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Strategies in Glioma-Surgery

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1. Introduction

1.1 Epidemiology and classification of gliomas

Malignant glioma is one of the most feared diseases in the industrialized nations. About 77% of all malignant tumors within the central nervous system are gliomas. There are about 18.000 newly diagnosed cases annually within the USA (9/100.000 inhabitants per year) and the disease causes about 13.000 deaths each year. Statistically this is a higher loss of life-time than all other tumor-entities together (Schwartzbaum et al., 2006).

About 45-50% of these gliomas are histologically classified as gliobalstoma multiforme (GBM) the most aggressive type of glioma which is classified as WHO grade IV (following the classification of Kleihues et al., 2000). 20-30% are so called anaplastic astrocytoma and the rarer anaplastic oligodendroglioma (WHO grade III), while about 16-8% are classified as low-grade gliomas (WHO grade I and II). Generally they show a less aggressive behaviour and a comparatively well differentiated appearance.

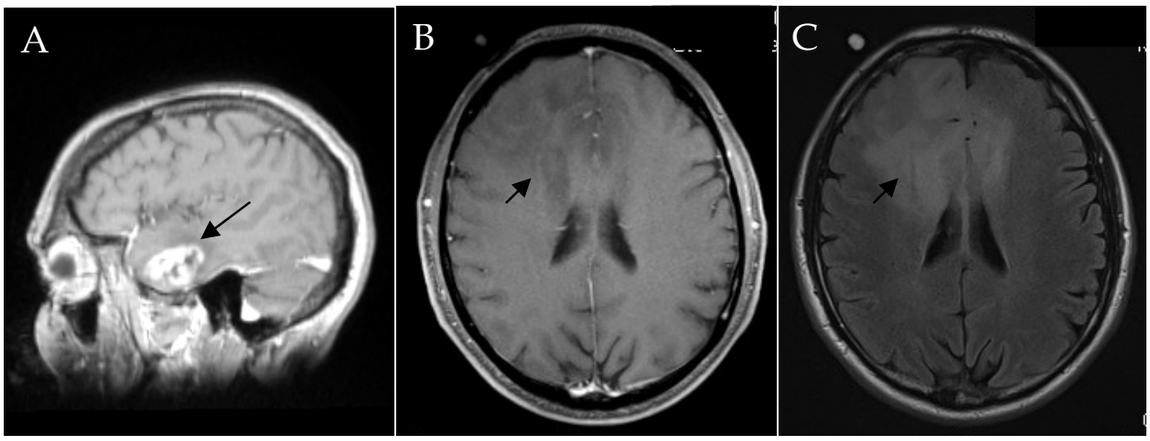

Fig. 1. A shows a sagittal gadolinium enhanced MRI scan of a Glioblastoma multiforme (WHO grade IV) with typical gadolinium enhancement of the tumor (arrow). Panel B shows a transversal gadolinium enhanced MRI scan of an Astrocytoma (WHO grade II). No contrast enhancement is noted (arrow). C shows the same tumor as FLAIR weighted image.

Among these are 10% differentiated astrocytoma, differentiated oligodendrogliomas and the mixed glioma (oligoastrocytoma) account for about 4-6%, 3-4% are so called ependymomas, and about 2% are pilocytic astrocytoma which is considered the only benign glioma (WHO grade I) (Wrench et al., 2002).

Astrocytic gliomas (anaplastic, differentiated and pilocytic astrocytoma) are believed to arise from astrocytic progenitor cells (type-I-astrocytes) whereas oligodendroglial tumors and mixed gliomas (oligoastrocytoma) arise from O-2-A progenitor cells. Ependymomas are derived from the ependyme of the ventricles (Schlegel et al. 2001)

1.2 Standard therapy and prognosis

Standard therapy of high-grade gliomas (WHO grade III and IV) includes gross total resection, concomitant radio-chemo-therapy with 60Gy and Temozolomide, followed by 6 cycles of Temozolomide, the so called Stupp-protocol (Stupp et al., 2005). The medium survival time for WHO grade IV tumors is about 15-18 months if this standard protocol is followed (Choi et al., 2008; Stupp et al., 2005). Before introduction of concomitant radio-chemo-therapy the survival time was about 12 months only with a 5-year survival rate of 3-4% (Davis et al., 1999; Barnholtz-Sloan et al., 2003). Following these authors the prognosis of WHO grade III tumors was better with a 5-years survival rate of 30-31% (Davis et al., 1999 und Barnholtz-Sloan et al., 2003). Recent studies (level I and II evidence) highlighted the role of the extend of surgical resection is an important predictor of progression-free and overall survival in the presence of high-grade glioma (WHO grade III and IV). More extensive surgery resulted generally in better outcome (Lacroix et al. 2001, Stummer et al. 2008, McGirt et al. 2009).

The less aggressive low-grade gliomas show generally a better prognosis of about 7-8 years survival after diagnosis, which however depends on the exact histological type (astrocytoma, oligodendroglioma; Schlegel et al., 2003). For these tumors no generally accepted standard-therapy protocol exists.

Pilocytic astrocytomas (WHO°I) show the best prognosis. They can be cured by complete resection. If this is not achievable patients should be followed closely and re-resection considered in case of progression (Bowers et al., 2001). Other treatment options include PCV chemotherapy and Radiotherapy. However, if a complete resection is achieved radiotherapy is generally not regarded as an option (Fisher et al., 2001; Karim et al., 1996).

More diffusely infiltrating low-grade gliomas like the differentiated astrocytoma (WHO°II), differentiated oligodendrogliomas (WHO°II) and oligoastrocytomas (WHO°II) show a significantly worse prognosis with a median survival of 3.2-7.7 years, depending on additional factors like age at diagnosis, largest tumor diameter, tumor crossing midline, histological type and neurological deficits at diagnosis (Pignatti et al., 2002). Although no level I evidence exists, several recent studies favour early surgery (soon after diagnosis versus surgery after progression or onset of symptoms) (Lang et al., 2006). Concerning the extend of resection the more recent evidence, mainly from retrospective case-series (evidence level V), supports a radical resection of diffuse low-grade gliomas if achievable at an adequate risk (Lang et al., 2006; McGirt et al., 2008; Schomas et al., 2009; Pouratian et al., 2010).

Radiotherapy can be applied, but again there remains controversy concerning the optimal timing (directly after surgery or if the tumor shows signs of progression) (Lang et al., 2006). Besides the comparatively long survival time after radiotheray leads to considerable side-effects by the neurotoxicity of the radiation (Klein et al., 2002; Olson et al., 2000; Laack et al., 2005).This supports later radiotherapy, whereas the authors of a mayor trial (EORTC 22845) favour early radiotherapy (van den Bent et al., 2005).

Chemotherapeutic options include adjuvant PCV after radiation and recent studies show some success of the treatment with Temozolomide, however larger studies are needed to assess the real benefits and risks (Baumert et al., 2008; Tosoni et al., 2008).

1.3 Factors limiting the surgical treatment of gliomas

Unfortunately, it remains clear that in spite of all these therapeutic efforts survival times of glioma patients are quite bad. So what is the reason for that?
A closer look on glioma-morphology and on historical treatment concepts might help to understand the problems of malignant glioma:
One issue is that gliomas are believed to arise from glial cells which are part of the normal brain histoarchitecture (astrocytic progenitor cells/type-I-astrocytes and O-2-A progenitor cells). Depending on the degree of mutation and degeneration these cells still closely resemble their normal progenitors and neighbouring cells. If a surgical resection of a glioma is encountered it can therefore be extremely difficult for the surgeon to identify the tumor-margin and to define the optimal extend of resection.
Another, even more problematic property of malignant gliomas is that they migrate along fiber tracts and vessels into the surrounding (often still functionally intact) brain tissue. In 1990 Kelly and colleagues could show by serial stereotactic biopsies that individual glioma cells can be found at a certain distance from the tumor, beyond the region of the tumor-oedema and even in the contra lateral hemisphere (Kelly et al., 1990). These cells are small and far distributed, they cannot be resected, because they are surrounded by functional brain tissue which should not be damaged and even the most sensitive imaging modalities (MRI and PET) are presently unable to detect most of them.
Therefore beside surgical resection other treatment modalities like radio- or chemotherapy which reach beyond the surgically resectable tumor margin are indispensible.

2. Surgical therapy of gliomas

2.1 Development of surgical techniques

The first intracerebral tumor was targeted surgically in 1884; the physician Alexander Hughes Bennett (1848-1901) indicated this surgery, while the operation was performed by the surgeon Rickman John Godlee (1849-1925). Although the patient died only a month after this procedure of meningitis this extensively discussed and well documented case marks the beginning of the surgical treatment of intracerebral tumors. Glioma surgery has gone a long way and seen many technical innovations since. In the following years the surgeons Williams Cushing (1869-1939), Fedor Krause (1859-1937) and Victor Horsley (1857-1916) paved the way for neurosurgery as an independent discipline in their countries (USA, UK and Germany). The problems of pain and infections were sufficiently solved by anaesthesia and antisepsis, yet the location of the concerned lesions in the scull remained problematic.
The discovery of x-rays by Wilhelm Konrad Röntgen (1845-1923) enabled a range of new diagnostic inventions. Further milestones were the development of cerebral angiography by Egas Antonio Aaetano de Moniz (1874-1955), computerized tomography by Johann Radon (1887-1956), Allen McLeod Cormack (1924-1998) and Godrey Newbold Hounsfield (1919-2004) and magnetic resonance imaging by Felix Block (1905-1983) and Edward Purcell (1912-1997)(Del Maestro et al., 2006; Eckart, 1990).
However surgeons soon discovered that the simple excision of glial tumors frequently led to recurrence of gliomas. In the 1960s this observation led to the development of super-radical

resections. In some cases the complete hemispherectomy of the tumor bearing hemisphere was performed. Although these operations have shown some limited success they were unable to finally cure glioma (Giese et al., 2003). This is in accordance to Kelly´s above described observations who found glioma cells far beyond the margins of the solid tumor and even in the contra lateral hemisphere (Kelly et al., 1990).
Nevertheless, even though surgery was found unable to cure glioma it did improve symptoms and survival. Furthermore most recurrent glioma arise at its primary resection site or in a distance of no more than 2-3cm there off (Giese et al., 2003). Accordingly larger recent pro- and retrospective studies could show that the extend of the surgical resection is an important predictor of progression-free and overall survival for the patients suffering from malignant glioma as already stated above (Lacroix et al., 2001, Stummer et al., 2008, McGirt et al., 2009).
Unfortunately tumors are generally surrounded by still functional brain tissue often even in the direct neighbourhood of functionally important centres in the brain such as speech-areas or motor cortical areas (53,9% of newly diagnosed Glioblastoma multiforme are located within or close to such centres; Duffau et al., 2004). In these locations the consequences of an over-radical resection can be severe neurological deficits, while the consequence of an incomplete resection is an impaired prognosis.
Neurosurgeons around the world have therefore focused their research to optimize the intraoperative visualization of glioma cells and to monitor brain function. A first important step was the introduction of microsurgical techniques by M. Gazi Yaşargil and others by application of the operating microscope (Yaşargil, 2010).
Conventional operating microscopes have a magnification of about 5-80x and furthermore offer optimal illumination of the operating field. Using these operating microscopes, experienced neurosurgeons can distinguish characteristic features of the brain tumors as different shades of colour, thrombotic blood vessels or necrotic areas. Besides the consistency of the tissue features valuable information for the discrimination of tumor and adjacent brain tissue.

Fig. 2. Operating microscope (A), cerebral cortex during surgery and microsurgical instruments (B).

2.2 Optimizing the extend of resection

2.2.1 Image-guidance and macroscopic imaging

Further important steps were introduction of image-guidance, which allows the surgeon to exactly locate an area of interest on the preoperatively acuised CT or MR images.

Disadvantages of this technical milestone are at one hand the restricted resolution which does not allow the identification of very small tumor residues. The resolution of image guidance can obviously not exceed the resolution of the imaging modality applied for guidance which is about 0.6mm^3 for state of the art CT scans or 1mm^3 for modern MR tomographs (Foroglou et al., 2009) . The other important disadvantage is the fact that image-guidance refers to the anatomical situation at the time of acquisition of the images.

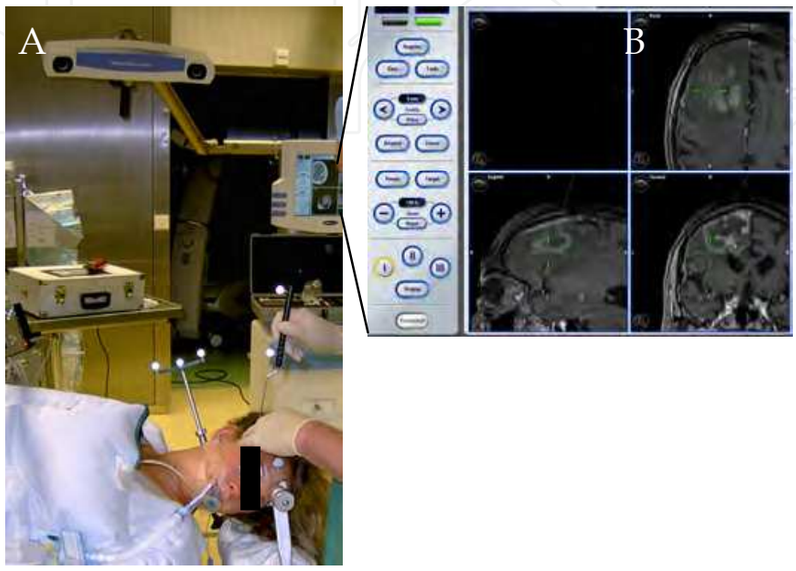

Fig. 3. Image-guiding system (A) and Screenshot of intraoperative image-guidance (B)

Unfortunately after craniotomy (opening of the skull) cerebrospinal fluid drains out and the intracranial pressure changes which results in gradual dislocation of the anatomical structures, an effect called brain-shift. Depending on the size of the craniotomy and the present intracranial pressure and the time after craniotomy this brain-shift can completely distort the neuronavigation.

Intraoperative imaging by ultrasound (Rygh et al., 2008) or intraoperative MR imaging (Foroglou et al., 2009) were introduced in order to counteract these problems and likewise optimize the extend of resection. However, the resolution of ultrasound imaging is even far lower than that of a CT or MRI scan and the procedure of an intraoperative MRI is expensive and time consuming.

Another imaging modality which can help to determine the real tumor size, especially if recurrent glioma and scar tissue formation have be discriminated, is the so called positron emission tomography (PET; Langleben et al., 2000). This technique uses radioactive marked variants of substrates of the cancer cells metabolism. These marked substrates (for example ^{18}F-desoxyglucose/FDG or ^{11}C-methylmethionin/MET) accumulate in the tumor with its high metabolic rate and the resulting in characteristic hot spots on the resulting images (Bénard et al., 2003; de Witte et al., 2001).

2.2.2 Neurophysiological monitoring

Besides resection control by image-guidance the integrity of some neurological functions of the tumor surrounding brain can be monitored directly.

By electric stimulation of motor areas and fiber tracts belonging to these areas the effector organ (muscle) can be activated. If these motor areas are stimulated during surgery, either transcranial or, if the concerned functional area is surgically exposed, by direct cortical stimulation, the induced activity of the effector organs (muscles) can be recorded by electromyography. A disturbance of motor cortical areas or corresponding fiber tracts leads directly to a disturbance of the measured activity in the effector organs and tell the surgeon that a further resection in the concerned area can be expected to result in neurological dysfunctions.

If surgery is performed near the sensory cortex or corresponding fiber tracts the same principle can be applied. The corresponding sensory organs (ears, eyes, perception sensors in the skin of a certain area etc.) can be stimmulated and the effect on the cerebral cortex is monitored by electro encephalograms or evoked potentials (Duffau, 2007).

More complex functions, like the human speech cannot be monitored by simple stimulation in the narcotized patient, as they involve several distinct functional areas within the brain. These tasks can however be monitored during awake operations (Duffau et al., 2009). For these awake operations nowadays most centres perform the craniotomy under general anaesthesia, after which the patient wakes up for the preparation of the brain tumor and is again sedated for wound closure (sleep/awake/sleep). By these means the patient can speak to the surgeon or an accompanying neuropsychologist during surgery and an impairment of the cortical areas responsible for speech production becomes directly apparent by dysfunctions of the normal speech. Normally the awake patient is asked to perform certain tasks like naming objects shown to him/her on a computer screen. Such awake procedures are less problematic than most people would expect, because the brain itself does not percept pain and the more painful craniotomy and wound closure can be nevertheless performed under general anaesthesia.

2.2.3 Intraoperative microscopy and fluorescent imaging

A further approach for to optimize the extend of resection is the staining of glioma tissue and optimization of the operating microscopes for enhanced intraoperative imaging. The most widely used technique is the staining of high-grade glioma tissue by 5-amino laevolinic acid (5-ALA; Hebeda et al., 1998; Stummer et al., 1998; Stummer et al., 2006). 5-AlA naturally occurs as an intermediate of the heame biosynthesis (Uehlinger et al., 2000) and external substitution of 5-ALA leads to accumulation of its fluorescent metabolite protoporphyrine-IX (PpIX) in many tumor cells including most high-grade gliomas. PpIX has a maximum absorption around 400nm (UV light excitation) and the resulting fluorescence (emission) is visible to the human eye and can likewise be visualized by modified operating microscopes (Hebeda et al., 1998; Stummer et al., 1998). Stummer and colleagues could show in their study, already cited above, that not only a more radical resection leads to prolonged progression free survival times of patients suffering from high-grade glioma, but that the application of intraoperative fluorescent guidance with 5-ALA could enhanced the rate of complete resections (as defined by an early postoperative contrast enhanced MR-scan) from 36 to 65% (Stummer et al., 2006).

In an ongoing project optical coherence tomography (OCT) has been used experimentally and in vivo to detect residual glioma tissue in the resection cavity (Boehringer et al., 2009).

Newer, yet experimental developments include the application of high performance fluorescent microscopes like confocal or multiphoton microscopes. which allow the identification of glioma cells down to the single cell level (Kantelhardt et al., 2009) and even gathering of functional information by time resolved fluorescent multiphoton microscopy

(Kantelhardt et al., 2007). Other techniques include infrared spectroscopic imaging (Steiner et al., 2008), or the staining of glioma cells by targeting the matrix metalloproteinases (MMP) which is present on the surfaces of high-grade glioblastoma cells (as on many tumor types) for the development of both drugs and MRI probes (Veiseh et al., 2007; Veiseh et al., 2009). Recently, the group of Tsien proposed using the MMP activity of tumor cells to incorporate dyes, nanoparticles and also drugs into tumor cells by unmasking a cell penetrating peptide sequence for guiding surgical resection and chemo therapy (Nguyen et al., 2010; Olson et al., 2010).
By the development of fluorescent nanoparticles (Quantum-dots) specifically targeting EGF-receptors, PDGF-receptors or other molecules believed to be specific for glioma cells within the brain, staining of living high- and low-grade glioma tissue was achieved in vitro (Kantelhardt et al., 2010). This is an important step, as the present gold-standard of intraoperative fluorescence imaging in gliomas 5-ALA does not stain low-grade gliomas.

2.3 Local chemotherapy

The second issue, remaining glioma cells beyond the margin of the tumor, was likewise a focus of neurosurgical research. The underlying idea is to deliver chemotherapeutics or radioactive substances directly into the tumor and, to the remaining glioma cells beyond the margin of the resection cavity. Several pass ways have been explored to reach this goal.

2.3.1 Intra-arterial delivery

Conventional administration of tumorocidic agents via vein or orally leads to a more or less equal concentration of the drug within the whole blood volume. Depending on the chemical and pharmacological specifities of the drugs penetration into different organs differs. Hydrophilic agents tend to stay in the blood stream, lipophilic ones generally penetrate much better into the different tissues. Likewise smaller molecules penetrate better than bigger ones. In case of a localized neoplasm a more specific administration of the tumorocidal agents is desirably. Malignant brain tumors rarely spread outside the central nervous system. The reason for this is not yet completely known. The fast progress of the disease for once limits the metastatic spread by limiting the survival time of the diseased patients. This might change when therapy regimes are available which prolong the survival times in highly malignant gliomas to several years. However most likely this is not the only reason, because other tumors, as malignant melanoma metastases much faster. The blood-brain barrier probably plays a major role in the restriction of the spread of malignant gliomas, either by hindering the migration of malignant tumor cells in the blood stream or by modulating the immune response in some way.
However, in order to minimize side effects and to enhance the concentration of chemotherapeutic agents in the tumor volume the local application of the drugs to an only locally growing tumor is an obvious idea. Every growing cell in the human organism needs sufficient supply of oxygen and nutrition, which are generally transported by the bloodstream. This is especially true for the fast growing and infiltrating tumor cells with their specific high metabolic turnover. As malignant glioma cells are derived from regular gill cells, or tumor stem cells which are themselves derived from regular stem cells as more recent theories go, they share a lot of specifities with normal glial cells in the brain. The higher consumption of substrates of the fast growing cells is one of the most striking differences. By administering tumorocidal agents via the bloodstream the antitumoral effects are multiplied due to the fact that the hyperperfused areas of the tumor, respectively

the metabolically most active or fastest growing areas in the tumor, get more of the tumorocidic agents than regularly perfused brain. The intra-arterial delivery of chemotherapeutics seems therefore a promising way to reach the most aggressive tumor cells. As many tumorocidal agents are furthermore eliminated in the liver it is desirable to bypass this organ. By intravenous or oral application a large amount of the tumoricidal agents may be cleared out of the circulation before even reaching the tumor, the so called first-pass effect. Intra-arterial administration in an artery directly leading to the tumor avoids this effect, therefore it is especially indicated for agents with a high systemic clearance-rate.

The chemotherapeutics are administered by an intra-arterial catheter in the carotid and/or the vertebral artery depending on the exact location of the tumor. If there are any doubts which vessel perfuses the tumor, an angiography can be performed prior to the administration of the tumorocidal agent. For the procedure (angiography and intra-arterial administration of the tumorocidic agent) the patient is punctated in the right femoral artery using the Seldinger technique (first punctation of the vessel with an canulae than a small wire is pushed through the lumen of the canula and than the catheter is placed guided by the wire). Than the administration-catheter is carefully maneuvered under radiographic control until it reaches the concerned artery and the tumorocidal agent is given via this catheter.

Preclinical studies in animal models and laboratory experiments were performed using different concentrations and combinations of chemotherapeutics. Furthermore intra-arterial treatment regimes were combined with intravenously or orally applicated drugs and radiotherapy. Some of the results were encouraging, so several pilot studies and phase I/II trials have been performed for low and high-grade gliomas, germ-cell tumors, primary CNS lymphoma, or primitive neuroectodermal tumor and brain metastasis (Doolittle et al., 2000). Among the substances used for intra-arterial administration are carboplatin, carmustine and other nitrosoureas, cisplatin, etoposide and methotrexate (Newton, 2005). Some authors described median survival rates for glioblastoma patients treated with intraarterial cisplatin and etoposide combined with radiotherapy to be dramatically longer than in patients treated with standard radio- and chemotherapies (Madajewicz et al., 2000; Osztie et al., 2001). However, limitations of the technique arise from the blood-brain-barrier and potentially significant complications such as neurologic toxicity like leukoencepalopathy, ototoxicity, seizures, visual loss; vascular complications like strokes or haematological complications like leukocytopenia or thrombocytopenia.

Osmotic blood-brain barrier disruption using isoflurane or propofol anesthesia showed some remarkable effects in the experimental setting as well as in a recent phase II study (Fortin et al., 2005; Hall et al., 2006). Unfortunately the disruption can also enhanced neurotoxic side effects. Especially an intraarterial administration of etoposide after osmotic disruption of the blood-brain-barrier showed unexpected severe complications (Fortin et al., 2000). Etoposide was thereafter administered before application of the blood-brain-barrier disrupting anaesthetics or it was given intravenously (Newton et al., 2002). Newer results suggest that the toxicities of carboplatin and tethotrexate based intraarterial administration regimes is comparatively low and well tolerated (Newton et al., 2005).

The safety of intra-arterial administration as a way to applicate some tumorocidal agents seems to be out of question by now. Yet no phase III study could demonstrate a survival benefit for patients treated with intraarterial chemotherapy compared to those receiving intravenous treatments.

2.3.2 Intratumoral injection

Another way of reaching high concentrations of antitumoral agents in malignant gliomas is to bypass the blood brain barrier instead of disrupting it. For this purpose tumoricidal agents are injected directly in the brain tumor tissue. In most cases, in the animal model as well as for the therapy of patients suffering from malignant gliomas, local injections are placed steriotactically to ensure the correct positioning of the agents. One or several bolus injections are placed on the same spot. The stereotactical technique allows the exact positioning of the needle in the lesion within the scull without the necessity to perform a large craniotomy. Prior to the procedure the exact position of the tumor within the scull has to be located. Therefore the skull is fixed in a rigid frame, than a CT-scan or MRI-scan is performed. By integrating the image data the exact location of the lesion within the frame is obtained. Now it is possible to calculate the angel and depth in which the tumor can be punctated. In the case of open surgery the injection can be placed under direct visualization.
The systemic side effects of such an intratumoral or interstitial chemotherapy should be minimized respectively the tolerated dose of the tumoricidal agents in the tumor can be elevated without further damage to other organs, because only a small portion of the substance will end in the blood vessels. In theory this locally enhanced concentration of the injected substances will be present for a prolonged period, because the distribution via osmosis in the interstitial space will take much longer than the systemic clearance-rate of most substances allows the agent to stay in the bloodstream. Laboratory studies have been undertaken to prove this hypothesis. The concentration of a tumoricidal substance as for example DTI-015/BCNU in ethanol in the tumor tissue was found to be up to 100-1000 fold higher if injected directly into the tumor compared to the intravenous administration (Hamstra et al., 2005). Furthermore substances not passing the blood-brain barrier can be used. Among the tumoricidal agents applied for intratumoral injections were not only the classical chemotherapeutics as BCNU, but also immunoactive substances as beta interferon (Rainov et al., 2004), vaccine candidates or modified viruses (Rainov et al., 2006) or radioactive agents as the beta emitter 201Tl-chloride (Ljunggren et al., 2004). However in many cases the effects in preliminary animal studies seem more dramatic than expected by the specific mechanism of the concerned drug. Patient based studies are still very rare. A possible explanation for the astonishing good results may be local toxicity or chemical alteration of the tissue surrounding the injection site (for example pH mediated), as optimal doses for the interstitial therapy are often not yet established. Nevertheless the approach is still an interesting alternative to systemic administration. Considering the promising results from laboratory studies it takes no wonder that the technique has already been used for the treatment of patients. Data from a phase I/II trial for local injection of DTI-015 in recurrent malignant glioma has been published already in 2003 (Hassenbusch et al., 2003). These results suggested that the stereotactic injection of BCNU is well tolerated and a feasible alternative for the treatment of inoperable recurrent Glioblastomas.

2.3.3 Convection enhanced delivery

The fact that the efficacy of a treatment could be elevated by multiple injections leads to the problem of multiple punctations. Voulgaris and colleagues (Voulgaris et al., 2002) therefore used an omaya reservoir to administer Doxorubicin in recurrent high grade gliomas on 10 days. Many others used infusions instead of injections in order to administer a bigger amount of antitumoral agents over a prolonged time. These techniques portend a novel technique: The convection enhanced delivery (CED). The term convection enhanced

delivery describes the interstitial application over a prolonged period via one or several previously implanted catheters by micropumps or sometimes gravity dependent infusion. Most researchers and physicians working on interstitial chemotherapy changed from single injections to this mode of delivery. They argued that the advantages of an interstitial therapy, higher dosage and lower systemic side effects, could be optimized by this technique. The catheters can either be placed under direct visualization following craniotomy or stereotactically, as described in the previous passage. A number of studies in animal models as well as in patients suffering from recurrent malignant gliomas have been performed to compare the dose distribution and safety of single or multiple bolus injections to CED. The first trials were performed in a nude mice flank tumor model of human malignant glioma. The in vivo effectiveness of CED was thus demonstrated. Further investigations on nude athymic mice using IL13 cytotoxin could show that the applied agent was distributed over a larger area by multiple injections compared to convection enhanced delivery, whereas the continuous infusion reached higher local concentrations in the target volume (Kawakami et al., 2004). Following this several phase I/II and III trials CED were initiated (Debinski et al., 2009). Nearly all antitumoral substances have been tested for intratumoral application. ACNU (nimustine) was administered in recurrent glioma and could induce necrosis and inhibit growth of the tumor (Wakabajashi et al., 2001). BCNU was administered in patients with recurrent glioma (Hassenbusch et al., 2003; Hamstra et al., 2005). Others were carboplatin or gemcitabine (Degen et al., 2003), several monoclonal antibodies (Wersall et al., 1997; Sampson et al. 2006), TP-38 a recombinant chimerical protein containing Pseudomonas exotoxin fused to transforming growth factor (TGF)-alpha (Sampson et al. 2005), a chimerical protein consisting of IL4 and Pseudomonas exotoxin or the IL13 cytotoxin (Rand et al., 2000) to name just some of the drugs. Likewise radioactive substances were locally applied as intracerebral brachy-therapy (gliasite^{R}, Chino et al. 2008). However although these trials could show some oncological effectivity severe problems were observed. The concerns mainly centered on ineffective tissue distribution and local adverse events due backflow and malpositioning of catheters or local infections (Bidros et al., 2010; Bonerba et al., 2010).

2.3.4 Local chemotherapy with implantable wafers

The problems with backflow and wound healing experienced in convection enhanced delivery of antitumoral agents resulted finally in the development of BCNU-wafers for implantation in the surgical resection cavity (gliadelR). A phase III study from 2003 showed that the intent-to-treat group showed a significantly better median survival of 13.9 to 11.6 months (Westphal et al. 2003). These BCNU wafers are presently the only intratumoral chemotherapy which got an approval from the FDA (Bonerba et al., 2010). Meanwhile the implantation of BCNU-wafers has been combined with the current standard therapy, the so called Stupp-protocol showing again favourable results (McGirt et al., 2009; Affronti et al., 2009). However others have reported about adverse events such as brain oedema, (transient) hydrocephalus, wound healing disorders (Bock et al., 2010; Giese et al., 2010).

Because of this the technique should be used after critical evaluation of the individual situation of the patient only.

Future developments might include a targeted local chemotherapy by chemotherapeutical agents coupled to specifically targeting nanoparticles or biomolecules and other upcoming substances.

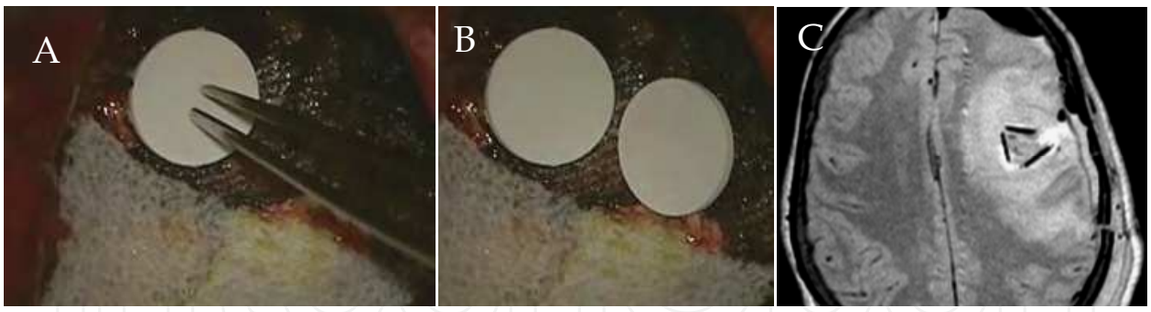

Fig. 4. A shows the implantation of an Gliadel[R] wafer. Two wafers in place (B) and a postoperative MRI scan showing 3 Gliadel[R] wafers in situ.

3. Conclusion

With about 9/100.000 newly diagnosed cases per year malignant glioma is one of most devasting diseases in the industrialized nations. Following the WHO grading system gliomas are classified from WHO grade IV (highly aggressive) to I (benign). Grade IV and III are called high-grade, while the less aggressive grade II is called low-grade gliomas.

The standard therapy of high-grade gliomas includes gross total resection, which has shown to improve the prognosis in recent phase III trials, concomitant radio-chemo-therapy with 60Gy and Temozolomide, followed by 6 cycles of Temozolomide, the so called Stupp-protocol. The medium survival time for WHO grade IV tumors is about 15-18 months if this standard protocol is followed, while the prognosis of WHO grade III tumors is slightly better (5-years survival rate of about 30%).

Low-grade gliomas show a better prognosis of about 7-8 years, and no standard-therapy protocol exists. All treatment modalities applied in high-grade glioma (surgery, radiotherapy, radio-chemotherapy, chemotherapy) are feasible and therapy is based on an individual decision. Recent case series however advocate early and complete surgery.

Nevertheless the prognosis of malignant brain tumors is generally still poor. The main reason for this is the ability of glioma cells to infiltrate the still functioning brain tissue beyond the margin of the solid tumor.

In order to further improve the prognosis many neurosurgeons have focused their research on optimization of the extend of resection. This goal is compromised by the fact that gliomas arise from glial progenitor cells which are part of the normal brain histoarchitecture. Depending on the degree of mutation and degeneration these cells still closely resemble their neighbouring (still functional) brain cells. CT- and MRI based image-guidance, intraoperative ultrasonography and MRI scanning were developed in order to guide the surgeon during resection. The accuracy of this image-guidance is restricted by the maximum resolution of the applied imaging modality (CT, MR, ultrasonography) and the accuracy of image-guidance is decreasing during the ongoing resection as the brain-shift alters the anatomy.

Another approach is the application of electrophysiological measurements and awake operations in order to control the integrity of neurological functions intraoperatievly. This is presently routineously applied if the glioma is in or close to a functionally important cortex areas like speech or motor areas.

Besides neurosurgeons have investigated novel optical technologies and dyes in order to differentiate glioma- and adjacent brain tissue. The staining of high-grade glioma tissue using 5-ALA is already in wide clinical use and recently the staining of living low-grade glioma tissue was achieved in vitro by specifically targeted nanoparticels. However further research is required before this can be introduced into clinical practice.

A completely different approach is the application of local chemo- or radio therapeutics.

Different modes for the local application of chemo- and radiotherapeutical agents were developed. The first approach was an arterial injection of chemotherapeutics with and without prior disruption of the blood brain barrier. Several studies could show that the therapy is generally well tolerated and safe, however it was not yet proven to be more effective than the conventional treatment. Therefore the blood-brain barrier was bypassed by direct injection into the tumors. This could be done once or repeatedly by stereotactic injection or under direct visualization at the end of an surgical procedure. In order to obtain even better results convection-enhanced delivery was developed, where the concerned chemotherapeutic is injected over a prolonged period of time by a pump or infusion. However results have yet likewise been suboptimal, most likely due to backflow and ineffective tissue distribution. The only local chemotherapy for malignant gliomas now in clinical use is the implantation of BCNU loaded wafers into the resection cavity at the end of surgical resection. This treatment option has recently been combined with the standard therapy (Stupp-protocol) for high-grade gliomas. Several studies could show its effectivity but likewise pointed out some dangers as the development of brain oedema, transient hydrocephalus or wound healing disorders. In future specifically targeted local chemotherapeutic agents could be developed to overcome these problems.

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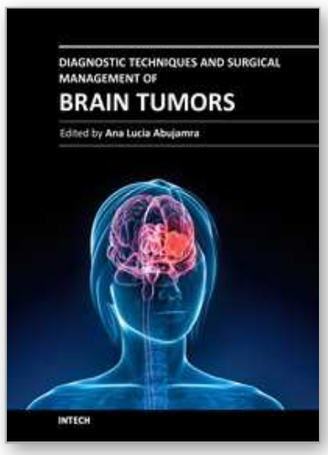

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