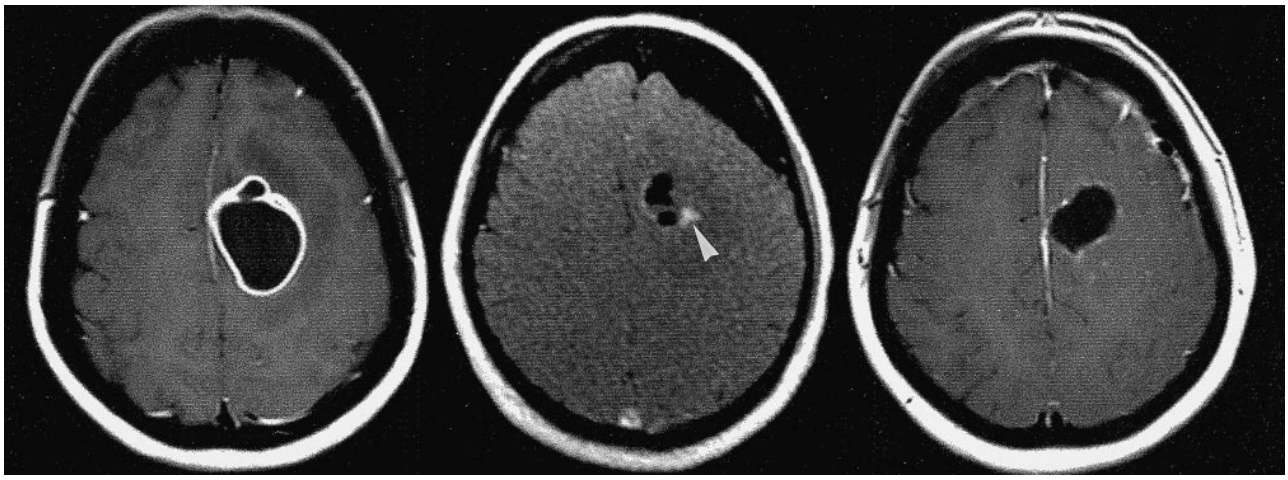

FIG 2. A 41-year-old woman with a recurrent glioblastoma multiforme.
Left, Preoperative T1-weighted image shows a left-hemispheric lesion (674/20/2).
Middle, Intraoperative MR image (532/15/3) shows residual enhancing tumor (*arrowhead*).
Right, Surgery was continued, and the residual tumor was removed, as shown in this early postoperative MR image (674/20/2).

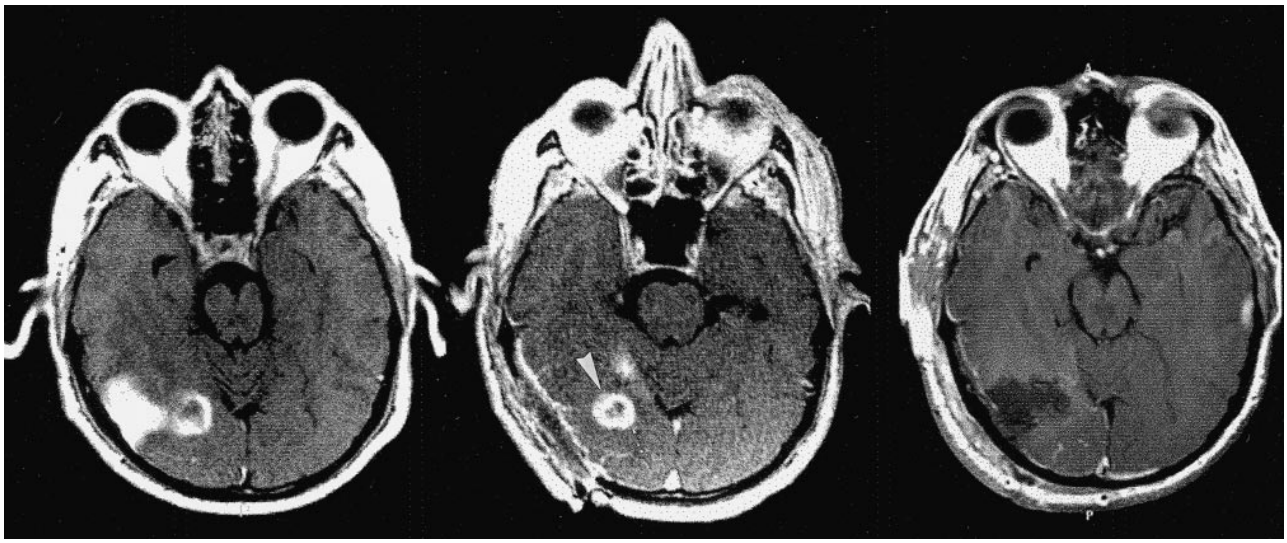

FIG 3. A 55-year-old man with a glioblastoma multiforme. The bulk of the tumor is above the level of these T1-weighted images.
Left, Preoperative MR image shows a right-hemispheric lesion (674/20/2).
Middle, Intraoperative MR image (532/15/3) shows residual tumor at the bottom of the resection cavity (*arrowhead*).
Right, Surgery was continued, and this residual tumor was removed, as shown in this early postoperative MR image (674/20/2).

(10, 14), which allows a much shorter setup time than the one used in our study.

Of course, the complete removal of all enhancing tumor tissue in patients with high-grade gliomas must not be confused with the removal of *all* tumor cells. It has been shown that isolated tumor cell infiltration extended at least as far as the hyperintense area on T2-weighted images (15) (ie, far beyond the contrast-enhancing tumor tissue). Nevertheless, many studies have found a beneficial effect of the removal of all enhancing tumor (1, 16–20) on patient survival and/or progression-free intervals in patients with high-grade gliomas, whereas some other studies were not able to confirm these findings (21, 22).

Because the follow-up period in our own patient group is not yet long enough, we cannot at this time reliably answer the question of whether the improved surgical results in our patients undergoing intraoperative MR imaging translate into longer survival times, longer progression-free intervals, and improved quality of life. The rate of complete removal of all enhancing tumor parts was only 36.6% when neuronavigation alone was used to assist the neurosurgeon. It is disappointing that by using neuronavigation alone, a complete removal of all enhancing tumor parts could be achieved in only approximately one third of the patients, although this is approximately twice as much as in a series of patients who had been operated on in the

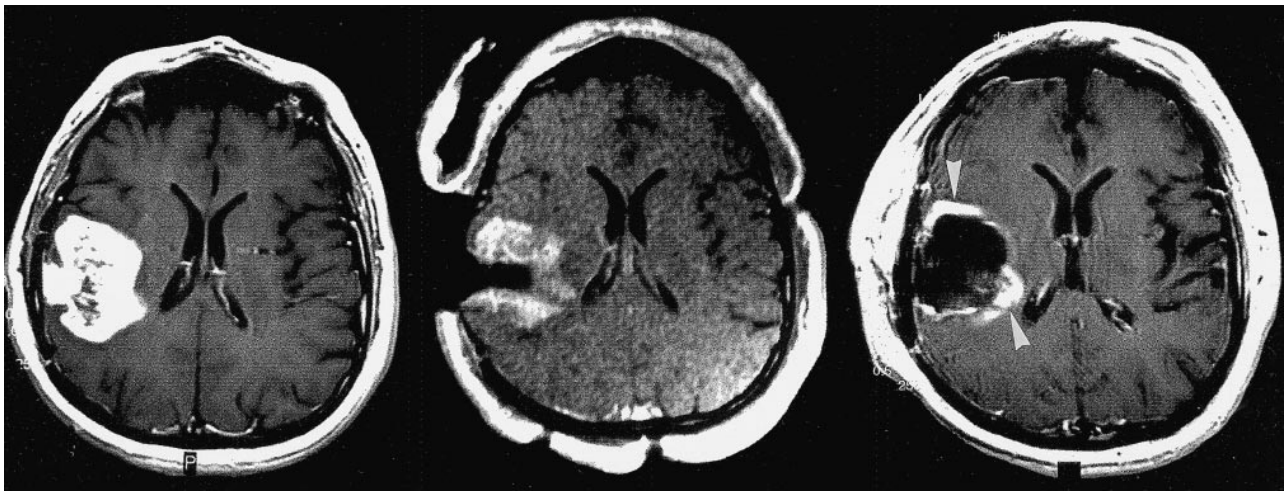

FIG 4. ''Failure'' of the intraoperative MR imaging approach in a 46-year-old man with an anaplastic glioma.
Left, Preoperative MR image shows a right-hemispheric lesion (674/20/2).
Middle, Intraoperative MR image (532/15/3) shows massive residual tumor. Surgery was continued with extensive further tumor resection.
Right, Early postoperative MR image (674/20/2), however, still shows residual enhancing tumor (*arrowheads*).

same institution without the use of neuronavigation (1). This relatively low rate of complete removal probably occurs because neuronavigation systems work with MR datasets that are acquired preoperatively. These datasets grow ''old'' during the course of the operation; this is known as the ''brain shift problem'' of neuronavigation. Brain shifts of 5 to 10 mm and more during the course of neurosurgery have been reported (23–25), explaining the limited usefulness of neuronavigation for the assessment of the completeness of tumor resection. This also emphasizes the need of an intraoperative imaging technique to correct for these distortions.

Conclusion

Intraoperative MR examinations improved the surgical results in a series of patients with high-grade gliomas. Although in a strict scientific sense an improvement in surgical results has been proved only for patients with high-grade gliomas in this study, we are confident that these findings can be applied to other enhancing intra-axial tumor entities in which the overall prognosis is better than in cases of high-grade gliomas.

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