Extirpation of glioblastomas: MR and CT follow-up of residual tumor and regrowth patterns.

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Extirpation of Glioblastomas: MR and CT Follow-up of Residual Tumor and Regrowth Patterns

Michael Forsting,1,4 Friedrich K. Albert,2 Stefan Kunze,2 Hans-Peter Adams,3 Dirk Zener,2 and Klaus Sartor1

PURPOSE: To optimize the timing of CT and MR after glioblastoma resection and to define the pattern of tumor regrowth. SUBJECTS AND METHODS: Sixty-eight patients with glioblastoma were studied prospectively with CT and MR. The first postoperative scan was obtained between day 1 and day 5; follow-up scans were obtained bimonthly. RESULTS: Residual tumor was shown most reliably on scans obtained shortly after surgery (MR, 77%; CT, 40.5%). After the fourth day up to 3 months postoperatively, surgically induced enhancement prevented recognition of residual tumor. Seventy-five percent of patients with residual tumor shown by early postoperative MR had progressive disease during follow-up, whereas only 36% of patients without evidence of residual tumor had MR signs of progressive disease. CONCLUSION: Early, enhanced, postoperative MR is the radiologic procedure of choice to determine the extent of glioblastoma resection. Gross total tumor resection as determined by early postoperative MR correlates with a prolongation of life.

Index terms: Glioblastoma multiforme; Magnetic resonance, postoperative; Computed tomography, postoperative; Brain neoplasms, surgery

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Most scientific studies addressing the role of surgery in the management of malignant cerebral gliomas in adults rely exclusively on the surgeon's impression of the degree of resection accomplished; subjective estimations of tumor bulk reduction form the basis of very recent reports (1–4). Also, most studies are retrospective reviews of the records of patients operated on by various surgeons (1). While computed tomography (CT) has been available for many years to monitor patients postoperatively, and while magnetic resonance imaging (MR) can now be used for the same purpose, both methods are diagnostically limited because they do not distinguish tumor enhancement from surgically induced enhance-ment. Among the few available CT-based studies, there is neither consistency in the methods of estimating residual tumor volume, nor consistency in the timing of postoperative radiographic studies (1, 5–9). Thus far, the systematic use of MR, and especially of paramagnetically enhanced MR in the evaluation of the cranial postoperative site, has remained largely uninvestigated (9, 10).

The purpose of this study was, first, to evaluate the natural history of contrast enhancement after brain tumor resection; and second, to find out which imaging modality would be optimal to monitor glioblastoma patients radiologically after surgery. The goal of the long-term follow-up part of our study was to define the regrowth pattern of glioblastoma after surgical excision.

Subjects and Methods

In a prospective study, 68 patients with glioma grade IV (WHO) were studied by CT and MR before and, at specific intervals, after surgery. All CT studies were performed before and after intravenous contrast enhancement; contrast scans were obtained immediately after bolus injection of 100 mL of iohexol 300 (Omnipaque; Schering AG, Berlin, Germany). MR was performed on a 1.0-T unit. T1-weighted images (T1WI) were obtained with a repetition time (TR) of 600 msec and an echo time (TE) of 20 msec. For contrast
enhancement, 0.2 mmol/kg gadolinium-DTPA (Magnevist, Schering AG) was injected intravenously; imaging was begun immediately after the injection of contrast material. With both CT and MR studies, the section thickness was 8 mm without intersection gap.

The first postoperative CT and MR scans (early postoperative imaging) were obtained as soon as possible after surgery, usually between day 1 and day 5. Early postoperative MR was performed in all patients, and additional early postoperative CT scanning was done in the first 42 patients. Later (follow-up) MR imaging was performed 2 weeks, 4 to 6 weeks, and then every 2–3 months after surgery in all patients.

The same postoperative imaging protocol was used to examine 10 patients who had astrocytomas grade II (WHO) without preoperative signs of blood-brain barrier disruption (control group). Thus, any early postoperative enhancement in this group had to be interpreted as being surgically induced.

To evaluate the natural history of postoperative contrast enhancement and to determine which imaging modality would be most suitable for postoperative monitoring, we analyzed the CT and MR scans of all 68 glioblastoma patients (group A) and of 10 patients with astrocytoma grade II (group B). To define the pattern of tumor regrowth, we analyzed the imaging data of 55 patients (group C), in whom the postsurgical follow-up was longer than 6 months; the median follow-up time in this group was 38.8 weeks.

Results

Residual Tumor and Natural History of Contrast Enhancement

Early postoperative MR showed no enhancement along the resection lines in all patients of group B (Fig. 1), indicating that no surgically induced disruption of the blood-brain barrier exists at this time. In 40.5% (17/42) of patients in group A, early postoperative CT revealed irregular (nonlinear) enhancement at the margins of the resection site; analogous changes were seen on MR images in 77% (52/68) of patients. These areas of abnormal contrast enhancement corresponded to enhancing areas already present on the preoperative scans and thus reflected residual tumor (Fig. 2). MR findings were equivocal, mainly due to motion artifacts, in 7% (5/68) of patients, while CT findings were equivocal in 40.5% (17/42) of patients. No signs of residual tumor were seen in 16% (11/68) of patients on early postoperative MR and in 19% (8/42) of patients on early postoperative CT.

The main tissue alteration confounding the interpretation of early CT studies was hemorrhage at the resection site and enhancement of the adjacent parenchyma, both of which were difficult to distinguish from infiltrating tumor (Fig. 3).

On MR we saw early (i.e., occurring up to 3 days after surgery) formation of methemoglobin in 44% (30/68) of patients (Fig. 4); the amount of methemoglobin was usually minimal. We could differentiate T1-shortening from methemoglobin and T1-shortening from Gd-DTPA only by comparing unenhanced and enhanced scans. About 20% of the patients revealed early meningeal enhancement, usually at the craniotomy site (Fig. 2). Beginning with the second postoperative week, widespread enhancement occurred along the resection lines. This type of enhancement was always more apparent on MR and was nearly impossible to distinguish from residual tumor (Figs. 2 and 5). Simultaneously, on MR images, increasing protein content plus formation of methemoglobin resulted in marked T1-shortening within the resection defect (Fig. 6). At this time, about 10% of the patients revealed new, partially gyriform, enhancement of the adjacent brain parenchyma, especially after temporal lobe resections (Fig. 6). Long-term follow-up taught us that these lesions were ischemic, since on later scans they appeared as small cortical infarcts that eventually became isointense with cerebrospinal fluid.

About 2 months after surgery, the "benign," linear enhancement had nearly resolved in most
patients. In some patients, however, we saw linear enhancement along the resection lines persisting up to 6 months after surgery. This phenomenon was easy to differentiate from enhancing tumor, since tumor appeared more irregular, nodular, or mass-like.

**Regrowth Pattern of Recurrent Tumor**

Table 1 shows the data of the 55 patients (group C) who were included in the follow-up study. In 44 of these 55 patients, residual enhancing tumor was visible on MR, while in the remaining 11 patients no tumor could be seen. A total of 41 patients had postoperative radiation, while 14 patients refused to have any additional therapy. None of the patients was treated with chemotherapeutic agents.

Table 2 shows the predictive values of residual tumor. Both the progression-free interval and the total rate of tumor recurrence were found to depend significantly on the type of surgery, that is, gross total versus subtotal or partial resection. In case of evidence of residual tumor on early postoperative MR, 75% of the patients developed progressive disease during follow-up; however, only 36% of patients developed progressive disease if there was no MR evidence of residual tumor. Furthermore, the progression-free interval doubled in those patients whose early postoperative MR showed no signs of residual tumor. In about 80% of the patients with enhancement of residual tumor on early postoperative MR and progressive disease, tumor regrowth unquestionably arose from these enhancing tumor remnants (Fig. 7). In the remainder of patients (20%), multicentric glioma involving both the primary site of tumor extirpation and other, more remote locations developed during follow-up (Fig. 3D). Only two patients without residual enhancing tumor seen on the first postoperative MR had local tumor regrowth; in two other patients of this group, multicentric gliomas that did not involve the initial tumor bed developed during follow-up.

**Discussion**

Glioblastoma multiforme and anaplastic astrocytoma account for at least 35% of all primary brain tumors, which translates into 6600 new cases annually in the United States alone (11). The overall survival rate of patients with these tumors is far from being satisfactory; the 24-month mean survival rate for patients with glio-
Fig. 3. Axial unenhanced (A) and enhanced (B) CT images and axial enhanced T1-weighted MR image (600/ 20/2) obtained on the first day (A–C) and 9 months (D) after extirpation of glioblastoma. A and B, On CT it is impossible to differentiate between tumor enhancement, postsurgical hemorrhage, and hyperperfusion of the adjacent brain parenchyma. Slight changes in position of the patient’s head during scanning make it more difficult to compare the unenhanced (A) and enhanced (B) scans; especially on the first day after surgery, many patients do not hold sufficiently still and are less cooperative as during later follow-up. C, MR obtained on the same day as CT clearly delineates residual tumor masses without artifacts from hemorrhage or hyperperfusion. D, MR obtained 9 months later shows a second glioma in the left parietal lobe.

Glioblastoma is 8%–12%, while the median postoperative survival time is 8 months (12, 13). One retrospective study showed a 5-year recurrence-free survival rate of 0% for patients with glioblastoma multiforme (14). Recent attempts at improving the median survival were focused primarily on the use of new chemotherapeutic regimens or different forms of radiation therapy, with little attention directed towards improving the surgical part of the treatment plan (2). When information on the extent of the surgical resection is given, it is primarily based on the surgeon’s impression and not on quantifiable, eg, radiologic criteria. However, to compare their relative usefulness, all therapeutic methods used in a multimodality treatment plan require quantification; judging their respective therapeutic benefits should not be based on subjective factors. Thus, if in the individual patient the results of treatment of a malignant glioma are to be assessed, the
extent of tumor resection should be determined radiologically.

Although CT and, more recently, MR have been used extensively to monitor patients after brain tumor surgery, there are problems with this approach. Perhaps the greatest of these problems is that the effectiveness of CT and MR is reduced by the diagnostic difficulty of distinguishing tu-
A, Aside from small residual enhancing tumor at the medial margin of resection site, there is marked hypointensity of adjacent temporal lobe with subtle but definite evidence of parenchymal or vascular contrast enhancement as an early sign of ischemic brain infarction.

B and C, Two weeks later, T1-shortening within the resection defect (arrows) probably due to methemoglobin formation and increased protein content is seen on unenhanced (B) and enhanced (C) MR. Also, there is marked gyriform enhancement of the adjacent temporal lobe (arrowhead in C) consistent with ischemic brain infarction.

TABLE 1: Clinical data of the 55 patients with a follow-up time of more than 6 months after extirpation of glioblastoma (group C)

<table>
<thead>
<tr>
<th></th>
<th>rT</th>
<th>No rT</th>
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</tr>
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<tbody>
<tr>
<td>Sex (male/female)</td>
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<td></td>
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<tr>
<td>Age</td>
<td>55.1 yr</td>
<td></td>
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<tr>
<td>Median follow-up time</td>
<td>38.8 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival time</td>
<td>35 wk</td>
<td></td>
<td></td>
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<tr>
<td>Residual tumor (yes/no)</td>
<td>44/11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation therapy (yes/no)</td>
<td>41/14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time 6–12 mo</td>
<td>20/55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time &gt; 12 mo</td>
<td>35/55</td>
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TABLE 2: Prognostic value of residual tumor after extirpation of glioblastoma

<table>
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<th></th>
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<tbody>
<tr>
<td>Tumor recurrence</td>
<td>33/44</td>
<td>4/11</td>
<td>.003a</td>
</tr>
<tr>
<td>Progression free interval (wk)</td>
<td>15.4</td>
<td>30.6</td>
<td>.005b</td>
</tr>
</tbody>
</table>

Note.—rT, residual tumor (based on early postoperative MR).
Statistical analysis: a Fisher's Exact test
b Student-Newman-Keuls test

The mechanisms underlying postoperative enhancement are not fully understood but may include local blood-brain barrier disruption, formation of neovascularity, and luxury perfusion (6, 8, 15, 16). Several hypotheses have been advanced to explain both the occurrence and the evolution over time of contrast enhancement at the resection site. The development of granulation tissue observed experimentally in a canine model appears to parallel most closely the enhancement pattern seen on CT (15, 17). Hyperemia of the injured brain parenchyma due to dysautoregulation may play an additional role (15). Animal experiments and serial CT scanning after brain tumor resection have shown delayed contrast enhancement appearing along the operative margins up to 5 days after surgery (6, 15). Despite these results, which suggested a potential of CT for postoperative follow-up imaging, CT did not become widely accepted for examining tumor patients after surgery. The main problem of interpreting early postoperative CT is to differentiate tumor enhancement from hemorrhagic fluid or blood within the area of resection and hypervascularity of the adjacent parenchyma due
to dysautoregulation. This similarity of tumor enhancement and other, non-neoplastic soft tissue changes was the main reason for the many equivocal CT scans in our series. While MR is now routinely used, especially in neurologic disease, no prospective studies evaluating the effectiveness of postoperative Gd-DTPA-enhanced MR in patients with glioblastoma multiforme have been done.

A comparison of Gd-DTPA with iodinated contrast agents reveals many similarities but several important differences. Runge et al (18) suggested that Gd-DTPA-enhanced MR is more sensitive than iodinated contrast-enhanced CT in detecting early disruption of the blood-brain barrier. Based on a moles per kilogram dose of administered contrast medium, MR is about 20 times as sensitive to Gd-DTPA as is CT to iodinated contrast agents. Even minute amounts of enhancing residual tumor should thus be visible on MR, amounts of tumor that would be invisible on CT.

Because of flow-related phenomena, vascular enhancement seen on MR differs from vascular enhancement seen on CT; on MR, large arteries

Fig. 7. Axial T1-weighted MR image (600/20/2) obtained preoperatively (A), on the first day (B), 4 months (C), and 10 months (D) after extirpation of glioblastoma.

A and B. Early postoperative MR (B) shows small residual enhancing tumor at the medial margin of the resection site.

C. Four months after surgery and radiation therapy, the residual tumor appears to be smaller but is still clearly visible.

D. MR obtained 10 months after surgery shows regrowth of the tumor, which unequivocally arises from macroscopic tumor remnants.
do not usually enhance significantly unless there is pathologic slowing of blood flow (19). Furthermore, the specifics of the contrast enhancement mechanism of Gd-DPTA, a substance visualized indirectly by its causing local changes in the magnetic environment of protons, should minimize the enhancement effect from hypervascularity as seen with iodinated contrast media.

In agreement with its theoretical advantages, MR did surpass CT in visualizing residual tumor after glioblastoma resection: in 76% of patients, residual enhancing tumor was easily detectable on early postoperative MR images, and diagnostic difficulties were encountered in only 7% of patients. Because of the characteristic signal changes due to hemoglobin degradation, differentiating tumor enhancement from postoperative hemorrhage during the first 4 days after surgery was easy; during the same period we also saw no "benign" enhancement related to the surgical trauma.

In two patients studied with MR in the immediate postoperative period, Elster et al (9) observed abnormal enhancement of the dura mater and brain. This is, in part, at variance with our results, but we do agree with these authors that meningeal enhancement may be observed shortly after surgery. In one of the figures in their paper, contrast enhancement is visible at the resection site, although it remained unclear after what kind of surgery this occurred. We consider it essential to start imaging immediately after contrast injection, or else contrast material might extravasate along the margins of the incision (9, 20). When using this technique, we never saw early contrast enhancement in glioblastoma patients during the first 4 days, and the same was true for the patients of our control group with preoperatively unenhancing astrocytomas grade II (WHO). In two patients, who for clinical reasons were scanned on the fifth postoperative day, we saw beginning linear "benign" enhancement along the resection margins.

Unexpectedly, we saw signal changes consistent with the presence of methemoglobin at the resection site in 44% of the patients within the first 4 days after surgery. This differs from the typical time course of hemoglobin degradation according to which it takes about 1 week after acute intracranial hemorrhage for methemoglobin to form. One reason for this deviation from the normal sequence of events might be the common practice of neurosurgeons of using of hydrogen peroxide ($H_2O_2$) for local hemostasis; $H_2O_2$ is a strong oxidizing agent that considerably accelerates methemoglobin formation. When MR imaging is performed before and after contrast enhancement, it is usually easy to differentiate T1-shortening due to residual enhancing tumor from early methemoglobin formation. Beginning with the second week after surgery, extensive linear enhancement is present along the margins of resection on both CT and MR scans, and it becomes nearly impossible to distinguish between surgically induced enhancement and enhancement due to residual tumor. On MR scans obtained during the second postoperative week, one faces an additional diagnostic problem: about 10% of patients develop ischemic lesions in the brain parenchyma next to the resection site, especially after temporal lobe surgery. This may explain the clinical worsening of some patients after surgery. If an early postoperative baseline MR study is available, one can usually recognize these ischemic lesions as such and thus avoid misinterpreting areas of abnormal enhancement as residual or early regrowing tumor. Another diagnostic dilemma characteristic for the second postoperative week is that blood present at the resection site now becomes hyperintense and may thus be difficult to differentiate from residual enhancing tumor. While, on MR images, blood becomes more visible during the subacute stage of hemorrhage, it becomes less apparent after clot lysis on CT. Elster et al (9) suggested, therefore, that MR performed during the first several months after surgery to check for residual of recurrent tumor must be viewed with skepticism. We agree in so far as it is indeed futile to start obtaining follow-up scans 2 weeks or later after surgery. We do think, however, that many diagnostic difficulties occurring during follow-up can be avoided if an early postoperative baseline MR study is obtained. This is true not only with regard to tumor recurrence but also with regard to complications of multimodal treatment plans, complications that might be confused with tumor recurrence (21).

A remaining problem may be that of meningeal enhancement. This type of abnormal postoperative enhancement can be visible (usually near the craniotomy site) on early scans, increases during the ensuing weeks and months, and tends to persist for up to 1 year, sometimes even much longer (9). Since superficially located glioblastomas are known to invade the meninges (22), postoperative meningeal enhancement may cause diagnostic problems, for example, distin-
guishing meningeal spread of the tumor from surgically induced enhancement. While dural spread in glioblastoma may occur, we never saw regrowth of tumor originating from the dura in our patients.

Although there is general agreement on the need to obtain a precise pathologic diagnosis of a malignant brain tumor there are still controversies regarding the extent of the surgical resection necessary (1, 23–26). A review of cooperative neuro-oncologic studies shows that 70%–80% of the patients were treated by subtotal tumor resection or had only a biopsy (27, 28). When planning the treatment of glioblastomas, the key question is whether recurrent tumor arises from residual tumor tissue or from microscopic tumor cells left in the surrounding brain parenchyma (29). Hochberg and Pruitt (30) reported that CT provides accurate information as to tumor volumes, and that 80% of tumor recurrences occurred within 2.0 cm of the initial tumor bed. In the series of Burger et al (31) some tumors were relatively discrete, having a rim of microscopic tissue infiltration extending less than 2 mm beyond the area of contrast enhancement on CT. Other tumors, however, were highly infiltrative, especially when neoplastic cells had entered compact fiber pathways (32). The growth patterns of malignant gliomas are related not only to the biologic behavior of the tumor cells, but also to their anatomic environment in the central nervous system. Glioma cells, for example, tend to invade superficially the pia mater and perivascular spaces and to spread along white matter fiber tracts, such as those of the corpus callosum and optic radiation (33). Peritumoral brain edema expands the extracellular space and may thus facilitate migration of invasive tumor cells (34). Unfortunately, when using presently available radiologic imaging techniques, one cannot precisely define the microscopic margins of residual glioma. It is equally impossible to distinguish clearly between tumor and peritumoral edema. What one calls “edema” should be better described as “tumor plus edema,” since tumor cells may extend beyond abnormally enhancing tissue as seen in MR (35). Paramagnetic enhancement marks the site of the blood-brain barrier breakdown, not necessarily the tumor margins, but it is helpful in distinguishing gross tumor margins from surrounding edema.

Cerebral gliomas should be treated in the same way as other neoplasms. The goals of surgery should be to obtain a histologic diagnosis, reduce tumor bulk, improve the neurologic status of the patient, buy time for other therapies to take effect, and possibly change tumor kinetics to make the tumor more sensitive to irradiation and chemotherapy (2). The fatalism in the surgical treatment of glioblastoma results from the belief that early tumor regrowth occurs independent of the type of resection, usually arising from (microscopic?) remaining tumor cells. Goldsmith (36) found only a slight increase, from 1.6 months to 3.9 months, in the survival time after gross total resection as compared to subtotal resection; however, he did not have available a radiologic baseline scan (CT or MR) showing the actual degree of resection. Ammirati et al (7) first reported a significant prolongation of life after gross total resection, as judged on postoperative CT, in a small group of patients with glioma grade III and IV. Our findings strongly support the idea of gross total resection: in nearly 80% of the patients, we saw regrowth of the glioblastoma to occur out of macroscopic tumor rests; there was never tumor regrowth out of the margins of resection that showed no enhancement on early postoperative MR in these patients. In two patients without evidence of residual tumor on early postoperative MR, local tumor regrowth did occur, but the progression-free interval had doubled.

These findings have important therapeutic implications. They suggest, that the aim of surgery in glioblastoma should be gross total resection. If functional considerations do not allow sufficiently aggressive surgery, the first target of adjuvant therapy should be any tumor rest left behind, as delineated by early postoperative MR. This opens an opportunity for stereotactic radiation therapy with a focused boost on the residual tumor (37) and could potentially result in a renaissance of the use of neutron beam irradiation for attacking tumor cells. If fast neutron beams can be directed more selectively at the residual tumor, provided the tumor was localized precisely with CT and MR, this mode of stereotactic therapy may prove to be more effective than standard photon therapy (37, 38). Another novel therapeutic approach might be stereotactically guided application of liposomes and chemotherapeutic agents into the neoplastic tissue.

During radiologic follow-up, about 20% of our patients had a tumor recurrence seemingly apart from the resection area (Fig. 3D). This high incidence of multicentric glioma—in the series of Hochberg and Pruitt (30), multicentricity occurred in only 4%–6% of patients—is probably related
to the way we follow our patients radiologically. These multicentric gliomas, whose occurrence possibly reflects a high potential of migration of the malignant cells, probably should be classified as a secondarily generalized neoplastic disease of the brain.

In conclusion, effective multimodality treatment of malignant gliomas requires quantification of all methods used. Thus, it is important to determine the extent of tumor resection as precisely as possible when assessing the results of surgery. We propose that postoperative imaging to look for residual enhancing tumor be performed within the first 3-4 days after surgery, preferably by using MR. This timing minimizes diagnostic problems associated with "benign" enhancement related to the surgical trauma. In contrast to Glantz et al (39), we believe that positron emission tomography is unnecessary for distinguishing persistent tumor from postoperative parenchymal changes.

A radical surgical approach, gross total tumor resection, appears to increase significantly both length and quality of survival when compared with a less radical approach (subtotal resection). Preferential local regrowth provides the rationale for coned-down volume radiation therapy that allows to spare much normal brain tissue. With serial MR, tumor recurrence can be detected earlier than before. Tumor extent can be defined better, and our knowledge regarding the biology of malignant gliomas is likely to grow, particularly when we start correlating radiologic findings with the results of neuro-oncologic basic research.

References