**DIAGNOSIS AND MANAGEMET OF GLIOBLASTOMA PATIENTS WITH RAPID EARLY PROGRESSION BEFORE THE INITIATION OF ADJUVANT ONCOLOGY TREATMENT**

**Project introduction including relevance and topical issues**

Glioblastoma (GB) is the most aggressive diffuse glioma that corresponds to grade 4 based on the 2016 World Health Organization Classification of Tumors of the Central Nervous System. GB is the most common primary brain malignancy with the incidence of 3 per 100,000 persons per year, accounting for 45% of malignant primary brain tumors and 54% of all gliomas. Despite the considerable improvements in surgical techniques, which enable more extensive degree of resection, wide application of more precise radiotherapy (RT) and novel chemotherapeutic agents, GB remains an incurable disease with a median survival of 15 months and 3-year overall survival (OS) of less than 10% in real clinical practice [1-4]. Clinical trials evaluating the role of modern targeted therapy did not prove superiority of this treatment strategy and results of GB treatment remains poor. The only one possible advance after 15 years is the treatment by tumor treating fields, however wide availability of this method is limited by enormously high price tag, patients motivation and some discussable issues in performed clinical trials [5].

Current standard of care is based on multimodality treatment combining surgery, RT and chemotherapy with alkylating agent temozolomide (TMZ). Adjuvant therapy is usually initiated up to 4-6 weeks after surgery to allow sufficient recovery time and enable wound healing. Standard post-surgery treatment of newly diagnosed GB patients has remained unchanged since implementation of the recommendations of the EORTC 26981–22981/NCIC CE3 trial (Stupp regimen) that finished enrolling patients in 2002 and was published in 2005. In this protocol, TMZ (75 mg/m2) is administered on days 1 through 42 with concomitant RT (60 Gy), followed by administration of TMZ alone (150 to 200 mg/m2) on days 1-5 in six consecutive 4-week cycles. Co-administration of TMZ improved survival from 12.1 months (with RT alone) to 14.6 months (with addition of TMZ) [6-8]. Continuing effort how to improve treatment outcomes is urgent clinical as well as research need.

Glioblastoma as a progressive disease

The phenomenon of postoperative rapid early progression (REP) has only recently been explored with increasingly available magnetic resonance imaging (MRI) for both postsurgery and preRT indication and is currently of high interest. REP diagnosis is based on a comparison of early postoperative MRI findings (up to 72 hours postoperatively) and planning preRT MRI. Farace at al focused on early MRI changes in glioblastoma in the period between surgery and adjuvant therapy [9]. Comparing early post-operative MRI with pre-adjuvant MRI acquired approximately 30 days later, they found that at least 30 % of MRI showed signs strongly suggestive of tumor progression during this period. Even higher proportion of patients with documented REP was recently described by Palmer et al when up to 50 % developed progression before initiation of adjuvant treatment without any effect of waiting time to initiation of RT (median time from resection to RT was 32.5 and 33 days in patients with and without REP (p=0.337) [10]. These results are in accordance with our retrospective analysis of 95 patients with GB treated during 2014-2017 where 52% patients developed suspected progression at MRI performed for radiotherapy planning purposes – Lakomy, Kazda et al, manuscript in preparation; presentation at European Association of Neuro-Oncology 2019 annual meeting). These patients may represent a subset of patients with a particularly aggressive phenotype of GB.

According to these and other several retrospective analyzes, it was consistently confirmed that the presence of early recurrence on planning MRI examination was associated with a more aggressive form of glioblastoma and worse overall survival [11-14]. Higher risk can be expected in patients after fewer radical resections [14]. What further affects the prognosis of patients with early relapse is also unclear. In one study, overall survival was significantly worse when MGMT methylation was not present in this group of patients [10]. Analysis of other potential biomarkers is insufficient. Given the large number of patients with REP and the retrospective analyzes available to date, it is important to prospectively analyze this more aggressive tumor group and try to more clinically influence the negative course of the disease in this particular group of patients.

Currently, it is not clear what is the optimal approach in patients with REP. Whether to indicate reoperation of recurrence, to choose accelerated RT regimes with or without concurrent chemotherapy or administration of more aggressive and intensive chemotherapy with combined alkylating cytostatics 7in the presence of MGMT methylation, marker of higher radiosensitivity [7]. Treatment of these patients today is not different from patients without REP, and if so, it is purely an individual approach. Clearly, these patients biased previous clinical trials where no routine preRT MRI examination was performed. Currently, these patients are usually excluded from clinical trials, moreover, recent studies often randomize patients after the competition of standard adjuvant chemoRT without any clear progression on the first post chemoRT MRI. REP in MRI planning is a significant negative prognostic factor that should be a stratification factor in future clinical trials. The basic problem is the postoperative prediction of early recurrence. In general, the progressive feature of GB is done by its microenvironment, molecular background of glioma cells, and miRNA profile that, as was shown also by the members of our team, is significant in GB oncogenic signaling and has potential to serve as a disease biomarker and a novel therapeutic target in oncology [15-21].

*Amino acid Carbon-11-labeled methionine PET (MET PET) is the most widely studied tracer for molecular imaging in glioma*

Positron emission tomography is currently becoming progressively more established part of brain imaging in both pretreatment as well as follow up examination. There is increasing evidence supporting implementation of PET imaging into brain cancer management [22]. However, modern PET facilities with an inhouse cyclotron are not widely available contributing to necessity of centralized care for offering of state-of-the-art comprehensive neurooncology care. Further developments and supports must be focused not only on construction of new PET camera facilities, but also on implementation of new advanced PET techniques in already established PET centers equipped by cyclotron (developments in MET, FLT, FET or FDOPA tracers for example) [23,24]. Amino acid tracers´ uptake reflects amino acid transport and proteosynthesis which are increased in most types of tumors including gliomas when compared to normal surrounding tissues. Resulted higher tumor-to-normal brain ratio (T/N ratio) provides higher contrast and tumor discrimination comparing to FDG even through lower absolute standard uptake values (SUV). However, because amino acid tracer transport is independent of blood brain barrier breakdown, there is visible PET uptake for tumors that do not enhance on MRI or for aggressive parts of tumor with no MRI contrast uptake yet.

MET PET plays an especially important role in improving diagnostic procedures for treating brain tumors. [11C] Methionine is not taken up by normal brain tissue to a marked degree, and the sensitivity of MET PET for detecting glioma tumors appears to be high (11–16). MET PET uptake by normal brain parenchyma is relatively low, and so MET PET shows promise for assessing cerebral tumor dimensions. It has been suggested that MET PET may more precisely outline the true extent of viable tumor tissue than MRI, whereas MRI has the capability to better delineate the total extent of associated pathologic changes, such as edema, in adjacent brain areas [25,26]. Utility of MET PET was also successfully tested in our institution [27].

MET PET tumor/normal tissue index of 1.3 was considered the threshold for malignant activity based on correlation to stereotactic histopathology examination. It is not clear which threshold value for the tumor/normal tissue index should become the reference value for determining GBM. For primary brain tumor, some reports have used 1.3 or 1.7 to determine the threshold value [28-30].

Usage of MET PET is limited by its short half-life to centers with its own cyclotron enabling the manufacture of radiopharmaceuticals. Patients with REP of GB need to start oncological treatment as soon as possible and it is not ethical to wait for other commercially available radiopharmaceuticals (FET, FLT and others) that have a longer half-life but are only available in limited ordering schedule. In the comprehensive neurooncological centers, however, the individual rapid preparation of methionine tracer, the most studied substance in brain tumors, is the unique option how to improve outcomes of patients with REP, particularly aggressive GB.

**Preliminary data**

This project proposal follows from our previous retrospective analysis of 144 glioblastoma (GB) patients treated in our institution from 2014 to 2017. 47 patients (30.5%) were treated according to Stupp regimen. Median overall survival was significantly better in patients treated according to Stupp regimen (23.3 vs. 8.6 months, p<0.001) proving high standard of treatment procedures in our institution resulting in comparable survival outcomes to other currently published series [5]. Rapid early progression (REP) was presented in 52% of 95 evaluable patients who underwent both post-surgery and pre-radiotherapy MRI scans. Their median overall survival (OS) was significantly worse (10.2 vs.18.5 months, p=0.001). These results are within confident intervals reported by Palmer et al (11.5 months /95% CI: 7.4-17.6/) vs. 20.1 months /95% CI: 17.8- 26.1/, p=0.013) [10]. We did not observe any significant impact of waiting time to start of RT. Patients developing REP had significantly worse progression free survival (progression after RT, calculating from the beginning of chemo/radiotherapy) as well (3.6 vs. 9.3 months, p=0.034). Presented own retrospective survival outcomes data will serve as a comparator in presented project.

**Hypothesis**

GB patients developing REP before start of adjuvant RT have dismal prognosis even in relation to generally poor outcomes of GB patients. Nevertheless, they were considered perspective patients since they underwent radical neurosurgery and headed to aggressive oncology treatment with the hope of longer lasting survival. The optimal treatment of these patients with REP is unknown, no previous prospective trial was performed in this specific cohort of early progressing patients. We hypothesize that new enhancing lesion on MRI or progressing residual disease after subtotal surgery is not the only one region of early progression and when RT is aimed solely by the enhancing MRI lesion, marginal miss may be reason of further rapid progression after RT (3.6 months PFS in our retrospective cohort). MET PET imaging reveal further regions of aggressive part of tumor and guiding RT not only by MRI enhancing lesion but also by PET scan may significantly improve outcomes of these patients.

**Project objectives**

1) Prospective assessment of the incidence of REP on planning MRI (MRI performed for planning purposes of RT, usually done 1 week before the start of RT); comparison of early postoperative and planning MRI exams

2) For REP group (Aim 1) examination of the potential of MET PET to reveal further regions of aggressive disease apart from enhancing lesions on T1 weighted MRI scan and to confirm early progression (differential diagnosis to postsurgery changes).

3) Ability of MET PET to optimize definition of target volumes for adjuvant RT (Boolean operators; PET - T/N ration ≥1.3 and MRI high risk regions)

4) Evaluation of the effect of RT optimization on early recurrence in terms of PFS (primary outcome used in power analysis) and OS versus our own historical retrospective cohort (2014-2017)

5) Evaluation of spatial patterns of failure (central vs. in-field vs. marginal vs. distant) in MET PET cohort in comparison to retrospective REP cohort.

6) Univariate and multivariate analysis of clinical factors (age, gender, extent of resection, KPS before RT, early recurrence, time to initiation of postoperative treatment, administration of concomitant chemoRT and adjuvant chemotherapy) and laboratory biomarkers (MGMT, IDH, ATRX, TERT, Ki-67, PD-L1) on PFS and OS in a whole group of 120 prospectively enrolled patients with GB.

7) Identification of basic clinical and laboratory biomarkers (Aim 6) of REP applicable to clinical practice

**Methods and approaches**

A cohort of 120 patients with histologically proven newly diagnosed GB (pathology part of co-applicants team) after surgery (neurosurgery part of co-applicants team) will be prospectively enrolled to the study at Masaryk Memorial Cancer Institute (MMCI, principal investigator team). Patients will be included into the study after signature of the Informed Consent.

*Inclusion criteria*: Newly diagnosed glioblastoma (WHO 2016 classification), minimal age of 18 years, performance status according to ECOG (Eastern Cooperative Oncology Group) 0-2, healed surgical wound, postoperative MRI no more than 72 hours after surgery, indication to adjuvant oncology treatment, signed informed consent form.

*Exclusion criteria*: prior brain surgery, prior brain RT, history of solid cancer except for non-melanoma skin cancer, any systemic illness or unstable medical condition that might pose additional risk for performance of oncology treatment and imaging (MRI, MET PET), active drugs as well as alcohol addiction or any other factors that might be considered interfering with study requirements. Known active infection (HIV, viral hepatitis A, B, C). Exclusion criteria apply also to pregnant or breastfeeding patients, as well as patients unable or refusing to sign the written informed consent. Patients without resection of glioblastoma (those with biopsy only) will be excluded from this study. Patients without indication to adjuvant RT. Patients indicated to reoperation. Contraindication to radio/chemotherapy or MRI/MET PET imaging according to institutional standard operation procedures.

The standard adjuvant treatment (examples of standard schedules summarized below) will be realized at the Department of Radiation Oncology and Department of Comprehensive Oncology Care, at MMCI. All patients irradiated at MMCI undergo planning MRI (with administration of contrast agent) for registration to planning CT as a process of accurate delineation of target volumes as well as organs at risk (software EclipseTM). All these procedures are standard part of modern RT procedure (RT planning). This planning MRI is usually acquired 1 week before start of irradiation, which is usually timed 5-6 weeks after surgery. Experienced neuroradiologist (Belanova, board exam in neuroradiology) will evaluate planning MRI for all patients and will delineate regions of potential rapid early progression (if presented; defined as a new contrast enhancing leasion, ≥25% increase in any dimension of the residual tumor or as a clear progression based on neuroradiologist judgement; all comparing to postoperative MRI).

Patients without evidence of REP will further undergo standard adjuvant oncology treatment according to established institutional and national guidelines as follow: 1) Stupp regimen [8] for patients in a good general condition, patient able to undergo long (6 weeks) chemoRT. Indication according to treating physician, no influence by presented study (total dose of 60 Gy, administered in 30 daily fractions over a period of 6 weeks. Concurrent temozolomide administered with RT at a dose of 75 mg per square meter of body-surface area per day for maximum of 49 consecutive days from day 1 until the final day of RT. Adjuvant temozolomide administered at a dose of 150 to 200 mg per square meter per day for 5 consecutive days of a 28-day cycle for up to 6 cycles or until disease progression. 2) Perry accelerated regimen [31] for patients ≥65 years old and those deemed by their treating physicians not to be suitable to receive long conventional RT (literally as in Perry study protocol) in combination with chemotherapy (total dose of 40.05 Gy, administered in 15 daily fractions over a period of 3 weeks. Concurrent temozolomide administered with RT at a dose of 75 mg per square meter of body-surface area per day for 21 consecutive days from day 1 until the final day of RT. Adjuvant temozolomide administered at a dose of 150 to 200 mg per square meter per day for 5 consecutive days of a 28-day cycle for up to 12 cycles or until disease progression. 3) For patients of any other condition (regardless the age), not suitable to undergo concurrent chemoRT, individual adjuvant treatment is indicated, usually accelerated RT alone (total dose 30-50 Gy in 10-20 daily dose, for example 10x3.0 Gy, 10x3.4 Gy, 15x2.67 Gy, 20x2.5 Gy and others) followed in some patients by palliative chemotherapy with temozolomide based on patient´s actual condition. All patients will be scheduled to regular follow-up with MRI (first MRI 2 months after the end of RT, the others every 3 months, otherwise ordered earlier based on clinical need) utilizing standardized RANO criteria.

Patients with the evidence of REP will be scheduled to MET PET (Rehak - Department of Nuclear Medicine, MMCI). MET PET examination (procedures based on previous experience with MET PET in our institution [27], 250 MBq, images acquisition 5 minutes after administration) will be performed maximally within 1 week after planning MRI. Maximum effort (in both, MET PET as well as RT planning) will be paid to avoid potential delay in the start of oncology treatment. Image transfer will be ensured utilizing standard Picture Archiving and Communication System (PACS) and software for RT planning (EclipseTM). Regions with high MET PET uptake (region of high SUV will be dedicated by Rehak) will be contoured and after coregistration to planning CT transferred to RT treatment planning software. The residual tumor volume defined by focal MET uptake will be delineated manually (EclipseTM) by Rehak. However, a threshold value for the tumor/normal tissue index of 1.3 (discussion about appropriate threshold value see above) will be considered for the tumor margin in all patients. For all the patients included in the trial, the same windowing will be used. Normal tissue for calculation of tumor/normal index will be represented by SUV in contralateral hemisphere in healthy brain including both grey and white matter and calculated not only from one slice but as a median value from several slices). An automated definition of tumor volume is not feasible because of the small size of focal MET uptake in most patients and the high uptake in normal tissue such as lacrimal glands or mucosa. Adjuvant oncology treatment for this patients with REP will be performed according to regimens described above, however, RT will be optimized based on information from MET PET: high MET PET uptake will be, together with contrast enhancing regions on T1 weighted MRI, integral part of delineation of gross tumor volume (first step in target volumes delineation during RT planning; this is basis for further standard expansion of target volumes to accommodate prescribed RT dose to regions of microscopic disease). Special attention will be on discordant regions of high MET PET uptake and no MRI contrast enhancement. Follow up will be realized on the same basis as for patients without REP.

The cellular and cytogenetic features together with the final histologic diagnosis according to the 2016 WHO classification of CNS tumors will be determined by a skilled neuropathologist (Kren, Muckova) and molecular biologists (Slaby, Sana, Souckova). Neuropathologist and molecular biologists will be blinded to radiologic imaging. Routine staining methods will be applied for standard histopathological evaluation (e.g. hematoxylin-eosin). Immunohistochemical analyses and molecular testing will focused on proliferation rate (Ki67), programmed death ligand 1 positivity, IDH, ATRX and TERT mutational status, MGMT promoter methylation status, and 1p/19q co-deletion. These markers will be evaluated retrospectively also in our historical control cohort of 95 patients (see above preliminary data as well as statistical consideration section below) in order to ensure valid comparison of groups (without vs. with MET PET) in multivariable analysis (Cox Proportional-Hazards Model)

All data will be collected in pseudonymized form in a database (full access Lakomy, Smrcka) and subsequent calculations and analysis (Lakomy, Smrcka and whole consortium) will be performed with the participation of an experienced statistician.

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