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REVIEW

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Treatment of malignant glioma: a problem beyond the margins of resection

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Abstract The treatment of malignant glioma remains problematic. Surgical removal followed by external beam irradiation represents a standard treatment that has demonstrated a prolonged time to progression and survival. However, the capacity to locally invade normal brain invariably leads to formation of a recurrent tumor most often immediately adjacent to the site of resection. This clinical everyday experience prompts the hypothesis that improved local control of the tumor may translate into a delayed time to progression and possibly survival, specifically because systemic chemotherapy for most of these tumors has failed to significantly improve survival. Local treatment strategies including chemotherapy, gene therapy, and immunotherapy are rapidly developing and progressing to clinical trials. Several theoretical considerations suggest that these approaches may be promising in the treatment of brain tumors.

Key words Glioma · Experimental therapy · Chemotherapy

Introduction: clinical pathology of malignant gliomas

Malignant gliomas represent the largest group of glial tumors in humans and with few exceptions are highly invasive tumors. The benefit of surgical removal has been a matter of intense controversy over the past decades. In 1991, Quigley and Maroon reviewed twenty reports comprising more than 5600 patients treated over a period of 30 years. Only four studies found an association between surgical resection and survival whereas most major series encompassing thousands of patients did not (Quigley and Maroon 1991). Even those studies that did identify a positive impact of surgery recognized other variables that ranked higher in significance than surgery. The modest impact of surgery on survival may be due to the overriding importance of other variables. In one such study, survival was increased four times in patients younger than 45 years versus 65 years (Winger and MacDonald 1989). Age and neurological performance have been confirmed as higher ranking predictors of outcome than surgery by several authors (Burger and Green 1987; Chang et al. 1983; Coffey et al. 1988; Devaux et al. 1993; Leibel and Sheline 1987; Nazzaro and Neuwelt 1990). Further analysis of many of the older studies revealed several shortcomings such as failure to control for patient age, functional status, tumor location, histological criteria, selection bias, selective utilization of radiation, and retrospective analysis. However, more recently, a significant correlation was found for survival and no residual contrast enhancement on postoperative magnetic resonance imaging (MRI) (Albert et al. 1994). There is now a general consensus that aggressive removal of macroscopic tumor could influence early regrowth from tumor remnants and possibly influence survival. It remains open whether any other surgical procedure which results in subtotal or close to total removal significantly impacts on survival. Nevertheless, an increasing number of authors have come to the conclusion that the extent of tumor resection may be a decisive prognostic factor (Ammirati et al. 1987; Andreou et al. 1983; Ciric et al. 1990; deTribolet and Frankhauser 1991; Hirakawa et al. 1984; Höllerhage et al. 1991; Murovic et al. 1986; Salcman 1987; Vecht et al. 1990; Wisoff et al. 1998). Postoperative external beam radiation therapy with a dose between 55 and 60 Gy applied to the tumor volume and a variable safety margin of adjacent brain has also been established as a standard treatment (Walker et al. 1979). A recent prospective study evaluating the impact of surgery versus biopsy alone in a cohort that received 60 Gy conventional radiotherapy could only demonstrate an advantage of surgery in those patients who showed a

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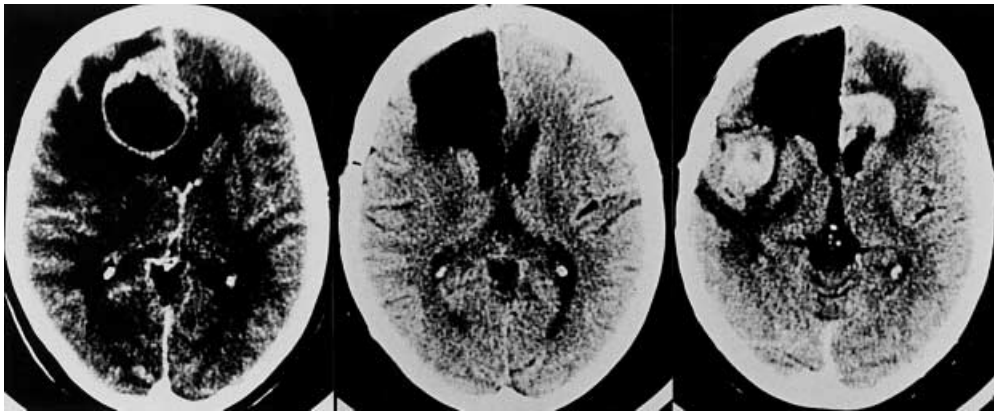

Fig. 1 Histologically confirmed glioblastoma WHO IV in a 56-year-old woman who presented with glioblastoma (*left*). A macroscopically complete resection was performed followed by conventional radiation therapy (*middle panel*). The patient underwent a second resection of a discontinuous temporal tumor 2 months later (not shown). Ten months later, multifocal, recurrent tumors were diagnosed immediately adjacent to the resection cavity (*right*). This pattern of local failure is observed in more than 90% of malignant gliomas

significant mass effect. In the absence of midline shift, no significant difference in survival was found between resected and non-resected patient groups (Kreth et al. 1999). Despite the established treatments these tumors will recur and subsequently cause neurological deterioration and death. Mean survival time remains poor and can be estimated between 12 and 18 months after diagnosis. Interestingly, after surgical resection of a glioma, invasive cells will invariably give rise to a recurrent tumor, which in 96% of the cases arises immediately adjacent to the resection margin or within 3 cm of the resection cavity (Burger et al. 1983; Gaspar et al. 1992). This pattern of local treatment failure most likely is due to a high density of remaining tumor cells within the proximity of the removed highly cellular part of the lesion, but may also be due to changes in the extracellular matrix environment after formation of glial scar tissue following resection (Fig. 1). In this sense, control of the disease by local treatment strategies applied to the resection cavity may reduce the rate of local failure and may increase the time to local progression and prolong survival time.

Strategies of local control

Local chemotherapy

Supraselective intra-arterial delivery

To increase local drug concentrations and reduce systemic toxicity intra-arterial administration of various agents has been evaluated in the treatment of gliomas. To further increase selectivity of intracarotid infusion, placement of microcatheters into branches of the middle cerebral artery has been used. These applications may be combined with local disruption of the blood-brain barrier, which again increases tissue concentrations of the drug and further allows reducing the total amount of drug required. To temporarily open the endothelial barrier, hyperosmotic substances or analogs of bradykinin (RMP-7) have been used and currently a multinational trial is investigating administration of carboplatinum following modification of the blood-brain barrier with RMP-7 (Gregor et al. 1999). The latter study demonstrated significant activity of these compounds in recurrent glioma patients, in particular in those who had not received prior chemotherapy. However, the intra-arterial application of these highly toxic compounds is associated with a significant risk. For example, administration of alkylating substances into the carotid artery has resulted in a leukoencephalopathy with significant morbidity (Shapiro et al. 1992). Supraselective infusion of carboplatinum into more distal vascular territories has demonstrated significant difficulties in the prediction of flow-related effects and steel phenomena that may alter the distribution of the agents. This compound, which has a high toxicity for the vascular endothelium, may result in local infarctions (Cristante et al. 1992). So far, no clinical study has demonstrated a clear treatment advantage of this method of drug delivery for malignant gliomas.

Intralesional deposition of biodegradable polymers

Another strategy to increase drug concentrations within the tumor while sparing systemic toxicity is to locally implant biodegradable polymers, which show slow-release of encapsulated drugs (Fig. 2). The first experimental implantations of such polymers in a clinical setting were started in 1987 (Brem et al. 1994). These polymers contained BCNU (Gliadel) because at that time this was the compound with which there was the most extensive experience in the context of glioma treatment. Subsequently, clinical phase I and II trials were completed and a randomized trial investigating implantation of Gliadel wafers containing 7.7 mg of carmustine for recurrent glioblastoma demonstrated

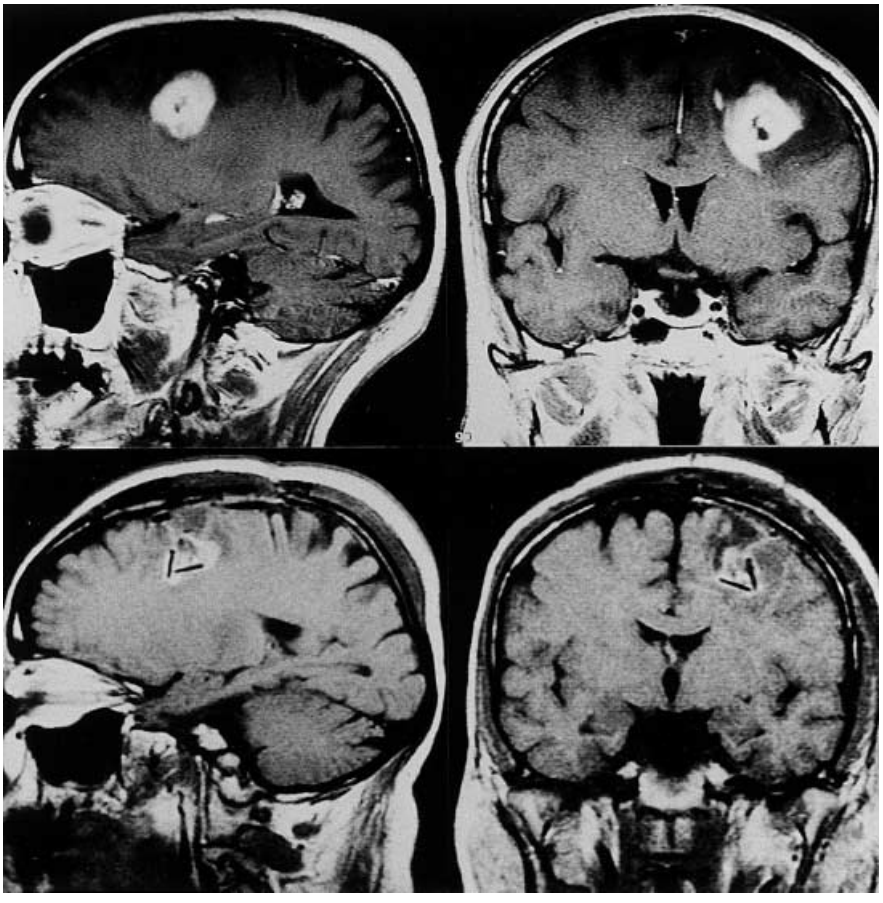

Fig. 2 Preoperative contrast enhanced T1 MRI of a histologically confirmed glioblastoma WHO IV showing a left frontal lesion with perifocal edema (*upper panel*). After what appears to be a gross total resection, biodegradable wafers containing carmustine were implanted into the resection cavity and can be identified as hypointense structures on postoperative MRI (*lower panel*)

prolonged survival compared to a placebo group (Brem et al. 1995). The polymer is designed to release the compound over a time interval of 3 weeks with over 50% of the drug being released within the first 24 h and 95% released by 120 h. As a first-line treatment of newly diagnosed malignant gliomas, this regimen has been investigated in a different randomized placebo-controlled trial after a pilot study had demonstrated promising preliminary results (Valtonen et al. 1997). In this multinational trial, over 250 patients had been enrolled and treatment results are expected in 2000. A small cohort study for the treatment of recurrent glioblastoma demonstrated that local application of chemotherapy is associated with a higher incidence of perioperative complications such as wound infections and seizures. This study was unable to detect a treatment advantage (Subach et al. 1999). However, independently of the results obtained from these recent trials, it is clear that this technology of drug delivery in the treatment of brain tumors is at the very beginning of a promising development. The polymer technology is largely independent of the compounds that may be encapsulated. In addition to other drugs that could be evaluated for intracerebral administration such as doxetaxel, mitoxantrone or platinum, different release kinetics and solubility characteristics would be desirable in the treatment glioma. A more prolonged release of compounds or sequential release of combined chemotherapy may be promising future developments.

Convection-enhanced delivery

Typically, the contrast-enhancing core of malignant gliomas is located within a much larger area of edema which is best visualized in T2-weighted MR images. It has been clearly demonstrated that this zone is not just an area of reactive brain tissue but rather reflects the extent of invaded brain. Biopsies taken from the contrast-enhancing center of a lesion towards the periphery yielded tumor infiltration throughout the T2 abnormal area and even within brain that showed no abnormal signal on MRI (Kelly et al. 1987). Gliomas produce a variety of factors regulating neovascularization and vascular permeability (Schmidt et al. 1999). Increased permeability of tumor vessels is the basis of edema which follows a directional flow from the bulk mass of the tumor to the periphery where it is subsequently absorbed and cleared (Reulen et al. 1988). The pattern of edema as a consequence of the bulk flow is modulated by the physical properties of anatomical brain structures. Large molecules may be passively transported and distributed within a large volume of brain following this continuous flow. Initially, the validity of this concept has been

demonstrated by placing catheters into non-resectable tumors followed by a positive pressure infusion (Liebermann et al. 1995; Laske et al. 1997). A small group of 18 patients diagnosed with recurrent glioblastomas was treated with transferrin-conjugated diphtheria toxin. Fifty percent of the treated glioblastomas responded with two cases of complete remission (Laske et al. 1997). Infusion rates vary considerably, obviously depending on the degree of pre-existing space occupied by a lesion (Reulen et al. 1988). However, 10 µl/min equaling 14 ml/day can be safely achieved. The preliminary evaluation demonstrates that experimental compounds can reach a large brain volume. This route of drug administration offers several advantages. Compounds are delivered regardless of their ability to penetrate the blood-brain barrier. Furthermore, interstitial delivery may prolong the half-lives of some compounds compared to intravenous or intra-arterial application. However, in contrast to other local treatment strategies, convection-enhanced delivery using edema flow will be reserved for selected patient populations, mainly with small moderately space-occupying tumors which are surgically inaccessible. The geometry of larger tumors may require placement of multiple catheters. Because removal of a brain tumor usually results in fast resolution of edema and a reversal of fluid flow now directed towards the resection cavity, this treatment can only be applied to non-resected tumors either as a treatment or as a pretreatment.

Currently a multicenter phase I trial is investigating convection-enhanced delivery of IL-4 conjugated *Pseudomonas* exotoxin (Fig. 3). This therapy is based on the observation that human malignant glioma cells express high affinity IL-4 receptors, which is a possible target for receptor-directed toxin therapy. An IL-4 fusion protein containing the translocation and enzymatic domains of Pseudomonas exotoxin has demonstrated complete remission of experimental tumors when injected directly into a lesion. In this xenograft model no evidence of toxicity was found (Husain et al. 1998).

Immunotherapy

For a long time, several investigators have tried to identify epitopes specific to glial tumors. However, local immunotherapies have shown little effect in clinical settings. Most epitopes present either on tumor cells or within the extracellular matrix of gliomas such as variants of CD44. The transferrin receptor, or tenascin are at best overexpressed in gliomas but have not proven to be truly glioma specific. Because of their molecular weight antibodies do not efficiently cross the blood-brain barrier. To circumvent this problem antibodies have been administered directly into tumors or tumor resection cavities (Wersall et al. 1997). Such antibodies binding to tumor epitopes may be conjugated with isotopes or immunotoxins and have been shown to retain these compounds within the area of the tumor for prolonged periods of time (Bigner et al. 1995; Reist et al. 1995; Riva et al. 1997). One such strategy has recently entered a clinical phase I trail. In this recent study, an iodine-131-labeled monoclonal antibody to the matrix protein tenascin, which is highly expressed in the matrix of malignant gliomas, was injected into the resection cavity of newly diagnosed malignant gliomas (Akabani et al. 2000).

Alternatively, immunomodulators and activated immunocytes such as lymphokine-activated killer cells and tumor-infiltrating lymphocytes have been applied locally (Fig. 4). These strategies face several limitations. Preliminary trials investigating direct infusion of, for example, IL-2 have demonstrated an extraordinary local toxicity (Köppen et al. 1991). Furthermore, a complex interaction of glioma cells and immunocytes has been demonstrated to result in rapid inactivation of T-lymphocytes, for example, through secretion of immunosuppressive factors such as TGF-β (Fontana et al. 1992). In addition, it has to be kept in mind that the interaction between immunocytes and glial tumor cells may be complex. Several cytokines released from activated lymphocytes also have growth or motility effects on glioma cells. This interaction is poorly understood to

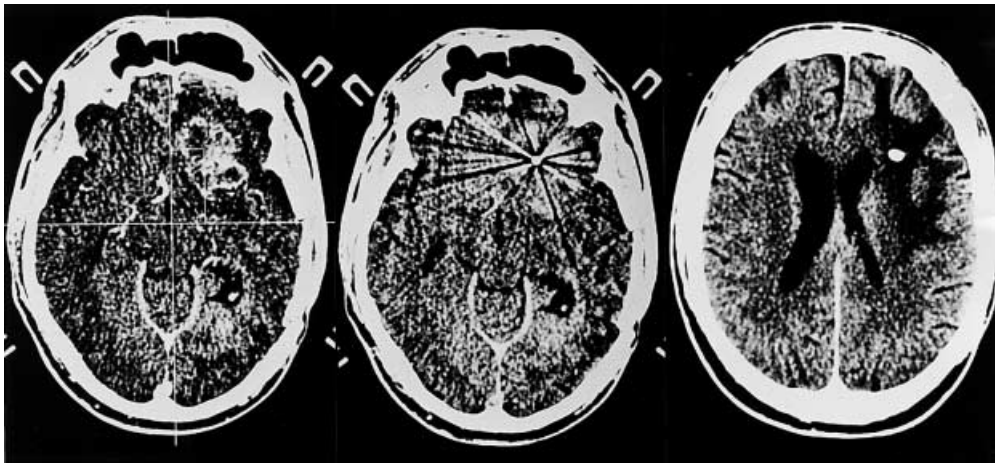

Fig. 3 Intraoperative contrast-enhanced CT scan of a non-resectable recurrent glioblastoma (*left*) which was confirmed by a stereotactic biopsy (*middle*). After biopsy, a catheter was placed into the center of the lesion (*right*) which was subsequently used for convection-enhanced delivery of an IL-4 conjugated Pseudomonas exotoxin

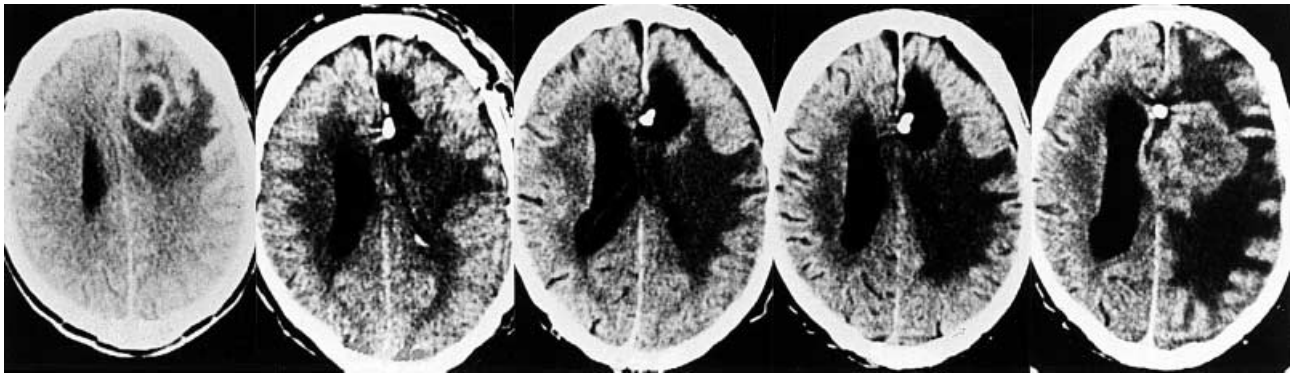

Fig. 4 CT-documentation of a case in which after resection of a tumor (*A*), a catheter was placed into the cavity through which IL-2 was applied directly (*B*). In the subsequent weeks (*C*, *D*) there was a massive, persistent, steroid-resistant edema and, nevertheless, several months later a recurrent tumor (*E*)

date. Despite these drawbacks several promising approaches are under pre-clinical investigation including ex vivo manipulation of effector cells, reversal of tumor derived immunosuppression, and induction of increased immunogenicity of glial tumor cells.

Gene therapy: a concept on hold

Due to the fact that malignant brain tumors are confined to their primary location in the central nervous system and do not metastasize, these tumors lend themselves to novel technologies and local treatment strategies. Systemic gene therapy today still remains polemic mainly because of biologic safety concerns. However, the central nervous system may represent a suitable target for a local gene therapy. Recent developments in cell biology have identified numerous potential targets for gene therapy-directed manipulation of cellular functions. This includes replacement of mutated tumor suppressor genes, induction of immunogenicity of tumor cells, or transduction of tumor cells with suicide genes, which selectively sensitize transduced cells to chemotherapy (Kramm et al. 1995). Two clinical phase III trails have evaluated the concept of suicide gene delivery for the treatment of newly diagnosed malignant glioma. For these trials, a retroviral transduction of the herpes simplex thymidine kinase gene (HSV-Tk) was used (Culver et al. 1992; Ram et al. 1997). After surgical removal of a tumor, a cell suspension of vector-producing murine fibroblast is implanted into the tissue surrounding the resection cavity. These vector-producing cells release a modified Molony leukemia retrovirus, which carries the HSV-Tk gene. Viral infection of surrounding tumor cells transduces the suicide gene. The retrovirus selectively infects proliferating cells. Within normal brain there are practically no proliferating cells which lend natural tumor selectivity to this method. The retrovirus is infection competent but replication deficient preventing uncontrolled propagation of the viral infection. Two weeks after implantation ganciclovir is intravenously administered which is activated in HSV-Tk transduced tumor cells by phosphorylation. This leads to DNA fragmentation and activation of an apoptotic cascade, the cellular suicide program, both in vector-producing cells and transduced tumor cells. This direct effect on transduced tumor cells is enhanced by the increased cell death of neighboring tumor cells. This so-called bystander effect is mediated by gap junction communication (Mesnil et al. 1996).

Both multicenter studies have been completed and have demonstrated the safety of this clinical application but failed to demonstrate a clear therapeutic effect. This failure may reflect the low transduction rates associated with the retroviral vectors available at the moment. In contrast to animal studies, where transduction rates of 50% where achieved in the clinical situation, these rates where estimated to be less than 0.1%. Furthermore, implantation of the vector-producing cells using injections spaced at approximately 1 cm may not be adequate tools to disseminate the virus wide enough to access tumor cells within invaded adjacent brain. This may be illustrated by the patterns of failure after treatment (Fig. 5). However, it is important to understand

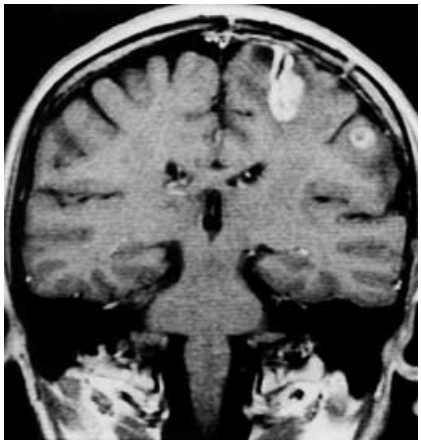

Fig. 5 A left parietal glioblastoma was initially resected and a local gene therapy was performed by implantation of vector producing cells into the walls of the resection cavity. After 10 months a recurrent tumor was diagnosed with a relatively small tumor mass directly adjacent to the resection cavity and a second, more distant, satellite lesion arising from an area that had not been implanted

that the development of viral vectors is rapidly progressing. Adenoviral- and HSV-based vector systems, for example, promise significantly higher transduction rates and may also be usable as replication competent systems (Alemany et al. 1999).

Radiation therapy

In addition to local chemotherapy and immunotherapy, various forms of interstitial radiation have established themselves as classical, neurosurgical local therapies. This modality, however, has very strict limitations regarding the size of the treatable lesion. For this reason, the lesions are frequently rather low-grade tumors (WHO grade I and II) and metastases. As radionuclides, iridium as well as iodine-125 have been used (Ostertag 1994), with I-125 seeds as temporary high-energy implants or permanent low-activity implants (McDermot et al. 1998). In certain selected situations, such as recurrent or small primary tumors as well as in high-grade gliomas, recurrent, small primary tumors receive implants as an adjuvant therapy and some increase in median survival for a highly selected group of patients seems to be demonstrable (McDermott et al. 1998). The diagnosis and treatment is always based on stereotactic procedures. More recently, a radiation point source has been introduced as a radiosurgical tool for interstitial radiation which is also inserted stereotactically and left in place for a short period of a few minutes and removed after application of the total dose (Cosgrove et al. 1997). It is generally accepted that these modalities will have little impact on the management of glioblastoma in general, except for some rare deep-seated lesions which are detected early while they are still small – and are only amenable to stereotactic treatment anyway – and residual tumors in deep locations or small recurrences.

The limits of local treatments

Despite the clinical fact that most gliomas recur locally, the true dissemination at the time of diagnosis spreads far beyond the immediately adjacent normal brain. Invasion of malignant gliomas does not seem to be a random process but rather follows certain pathways of preexisting anatomical and biochemical pathways in the central nervous system. Beyond the edge of a lesion that may appear, well-delineated invasive cells can be found following small blood vessels were a perivascular cuff-formation may be observed. More evident, tumor cells show high affinity to myelinated fiber tracts in which single glioma cells show intrafascicular, perifascicular, and interfibrillary migration. The consequence of this cellular behavior results in the spread of a tumor, for example, along the optic radiation or through the corpus callosum (Fig. 6). When a glial tumor reaches the ependymal and subependymal layer lining the walls of the ventricle, very distant spread of the tumor may occur

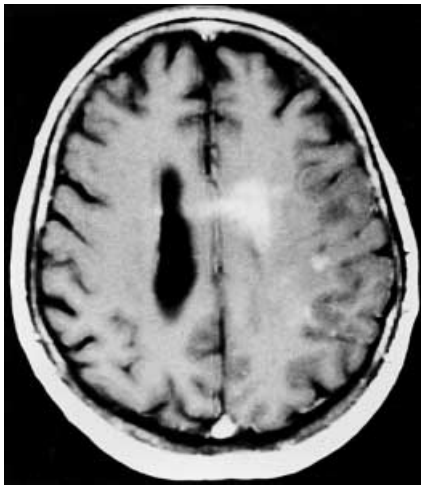

Fig. 6 This T1 MRI with gadolinium demonstrates a finger-like extension of a left fronto-parietal glioblastoma which projects along the myelinated fiber tracts of the corpus callosum into the contralateral hemisphere. This pattern of spread limits surgical options and will eventually result in a bilateral tumor mass

rapidly, sometimes even into the contralateral ventricle (Fig. 7). Furthermore, dissemination along the CSF pathways may occur (Fig. 8) (Giese and Westphal 1996).

Single invasive cells may be found several centimeters away from the macroscopically visible margin of a glioma. These invasive tumor cells are clonogenic. Glioma cells from up to 4 cm beyond the visible tumor can be isolated and grown in tissue culture (Silbergeld et al. 1997). This implies that after surgical resection of a glioma, single invasive cells can give rise to a recurrent tumor. Further illustrating the extent of spread, a series

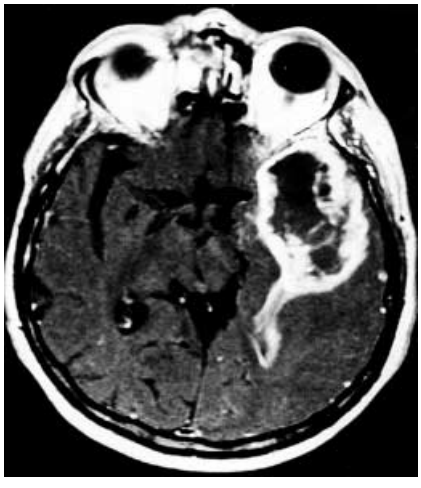

Fig. 7 Whereas this newly diagnosed left temporal glioblastoma appears to be well circumscribed with regard to its contrast-enhancing portion, a fine enhancement of the ventricular walls indicates subependymal spread with a rather distant dissemination of the tumor as far as the posterior horn of the left ventricle. In this case, already at the time of diagnosis this tumor is not amenable for local treatment strategies anymore and rather involves the entire left hemisphere

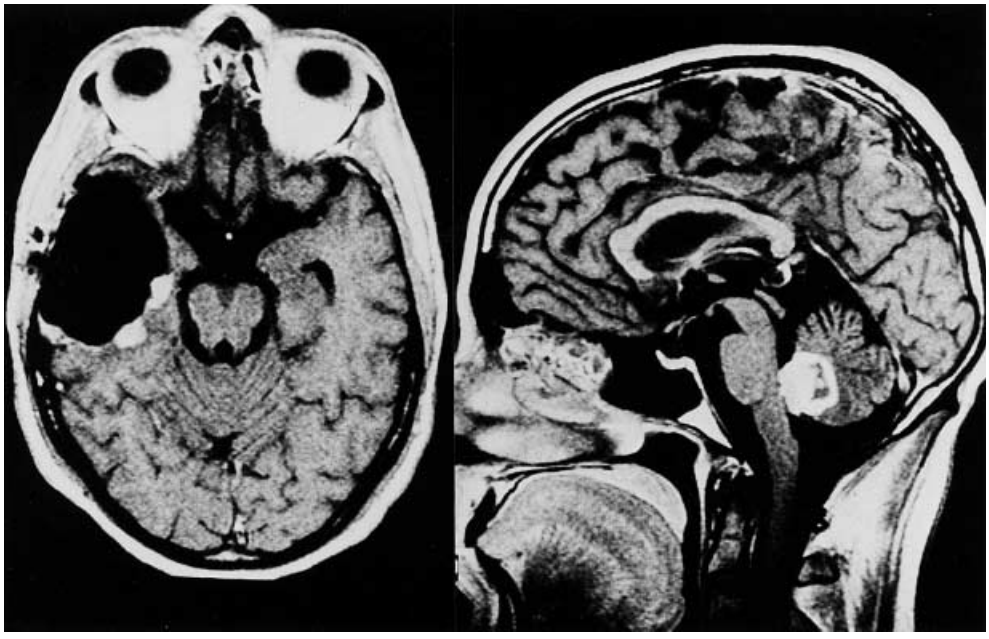

Fig. 8 This MRI illustrates a biopsy proven right temporal glioblastoma which was treated with a gross total resection and postoperative conventional radiation therapy. Eight months later the tumor recurred locally. At this time the patient became symptomatic due to a cerebellar metastatic lesion which was reoperated and confirmed to be a glioblastoma. Spread along the CSF pathways is rare but does occur after surgical entry of the ventricular system for removal of malignant brain tumors

of 100 consecutive untreated glioblastomas demonstrated evidence for histological tumor spread to the contralateral hemisphere in 47% of the cases (Matsukado et al. 1961). In this sense, control of the disease by local treatment strategies, for example, applied into the resection cavity, may reduce the rate of local failure and may increase the time to local progression. However, considering the distant spread of the disease, gliomas can hardly be called a local disease. It is not surprising that with local therapies such as the application of local chemotherapy or with the current gene therapy protocols, investigators have started observing cases of more distant satellite lesions resembling multi-focal disease when tumors recur. These patterns of recurrence reveal the true potential of glioma migration and invasion suggesting that, given time, these tumors will possibly spread throughout the entire brain. With the exception of convection-enhanced delivery, most local therapies surely do not reach a large enough volume of brain to account for the invasive front of a glial tumor. As attractive as local treatment strategies are today, their perspective in the long run will be limited in the absence of collateral anti-invasive concepts.

Perspectives: how to hit a moving target

Anti-invasive therapies for malignant glioma face the conceptual limitation of a widely disseminated disease at the time of diagnosis. Attempts to limit further spread may be of little value unless the process of invasion itself can be exploited to render the tumor cells susceptible to other tumoricidal therapies. To date, few such approaches exist and treatment of invasive glioma cells is challenged by some adverse cellular behaviors inherent to the biology of these cells.

There is accumulating evidence that these cells show a relative resistance to several modes of treatments. Several experimental systems have demonstrated that there may be an inverse correlation between cell motility and the proliferation of a cell population. Glioma cells, when stimulated to migrate by permissive matrix substrates or soluble motility factors, show a temporarily lowered proliferation rate (Giese et al. 1996a; Giese et al. 1996b). Control of motility is tightly controlled by matrix adhesion (Giese et al. 1994; Giese et al. 1995; Giese et al. 1996b; Palacek et al. 1997). Adhesion is mediated by integrin receptors which activate a signaling complex of tyrosine kinases such as pp125 FAK eventually resulting in a signaling cascade with downstream activation of MAP-kinase and other kinases associated with the regulation of the cell cycle (Luna and Hitt 1992; Zhu and Assoian 1995). The signal transduction cascades used by both integrins and mitogenic factors converge at some point and, therefore, proliferation and migration need to be coordinated as separate cellular phenotypes. There is recent evidence that glioma cells may also be less prone to undergo apoptosis when stimulated to migrate. This allows for the speculation that invasive glioma cells may have an increased resistance to antiproliferative, apoptosis-inducing treatments such as radiation, chemotherapy or the current protocols for gene therapy. These data suggest that invasive glioma cells represent a specific challenge to treatment not only because of their tendency to disseminate but also because of their specific biology. Identification of genes associated with the invasive phenotype may offer modes to specifically interfere with this cellular behavior. Recently, we have identified such a gene, thromboxane synthase, overexpressed in highly migratory glioma clones (McDonough et al. 1998). Specific inhibitors of this gene will abrogate migration of glioma cells (Giese et al. 1999). Interestingly,

inhibition of motility is paralleled by an increased sensitivity to induced apoptosis. In this sense, an anti-invasive treatment renders migratory cells susceptible to a cytoreductive treatment and may specifically target invasive cells.

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