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Clinical Study

Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma

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Summary

Objective: Recently a randomized placebo-controlled phase III trial of biodegradable polymers containing carmustine has demonstrated a significant survival benefit for patients treated with local chemotherapy. A local chemotherapy applied directly to the resection cavity may act directly on residual tumor cells in adjacent brain possibly leading to a local control of the tumor and increased survival.

Methods: We have analyzed the pattern of recurrence using serial MRI studies of 24 patients treated with GLIADEL® Wafers or placebo wafers following resection of glioblastomas.

Results: Of 24 patients 11 received carmustine wafers and 13 placebo. The age distribution and Karnowsky performance scores of the two populations were not different. However, the median survival (14.7 versus 9.5 months; $P = 0.007$) and the time to neurological deterioration (12.9 ± 4.85 vs. 9.4 ± 2.73 months; $P = 0.035$) was significantly longer in the treatment group *versus* the placebo treated control. Preoperative and follow up MRI studies were evaluated in a blinded fashion. Out of 24 patients that entered the analysis 11 showed clearance of all contrast enhancement following resection of glioblastomas. Seventeen tumors progressed locally and 7 showed different patterns of distant failure. Within the carmustine treated group 8 patients showed a local treatment failure with recurrent tumors immediately adjacent to the resection cavity or progression form a residual tumor. Three patients showed a multifocal distant and local pattern of failure after complete or subtotal removal. In no case the local chemotherapy resulted in a distant recurrence only. However, the time to radiographic progression was 165.1 ± 80.75 days for the GLIADEL® Wafer group and 101.9 ± 43.06 days for the placebo group ($P = 0.023$).

Conclusion: In this subgroup analysis of a phase III trial population both the clinical progression and radiological progression were significantly delayed in patients treated with local chemotherapy, resulting in an increased survival time. Local chemotherapy with carmustine containing wafer implants did not result in an altered pattern of recurrence and did not promote multifocal patterns of recurrence.

Introduction

GLIADEL® Wafers [poly (carboxyphenoxy-propane/sebacic acid) anhydride wafers containing 3.85% carmustine] are designed to slowly release carmustine over a period of ∼2 weeks after placement into the resection cavity. This will result in high concentrations of carmustine locally elevated up to 100 fold over levels achieved with systemic delivery of biodegradable carmustine (BCNU). However, systemic BCNU remains below detection, sparing systemic toxicity from these compounds [1]. Efficacy of local chemotherapy with GLIADEL® Wafers has been demonstrated in patients with recurrent glioblastoma in

a double-blind, randomized, placebo controlled study. For patients undergoing surgery for recurrent glioblastoma multiforme, GLIADEL® Wafers increased survival compared to placebo wafers (median survival 7.2 months for the GLIADEL® Wafer treated patients vs. 5.4 months for the placebo wafer treated patients) [2]. Recently, an international, placebo-controlled, double-blind, randomized, prospective phase III trial for malignant glioma has also demonstrated the efficacy of GLIADEL® Wafers for treatment of malignant glioma at the time of primary diagnosis and surgery [3]. This study demonstrated that the median survival in the intend-to-treat group was 11.6 months for placebo patients and 13.9 months for the GLIADEL® Wafer group ($P = 0.03$) with a risk reduction of 29%.

Conceptually, a chemotherapy applied directly into the resection cavity should act directly on residual tumor cells in adjacent brain possibly leading to a local control of the tumor, which may increase time to local progression and therefore possibly prolong survival [4]. This may be limited by the highly invasive nature of malignant gliomas that have been demonstrated to show rather distant dissemination several centimeters beyond the macroscopically discernible margin of the tumor (reviewed in [5]). Presumably, the passive diffusion of compounds applied into the resection cavity will only allow treating a rather limited volume of brain [6]. One possible consequence of an effective local control may therefore be distant recurrence of the disease, which ultimately will lead to the demise of the patient. This study presents a subgroup analysis of the radiographic pattern of recurrence after implantation of GLIADEL® Wafers in 24 patients with glioblastomas enrolled at three of the participating German centers. Eleven of these patients received GLIADEL® Wafers and 13 received placebo. Preoperative and follow up MRI studies were evaluated in a blinded fashion. The extent of tumor resection and the pattern of subsequent tumor recurrence or tumor progression were analyzed and correlated with survival and time-to-neurological progression. This analysis demonstrated that in agreement with the results of the phase III trial local chemotherapy did result in a prolonged survival of this subgroup of patients and a prolonged time to clinical progression. The patterns of recurrence were not different in GLIADEL® Wafer treated *versus* placebo treated patients, but the time to radiographic local progression was prolonged in the GLIADEL® Wafer treated patients.

Methods

Study design

This subgroup analysis represents 24 patients enrolled at three of the German centers participating in a prospective, randomized, placebo-controlled, multicenter, multinational, double-blinded trial, which was conducted in 240 patients with the intra-operative diagnosis of malignant glioma. To be eligible, the patient had to have the intra-operative diagnosis of malignant glioma; be between the ages of 18 and 65; have radiographic evidence on cranial magnetic resonance imaging (MRI) of a single, contrast-enhancing, unilateral, supratentorial, cerebral tumor; be treated within 2 weeks of the baseline MRI; and have a Karnofsky performance score (KPS) of 60 or higher. Patients with prior cytoreductive therapy, multifocal disease, prior radiotherapy to the brain, known hypersensitivity to nitrosoureas, and clinically significant laboratory abnormalities were excluded.

The preoperative MRI scans and follow up MRI were evaluated retrospectively in a blinded fashion. Based on an early contrast enhanced MRI scan within 48 h following tumor resection the clearance of all contrast enhancement or the location of residual tumor was determined. Tumor progression was defined as new contrast-enhancing lesion after a complete resection, in an area of no enhancement on previous scans, or as an increase of volume of a residual lesion by at least 25% volume. The location of a recurrent or progressing lesion was scored as local to the resection cavity (immediately adjacent), distant/diffuse (>1.5 cm), or multifocal.

Treatment plan and statistical evaluations

The design, safety evaluations, and statistical analysis of the phase III trail were described in detail in Westphal et al. [3]. In brief, patients with the intra-operative diagnosis of malignant glioma were randomized to receive either GLIADEL® Wafers or placebo wafers followed by external field radiation of 55–60 Gy 2 weeks after resection. Following tumor resection up to 8 wafers were implanted. Patients did not receive systemic chemotherapy unless a diagnosis of tumor progression was made, at which time any therapy could be employed. Patients were followed with periodic clinical evaluations at prespecified intervals. All 24 patients

of this subgroup analysis had complete follow up MRI studies and clinical evaluations. At the time of data analysis all patients had died as a consequence of tumor progression.

Neuroradiologic evaluation

Magnetic resonance imaging was the standard imaging modality for this study. The MRI protocol consisted of an axial proton density/T2 double echo sequence, a coronal T1 weighted spin-echo (SE) sequence with and without contrast material [different approved gadolinium chelates, additional sagittal and axial T1 weighted SE sequences and a fluid attenuated inversion recovery (FLAIR) if available]. Slice thickness was 5 mm in each case. A T1 weighted 3D gradient echo sequence with slice thickness ranging from 1.5 to 3 mm after contrast application was also performed. The parameters were adjusted to the local requirements of each center. Imaging was done at baseline prior to the resection, within 48 h postoperatively, and at 3 months intervals postoperatively. The baseline studies were used to approximate the volume of contrast-enhancing tumor by determination of the largest diameter on axial, coronal, and sagittal planes. The postoperative scans were used to determine the extent of resection and as a basis for documenting recurrence on subsequent scans.

Histological analyses

The local neuropathologist at each center determined the presence of a malignant glioma by intra-operative frozen sections. A definitive local diagnosis was obtained from paraffin embedded material adhering to the WHO guidelines. Slides were sent for central neuropathological review [3]. All patients included in this subgroup analysis had a diagnosis of glioblastoma WHO grade IV.

Statistical analysis

The subgroup analysis is based on the phase III study that was conducted using stratified blocked randomization by clinical center. Survival was defined as the duration between the date of randomization and date of death, or the date of last contact. A number of secondary endpoints were specified in the phase III trial. Time-to-progression was assessed in three different ways: time-to-KPS decline, time-to-neurological progression, and clinical criterion. A decline in the KPS score was defined as a KPS $<60\%$ for two consecutive assessments. In the case of neurological progression, progression was determined by decline in the neurological evaluation of 10 pre-specified neuroperformance measures [vital signs, level of consciousness, personality, speech, visual status, cranial nerve examination (III, IV, VI), cranial nerve examination (other), sensory status, cerebellar examination, and other signs]. An ordinal scale was used to assess these neuroperformance measures: 1 – normal, 2 – slightly abnormal, 3 – moderately abnormal, 4 – severely abnormal, 5 – not able to perform, and 6 – not done. Deterioration was defined as decline in the scale for two consecutive assessments [3].

Results

Patient population characteristics at baseline

Twenty-four patients randomized to treatment (11 patients were treated with GLIADEL® Wafers and 13 with placebo wafers) in three German study centers were equivalent to 10% of the patient population of the phase III trial. All 24 Patients had a histological diagnosis of Glioblastoma WHO grade IV. There was no statistical difference in age (GLIADEL® group 53.9 ± 9.72 vs. placebo group 60.5 ± 7.99; $P = 0.08$), and KPS (GLIADEL® Wafer group 88.5 ± 12.81 vs. placebo group 85.5 ± 12.14; $P = 0.56$) of the patients in the two treatment groups.

The median survival time for the GLIADEL® Wafer group was 14.7 months and was statistically significantly longer than for the placebo group (9.5 months; $P = 0.007$). At the time of evaluation all patients had died as a consequence of tumor progression.

Time-to-neurological progression analysis

In the GLIADEL® Wafer treated group the mean time to deterioration of the KPS was longer (12.9 ± 4.85 vs. 9.4 ± 2.73 months; $P = 0.035$) as compared to the placebo wafer treated group. The mean time to deterioration for each of 10 individual neuroperformance measures was calculated from the date of randomization to the date of neurological deterioration. In the GLIADEL® Wafer treated group the time to deterioration for 7 of 10 performance measures were statistically longer than in the placebo treated group. For time to

Table 1. Time-to-neurological progression analysis

Neuroperformance measure	Mean time without deterioration (weeks)		*P*-value
	GLIADEL® $n = 11$	Placebo $n = 13$	
Vital signs	62.7 ± 17.25	41.8 ± 11.22	0.002
Level of consciousness	53.5 ± 22.57	40.4 ± 11.02	0.076
Personality	42.6 ± 27.29	30.9 ± 14.77	0.194
Speech	50.1 ± 25.79	33.3 ± 16.53	0.066
Visual status	53.8 ± 23.13	33.8 ± 15.42	0.019
Cranial nerves II, IV, VI	61.6 ± 17.56	41.87 ± 11.22	0.003
Cranial nerves, other	62.7 ± 17.25	34.5 ± 14.51	0.001
Motor status	49.9 ± 22.24	25.2 ± 15.89	0.004
Sensory status	56.6 ± 21.24	35.4 ± 15.58	0.024
Cerebellar status	55.46 ± 26.02	33.1 ± 14.33	0.014

deterioration of 'level of consciousness', 'personality', and 'speech' no statistically significant difference was found, although for all three measures the mean time to deterioration was longer in the GLIADEL® Wafer group than the placebo wafer group (Table 1).

Analysis of recurrence and progression pattern

The blinded evaluation of preoperative gadolinium enhanced MRI and postoperative MRI performed within 48 h after tumor resection and implantation of wafers into the resection cavity demonstrated that in 11 of 24 patients (46%) a clearance of all contrast-enhancing tumor was achieved. Of these 11 patients 5 had received GLIADEL® Wafers and 6 placebo wafers. In 13 cases (54%) the early postoperative MRI revealed areas of contrast enhancement that were diagnosed as residual tumor based on a comparison with preoperative tumor volumes and location as well as persistent perifocal edema and increasing lesions in follow-up MRI studies. However, in all cases with residual tumor a resection greater than 85% of the original tumor volume was achieved, in 20 cases resection was greater than 95%.

The analysis of residual tumor on postoperative MRI was confounded by the fact that implantation of wafers into the resection cavity caused morphological changes of the brain immediately adjacent to the implanted material. On early postoperative MRI studies within 48 h post surgery wafers appeared as an artificial loss of MRI signal with a shape corresponding to the wafers morphology (Figure 1a). Usually follow-up scans, 3 months postoperatively showed resorption of the wafer material (Figure 1b). In some cases, isointense linear structures probably corresponding to wafer remnants could still be detected in the resection cavity at 3 months. Implantation of wafers resulted in a thin contrast-enhancing ring surrounding the resection cavity in eight of the 24 patients. Sometimes a cystic transformation of the resection cavity was observed, however, this did not require any surgical intervention (Figure 1b). Typically, this phenomenon was found at three month postoperatively but declined on follow-up scans. This sequence of morphological events was observed for both carmustine containing wafers (six patients) but also placebo wafers (two patients). This phenomenon was difficult to delineate from manifestation of a recurrent tumor in some cases and follow-up studies were necessary to differentiate tumor regrowth from secondary reaction to wafer implantation (Figure 1c).

Follow up MRI studies were analyzed for the pattern of recurrent tumors or progression of residual lesions. Patterns were classified as 'local, diffuse, multifocal or distant' to the resection site. For those cases ($n = 11$) in whom a complete resection was achieved with no evidence of residual contrast enhancement, the pattern of tumor recurrence was scored as 'local' when a recurrent tumor was found within the wall of the resection cavity (Figure 2a). A 'non-local' recurrent tumor was diagnosed in cases of multifocal recurrence, which may have been distant to the resection site or 'local' but with an additional lesion with no spatial relationship to the resection site. A non-local pattern was also diagnosed when a recurrent tumor involved a large field surrounding the resection cavity involving areas >1.5 cm from the resection cavity on MRI scans with first evidence of recurrence (Figure 2b).

After complete surgical removal a local recurrent tumor immediately adjacent to the resection site was diagnosed in 5 patients that had received GLIADEL® Wafers and in 4 patients with placebo implants.

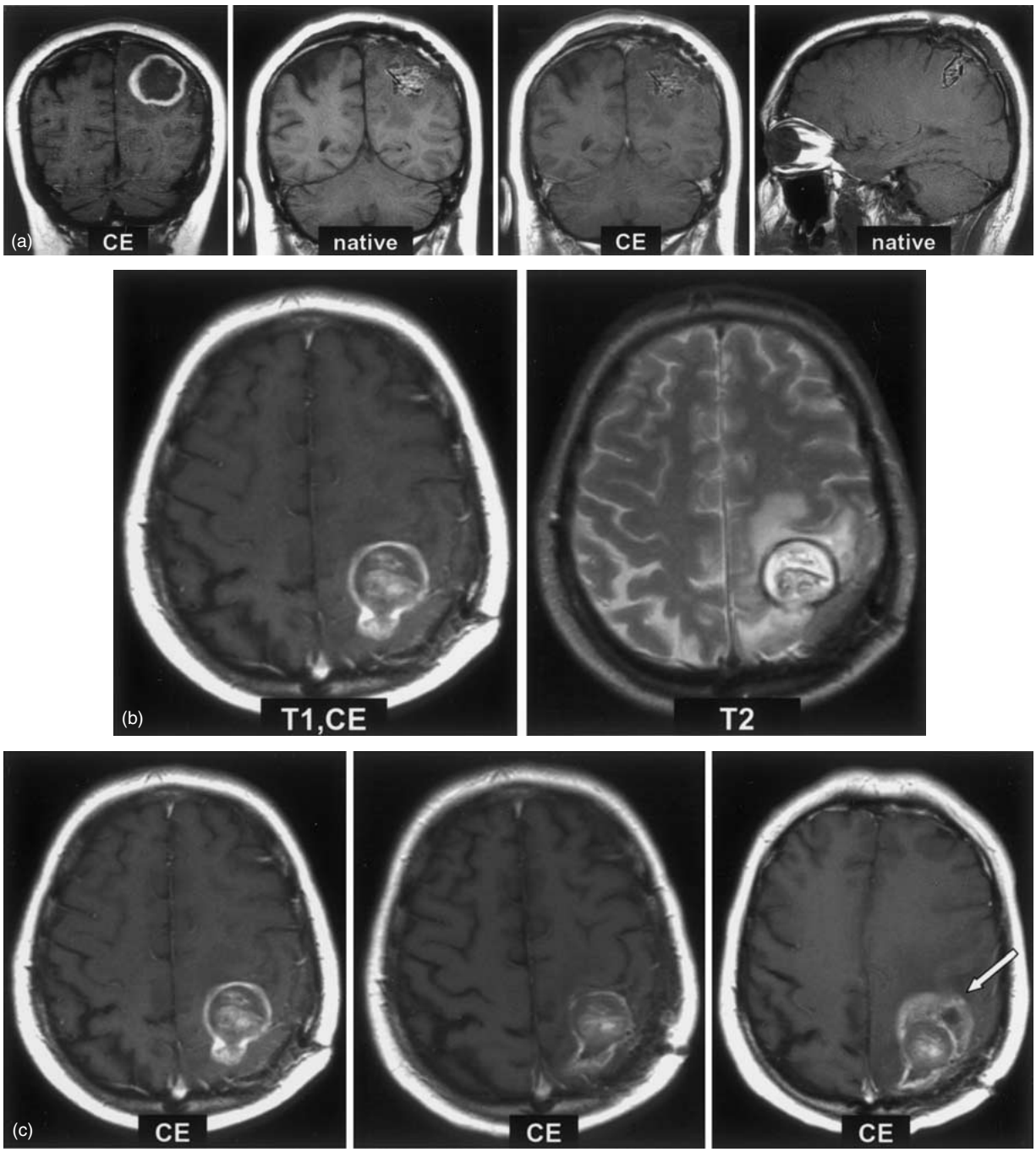

Figure 1. Imaging characteristics of wafer implants on MRI. (a) 45 year-old male diagnosed with a left post central glioblastoma (left image) was randomized to implantation of placebo wafers. Postoperative T1 weighted images show hemorrhagic transformation of the resection cavity without residual enhancing tumor. Wafers are visible as signal free, platelet shaped structures placed adjacent to the resection margins. (b) At 3 months post OP, enhancement of the resection margin is prominent. Remnants of incompletely resorbed blood degradation products and wafer material are noticeable in the center of the cavity, now showing a cystic configuration. Methemoglobin, causing a clear signal decrease, is also located at the resection margins forming a dark ring in the T2 weighted image (right). (c) Time course until tumor recurrence 3, 6, and 8 months post OP (from left to right). At 6 months, enhancement of the resection margin is less prominent and keeps its configuration and size even until local recurrence of the tumor at the rostral margin (arrow) appears.

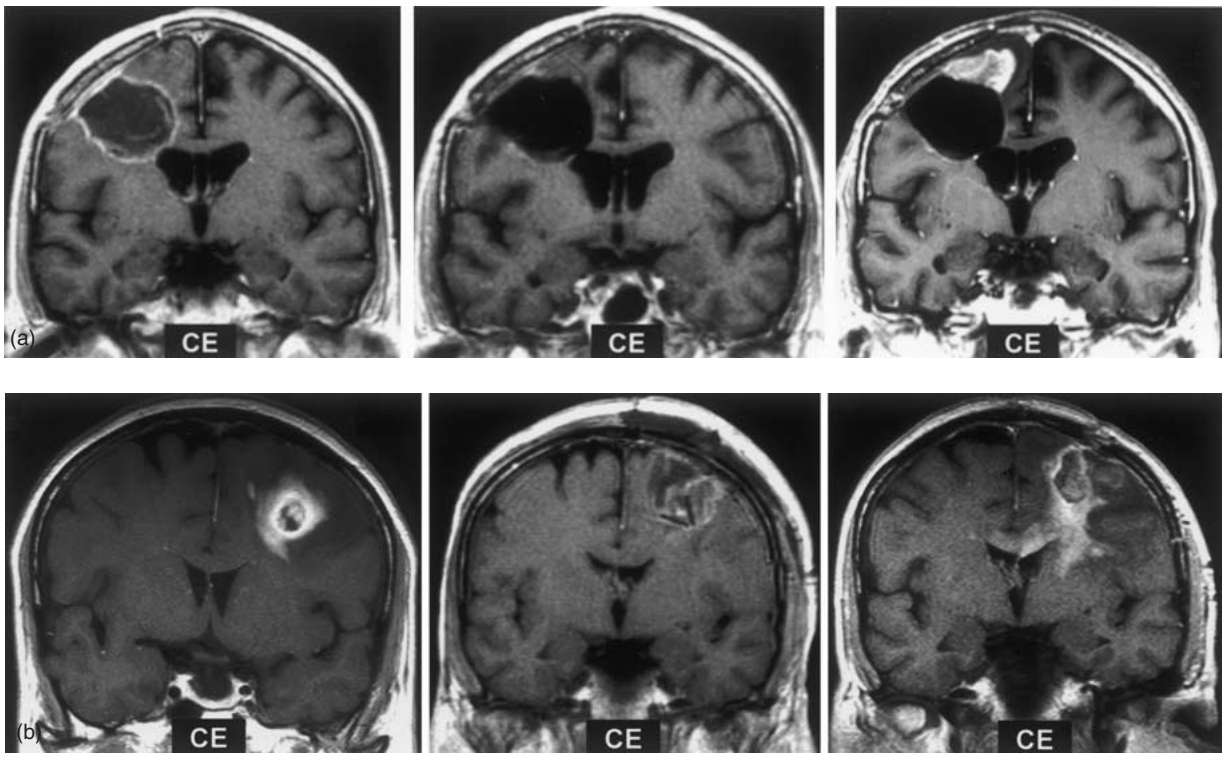

Figure 2. Local *versus* diffuse recurrence after complete resection. (a) Morphology of the resection site at 3, 6, and 9 months (left to right) after resection and carmustine wafer implantation in a 58-year-old male. Coronal T1 weighted images after application of contrast material show enhancement of the margin of the resection cavity, which fully resolved after 6 months. Nine months after resection, a well delineated recurrent tumor occurred at the apical margin. (b) Early diffuse recurrence in a 55-year-old female, preoperative, one day after resection and 3 months later (T1 weighted, contrast enhanced coronal images). One day after surgery, placebo wafers are visible in the resection cavity. No residual tumor is detectable, the signal intense rim is composed of hemorrhagic transformation and early leptomeningeal enhancement. Three months later, a contrast-enhancing tumor invades the deep white matter of the hemisphere and the corpus callosum, with a contiguous pattern form the lower margin of resection.

Recurrent tumor distant to the resection cavity after complete resection occurred in two patients, both had received placebo treatment (Figure 3).

In the 13 patients with residual tumor detectable on postoperative MRI, progression of the disease occurred at the site of the residual tumor in 12 cases, in 8 cases a localized tumor mass increased, in 4 cases a large non-local area of contrast enhancement occurred also involving the resection site. In one case local progression was associated with multifocal distant lesions. Local progression of the disease in cases with residual tumor occurred in 6 patients that had received local chemotherapy and in 7 patients of the placebo group (Figure 4). One patient of the GLIADEL® wafer group showed multifocal progression with a new contrast-enhancing lesion distant to the original site associated with local progression. A single patient 3 months after a clinically silent small local recurrence of a right temporal glioblastoma showed arachnoid dissemination with one cerebellar and three spinal metastases. This patient had received local chemotherapy.

For both patient groups, those with complete resection or residual tumor, local progression was found in 17 of 24 cases (GLIADEL® Wafer group 8 vs. placebo group 9). A pattern of non-local failure was found in 7 of 24 cases (GLIADEL® Wafer group 3 vs. placebo group 4). In no case did failure occur exclusively at a site not related to the site of the original tumor.

The preoperative tumor volume in the GLIADEL® Wafer group was larger than in the placebo group (74.9 ± 43.5 vs. 37.3 ± 23.5 ccm, $P = 0.013$). However, no association of the preoperative tumor volume and a 'local' *versus* 'non-local' pattern of recurrence was found (60.9 ± 43.6 vs. 39.1 ± 14.0 ccm, $P = 0.28$).

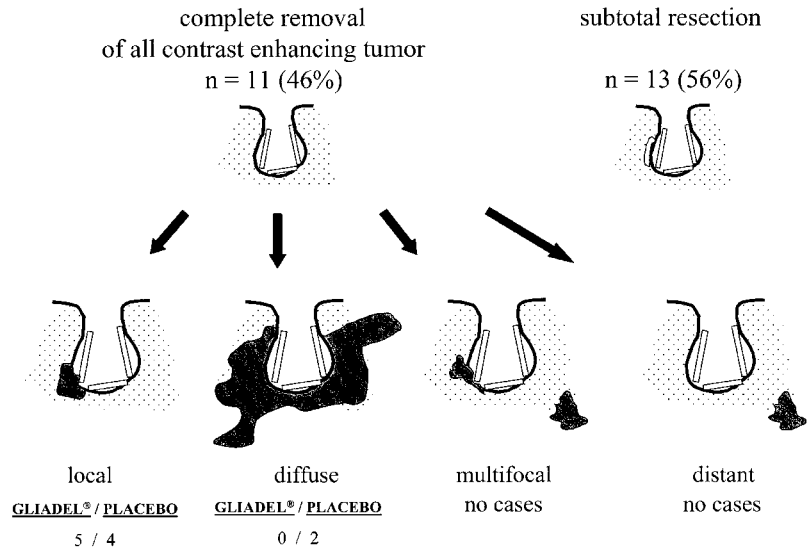

Figure 3. Pattern of recurrence following implantations of polymer wafers. Pattern of recurrence after complete resection of glioblastomas and local implantation of carmustine or placebo wafers.

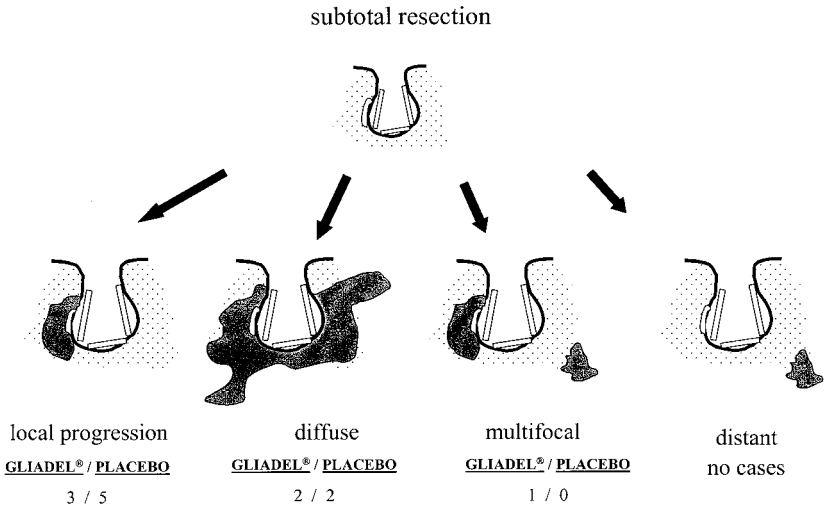

Figure 4. Pattern of progression after subtotal resection of glioblastomas and implantation of carmustine or placebo wafers.

Time-to-progression

The mean time to first detectable radiographic evidence of a recurrent lesion or progression of a residual tumor by at least 25% volume increase was 165.1±80.75 days for the GLIADEL® Wafer group and 101.9 ± 43.06 days for the placebo group ($P = 0.023$) (Figure 5). Patients with no evidence of tumor recurrence or a stable residual tumor beyond postoperative day 200 were all in the GLIADEL® Wafer treatment group (four patients, two of which had residual tumor), with the exception of a single patient in the placebo group, who was progression free for 204 days after a complete resection of a parieto-occipital glioblastoma.

Discussion

With few exceptions, malignant gliomas represent highly invasive tumors. The benefit of surgical removal

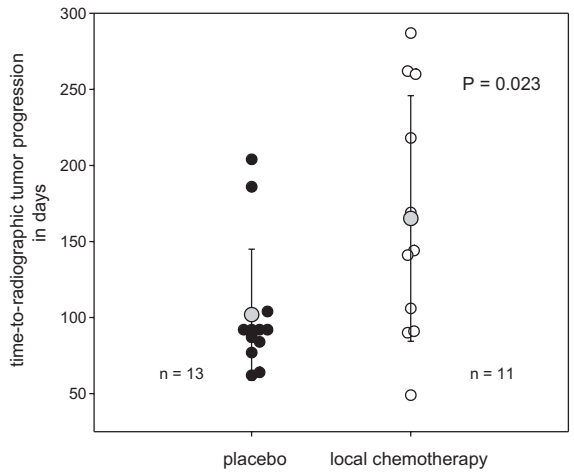

Figure 5. Time to radiographic recurrence or progression following complete or subtotal resection and implantation of carmustine or placebo wafers. Gray circles, mean values; Bars, S.D.

for these malignant and diffuse tumors has been a matter of intense controversy over the past decades. Several studies in the past encompassing thousands of patients had failed to conclusively demonstrate that resection translates into a survival benefit, suggesting that the impact of resection may be relatively small compared to other prognostic factors [7]. More recent studies now postulate that survival may be correlated with the absence of residual contrast enhancement on postoperative MRI [8]. In fact, extent of resection has now been demonstrated to positively correlate with survival time [9]. These results would further argue that aggressive treatment of macroscopic residual tumor is justified to influence early regrowth of malignant gliomas [10–14]. Interestingly, recurrent tumors will arise at the resection margin or within 2–3 cm of the resection cavity in greater than 95% of patients [15,16]. This pattern of recurrence has prompted the idea that local control of the disease by treatment strategies applied directly to the resection cavity may reduce the rate of local failure and may increase the time to local progression and possibly prolong survival time.

Clearly, local recurrence is the most frequent pattern of failure after surgical treatment of malignant gliomas, but the mechanisms that lead to local regrowth of tumors are poorly understood. Presumably, the density of tumor cells remaining after resection of gross tumor is higher at the margins of the cavity and decreases with distance from the core lesion [17,18]. A uniform proliferation rate of the remaining invasive tumor cells would, therefore, lead to regrowth of the mass immediately adjacent to the resection cavity. A local chemotherapy applied directly into the resection cavity results in high local concentrations of the treatment compounds and may retard growth of tumor cells located within the area reached by the compounds. The data from the international phase III trial as well as an independent study for a smaller group of patients have demonstrated that local implantation of GLIADEL® Wafers provides a significant survival benefit to patients with newly diagnosed malignant gliomas and also improved the clinical course of the patients determined by different neuroperformance measures [3,19]. Earlier, a small but statistically significant survival benefit had been demonstrated for treatment of recurrent malignant gliomas following initial resection and radiation therapy [2]. The analysis of our subgroup of patients from the phase III trial reflects these overall results. Release of carmustine from implanted wafers is a passive process and delivery to the adjacent brain relies on passive diffusion. Furthermore, resection of a mass lesion terminates the bulk flow from the center of a tumor directed to the periphery and may even lead to a reversed flow of interstitial fluid into the resection cavity [20]. Presumably, this limits the treatment volume of invaded brain. While local recurrence is the predominant pattern, malignant gliomas may also recur with satellite lesions, sometimes far from the initial site of the tumor and even in the contralateral hemisphere. At time of presentation these lesions are relatively rare and account for less than 10% of malignant gliomas [21,22]. In later stages of the disease multifocal tumors appear to become more frequent and clearly demonstrate that invasive cells will ultimately determine the course of these patients [23,24]. Effective local control of a malignant glioma may ultimately result in more distant recurrent tumors and possibly an increase in a multifocal pattern of recurrence. Multifocal recurrent gliomas leave few treatment options and preclude the possibility of a reoperation. The prolongation of the recurrence free interval by a locally acting strategy would therefore largely depend on the growth kinetics of more distant invasive parts of the tumor. However, our analysis in this small group of patients did not show that local carmustine treatment changed that pattern of recurrence from a predominant local to a more distant pattern despite a prolongation in survival time and a prolonged radiographic recurrence free interval in this patient population. In none of the 24 cases did progression of a tumor occur only at a distant site in the presence of a locally controlled implantation/resection site. This suggest that the potential of this treatment

strategy may not have been reached yet. In animal studies, an increase of the carmustine concentration to 20% resulted in an increased tumor control and survival, whereas a change to prolonged drug release kinetics seemed to be less effective [25]. However, in human recurrent glioblastomas an increase of the carmustine concentration did not result in improved survival compared to a 3.85% of BCNU wafer loading [26] However, there may be a subgroup of tumors that will recur as a local-well defined nodule. These tumors may be more suitable for a local treatment strategy than tumors that recur as large diffuse lesions (compare Figure 2b). At present there are no predictive parameters that will allow identifying these growth characteristics at the time of initial diagnosis.

On serial MRI BCNU containing wafers appear as linear shaped structures of decreased signal on postoperative day 1–2 T1 studies and do not enhance [27]. On 3 months MRI, the wafers in most cases were not detectable. However, in 8 of 24 patients a fine linear contrast enhancement of the walls of the resection cavity was observed on 3 months MRI. This phenomenon was not limited to patients treated with carmustine containing wafers, but also occurred in two cases of placebo treatment. This signal typically decreased on follow up studies. Most likely this perifocal reaction reflects a non-specific response of adjacent brain to the polymer implant. Microscopically Brem et al. have observed a local inflammatory response, gliosis and neovascularization in adjacent brain after wafer implantation into monkey brain. This local response including a 1–2 mm rim of necrosis was more pronounced to carmustine containing wafers than to the placebo wafers [1]. This may explain why a perifocal reaction was more frequently observed in patients that had received Giladel® wafer implants. Because of the imaging characteristics of wafer implants, the location and time of recurrence could in some cases be determined by comparison of the progression pattern on later MRI studies after the wafer associated changes subsided. Therefore, the data on radiographic time-to-progression must be interpreted with caution in this condition.

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