Non surgical treatment of adult supratentorial astrocytomas (glioblastoma multiforme, anaplastic astrocytoma, „low grade" glioma)

PhD theses

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1. Introduction

Classification of the tumors of the central nervous system – about neuroepithelial tumors in general

The 4th edition of the WHO classification of CNS tumors has published in 2008 and is still valid. Accordingly, the percent prevalence rate of primary CNS tumors is:

1.	Neuroepithelial tumors	44%
2.	The tumors of the meninges	31%
3.	The nerve sheath origine tumors	8%
4.	Tumors of the sella region	7%
5.	Limphomas	3%
6.	Others	7%

44% of all CNS tumors are neuroepithelial tumors, and among them the most frequent group of tumors are astrocytomas. 3% of neuroepithelial tumors are ependimal origine (ependimoma, mixopapillar ependimoma, anaplastic ependimoma, subependimoma) while oligodendroglial tumors are represented in 2%. The neuroepithelial tumors include the choroid plexus tumors, neuronal and mixed neuronal-glial tumors (mixed glial oligoastrocytoma), certain tumors of the pineal region, embryonal tumors (the most common representative is medulloblastoma), and rarer tumors such as astroblastoma, angiocentric glioma and third ventricul choroid glioma. Over the past decade as a member of the working group I researched properties and therapeutic opportunities of tumors of astrocistic and ependimal-subependimal origine.

1.1.Non-surgical treatment of malignanat astrocyitomas

Despite the development of neuroradiology, surgical technique and post-operative management, the treatment of adult malignant gliomas is still not resolved. For many decades radiotherapy was the only method used in daily practice in the postoperative treatment of malignant astrocytomas. In 1980 Walker and his cooperatives in multicenter, progressive, randomized trial justified that the after the radiation therapy itself or radiotherapy and nitrosourea-based chemotherapy coadministration, the survival of patients became significantly longer than in the non-treated or the group treated by only chemotherapy. In 2009 Stupp et al published 5 years results, of EORTC - NCIC study. Accordingly, during the irradiation, and after irradiation applied 6 cycles of temozolomide significantly improve survival compared to glioblastomas treated only with adjuvant chemotherapy. The so-called Stupp protocol has become a standard treatment modality in the management of postoperative glioblastomas. Between 1998 and

2004, under the leadership of Professor Áfra I have participated in several retrospective studies. As a member of National Institute of Neurosurgery and of neurooncology working group, I paricipated in the design and realization of several prospective study also, looking for most effective way of postoperative treatment of malignant gliomas and its reccurences. In 1998 I made a summary and evaluation of 1478 operated patients with histologically approuved glioblastoma multiforme. All of patients are detected and treated at our Institute. Using matematical and statistical methods I compared the survival times according to how radically the tumor is removed and according to applied postoperative treatment. Two articles are published with the largest number of patients in Hungarian relation using above mentioned database.

1.2.Non-surgical treatment of reccurences of malignant astrocytomas

In spite of surgical removal and postoperative irradiation most of malignant gliomas recur, in that case mainly chemotherapy is used. In the case of recurrence unified procedure or elective chemotherapy drug is not available. Primarily agents known from adjuvant treatments are applied which are mostly nitrozourea based chemotherapy combinations. For adjuvant treatment of malignant gliomas, a combination of BCNU-DBD or DBD itself has shown a relatively favorable outcome. Levin and cooperatives found the combination of PCV (procarbazine, CCNU, vincristine) more effective for treating anaplastic astrocytomas, and later Cairncross and cooperatives while other working groups proposed the same PCV chemotherapy treatment primarily for treating "aggressive" oligodendrogliomas.
Gutin and Posner offer BCNU in order to treat malignant astrocytomas and glioblastomas while in the case of oligodendrogliomas the combination of PCV is mainly offered by them. Based on our own previous experience and the literature mentioned above we applied primarily BCNU- DBD for treating recurring glioblastomas and A3 while PCV therapy was mostly applied for recurrent anaplastic astrocytoma and oligodendroglioma. In 2002, first in Hungary we published our achievements with so considered alkylating agent called temozolomide (Temodal®) (5,6). The medicine itself became available in countries outside the USA in 2000. Temozolomide is easily tolerable, orally applicable in pill form, which penetrates the blood-brain barrier well, and it has a favorable toxicity profile as well as a good antitumor activity in the case of recurrent glioblastomas, anaplastic astrocytomas and other malignant tumors (eg, melanoma). To measure the efficacy of temozolomide in the treatment of patients with recurrent glioblastomas, anaplastic astrocytomas and oligoastrocytoma I compared the received data to our previously acquired data which had been received when we had applied the BCNU-DBD combined chemotherapy. Between 2002 and 2004, I participated directly in the publication of four studies dealing specifically with the questions of chemotherapy treatment of recurrent malignant gliomas.

1.3.Treatment of low-grade gliomas (LGG)

In contrast to the low-grade gliomas (A II) the necessity of tumor irradiation or of appplied dose the view is not uniform. Many authors consider post-operative radiotherapy appropriate (possibly starting within 6 weeks), number of authors oppose it, referring to relatively often experienced long survival without radiotherapy. Many authors apply additional treatment when the tumor progresses or follow the so called "wait and see" policy. These authors believe that in the case of relatively slow tumor growth and opportunities offered by the repeated imaging surveillance, the surgery is sufficient when the patient's condition or the neuroradiological progression requires it. In contrast, from the studies of Recht et al., and later Pignetti et al. it turns out that between early (after the diagnosis) or after a long wait operated patients there is no significant difference in survival, however, the majority of tumors in the "late" group had been malignantly transformed. In the hope of clarifying the disputed questions four prospective randomized study has been performed in the past decade:
The EORTC study number 22845 randomized 314 patients. According to this study after the radical removal of the tumour half of the patients were irradiated while another half of the patients received the radiotherapy after the appearance of recurrency. The result did not completely fitted the previous expectations. The overall survival (OS) did not show a significant difference though five year progression free survival (PFS) was better in the post operatively irradiated group.
The EORTC trial 22844 randomized 379 patients to receive irradiation postoperatively (or postbiopsy) with either 45 Gy in 5 weeks or 59.4 Gy in 6.6 weeks with quality-controlled radiation therapy. No significant difference was found between the two groups in terms of survival or the progression free survival.
A NCCTG Radiation Therapy Oncology Group/Eastern Cooperative Group randomized 203 patients to compare survival and toxicity in adult patients treated with low-dose (50.4 Gy/28 fractions) versus high-dose (64.8 Gy/36 fractions). Neither here significant difference was found in 5 year overall survival or progression free survival. A Southwest Oncology Group study randomized 54 adults with incompletely resected LGG to RT alone or RT plus CCNU (lomustine) chemotherapy. There was no difference in outcome between the 2 treatment groups.
There is no established consensus regarding low-grade gliomas treatment strategies, a lot of questions are unanswered. In our institute between 1999-2003 the low-grade (A II) tumors were treated in different ways searching for the best solution. Our research achievements were reported in two studies, which dealt with various methods of treatment of low-grade gliomas.

1.4.Treatment of malignant brain tumors accompanying edema with methylprednisolon

Peritumoural oedema often causes increased intracranial pressure. In the background of peritumoural oedema a damaged blood-brain barrier can be found. The increased permeability of the capillary blood vessels plays an important role in int he

development of oedema (vasogen type of oedema). Its precise mechanism is still not known, there is some evidence according to which phosphorilation of VEGF's (Vascular Endothelial Growth Factor) occludin leads to opening of the tight junctions (zona occludens). There is some further evidence according to which the VEGF induces the endothelium fenestration and it increases the permeability of capillary blood vessels this way. The expression of VEGF in gliomas is directly proportional with the tumour malignancy. In low grade gliomas the expression of VEGF is low. Fiftyfold greater amount of VEGF mRNS is registered after malignant transformation of low grade gliomas. The new antiangigenetic drug bevacizumab (Avastin), which is used in the treatment of glioblastomas, decreases not only de novo angiogenesis, but also the oedema generated by VEGF. It is characteristic about the mechanism of action of glucocorticoids such as dexamethasone or methylprednisolone that it reduces the expression of VEGF and thus are reducing oedema effect. In 1961Galicich, French and Melby reported about the brain oedema reducing effect of glucocorticoids, especially the dexamethason.
In the past decades dexamethason has been routinly applied for reducing brain oedema in the form of a single big dose or permanent infusion. In that time metilprednisolon (MP) was rarely used for brain oedema treatment. Miller et al treated ten patients preoperatively. On avarage 55 days Lieberman et al applied MP in a bigger dose (200-2000 mg per day) at patients because of inoperable tumour. Glucocorticoids' oedema reducing effect is partly reached by dephosphorilation of occludin and partly by upregulation of occludin. Given in equivalent dose MP seems to have similar effect to treatment by dexamethason.

2. Objectives

1. Examination of effect of high dose methylprednisolon on peritumoral brain oedema
I sudied high dose methylprednisolon applied intravenously in the treatment of peritumoral brain oedema, primarily in terms of changing in neurological signs, mapping possible complications.

2. Collecting, processing and analysing the data of 1478 patients with histologically verified and reviewed primary glioblastoma multiforme treated in our institute during forty years from 1955 to 1994
Using statistical and mathematical methods I examined the data of 583 only operated (no irradiation or chemotherapy) patients if there is any connection between some anamnestical data and survival time. I conclude and compare the treatment results of 1478 patients operated and posopertaively treated with only operated patients' survival data.

3. Examinations of treating possibilities of recurrent supratentorial malignant gliomas
During my work I searched for the answers to the questions below:

I examined the efficiacy of BCNU-DBD and PCV (procarbazin – CCNU – Vincristin) combined therapy in the case of operated and irradiated recurrent malignant gliomas (materials of ten years – 73 cases). I examined the effect of temozolomid treatment in the case of recurrent malignant glioma (materials of two years – 40 patients). I analysed and compared the survival of recurrent malignant glioma groups treated by the combination of temozolomid and BCNU-DBD.

4. Treatment of low-grade glioma – searching for the best therapeutic modality

I searched for the answer to the following question:
What is the connection between some anamnestical data and postoperative survival (40 years and 348 cases)?
I examined the role of early irradiation in the treatment of low-grade glioma (12 years, 97 cases).
I performed a retrospective analysis in terms of survival data, in the case of non-operated WHO grade II astrocytomas when stereotactic biopsy and following irradiation were performed (12 years, 38 cases).

3.Methods

3.1Methilprednisolon treatment of peritumoral oedema

Examinations were performed by involving 22 patients (14 males, 8 females).
Before operating the tumour in 17 cases we performed treatments while further 2 or 3 patients were treated besides local irradiation and chemotherapy. Patients previously treated by steroid are not involved in our current review. Hystological disrtibution of tumors is 14 malignant gliomas and 8 metastatic tumor. The dose of methylprednisolone was defined by the size of oedema shown by CT pictures, the patient's state of consciousness and the focal neurological signs and their degree of seriousness. The initial dose was 250, 500 or 1000 mg per day in intravenous bolus.
This dose had been applied preoperatively for 2-5 days and it was continued postoperatively for 3 days, the dose was reduced giving half a dose in every other day. Medical treatment was left off on the fifth postoperative day. In non-operative cases the treatment was started with infusing high-dose methylprednisolon (1000, 500 or 250 mg) then the dose was gradually decreased and the preoperative medication was continued for some months in the dose of 32-100 mg applied on average every other day. The Unified Neurological Stroke Scale was applied to register the neuroligical state. The patients had been examined and their state had been expressed with scores twice a day before the therapy then the same process was perfomed during the therapy after 6-12 hours then from the second day. The general state of the patient had been registered before the treatment, also before the operation and it was also registered after the treatment as well according to the Karnofsky Permomance Score (KPS). At 17 patients treated prior to surgery, blood

glucose was monitored twice a day, potassium and sodium ion concentration were also examined as well as the level of serum albumin.

3.2Glioblastoma multiforme database (1955-1994)

Surgery and possibly optimal removal was performed in all cases. Stereotactic biopsy is not involved in this material. All the tumors were primary supratentorial or lobe glioblastomas though in several cases the tumor reached the corpus callosum or the basal ganglias. Histological dyagnosis was performed according to the criteria of WHO's modified publication. Isolation according to the histological subgroups (e.g. gliosarcoma) was not regarded necessarry: in their biological attitude they were not basically different from primer glioblastomas and their number (1,76 per cent) was not significant. Anaplastic astrocytomas and tumors which proved to be glioblastomas for the second operation are not in the current review. In this review we deal with anamnestic data, clinical symptoms, the time till the operation, furthermore we deal with the most common diagnostic processes like angiography and isotope and we also deal with the data of CT and MRI changes. Beside the distribution by age and sex particular attention was paid to the appearance of disease and its acute forms compared to the operative record (haemorrhage, cist). The complete clinical course and postoperative survival of 1207 patients are known. In the case of 583 patients only surgery was performed while 624 patients were treated in a postoperative way. The basis of postoperative treatment was radiotherapy. The planned complete radiation couldn't be applied in several cases. In the current review the patients who received the minimum 30 Gy were regarded irradiated. The most most common dose was 50-60 Gy. During the three decades a lot of cytostatic drug effect was examined, some of them were only examined in smaller groups.
Nitrosoureas commonly derivatives as BCNU or CCNU was, furthermore dibromdulcitolt (DBD), procarbazine (PZB) and vincristine (VCR) used in the form of mono- or combination therapy. The arrangement and processing of the data, the editing of the graphicons, and mathematical-statistical analysis were made using Excel 7.0 (Microsoft), Statistica for Windows 4.5 (StatSoft) and SigmaPlot 1.02 (Jandel Corporation) softwares, while Kaplan-Meier estimator, Cox regression analysis and Kolgomorov-Smirnof test served as tools for understanding connections behind the data.

3.3.Traetment of recurrent malignant gliomas

3.3.1Chemotherapy (BCNU, PCV)

Between 1992-2003 at the National Institute of Neurosurgery 73 patients were treated by chemotherapy because of recurrent malignant glioma or because of recurrency after reoperation. In all cases postoperative chemotherapy was applied. 63 patents were treated by chemotherapy after first operation and irradiation when recurrent tumor appears, while 10 patient recived chemotherapy after reoperation

and radiotherapy when new recurrent tumor appears. Beside clinical signs the recurrency was justfy with CT and or MRI examination. None of the patients was previously treated by chemotherapy. 43 patients recived BCNU-DBD, while 30 patients were treated with PCV combination. In the BCNU group at 20 patients pimary histological diagnosis was glioblastoma, out of 23 A3 9 were originaly A2. In the PCV group out of 30 patients 16 were A3, while 14 were oligodendroglioma or oligoastrocytoma buti in 11 cases the tumor was originaly O2. On admission all patients had normal hemopoetic, renal and hepatic function. During BCNU-DBD treatment chemotherapy started with BCNU 150mg/m^2 iv. infusion on day 1, which was followed next day by DBD 1000mg/m^2 given oraly. The course was repeated every six weeks, altogether 2-8 times. After 3 weeks and before the next treatment complete laboratory control was performed. PCV treatment started with vincristine 1,5mg/m^2 iv. (2 mg maximum) and the same day 100mg/m^2 CCNU was given oraly followed by procarbazine 60mg/m^2 on days 8-22 and finishend by the same dose of vincristine on day 30. The course was repeated after one month, mostly six times. Before every course laboratory examination was performed. Generally both of treatment type was well tollerated, but if necessary (2. grade of myelotoxicity) the doses was lowered by 25% or the treatment was postponed for six weeks. The results of treatments were evaluated according to criteria of MacDonald et al, ont he basis of clinical examination and contrast enchanced area on CT. Thus complete response (CR) corresponded to total disapperence of contrast enchanced area, partial responce (PR) to a reduction by at least 50%. In both cases patients clinicaly improved or remain stable. Steroids were stopped or their dose could be reduced. Stable disease (SD) or progressive disease (PD) meant stable or progressive illnes. Survival curves were stimated by the Kaplan – Meier technique and generalised Wilcoxon test modified by Gehan was used for obtaining p-value.

3.3.2.Chemotherapy (temozolomid)

At our Institute 40 patients with recurrent malignant gliomas had been treated between June 1999 and September 2001. Previously macroscopicaly total removal of the tumor is done followed by 60 Gy fractionated radiotherapy. Reoperation and previous chemotherapy was not performed in any of cases. Recurrency was justfy with contrast CT and/or MRI examination. Before the treatment with temozolomide every patient had the Karnofsky value of minimum 60 and the laboratory examinations showed normal hemopoetic, kidney and hepatic status. 19 female and 21 male were involved in the study. 26 patients had primary histology of glioblastoma, in 14 cases A3 or mixed oligoastrocytoma was diagnostized. During the treatment 200 mg/m^2 temozolomide was given every day for 5 consecutive days after proflilactic use of antinausea drug. The treatment was repeated after 28 days but before it, laboratory examination of blood counts, liver and renal function was performed. The tretment had to be stopped in four cases after 1 or 2 course, in 3 cases because of myelotoxicity side effect (anaemia, neutropenia) while in one case because of allergy. The othe patients did not have the dose lowered. The patients

received 2-12 course, an average of 5,4 cycles. Because of the possible occurrence of nausea, and vomiting, treatment was not interrupted. The response to chemotherapy was determined by contrast-enhanced area on CT and clinical criteria established by MacDonald et al. Neurological examination, CT scan or MRI control shooting occurred monthly. The survival were stimated by the Kaplan – Meier technique and generalised Wilcoxon test modified by Gehan was used for obtaining p-value.

3.3.3.Analysing and comparison of groups treated by BCNU-DBD and temozolomide (2000-2003)

75 consecutive patients with recurrent malignant glioma were treated in our institute with orally given temozolomide for five consecutive days and the course was repeated every twenty eight days. Among our patiens there were 38 females and 37 males. The Karnofsky Performance status (KPS) was above 70 per cent at every single patient. 40 patients originally had glioblastoma multiforme while at the others either A3 or oligoastrocytoma or oligodendroglioma was the primary histology. At each patient radical removal of tumor was performed followed by 60 Gy dose irradiation. 10 patients earlier received posoperative chemotherapy at the first recurrence. In the cases of oligoastrocitoma or oligodendroglioma PCV (procarbazin, CCNU Vincristin) were applied while in the cases of astrocytomas BCNU was given. In these cases temozolomide was used as second line drug. Patients received 2-16 course on average 6,2. Eleven patients received 12 or more courses. Temozolomide was applied in 200 mg/m^2 per day for five consecutive days repeated every twenty eight days. Each patient received profilactic antiemetic drug.
According to WHO criteria the third grade myelotoxicity was registered in two cases, the fourth grade myelotoxicity was noted only at one patient. First or second grade thrombocytopeny és neutropeny was observed at five patients where the treatment was postponed for one or two weeks. Nine patients suffered from nausea. Neurological examination was performed every month while CT or MRI scan every second month. The response to treatment was evaluated according to criteria established by Macdonald. At the moment of analysis 24 patients were still alive. 46 further patients were treated by BCNU-DBD combination. 11 out of 26 AA patients were originally diagnosed with A2 astrocytoma while all the twenty patients with glioblastoma multiforme were primarily diagnosed with GBM. The survival curves were evaluated using Kaplan-Meier method and the statistical analysis was performed using Kolmogorov-Smirnow test.

3.4 Treatment of low-grade glioma: searching for the best therapeutic modality

3.4. 1. Connection between some anamnestical data of supratentorial low-grade gliomas and survival time

At the Natinal Institute of Neurosurgery during forty years (1955-1994) 348 low-grade and 383 anaplastic supratentorial, lobar diffuse astrocytomas have been operated on in adults. In all cases open surgery with optimal tumor removal was performed. Histological grading followed the reviewed WHO classification. Low-grade or Grade II astrocytoma corresponds to non-pilocytic, „ordinary" or A II astrocytoma. The A II astrocytoma is composed of astrocytic tumor cells with pleomorphism and moderate hypercellularity, but importantly no mitoses, endothelial proloferation or necrosis is found. Anaplastic or grade III astrocytoma shows focal or diffuse anaplasia: incresed cellularity pleomorphism, nuclear atypia and mitocic activity. Endothelial prolipheration or necrosis are however absent. Age, sex, localisation, the most frequent presenting symptom, the length of epileptic history, the frequency and the type of seizures were registered. In twenty-one patients whose epileptic history was longer than 3 years on the CT scan hypodensity without contrast enhancement could be observed 3-9 years before surgery. Repeated CT at the time of surgery revealed a hypodense lesion again in ten cases while in eleven cases CT showed enhancement and/or enlargement of the abnormality. During the same period a further 29 patients were operated on after a history of seizures longer than 3 years following verification of the tumor by CT prior to surgery. Out of 21 and 29 cases histology revealed anaplastic astrocytoma in 11 and 10 patients, respectively. Another 51 patients' CT scan showed a hypodense lesion also after shorter history of epilepsy (one day to twenty-four months) and at surgery low-grade astrocytoma was proved. Reoperations were performed in 29 out of all 101 patients and malignant tranformation occured in 23 cases, but marked enhancement appeared on further 19 late CT as sign of dedifferentitation. We compared the survival of low-grade gliomas in the patients with short and long epilepsy history. Survival curves were calculated according to the Kaplan-Meier method and the generalised Wilcoxon test was used for obtaining p values.

3.4.2.Role of early radiotherapy in the low-grade gliomas

166 consecutive patients were identified using our prospectively maintained database as having low-grade nonp-pilocytic supratentorial astrocytoma operated at our institute between 1985 and 1997. The neuroradiological, clinical, histological, treatment parameters and follow-up information were analysed, supplemented by medical record review, direct physician and patient contact, as needed. Available histological slides were re-examined by two certified neuropathologists. Only those with a complete agreement on tissue diagnosis of WHO Grade II astrocytoma were included in the study, limiting our original pool to 106 cases. In most cases reason for exclusion was the presence of various degree of oligodendroglial features. Six patients were lost for follow-up in the study period (4,6 per cent), and there were 3 posoperative deaths (2,8 per cent). Data gathered for each patient included sex, age, type and duration of symtoms, initial preoperative CT finding, tumor localisation, tissue diagnosis, date and extent of surgery, Karnofsky perfomance score (KPS) after surgery, timing, dose and technique of RT, date of tumor progression, tissue diagnosis at recurrence, and last known status. Extent of surgery was assessed based

on postoperative CTs and operative notes, except for the last 11 cases where MRIs were also available. Cases were grouped as subtotal when the tumor removal was smaller than 90 per cent and total when the resection was bigger than 90 per cent.
Timing of RT was considered early if the patient received RT following histological confirmation, dealyed when it was postponed until progression. RT was given within six weeks after surgery in 36 patients (37,1 per cent). The median dose of RT was 54 Gy (range 50-60 Gy) administered over 5-6 weeks using conventional fractionation (2 Gy peer day). The two groups of patients (early vs late) were well-balanced according to basic characteristics. Patients were regularly controlled by CT scan every 6-12 months or when their clinical status required it. Progression was established on the basis of clinical or radiological deterioration. Patients with clinical worsening were pre-ordered for MRI or CT scan and tumor progression could be shown in all the cases. Survival time was calculated from the time of diagnosis to the time of death or the follow-up was closed in the time of completing the study. Progression free survival time (PFS) and disease specific survival (DSS) were calculated in every patient using the Kaplan-Meier method, but long-rank test was used for equivality examination. For uni- and multivarious analysing we used the Cox proportional modell.

3.4.3.Clinical examination following stereotactic biopsy of low-grade gliomas and irradiation

Only those patients were involved in the study in whom could be shown the central region, the midline or insula involvement and in whom WHO Grade II astrocytoma could be verified histologically. Every single patient received radiotherapy after stereotactic biopsy. Between 1995 and 2007 38 patients fitted the the requirements above. Karnofsky performance score was calculated from medical reports. 18 males and 20 females participated in the study. Stereotactic biopsy was performed after CT and MRI examination. The pictures shown on CT and MRI were characteristic to low-grade gliomas, hypodensity or mixed density could be seen without contrast enhancement. The histological diagnosis was established according to WHO criteria. Those cases were not suitable for surgery because of localisation, on the other hand each of every tumor was bigger than 3 cm in diameter, causing no mass effect. Every patient received 54 Gy dose of radiotherapy, which was started six weeks after histological diagnosis. The follow-up of the patients were based on regular outpatient examination and telephone interviews. The average follow-up time was 65,5 months.

4.Results

4.1. Methylprednisolon treatment of peritumoral oedema

The first clinical signs of the effect of high dose methylprednisolon infusion can be seen 24-36 hours after the administration of drug. The neurological signs and vigility in the preoperatively treated patients improved in all but one patient. Neurological improvement was mostly expressed by the improvement of paresis, which became partial, or disappeared and also the seriousness of aphasia was decreased. Six seriously paretic patients became able to walk. The status of patients treated by irradiation or chemotherapy significantly improved beside continuous MP administration and allowed completing of the planned treatments and later reducing and quitting the steroid application. Patients fitted in for operation were not controlled with regular CT examination, registration of marked neurological improvement often proved to be sufficient. Those patients who received chemotherapy were regularly controlled with CT examination, which demonstrated a significant reducing of peritumoral oedema.
Significant side effects were not noted. Operative infections were not present. Differences in ions household could not be shown, hypertension or gastrointestinal complication were not experienced either.
Psyshiatric involvement did not appear during the treatment. Special attention was paid to the changes of blood sugar value. During a short intense treatment the blood sugar value did not show a significant difference in any of the cases.

4.2.Glioblasztoma multiforme database – 40 years, 1478 cases

Distribution according to the gender of 1478 patients were the following: 861 males (58,22%), 617 females (41,78%), which corresponds to the ratio of 1,4: 1. Age of patients variates between wide boarders, the youngest patient was aged 15 and the oldest was aged 82. The average age was 53,4 years while the median value was 55 (STD 10,73). The disease is more common in old age, the maximum incidence in our study was in the 6th decade. The most of the tumors were found in temporal (692 = 46,7%) and frontal localisation (452 = 30%). The parietal localisation was presented in 306 cases (20,7%) while occipital localisation was registered in 28 cases (1,8 %). In particular, a moderate leftist overweight (52.13%) appeared. 28 tumors showed bifrontal extension (1,8%). Among the complaints included in history we marked only the first and dominant complaint. We did the same with symptoms, the first and the most dominant symptom was registered – depending on localisation, aphasia and paresis often appeared together. The most often first and mostly not a single complaint was headache (46,5%). It was followed by early and late epileptic seizures (18%). In further order the important place was occupied by aphasia and paresis. Both of symptoms are used in general meanings, so to say the aphasia could be initially only motor aphasia, only sensor aphasia or mixed type.

We did the same with the paresis and psychic symptoms which are used in general meaning. These complaints appeared rather in older age. Rarely we noted as a first symptom the numbness, walking ataxia and visual disturbance, furthermore vomiting and dizziness. Between the beginning of complaints and dignosis or operation, the elapsed time was changing, but the most characteristic was the short mostly very short preoperative history was characteristic: in 1185 cases the peoperative history was shorter than 3 months, within this in 531 cases the preoperative history was shorter than 1 month. In 36 cases the preoperative history was more than ten month long. The calculated average value of preoperative histroy was 3,45 months while the median value was 1,5 months. In this group of patients the quality distribution of anamnestic data was also characteristic. In the case of long preoperative history the main complaint was epilepsy (temporal of focal seizure) while in 8 cases continuous headache was noted. Different attention is required for acute beginning, which means suddenly appeared complaints and symptoms. Sometimes acute beginning is followed by temporary improvement, so one or two month can be passed till we recognise the tumor. The suddenly appeared complaints can be connected with haemorrhage of the tumor, sometimes with appearance of cyst or its growth. We registered suddenly developed symptoms in 93 patients, tumor haemorrhage after a sudden beginning in 41 cases while significantly grown cysts were found in 131 cases at the operation. The neurological signs registered on admission were mostly focal in the form of counterpart paresis or plaegia. The paresis is often associated with speech disturbance which itself is rarely registered. Similar to speech disturbance localisation bound appeared hemianopsia. Walking disturbance rarely can be seen as a first symptom. The fundus slump was registered in 496 cases, mostly before CT era. Between 1955 and 1984 among 1006 patients in 397 patients congestive papilla was found while between 1985 and 1994 among 472 patients only 99 patients had congestive papilla. Expressed in per cent 39,4% and 20,9%. The most important tool for long time was carotis angiography. Less than 50% (n=556) of the patients which were undergone angiography had picture which refer to malignancy while in 581 patients pathological angiogenesis was not shown. In the smallest number isotopic examination was performed, which showed intensive isotop pickup in the most cases (289 cases), only 3 isotopic examination of glioblastoma had a negative result. Nowadays the main examination in tumor diagnostics is MRI scan complemented by giving contrast while it was CT scan complemeted by contrast in the time of making the database. In the given group of tumor patients 674 patients were examined by CT scan. Valuable contrast enhancement, mostly ring shaped is registered in 668 glioblastomas. In one case just weak contrast enhancement could be seen while in four cases no contrast enhancement was seen at all. It is important to mention that in 8 patients the CT examination performed after the first epileptic seizure did not show any kind of pathologic difference, in one case the MRI examination was negative too. However several weeks or months later repeated imaging in every occasion showed contrast enhancement lesion which was later histologically proved to be glioblastoma. The data above was presented based on the total patient records (1478). Further analysis was completed using data of only operated patiens (583 patients). Using statistical

methods connection between some anamnestical and clinical data with survival was examined. According to the Wilcoxon test only the median survival of the youngest and oldest groups of patients – younger than 40 and older than 68 years – showed a significant difference, p=0,039. Using Cox regression multivariant modell age depending survival showed strong significancy in favour of younger age (p=0,0076). Among the anamnestic data we examined the relevancy of the time from the first symptom to diagnosis or to operation. The longer period of time was associated with favourable postoperative survival (p=0,02). The acute onset of disease however did not influence the survival time of the patients (p=0,078). We also compared the possible influence of the epileptic onset to survival, but the difference was not significant (p=0,075). Postoperative treatment significantly influenced the survival of the patients. While the median survival time of postoperatively non-treated patients was 4 months, the median survival of patients postoperatively irradiated or irradiated and treated by chemotherapy was 8 and 10 months. The difference is strongly significant (p<0,01), but the difference between the survival time of the irradiated patients and patients treated by radio- and chemotherapy was not significant. The chemotherapy itself without irradiation did not have a meaningful effect. The median survival of the patients treated by only chemotherapy was 4 months, which was practically equal with the survival of the patients who did not receive any postoperative treatment. The overall survival of the reoperated patiens proved to be longer than of those who were operated once. This can even be understood if the survival was longer only for 2-4 months, and rarely we could reach longer (6-10 months) survival yet after the reoperation useful survival was rarely reached. Almost every reoperated patient received radio therapy or combined treatment. The status of the patients after the operation considerably influenced the final outcome. Using Karnofsky performance value we compared the survival of the patients whose Karnofsky value after operation was 60% or more with those whose Karnovsky value was lower than 60%. The difference between median survival in two groups was significant in favour of patients with higher Karnofsky value (p=0,001). The assesement if the the infiltrative glioma is totally or subtotally removed cannot be stated realisticly even though we considered important to examine the influence of total or subtotal removal on survival using operating record. Comparison of almost equal groups showed a significant difference in favour of total removal in the reported cases (p<0,001). After biopsy or partial removal of the tumor the survival times were significantly shorter, but because of this proportion of the number of the cases the statistical comparison was not possible. According to the age a significant difference could be shown in the meaning of the survival. Patients younger than 40 years (median 35 years) had median survival of 9 months while patients older than 60 years (median 64) had a median survival of 6 months, which is significantly different in favour of the first group (p<0,001).

4.3. Treatment of recurrent supratentorial malignant gliomas

4.3.1. Chemotherapy (BCNU – DBD, PCV)

16 out of recurrent antiplastic astrocytomas responded (CR or PR) to BCNU-DBD treatment, further 4 patients remained stable or the disease progressed (SD or PD). In the glioblastoma group, who recieved the same treatment, only 6 patients partially improved while the other patients' status remained stable or progressed. In the AA group the average survival was 13,3 months and median survival was 14 months while in the glioblastoma group the average survival was 8,3 months and median survival was only 7 months. The difference was statistically significant (p=0,0091). The survival data in the group of anaplastic astrocytomas and oligodendrogliomas, which were treated with PCV, were favourable. Among AAs 6 patients did not respond to the treatment while among OAs just 1 patient remained stable while the others showed significant survival after partial or complete response. It can be seen in average and median survival too: 17,3 months on average and 14 months on median survival, on the other hand the average survival of OAs was 28,1 months, median survival was 27 months. The survival of anaplastic astrocytomas treated with BCNU-DBD or PCV did not show a significant difference. Neither of the combinations caused any significant toxicity, mortality caused by chemotherapy did not occur. During the treatment with BCNU-DBD in three cases we detected first degree myelotoxicity which was manifested in trombocytopaenia. During the treatment with PCV in 9 but 1 cases we saw first or second degree toxic complication manifested in leucopaenia. To avoid the complications the 25% decrease of doses proved to be sufficient or the treatment was postponed for 1 or 2 weeks. Damage in the function of kidney or liver did not occur.

4.3.2.Chemotherapy (temozolomid)

19 females and 21 males were treated, the average age of the first group was 43,2 years while in the other group it was 46,3 years. 26 patients had primarily diagnosed glioblastoma while in 14 cases A3 or mixed oligoastrocytoma was the primary histology. Complete response was recorded in 3 cases, partial response in 11 cases, further progression in 4 cases while the 50% of the patients remained stable according to the CT and MRI. The decrease of the complaints and clinical improvement was noted in 4 patients, where the MRI showed stable disease. PFS was averagely 6,25 months and the average survival was 9 months. Based on primary histology the average survival in the cases of glioblastomas was 6,8 months and in the cases of anaplastic astrocytomas or mixed oligoastrocytomas it was 12,2 months. The difference was not significant. The overall survival counted from the first operation was 22 months due to the longer first period.

4.3.3.Retrospective analysis and comparison of the patients treated with BCNU-DBD és Temozolomid

The treatment needed to be stopped in 4 out 75 patients because of myelotoxical side-effects (anaemia, neutropenia) and in one case the treatment was stopped becuse of allergy. In the other patients the therapy could be continued without changing the dose. Complete remission was noted in 7 cases, partial remission in 14 and progressive disease was recorded in 14 cases while in 33 cases stable disease was observed. In 9 out of 33 stable disease cases marked neurological improvement was observed. In 3 patients with glioblastoma multiforme total remission, in further 6 patients partial remission, in 12 cases progressive disease and in 17 patients stable disease was observed. In 1 patient with malignant oligoastrocytoma after second course cystic tranformation of the tumor occured which made its recurrancy operable. Postoperative CT scan showed small residuum and after further 2 courses complete remission could be seen. 3 patients with recurrent AA was treated primarily with BCNU without any effect, later we started temozolomid treatment and stable disease could be reached. At the patients with glioblastoma multiforme the progression free survival was 6,8 months, and at the patients with AA and OA it was 9,45 months. Median survival for the GBM patients was 8,75 months and in the other group it was 11,15 months. The overall survival in the GBM group was 17,43 months and in the AA and OA group it was 70,32 months. In terms of overall survival significant difference could be seen between the 2 groups, but in terms of PFS the difference was not significant, we did not find any difference in the survival after recurrency either. According to the prospective randomized study performed by EORTC Brain Tumor Group the BCNU-DBD adjuvant combined postoperative chemotherapy significantly increases the survival of patiens with GBM and malignant astrocytoma. 46 patients suffered from malignant astrocytoma were treated in our institute according to EORTC protocoll. The survival times of this group was compared with the group of patients treated with temozolomid. The significant difference was not found, but in the group treated with temozolomid the less side effects were observed, moreover in 3 patients with recurrent GBM complete remission could be reached. In 6,15% of cases the treatment was stopped because of first and second degree myelotoxicity. In those cases the treatment was postponed for 1 or 2 weeks. Most of the patients toelrated well the treatment with temozolomid.

4.4. Results of low-grade gliomas treatment options

4.4.1. The result of the examination of connection between anamnestical data and survival times

The majority of cases with long-term epileptic history has been observed and operated on before the advent of CT. Survival of patients with a history of seizures longer than 3 years and of shorter preoperative history were compared. Five years survival rate was 44 and 39,2%. Median survival time of low-grade astrocytomas

with a long preoperative history was 53,5 months, while those with shorter history proved to be 51 months taking time to reoperation only. The difference was not significant. It is with reoperation of LGGs that markedly longer survivals could frequently be achieved. Accordingly the total survival time resulted in a median survival of 57,5 and 67,5 months, respectively which demonstrated a significant difference in favour of patients of a shorter history of seizures (p=0,03). The 5-year survival rate improved up to 50 and 62,7%.

4.4.2.Role of early radiotherapy in the treatment of low-grade gliomas:long term results of 97 patients

The median follow-up time of the surviving patients from tissue diagnosis to the last known status was 79 months (range: 28-154). Mean age of patients was 37 years (range: 14-85). Initial symptom was epilepsy in 81 cases (83,5%), 16 patients had different complaints as hemiparesis or headache. The location of the tumor was frontal and/or temporal in 85 cases (87,6%). Surgical removal was extensive and subtotal in 60 (61,9%) and 37 (38,1) patients, respectively. Postoperative KPS remained above 70 in 86 patients (88,7%) while in 11 cases (11,3%) it was between 30 and 70. Some degree of contrast enhancement on the preoperative CT was observed in 15 cases (15,5%). One patient died of parotid carcinoma, while all other deaths were related to astrocytoma progression. A strong, non-significant trend toward better PFS was also observed for patients with young age, KPS above 70, and epilepsy as initial symptom. On multivariate analysis, only the timing of RT was found to be associated significantly with better PFS (p=0,0068). The 5-year PFS rate following subtotal removal was 60,0% with, and 12,4% without RT. In the total resection group no significant difference in PFS was observed between early irradiated and deferred patients. The 5-year PFS rate was 46,2% and 54,1%, respectively (p=0,6812).

Disease specific survival (DSS)
Young age at presentation, and extent of surgery were associated with better survival on univariate analysis, but showed only a trend to significance in a multivariate Cox-regression model. The other parameters had no significant effect on survival. Following less than total resection early RT significantly improved survival.

Treatment and survival following progression
At last assessment 35 out of 97 patients (36,1%) were alive, 30 (30,9%) without recurrence. Nineteen patients (28,4%) received palliative care only, because of poor condition, exhaustion of treatment options, or lack of consent. Thirty-four patients (50,7%) have been reoperated, there was one postoperative death in this group. Nineteen patients (28,4%) received RT following reoperation, two patients did not consent to RT and in 12 other cases RT was already exhausted. Twenty-nine of the 34 reoperated tumors (85,3%) showed anaplastic features on histology, there were 23 (67,6%) anaplastic astrocytomas and six (17,7%) glioblastomas. In five cases (14,7%) histology remained unchanged. In the 14 cases treated by radio- or

chemotherapy without histological confirmation, tumor dedifferentiation was presumed based on the appearance of hyperdensity and marked enhancement of the originally hypodense and non-enhancing tumor. For the analysis of outcome following progression, we grouped patients based on whether they received delayed RT (with or without reoperation), or not. The latter group consisted of patients that were reoperated only, received chemotherapy, or no further treatment. Mean post-recurrence survival time with or without delayed RT was 37,1 and 13,9 months, respectively. The 3-year actuarial survival following progression was also significantly improved with delayed RT.

4.4.3.Clinical results of treatment of low-grade gliomas after stereotactic biopsy and radiotherapy

In 21 out of 38 patients epilepsy was registered (55%). Beyond regular neurological examinations during the follow-up every single patient was examined with CT and MRI. Decrease in the size of the tumor was noted in 25 patients (65%). Contrast enhancement was seen in 2 cases in the third and fourth year after after the beginning of the treatment (5%). These patients received chemotherapy. 11 patients remained stable (30%). 5 year progression free survival was 56,78 months (range: 12-101), 5 year DSS was 66,73 months (range: 24-101). KPS improved in 10 patiens and remained stable in all the other patients. Maintaining the antiepileptic treatment 9 patients became seizure-free while in 7 cases the seizure frequency and intensity decreased (16=76,2%), and in 5 cases it remained unchanged (23,8%).

5.Conclusions

1.I was the first in Hungary to examine and publish the effect of methylprednisolon treatment on peritumoral oedema. The registered, significant and fast clinical improvement in the examined patient group can be explained with the oedema reducing effect of the drug. At the same time - in accordance with literary data- significant side effects were not experienced.

2.Based on the analysis of the biggest GBM database in Hungary I can claim that age always significantly influences expected survival after either the total removal of the tumor or radio- and combined treatment.

3.Based on experiences gained on significant number of patients treated with recurrent malignant gliomas I was among the firsts to call attention to advantagous properties of temozolomid. I found that the effect of temozolomid is similar to- or the same as the effect well known chemotheraputic drugs.

4.The early radical removal of favourable localisation of low-grade gliomas can prevent a possible late malignant transormation and recurrency. In the cases of

unfavourable localisation of low-grade gliomas temporary result is expected after individual consideration applying biopsy and oncological treatment. According to our experience in the cases of subtotally or partially removed tumor early radiotherapy significantly improves the progression free survival and disease specific survival time. In the cases of totally removed LGG tumor the early irradiation does not benefit. Based on our resutls we can conclude that after the subtotally or partially removed LGG tumor the early radiotherapy is suggested while in the cases of totally removed LGG the postponation of radiotherapy till recurrency is a possible therapeutic option.

6. My own publications

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