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High-dose Tamoxifen Treatment Increases the Incidence of Multifocal Tumor Recurrences in Glioblastoma Patients*

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Abstract. *Background: Multifocal tumor recurrences in glioblastoma patients are described in 4% - 14% of cases. Two recent studies, treating newly diagnosed glioblastoma patients with continuous high-dose tamoxifen (TAM), reported an increased incidence of multifocal tumor recurrences in 45.5% and 33% of study patients. Patients and Methods: Fifty newly diagnosed patients with glioblastoma were treated with 3 cycles of carboplatin, continuous high-dose TAM and radiotherapy. Tumor progression was determined on follow-up MRI studies at 3-month intervals and categorized as either local or multifocal. Results: Multifocal tumor recurrence was found in 16 (33%) out of 49 study patients. Compared to tumors which remained local, multifocal tumor recurrences were characterized by a significantly longer median time to tumor progression (41 vs. 23 weeks, Breslow test: p=0.0123). Multifocal tumor recurrences were mainly observed after an initial response to the study treatment (81%), whereas local regrowth was more often associated with initial treatment failure, i.e. progressive disease (64%). Conclusion: The association of the pattern of tumor recurrence with the type of response to TAM treatment suggests that acquired resistance to TAM might be an important contributing mechanism in the development of multifocal glioblastoma disease.*

Glioblastomas tend to recur at the location of their initial presentation. In patients postoperatively treated with either radiotherapy (RT) only or with RT combined with chemotherapy including drugs such as cisplatin and carboplatin (CP), multifocal tumor recurrences were observed in 4-14% (1-6).

The anti-estrogen tamoxifen (TAM) is widely used in the treatment of breast cancer patients (7-9). It also acts as an inhibitor of protein kinase C (PKC), which shows a 10- to 100-fold increased activity in malignant gliomas compared to non-neoplastic astrocytes *in vitro*. Therefore an anti-neoplastic effect of this drug was suggested for malignant gliomas (10). Subsequent clinical trials in patients with recurrent glioblastomas, who had failed several previous treatment modalities, demonstrated a response to continuous TAM treatment in approximately 30% of the cases (11-13). Response to TAM therapy resulted either in a cessation of tumor growth or, in some cases, in a complete remission of the tumor. The duration of response to this treatment was variable, but exceeded 12 months in several patients. Several recent clinical studies have confirmed these relatively low response rates of approximately 30% (14-21). Neither a combination of TAM with other chemotherapeutic drugs such as BCNU (20), CP (18, 21), procarbazine (14) or Interferon α (16), nor an adjuvant TAM treatment prior to recurrence of the tumors (18-21) improved these treatment results with respect to median survival times or response rates (Table I).

Reports of serious side-effects with high-dose continuous TAM treatment demonstrated deep venous thrombosis occurring in 9% of patients (12-21). Other less severe side-effects were hot flashes at the beginning of treatment, secondary amenorrhea, transient ovarial cysts, vaginal bleeding and blurred vision.

None of the earlier studies mentioned an increased incidence of multifocal tumor recurrences. However, Muanza *et al.* (19) treated 12 newly diagnosed glioblastoma patients with TAM (120 mg / m^2) combined with conventional radiotherapy in the absence of any additional chemotherapy, and reported that 45.5% of patients suffered a tumor relapse,

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which was distant from the site of the primary tumor. In our study, we observed multifocal tumor recurrences in 33% of the study patients (21). Interestingly, our *in vitro* studies supported the hypothesis of a causal link between a continuous high-dose TAM-treatment and more frequent occurrence of multifocal tumor recurrences in glioblastoma. *In vitro* treatment of glioblastoma cells resulted in a more migratory and proliferative subpopulation, which may be the basis of a more invasive phenotype *in vivo* (22). The clinical course of patients with multifocal tumor recurrences was analyzed with respect to clinical signs of an initial response or resistance to an experimental tamoxifen treatment.

Patients and Methods

Study design and patients' characteristics. The study design, inclusion and exclusion criteria, the patients' characteristics as well as the study treatment performed in our clinical study were previously described in detail (21). In brief, between January 1995 and June 1998, 50 patients (29 males and 21 females, median age: 55 years, mean age: 51.2 years), with newly diagnosed glioblastomas WHO grade IV, were enrolled in a phase II study approved by the ethical committee of Hamburg, Germany (petition no. 986).

Study treatment consisted of a standard tumor resection. One week after surgery, a continuous high-dose, open-end TAM treatment (200 mg/d, Nolvadex®, Zeneca GmbH, Plankstadt, Germany) was initiated. Seven to 10 days following the initiation of TAM treatment, 3 cycles of *i.v.* CP (Carboplat®, Bristol-Myers Squibb GmbH, Munich, Germany) at a dose of 300 mg/m^2 were administered at 3-week intervals. A conventional RT (daily fraction of 1.8 Gy, total radiation dose of 59.4 Gy) was given within 1 week of the last CP cycle. In most cases, dexamethasone treatment was discontinued within the first two weeks after surgery.

Neuroradiological evaluation and criteria for termination of study treatment. Magnetic resonance imaging (MRI) 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. The 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. Imaging was done at baseline prior to the resection, within 48 hours postoperatively, prior to each cycle of CP, 2 weeks after completion of RT and at 3-month intervals thereafter. The postoperative scans were used to determine the extent of resection and as a basis for documenting recurrence on subsequent scans.

Treatment was discontinued either at the time of documented inefficacy, *i.e.* tumor recurrence or progress on MRI scan (TAM: 46 patients, 92%; CP: 7 patients, 14%; RT: 5 patients, 10%), or until serious side-effects occurred (TAM: 4 patients, 8%; CP: 1 patient, 2%).

Criteria for multifocal tumor disease. The combination of the following criteria was accepted as signs for the development of a multifocal tumor disease:

1. New contrast-enhancing lesion on T1-weighted MRI with a diameter of at least 2 mm not detectable on a previous scan.
2a. Distance of this new lesion from the original tumor location greater than 30 mm without signs of contrast enhancement in between foci, if the new tumor developed in the same hemisphere or
2b. Distance of this new lesion from the original tumor location larger than 20 mm without signs of contrast enhancement in between foci, if the new tumor developed in the contralateral hemisphere or infratentorial.
3. Lack of a hyperintense signal on T2-weighted MR-image between a new lesion and the original site of the tumor.

In cases of newly developing, contrast-enhancing lesions measuring less than 2 mm in diameter, but fulfilling the other two criteria mentioned above, diagnosis of multifocal tumor disease was made if a subsequent MRI scan demonstrated a progress of these lesions.

A primary multifocal tumor formation was excluded based on the preoperative MRI scans.

Criteria to define response to study treatment. Response to study treatment was defined according to the criteria given by Macdonald *et al.* (23): *Complete response* (CR): disappearance of all contrast enhancing tumor on consecutive MRI scans at least 1 month apart, off steroids, and neurologically stable or improved. *Partial response* (PR): ≥ 50% volume decrease of contrast enhancing tumor on consecutive MRI scans at least 1 month apart, steroids stable or reduced, and neurologically stable or improved. *Progressive disease* (PD): ≥ 25% increase of contrast enhancing tumor or any new tumor on MRI scans, or neurologically worse, and steroids stable or increased. *Stable disease* (SD): all other situations.

According to this definition, a CR or PR cannot occur in patients who underwent gross total resection (gtr) and who therefore did not present any residual tumor on postoperative control-MRI scan. The response status of such patients (n=13) was classified as SD or PD.

Clinical signs of intrinsic or acquired drug-resistance to TAM. According to Johnston (24), an intrinsic drug resistance to TAM is defined by a failure of the tumor to respond to TAM and by a continuous progress of the tumor under TAM therapy. The criteria for acquired drug resistance to TAM are either a tumor relapse after prior response to study treatment or a spontaneous regress of a tumor mass after TAM withdrawal.

Statistical analysis. A statistical Breslow analysis was used to compare the time- intervals to tumor recurrence and survival times between the subgroups of our study. The correlation between the pattern of tumor recurrence and the response to study treatment, classified according to the above criteria, was calculated two-tailed, by using the non-parametrical Spearman-Rho-test.

Results

Incidence and pattern of multifocal tumor recurrences. All but one patient, who had died before tumor recurrence (fatal pulmonary embolism 13 weeks after surgery), eventually experienced tumor progress or tumor recurrence. The median time to tumor progression (TTP) was 30 weeks (CI:

Table I. *Phase-II studies investigating the efficacy of TAM as monotherapy or combined with other drugs in the treatment of adult patients with malignant gliomas.*

Author	n=	primary/ recurrent tumor	Tamoxifen + added drug	WHO grade: median survival time	response rate
Couldwell *et al.*, 1996 (17)	32	recurrent	monotherapy	III: 185 weeks IV: 76 weeks	44%
Chang *et al.*, 1998 (16)	18	recurrent	Interferon α-2a	II-IV: 26 weeks	22%
Mastronardi *et al.*, 1998 (18)	40	primary	Carboplatin	III+IV: 56 weeks	?
Brandes *et al.*, 1999 (14)	55	recurrent	Procarbazine	III: 57 weeks IV: 27 weeks	29.5 %
Chamberlain and Kormanik, 1999 (15)	24	recurrent	monotherapy	III: 56 weeks	62 %
Napolitano *et al.*, 1999 (20)	46	primary	BCNU	IV: 58 weeks	?
Muanza *et al.*, 2000 (19)	12	primary	monotherapy	IV: 33 weeks	0%
Puchner *et al.*, 2000 (21)	50	primary	Carboplatin	IV: 55 weeks	30%

Table II. *Multifocal tumor recurrence after high-dose TAM treatment in 16 patients.*

Pat. No.	Sex	Age	location of initial tumors	tumor removal	TTP (w)	location of multifocal recurrent tumors	number of recurrent tumor foci	treatment of recurrent tumors	survival time (weeks) treatment	response to study
02	f	26	central, r	ntr	66	periventricular	2	reoperation of local recurrence, stereotactic radiosurgery, fotemustine	113	CR
03	f	35	frontal, r	ntr	94	periventricular	5	reoperation of local recurrence, stereotactic radiosurgery	150	CR
05	m	30	central, r	mr	41	periventricular	4	none	50	CR
06	f	41	frontal, l	ntr	54	periventricular	1	stereotactic radiosurgery	77	SD
11	m	45	frontal, l	mr	33	periventricular	1	none	36	PR
14	m	35	temporal, r	ntr	31	subdural	4	reoperation of new tumor, fotemustine	55	SD
15	f	46	frontal, l	mr	19	periventricular	2	none	42	PD
22	f	55	frontal, r	ntr	89	periventricular	1	reoperation of new tumor	118	PR
29	f	30	central, l	mr	43	periventricular	2	none	45	SD
31	m	60	central, r	ntr	59	periventricular	1	reoperation of local recurrence	119	SD
34	f	63	temporal, r	ntr	33	periventricular	1	none	59	SD
36	f	55	temporal, r	gtr	47	periventricular	1	fotemustine, reoperation of local recurrence	78	SD
37	m	68	central, r	gtr	47	periventricular	2	fotemustine	83	SD
38	f	62	parietal, r	gtr	22	contralateral parenchyma	1	none	22	PD
42	m	35	temporal, l	gtr	33	frontal lobe, skull base	2	reoperation of local recurrence	45	SD
52	m	63	temporal, l	ntr	21	periventricular	1	none	31	PD

TTP = time to progression (weeks); gtr=gross total resection (no residual tumor); ntr=near total resection (>90% removed); mr=major resection (50-90% removed).

25 - 35 weeks, mean: 38 weeks). Thirty-three patients (67%) developed a recurrent tumor or progression of a residual tumor at the primary site and 16 patients (33%) showed multifocal tumor recurrence. Multifocal tumor recurrences (median TTP: 41 weeks, mean TTP: 46 weeks) occurred significantly later (Breslow test: $p=0.0123$) than locoregional tumor regrowth (median TTP: 23 weeks, mean TTP: 34 weeks). However, the median survival time (MST) of patients with multifocal tumor recurrence (median: 55 weeks, mean: 70 weeks) was not different from patients with local tumor recurrence (median: 53 weeks, mean: 72 weeks).

Seven patients with multifocal tumor recurrences were reoperated and had histological confirmation of a recurrent glioblastoma (Table II). Autopsy was performed in 3

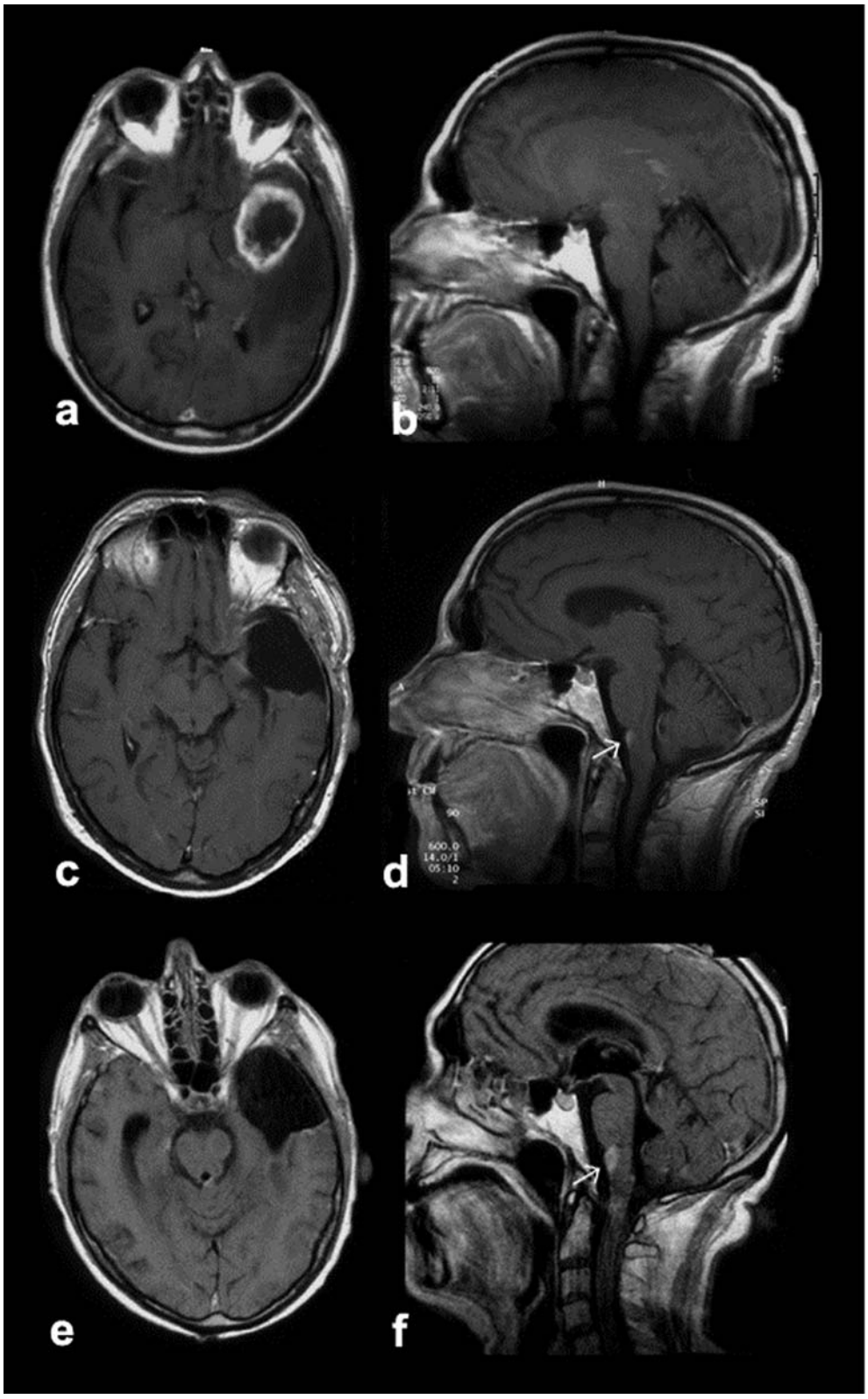

Figure 1. *Contrast-enhanced MRI of a 63-year-old male patient (Table II, pat. no. 52) showing a typical glioblastoma in the right temporal lobe (a). The brainstem showed no evidence of tumor invasion (b). Ten weeks after gtr, no local recurrence was detected (c). However, in the anterior brainstem, a small contrast-enhancing lesion had developed (→, d). A control MRI 24 weeks after surgery confirmed sustained local tumor control (e), but a progress of the brain stem lesion (→, f).*

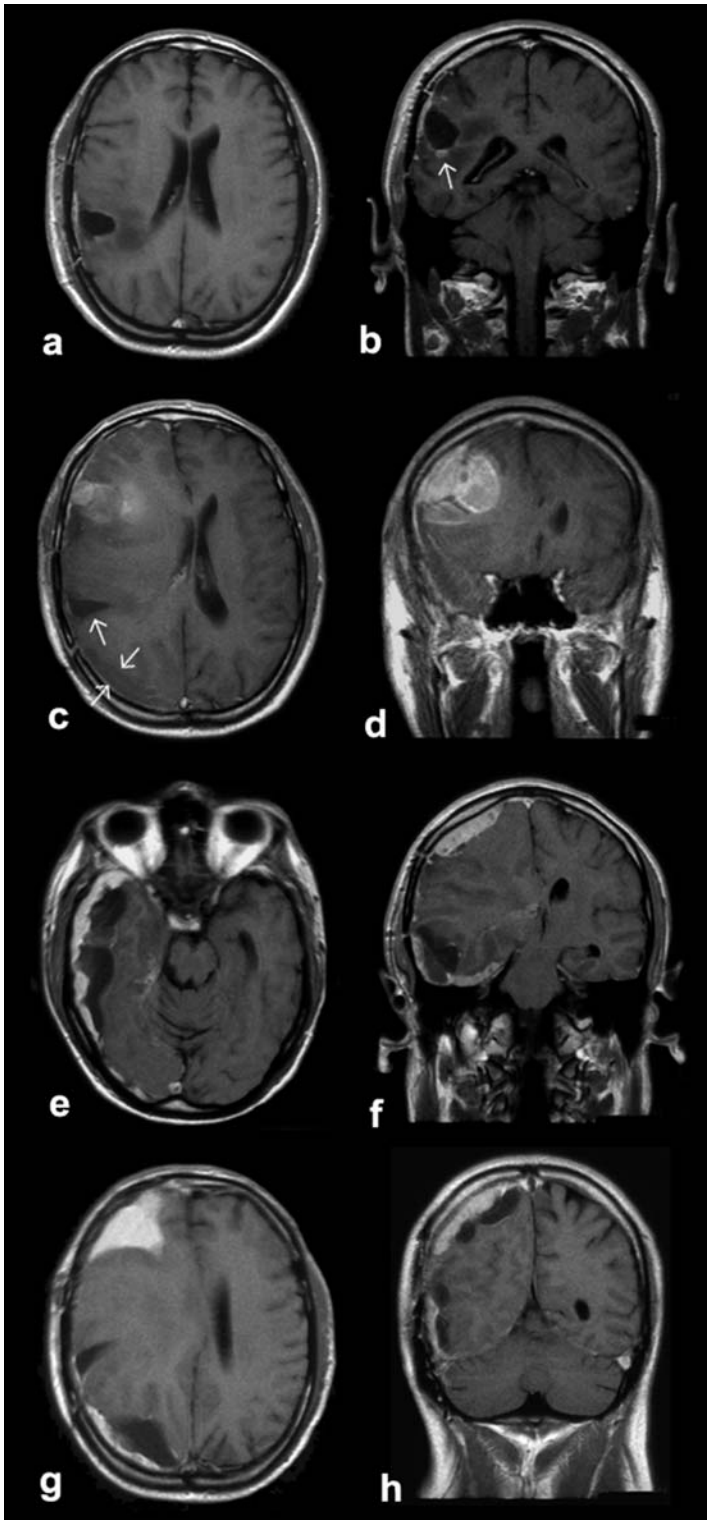

Figure 2. *A 35-year-old male patient (Table II, pat. no. 14) underwent complete resection of a right temporal glioblastoma. Nine weeks after surgery, an MRI scan showed a small nodular structure adjacent to the wall of the resection cavity, which was interpreted as a residual/recurrent tumor (a+b). Thirty-one weeks after surgery, the patient complained about a rapid onset of progressive headache. A large right frontal recurrent tumor was found, which appeared to be extracerebral, originating from the meninges. No local progression had occurred at the site of resection (↑). A parieto-occipital subdural fluid collection (→ ←) was observed (c+d). At reoperation the recurrent tumor was completely removed. However, after 5 weeks the patient again presented with similar symptoms. A MRI scan now revealed a more extensive recurrent tumor within the subdural space, a very unusual growth pattern for recurrent glioblastomas (e-h).*

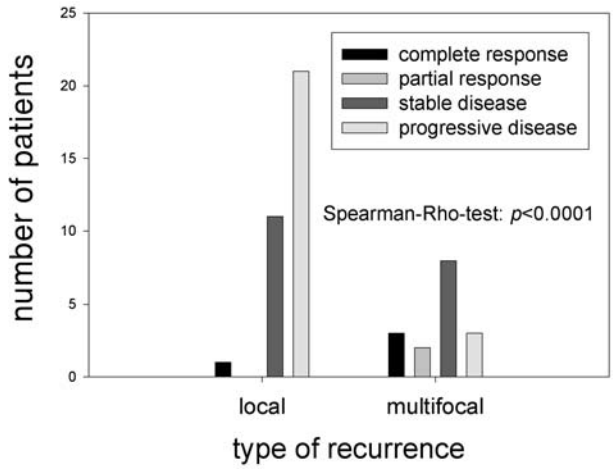

Figure 3. *Pattern of glioblastoma recurrence correlated with response to study treatment (23); Spearman-Rho-test: $p<0.0001$, $r=0.478$. (Gtr at surgery was achieved in 3 SD- and 1 PD-patient developing a multifocal tumor recurrence and in 7 SD and 2 PD patients developing a local tumor recurrence).*

additional patients. In the remaining 6 patients, the diagnosis of tumor recurrence was purely based on the described neuroradiological criteria which, however, were considered as characteristic. In the majority of patients (13/16), new tumors developed adjacent to the ventricular system suggesting a tumor spread by subependymal tumor cell migration or dissemination through the CSF pathways (Figure 1). In one patient, an aggressively and very rapidly growing tumor recurred, occupying the entire subdural space of the ipsilateral hemisphere (Figure 2). Five patients developed multifocal tumor disease despite sustained local tumor control at the original site of resection (Figure 1). Many of the multifocal tumor recurrences were characterized by a relatively small or even missing perifocal edema, although none of these patients received dexamethasone (8/16). In addition, the tumors frequently showed a homogeneous contrast enhancement without signs of central necrosis (14/16). These observations suggest that continuous high-dose TAM treatment has an anti-edematous effect.

Correlation of relapse pattern to the response to study treatment and TAM resistance. Based on the criteria of Macdonald *et al.* (23), 4 patients showed a CR, 2 patients a PR, 19 patients a SD (10 of them after radiographically confirmed gtr) and 24 patients a PD (3 of them after radiographically confirmed gross total resection (gtr)). As demonstrated in Figure 3, the rate of patients initially responding to study treatment was higher in patients subsequently developing multifocal tumor recurrences than among those experiencing local tumor regrowth. This correlation between the pattern of tumor recurrence and the response to study treatment was statistically significant (Spearman-Rho-test: $p<0.0001$, $r=0.478$). Because only a PD could be considered as a definitive sign of a missing response to study treatment, an intrinsic TAM resistance could be assumed in only 3 of the 16 patients (19%) developing multifocal tumor recurrences. In the other 13 patients (81%), an acquired resistance to TAM seemed to be the more likely underlying mechanism. In contrast, 64% (21 out of 33) of patients with a local tumor regrowth showed signs of an intrinsic TAM resistance and only 36% (12 out of 33) of an acquired TAM resistance.

Regress of a recurrent glioblastoma after TAM withdrawal as clinical sign of acquired TAM resistance. In one patient, regression of a recurrent tumor mass was observed after discontinuation of the experimental TAM treatment. A 57-year-old male patient presented with a right occipital single focus contrast-enhancing and ring-shaped lesion. Complete removal was confirmed on postoperative MRI and high-dose TAM treatment, CP and 59.4 Gy of radiation therapy were administered (Figure 4a). Follow-up MRI scans at 10 weeks, 29 weeks and 41 weeks after surgery showed no evidence of tumor. Fifty-three weeks after surgery, the patient complained of headache and fatigue. A control MRI scan showed a large recurrent tumor at the site of initial presentation with no additional areas of contrast enhancement and a marked perifocal edema (Figure 4b). Because of documented tumor progression, the high-dose TAM treatment was discontinued and the patient was given dexamethasone (3 x 4 mg). A second-line chemotherapy was recommended but a five-week follow-up MRI prior to the first cycle of fotemustine demonstrated a 50% decrease of the contrast-enhancing tumor volume on T1-weighted MRI. Furthermore, a resolution of perifocal edema was observed on T2-weighted MRI, paralleled by a significant decrease of the space-occupying effect of the lesion (Figure 4c). Therefore, fotemustine therapy was postponed. Stable disease was documented for two more months, followed again by local progression. The subsequent chemotherapy using fotemustine resulted in a temporary tumor control. However, the patient died of tumor progression 104 weeks after the initial operation.

Discussion

Local progression is the predominant pattern of treatment failure in glioblastoma and multifocal tumor recurrences are a relatively rare phenomenon. According to the literature, this growth pattern is observed in only 4%-14% of glioblastoma patients treated with surgery and radiotherapy or an additional chemotherapy (1-6). Multifocal recurrent glioblastomas are thought to occur more frequently with prolonged course of the

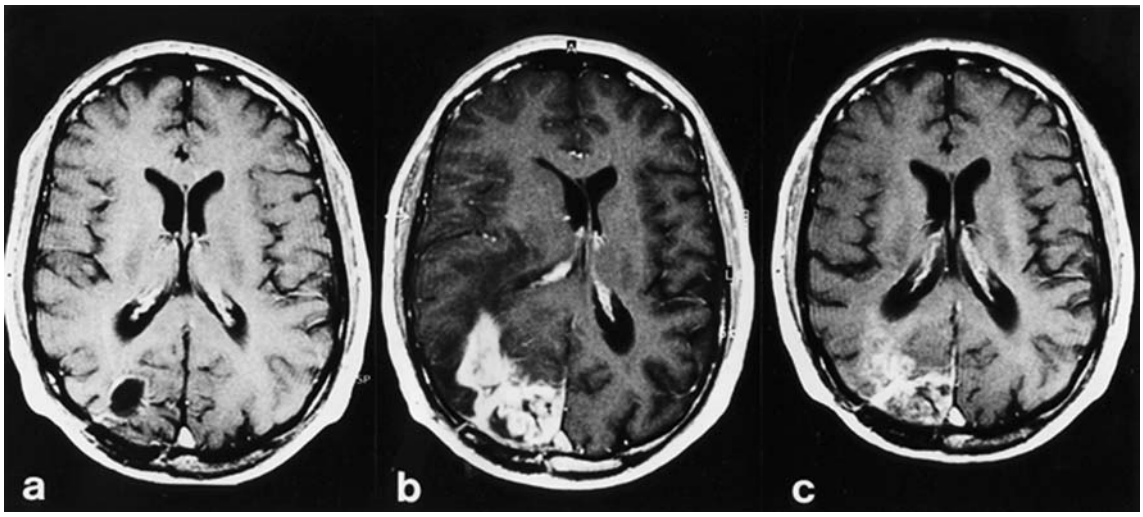

Figure 4. *MRI scan of a 57-year-old study patient who underwent gtr (a). Fifty-three weeks after surgery, a large locoregional tumor relapse was diagnosed (b), which led to termination of TAM therapy. The tumor responded to TAM withdrawal by a remarkable tumor shrinkage documented by another MRI scan 5 weeks after TAM withdrawal (c). More details of this case are described in the text.*

disease and extended survival (25). This may be based on the fact that glioblastomas present tumors that, at the time of diagnosis, have spread far into the adjacent brain, possibly affecting the whole CNS (26). Obviously, at the time of diagnosis, these tumors are not restricted to the area demonstrating radiographic changes (27). The microscopic invasive tumor may manifest with multiple macroscopic lesions in the form of a multifocal glioblastoma, prior to regrowth of a lethal mass at the initial site (25, 28).

An increased incidence of multifocal tumor recurrences in glioblastoma patients treated with TAM may be explained by the longer survival time of patients suffering this pattern of recurrence compared to those experiencing local tumor recurrences. This, however, is not the case in our study, or in that of Muanza *et al.* (19, 21). In our study, the MST of patients with multifocal tumor recurrences (55 weeks) did not differ from those with local recurrences (53 weeks). In the study of Muanza *et al.* (19), no responder to TAM therapy was identified and the MST of the entire study population was rather low (33 weeks), strongly arguing that the appearance of multifocal tumor recurrences in 45.5% of patients cannot be explained by an extended survival.

These clinical observations raise the question of a causal link between the high incidence of multifocal tumor recurrences and the treatment regimen of the glioblastoma patients in both studies (19, 21). Analyzing the two treatment regimens of these studies, TAM seems to be a common denominator, because the effects of surgery and radiotherapy on the recurrence pattern of glioblastomas are well-known and carboplatin was not included in the study of Muanza *et al.* (19).

If TAM is the agent responsible for an increased incidence of multifocal tumor recurrences in glioblastoma, the question arises as to how TAM may mediate these effects. According to Johnston (24), two different types of drug resistance can be distinguished. An *intrinsic* resistance is defined by a failure of the tumor to respond to TAM and by a continuous progress of the tumor despite TAM therapy. An *acquired* resistance is characterized by an initial response of the tumor to TAM therapy before resistance and regrowth. In advanced breast cancer, 50% of patients show characteristics of an intrinsic TAM resistance and 50% of an acquired resistance (29). Interestingly, this ratio of patients with intrinsic and acquired drug resistance to TAM was very similar in our group of glioblastoma patients (49% intrinsic, 51% acquired).

However, when stable disease under a tamoxifen regimen is considered to be a sign of response to study treatment rather than treatment failure, multifocal tumor recurrences developed in 81% of patients who had demonstrated an initial response to the study medication. This indicates that drug resistance to TAM in these cases may not be intrinsic but acquired (Figure 3). In contrast, patients with a local pattern of failure more often showed progressive disease as a sign of intrinsic TAM resistance (64%). Therefore, we suggest that the acquired drug resistance to TAM may be an important contributing mechanism to the high incidence of multifocal tumor recurrences, after the experimental treatment performed in our study and that of Muanza *et al.* (19).

Further evidence for this assumption may be provided by the TAM withdrawal effect, which was observed in one of

our study patients. A tumor growth-promoting effect of TAM has been described as another effect of acquired drug resistance in breast cancer and was observed in a small number of patients (24). In the clinical setting of breast cancer, this phenomenon could be demonstrated indirectly by tumor regressions following TAM withdrawal (30-32). These observations are paralleled by experimental data *in vitro* and *in vivo*. *In vitro*, TAM resistance in a TAM-sensitive MCF-7 breast cancer cell line could be induced by permanent TAM exposure. TAM-resistant strains of this cell line show an increased growth rate in the presence of TAM, in contrast to a growth inhibitory effect on the parental cell line (33). Experiments, in which MCF-7 xenografts established in ovariectomized nude mice were treated with long-term TAM regimens, showed a similar phenomenon. Acquired drug resistance resulted in a growth-stimulatory effect of TAM and a growth inhibition following subsequent TAM withdrawal (34, 35).

Such a phenomenon was also observed in our study. After TAM withdrawal, one of the study patients demonstrated a remarkable regression of a locoregional recurrent tumor, which had developed under continuous high-dose TAM therapy given for 52 weeks. The patient was treated with dexamethasone following TAM withdrawal. Well aware that dexamethasone may have some growth-inhibitory effect in a few glioblastoma patients (36), we consider it unlikely that, in our case, the dexamethasone treatment contributed to this remarkable decrease in tumor volume with a sustained effect for 3 months.

In addition to the clinical observations described above, we have previously reported *in vitro* evidence that TAM resistance may occur in glioma cells and that resistance results in a distinct phenotype of glioma cells (22). These data demonstrated that acquisition of TAM resistance can be induced by long-term sublethal exposure to TAM of established glioblastoma cell lines. TAM-resistant glioma cell subpopulations were characterized by a more migratory phenotype and a more rapid growth pattern compared to the non-resistant parental cell lines. These data suggest that acquisition of resistance to TAM may increase the invasive behavior of glioma cells, promoting rapid dissemination of the disease and enhance proliferation resulting in a rapid growth rate. Clinically this may lead to the manifestation of multifocal tumors.

Although acquired drug resistance to TAM may be a contributing mechanism in the development of multifocal tumor recurrences after initial response to TAM and a tumor decrease after TAM withdrawal, it is not an obvious explanation for the phenomenon that 3 of our study patients (6%) developed a multifocal tumor recurrence even after a very short time, obviously defining their tumors as intrinsically resistant to TAM. In those few patients, TAM may have caused an explosive and multifocal tumor progress. The mechanism of this suggested contra-productive drug effect seems to be independent of the type of drug resistance, though unclear at present.

Looking at the fate of those patients and the results of the study of Muanza *et al.* (19), who described a rate of 45.5% of patients developing multifocal tumor recurrences but not responding to TAM treatment, the question arises as to whether TAM might have worsened the prognosis of these patients by acting paradoxically *i.e.* in a tumor growth and invasion-promoting way. This, however, necessitates reassessment of the role of TAM in the treatment paradigm of glioblastoma, regardless of whether methods to predict a response to TAM in the individual patient are available or not (37-40).

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