Temporal changes in magnetic resonance imaging characteristics of Gliadel wafers and of the adjacent brain parenchyma

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Carmustine is used in the treatment of glioblastomas as locally applied chemotherapy in the form of biodegradable wafers, which are lined on the walls of the resection cavity at the end of the resection, to increase local concentrations and decrease systemic toxicity. A total of 44 patients with glioblastoma with gross macroscopic tumor removal were included. MRIs were performed at various times postoperatively (within 24 hours, 1 week, 1 month, 2 months, 3 months, 6 months, 9 months, and 1 year). MR protocols included a T2-, diffusion-weighted, and T1-weighted sequences with and without intravenous administration of gadolinium. On T1, the wafers change from their initial hypointense to an isointense appearance after a period during which they appear to be hypointense, with a hyperintense rim most prominent less than 1 month postoperatively. On T2 they change from a hypointense to an isointense appearance. Restricted diffusivity reshaping the silhouette of the wafer’s surface at the rim of the resection cavity can be found as early as day 1 postoperatively; however, 1 month after implantation, they all show areas of restricted diffusion, which may remain up to 1 year. Contrast enhancement at the rim of the resection cavity can already be found at day 1 postoperatively, with a peak shortly after 1 month after surgery. These changes can easily be mistaken for an abscess and hamper the early differentiation between residual tumor tissue and normal postoperative changes. However, early changes in either appearance do not predict overall survival or the progression free interval.

Keywords: diffusion-weighted imaging, follow-up, GLIADEL wafer, glioblastoma multiforme, MR imaging.

Glioblastomas are the most common primary neoplasms of the central nervous system. They are more common in men than in women and have the highest incidence during the sixth decade of life, with 5–8 new cases of malignant gliomas per 100,000 people per year. Glioblastomas rarely metastasize; instead, the majority of tumors recur locally within centimeters of the original tumor site. Several factors limit the efficacy of systemic chemotherapy, including (1) the capillary tight junctions of the blood-brain barrier (BBB) prevent entry of therapeutics from the general circulation into the brain depending on its molecular size, (2) the electric charges on drugs, and (3) the lipophilicity of drugs. Therefore, very few chemotherapeutic drugs applied systemically reach cytotoxic concentrations intracerebrally. Several methods have emerged to overcome this: high-dose drug regimens, liposomal drug delivery, and disruption of the blood-brain barrier with biochemical or osmotic agents.

Despite new therapies, survival rates remain generally very poor. With the introduction of the Stupp regimen in 2005, the median survival became 14.6 months, and overall survival was 9.8% at 5 years. Carmustine (BCNU: 1,3-bis[2-chloroethyl]-1-nitrosourea) has been used to treat malignant gliomas for a long time because of its efficacy against malignant...
glia formation. Systemically applied BCNU is effective against glioma, but its clinical implementation is limited because of the high toxicity of nitrosoureas. In addition, they are rapidly cleared from tissues, thereby limiting its bioavailability for brain tumors. To avoid systemic toxicity and to increase local cytotoxicity, efforts have focused on delivering chemotherapy directly to the perilesional tumor-infiltrated parenchyma. For this reason, a biodegradable wafer containing 7.7 mg BCNU has been developed for local delivery (prescribing information, Gliadel, Guilford Pharmaceuticals). Up to 8 BCNU wafers, depending on the size of the surgical resection cavity, are lined on the walls of the resection cavity at the end of open surgical resection for gliomas. Through this local application, high concentrations (0.5–3.5 mM) of BCNU can be delivered to the tumor bed over a period of up to 3 weeks. Thus, local concentrations of BCNU can be 4–1200 times greater, as with a systemically applied administration, with markedly reduced systemic adverse effects.

To date, more than 20,000 cases of BCNU wafers have been implanted. Clinical studies indicate that they improve survival in patients with recurrent or newly diagnosed malignant glioma. Median survival was 13.9 months for the BCNU wafer-treated group, with an overall survival of 9.2% at 3 years. Applying chemotherapy systemically leads, in general, to a potential treatment gap, which is typically in the order of 14 days after tumor resection and subsequent chemoradiotherapy. In the absence of treatment, tumor burden can significantly increase. Because the BCNU wafers are lined in the resection cavity at the end of the resection, there is no treatment gap between surgery and concomitant chemotherapy. However, compared with the recently published data on long-term survival among patients treated with the Stupp regimen, data on long-term survival beyond 3 years in the BCNU wafer-treated patients is currently still missing. Recently, the combination of both regimens (temozolomide plus BCNU wafer and radiation) has been introduced, which led to a median survival of 20.7 months with an overall survival of 36% at 2 years.

BCNU wafers are the only local chemotherapy approved by the European Medicines Agency and the FDA as an adjunct to surgery and radiotherapy in patients with newly diagnosed WHO grade III and IV malignant glioma and as an adjunct to surgery in patients with recurrent glioblastoma. Local therapy can result in distinctive adverse effects. In addition to an increased risk of wound-healing problems and cerebrospinal fluid leakage, new onset of seizures and an increase in local edema have been described. These are thought to be a result of local changes resulting from an inflammatory reaction caused by the chemotherapeutics and can result in life-threatening local cyst formations. Furthermore, the wafers, the resection cavity, and the adjacent parenchyma at the rim of the resection cavity change appearance on MRI over time and can be mistaken for infection or recurrent disease.

To date, no structured analyses regarding MR appearance has been published. To prevent a misreading of MRIs in BCNU wafer therapy, we therefore reviewed our patients’ charts and MR images for distinct local changes and assessed their clinical relevance.

Materials and Methods

Patient Population

Forty-four patients with glioblastoma were included. Inclusion criteria were gross macroscopic tumor removal, intraoperative alignment of biodegradable wafers containing 7.7 mg BCNU along the wall of the resection cavity, postoperative MRI performed within 24 h, and clinical and MRI follow-up. Because of varying periods of the follow-up MRIs, we pooled them into groups. Wafers were only applied once, either during the initial resection or if patients presented with recurrent disease without prior application of BCNU wafers. Accordingly, the concomitant therapy regimen varied. Patients presenting with a new high-grade glioma received the classical combination of radiation and oral temozolomide (Stupp scheme), whereas recurrent gliomas received radiation (if initially not radiated, 1 case) or temozolomide only. All patients were followed until their date of death to also monitor overall survival. Written informed consent was obtained by the time of the surgery, and the study was approved by the local institutional review board.

MRI Assessments

We reviewed all available MR images over time. In our institution, all patients undergoing brain tumor surgery receive an MRI 24 h after the resection. The usual follow-up is a 3-month interval, including a new MRI scan and consultation in our neurosurgical outpatient clinic. In the initial phase, because of unexpected changes on MR images, some patients underwent consecutive MRIs within a shorter period. Because patients were scanned either in our institution or at an outpatient MR facility, protocols and sequences used varied; however, all exams included a T1-weighted sequence with and without intravenous administration of contrast agents and a T2-weighted sequence. In most cases, a diffusion-weighted sequence (B=1000/s) was obtained. Patients with recurrent disease requiring further or repetitive surgical resection were excluded, because usually the remaining wafers were removed intraoperatively. In 2 cases during the learning curve, however, we obtained histology: one time, because of suspected abscess formation and, in the other, because of recurrent disease (thus, a biopsy specimen was also acquired underneath 1 wafer).

Statistics

Analysis was performed using SPSS. The overall survival was evaluated from surgery to death or censored...
after the last MR time with use of the Kaplan-Meier method. A log-rank test compared the survival curves for possible criteria of survival. In addition, a multivariate Cox model of proportional hazards was performed. The criteria were included according to their P values (highest log-rank P values to the lowest) and only one at a time. P values ≤0.05 were considered to be statistically significant. For exploratory analyses of correlations between the findings in the MRI or changes during the series of images, we conducted Pearson correlations.

**Results**

**Cases**

Overall, we analyzed 125 time points from 44 patients. In all but 2 cases, a 24 h postoperative MRI was available (in the remaining 2 cases, the postoperative MRI was performed within 72 h). Depending on the field strength (1.5 or 3 Tesla) and resolution of the sequence used, discrete changes can be found; otherwise, the main signal of the wafer dominates the appearance (for changes over time, see Figs 1–3).

**MRI Features at 24 Hours**

In the MRI performed within 24 hours after tumor resection, the wafers appeared hypointense in T1 and T2 in the majority of cases. Already in this first postoperative image, a hyperintense rim of the hypointense wafer (in the center) was found (7%) on T1-weighted images (T1WI), whereas they all appeared hypointense on T2-weighted images (T2WI; 100%). Restricted diffusion was already found in 18 cases (43%) in the parenchyma adjacent to the wafer at the rim of the resection cavity. Restricted diffusion differed from the appearance and pattern typically found after the resection of high-grade gliomas and could be differentiated from these perioperative strokes because it was reshaping the silhouette of the wafer’s surface at the rim of the resection cavity. Contrast enhancement was found in only 7 patients (17%), 2 of whom had undergone the second resection for recurrent disease. The resection cavity appeared to be hypointense in T1WI and hyperintense in T2WI because of a mixture of residual blood products and saline, with which the resection cavity was filled at the end of surgery. Hypointense areas were found at the ventral border of the resection cavity representing residual air.

**MRI Features within 1 Week**

Within the first week, only 50% of the wafers remained solid hypointense in T1, whereas the others showed a hyperintense rim around the hypointense center. On T2WI, they remained hypointense in 90% of cases. In 70% of cases, a new area of restricted diffusion reshaping the silhouette of the wafer’s surface was found at the rim of the resection cavity. The wall of the resection cavity showed contrast enhancement after intravenous administration of gadolinium in 30% of cases.

![Fig. 1. Distribution of the appearance of the Gliadel wafers in T1-weighted imaging (T1WI). These wafers change from a hypointense-dominated appearance into an isointense appearance after a period during which they appear to be hypointense with a hyperintense rim most prominent less than 1 month after implantation. None of these changes was a predictor for other changes depicted with MRI or long-term survival.](https://academic.oup.com/neuro-oncology/article-abstract/14/4/482/1053489)
MRI Features at Less Than 1 Month

In MRIs performed within less than 1 month, 83% of the wafers showed a hyperintense rim around the hypointense center on T1WI, and the remaining were still solid hypointense. On T2WI, about half of the wafers changed into a more isointense appearance, and the remaining were hypointense. Restricted diffusion, when performed, was found in all cases, reshaping the silhouette of the wafer's surface at the rim of the resection cavity. The wall of the resection cavity showed contrast enhancement after intravenous administration of gadolinium in 67% of cases. The resection cavity had restricted diffusivity in 75% of cases.

MRI Features at 1–2 Months

After approximately 1 month (33–46 days postoperative) (Fig. 4), 38% of the wafers showed a hyperintense rim around the hypointense center on T1WI, 50% were hyperintense, and 12% were iso- to hyperintense; 75% remained hypointense on T2WI, and 25% changed into an isointense appearance. We found restricted diffusivity reshaping the silhouette of the wafer's surface at the rim of the resection cavity in 75% of cases. The wall of the resection cavity showed contrast enhancement after intravenous administration of gadolinium in all cases, when given. In only 12% of cases, the resection cavity had restricted diffusivity.

MRI Features at 2–3 Months

After approximately 2 months (48–69 days postoperative), 43% of the wafers showed a hyperintense rim around the hypointense center on T1WI, 14% appeared to be isointense, 14% appeared to be iso- to hyperintense, and 29% appeared to be hyperintense. On T2WI, 43% appeared to be hypointense, 43% appeared to be hypo- to isointense, and 14% appeared to be hyperintense. Restricted diffusion was found in 86% of cases, reshaping the silhouette of the wafer's surface at the rim of the resection cavity. In 71% of the cases, the wall of the resection cavity showed contrast enhancement after intravenous administration of gadolinium. The resection cavity had restricted diffusivity in 29% of cases.

MRI Features at 3–4 Months

After 3 months (79–107 days postoperative), in the usual, regular follow-up MRI, 10% of the wafers were hypo- to isointense, 10% were isointense, 50% were iso- to hyperintense, and 30% were hyperintense on T1WI. On T2WI, 10% remained hypointense, 70% were hypo- to isointense, and 20% were iso- to hyperintense. Restricted diffusion, when performed, was found in 88% of cases to be reshaping the silhouette of the wafer's surface at the rim of the resection cavity. The wall of the resection cavity showed contrast enhancement after intravenous administration of gadolinium in 89% of cases, when given. The resection cavity showed no restricted diffusivity in all cases.

MRI Features at 4–6 Months

Approximately 4 months after surgery (118–205 days postoperative), the wafers appeared to be hypointense in 35% of the wafers, hypointense with a hyperintense
rim in 35%, isointense in 10%, and iso- to hyperintense in 20% on T1WI. On T2WI, they appeared to be hypointense in 32%, hypo- to isointense in 37%, isointense in 10%, and iso- to hyperintense in 21%. Restricted diffusion, when performed, was found in 78% of cases to reshape the silhouette of the wafer’s surface at the rim of the resection cavity. The wall of the resection cavity showed contrast enhancement after intravenous administration of gadolinium in 95% of cases, when given. The resection cavity showed restricted diffusivity in 6%.

MRI Features at 9–12 Months

Approximately 9 months after surgery (257–334 days postoperative), the wafers appeared to be hypointense with a hyperintense rim in 29%, isointense in 29%, iso- to hyperintense in 29%, and hyperintense in 13% on T1WI. On T2WI, they appeared to be hypointense in 29%, hypo- to isointense in 57%, and isointense in 14%. Restricted diffusion, when performed, was found in 50% of cases to be reshaping the silhouette of the wafer’s surface at the rim of the resection cavity. The wall of the resection cavity showed contrast enhancement after intravenous administration of gadolinium in 86% of cases. The resection cavity showed restricted diffusivity in 33%. After that time, the wafers turned isointense on T1WI and T2WI. Restricted diffusion disappeared, whereas there was still enhancement of the wall of the resection cavity.

Correlation to Survival

Neither restricted diffusion reshaping the silhouette of the wafer’s surface at the rim of the resection cavity nor contrast enhancement of the wall of the resection cavity was a predictor for recurrent disease or overall survival.

Fig. 3. Temporal course of the restricted diffusivity in the resection cavity and the adjacent brain parenchyma underneath the wafers and contrast enhancement of the rim of the resection cavity. Restricted diffusivity reshaping the silhouette of the wafer’s surface at the rim of the resection cavity can be found as early as postoperative day 1. One month after implantation, they all showed this area of restricted diffusion, which may remain up to 1 year after surgery. Contrast enhancement at the rim of the resection cavity appeared to be delayed, compared with changes of restricted diffusivity; however, we sometimes observed it on postoperative day 1, and we also noticed a peak a little over 1 month after surgery. Especially 1 month after surgery, the resection cavity showed the peak of restricted diffusivity, which usually disappeared 6 months after surgery. Together with the contrast enhancement of the rim of the resection cavity, it could easily be mistaken as an abscess. Changes in diffusivity in the resection cavity or the parenchyma adjacent to the wafers occurred during the period in which we think BCNU is delivered from the wafer into the tumor bed (over a period of up to 3 weeks), whereas the appearance of contrast enhancement at the rim of the resection cavity showed a peak shortly after these changes.
Fig. 4. Postoperative MR images of a patient after the resection of a left parietal glioblastoma multiforme: postoperative day 1 (A), 1 month after surgery (B), approximately 2 months after surgery (C), approximately 3 months after surgery (D), approximately 6 months after surgery (E), approximately 9 months after surgery (F); diffusion weighted images (left column), T1WI with intravenous administration of gadolinium (middle), and T2WI (right column). The wafers in T1WI and T2WI on postoperative day 1 appeared to be hypointense, best appreciated in T2WI. Note the susceptibility artefacts resulting from residual air and changes caused by blood products in the resection cavity. In the adjacent brain parenchyma underneath the medial, dorsal, and lateral wafer, restricted diffusivity reshaping the silhouette of the wafer’s surface can be found. One month after the resection (B), the wafer appeared to be hypointense in T1WI, with a hyperintense rim. There was enhancement of the wall of the resection cavity. In T2, the wafers can still best be appreciated as hypointense discs (B) with a tendency to a more isointense appearance compared to the immediately performed postoperative MRI (A). The restricted diffusivity underneath the wafer was no longer present in this case; however, the resection cavity developed restricted diffusivity, which together with the contrast enhancement of the rim of the resection cavity, can easily be mistaken as the typical MR appearance of an abscess.
survival. None of the changes depicted in either MRI technique were correlated to any other changes in appearance in other techniques (Pearson correlation).

In one case, during the initial learning curve, a biopsy sample was taken to rule out infection or early recurrence based on suspicious findings in an MRI that were related to changes caused by the Gliadel wafers. In the other case, a biopsy sample was taken during removal of recurrent disease in the tissue underneath a wafer. The contrast enhancing area demonstrated typical signs of an aseptic inflammation. There was no infection or abscess in either case. Four cases (9%) required surgical treatment because of development of space-occupying cysts in the resection cavity, which are not in the scope of this article. This again was not correlated to any changes depicted in either MRI technique.

The mean survival among our patients was 316.5 days (10.4 months, standard deviation, 40 days) (Fig. 5), which is in the range of previously published work. Two patients died of non-tumor-related causes (pulmonary embolism and ileus) within the first 2 weeks.

Discussion

Gliadel wafers underwent characteristic changes over time. On T1WI, they changed from their initial hypointense into an isointense appearance after a period during which they appeared to be hypointense, with a hyperintense rim most prominent less than 1 month after implantation. On T2WI, they changed from a hypointense appearance to an isointense appearance over time. Restricted diffusivity reshaping the silhouette of the wafer's surface at the rim of the resection cavity was found as early as postoperative day 1. One month after implantation, all cases showed this area of restricted diffusion, which remained in some cases for up to 1 year after surgery. These changes can be differentiated from postoperative strokes, known to occur very frequently after glioma resection, as ischemic areas of restricted diffusion occur in a wedge, circle, or triangle shape, affecting a vascular territory exceeding the size of the wafers. Furthermore, because usually more than 1 wafer is implanted, changes occur in the parenchyma adjacent to the wafers and not just at one rim of the resection cavity. Contrast enhancement at the rim of the resection cavity appeared to be delayed, compared with changes of restricted diffusivity; however, we also sometimes found it on postoperative day 1, and we noticed a peak a little over 1 month after surgery. Changes in diffusivity in the resection cavity or the parenchyma adjacent to the wafers occurred during the period in which BCNU is thought to be delivered from the wafer into the tumor bed (over a period of up to 3 weeks), whereas the appearance of contrast enhancement at the rim of the resection cavity showed a peak shortly after these changes. Early changes in either appearance seem not to affect overall survival or progression-free survival. The appearance of the resection cavity, the adjacent parenchyma, and contrast enhancement are problematic for 2 reasons. First, in immediately postoperative MRI, differentiation between residual tumor tissue and normal postoperative changes can be difficult if there is contrast enhancement; however, the enhancement is usually just a very small rim in this initial phase, compared with a nodular appearance in recurrent disease and can thus be differentiated most of the time. Second, especially 1 month after surgery, the resection cavity showed the peak of restricted diffusivity, which disappears usually 6 months after surgery. Together with the contrast enhancement of the rim of the resection cavity, it can easily be mistaken as an abscess, which was the case in one patient in our initial learning curve series. Laboratory findings were inconclusive, and a biopsy sample was taken to rule out infection.

The initial postoperative phase constrains accurate MRI, because the above-described changes can easily be mistaken as infectious changes. To avoid unnecessary biopsies, knowledge of possible changes related to implantation of these wafers is mandatory in reading the MRIs of these patients. Previous studies reported on some changes during follow-up, mainly cyst formation in the resection cavity. However, this is the first study, to our knowledge, to describe a structured analysis of the MR appearance of wafer-induced changes on MR images. In cases with contrast-enhancement and restricted diffusion within the resection cavity, clinical presentation, laboratory changes, and the time since implantation of these wafers should be reviewed. We suggest both a follow-up MRI prior to performing a biopsy and analysis of the wafers’ appearance in other sequences and also a review of all the images performed previously. In these cases, follow-up MRIs should be performed during shorter periods to depict these changes early and, thus, allow differentiation of changes caused by the wafers and infection. This is particularly important one month after surgery, but also at the first regular follow-up MRI, which is usually performed 3 months after surgery.

Another diagnostic challenge besides the wafer-induced changes is the differentiation of tumor recurrence from radiation-induced changes. This might further interfere with interpretation of the images, because they might show similar characteristics. However, tumor recurrence usually presents as nodular lesions at the rim of the...
resection cavity, compared with a circular rim enhancement caused by the wafers. Edema, best seen on T2WI, might be present in both circumstances. In cases of radiation necrosis, a nodular enhancement might be depicted; however, in these cases, MR perfusion and/or MR spectroscopy might be able to differentiate these changes. Because we followed up with patients receiving various perioperative therapy regimens besides locally applied Gliadel (first time presenters and those with recurrent glioblastomas), changes found in this study are most likely caused by these wafers. Combination with other therapies might influence the MR appearance of the resection cavity and adjacent brain parenchyma; however, we did not find such differences in the differently treated patients, and similar changes have previously not been described with other treatment regimens (such as the Stupp scheme) in the literature. Thus, we conclude that the changes found in our study were caused by Gliadel wafers.

Contrast enhancement presented as a rim at the wall of the resection cavity (Fig. 4) and was not of nodular appearance. Complete macroscopic resection was an inclusion criteria; thus, any new contrast enhancement was closely observed. If a nodular contrast enhancement was found, another MRI was performed within a short period (usually within 4 weeks), and if further progression was found, another resection was considered. However, changes suspicious for recurrent disease were very obvious and clearly distinguishable from Gliadel wafer-induced changes.

We conclude that by recommending careful follow-up MR imaging at the same institution or an institution familiar with these changes, in addition to shorter periods between follow-up scans in the learning phase of image interpretation of Gliadel-induced changes.

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References


