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18F-FDOPA based radiation planning in modern care of glioblastoma multiforme

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Doctoral thesis summary

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1. Introduction

Glioblastoma multiforme (GBM) is the most aggressive form of malignant glial tumors of the central nervous system (CNS). GBM accounts for approximately 15% of primary CNS tumors, with an incidence of 3 cases per 100,000 people. The average survival time for patients with GBM is between 12 and 15 months, the five-year survival of the disease is less than 10% nowadays.

Treating the disease is a complex oncological task. If it's possible after complete surgical removal, Temozolomide and Avastin based chemotherapy and 3D-based radiotherapy should be performed. In addition to modern treatment procedures, the majority of GBM patients experience local recurrence within a year, which based on international and domestic data, manifests itself predominantly 1-1.5 cm around of the primer tumor location.

Modern 3D-based radiotherapy is considered as a basic treatment for patients with GBM. During the implementation of modern 3D radiation therapy, the determination of the area to be irradiated is based on 3D cross-sectional information of computed tomography (CT) and magnetic resonance imaging (MRI). For determination of gross tumor volume (GTV) pre-surgical and post-surgical gadolinium-based T1-weighted and T2-weighted MR imaging in combination with CT fusion are used. Following the latest contouring and tumor definition recommendations, the resection cavity is also part of the GTV volume.

Accumulation of gadolinium in brain tissue is caused by damage to the blood-brain barrier, which may complicate the diagnosis of post-surgical changes and residual tumors. The accumulation of contrast does not always correspond to the actual extent of the tumor. Due to the propensity to recur and due to tumor infiltration, the GTV area is expanded by 2 cm during the determination of clinical tumor volume (CTV) taking into account anatomical corrections. In addition to the determination of the target volume according to the conventional protocol, positron emission tomography (PET) based functional imaging which provides biological (BTV) information is gaining more and more importance. Anatomical information based on CT and MR imaging is limited compared to morphometabolic information in PET imaging as CT and MR are primarily able to display structural anatomical changes as opposed to morphometabolic imaging information provided by PET imaging. The additional information provided by PET imaging can be used to assess the effectiveness of the treatment, to noninvasive grading, to establish a differential diagnosis, and to determine the extent of the tumor more accurately. In modern irradiation planning the integration of PET

information into the target volume definition increases the extension of the target area, the accuracy of tumor definition and localization.

In contrast to imaging with 2-deoxy-2- (fluorine-18) fluoro-D-glucose (18F-FDG) radiotracer which is based on glucose metabolism, amino acid analog PET radiotracers are characterized by high accumulation in tumor lesions and low accumulation in “normal” brain tissue. 3,4-Dihydroxy-6- (18F) fluoro-L-phenylalanine (18F-FDOPA) is one of the most intensively used amino acid analog radiotracers for diagnosis os CNS malignancies. The increased accumulation of mentioned radiotracer in malignant cells is mostly due to the increased protein transport of tumor cells.

For different tumor types and tracers, standardized recommendations were described by the European Association of Nuclear Medicine (EANM), European Association of Neurooncology (EANO), Response Assessment in Neurooncology (RANO) practice guidelines Society of Nuclear Medicine and Molecular Imaging (SNMMI) procedure standards for imaging gliomas.

Regarding the current report of the PET/RANO group, the majority of the available data connected to contribution of PET imaging to radiotherapy planning and monitoring are based on studies with (11C-methyl)-l-methionine (MET) and O-[2-(18F)-fluoroethyl]-l-tyrosine FET. During radiotherapy target delineation, MET, FET, and FDOPA studies suggested that BTV characterized by mentioned radiotracers is larger than contrast enhancement in World Health Organization (WHO) grade III/IV gliomas.

2. Objectives

The treatment of patients with glioblastoma multiforme is a multifactorial, complex task that is a major challenge despite evolving diagnostic and therapeutic tools. At Somogy Megyei Kaposi Mór Oktató Kórház Dr. Baka József Diagnosztikai, Onkoradiológiai Kutatási és Oktatási Központ due to the advanced infrastructural background, the modern diagnosis and treatment of patients are carried out in the highest technical quality, based on the application of the most modern principles.

Aspects of the treatment characteristics of patients with glioblastoma are recorded at the system in each case. Our work can be divided into two main parts, during which we aim to examine the following key aspects:

Objective I.

- We want to illustrate the role of MRI imaging in assessing the extent of surgical intervention in patients with primary malignant brain tumors, which can be related to the overall survival of patients.

Objective II.

- We want to illustrate the use of PET / CT, PET / MR in primary malignancies of the brain, according to the examination and follow-up protocol

Objective III.

- We would like to present the added value of 18F-FDOPA in the planning process of radiotherapy, as well as the assessment of the region of possible recurrence compared to the initial 18F-FDOPA PET/MRI in primary malignant brain tumors.

3. Presentation of the publications on which the dissertation is based

3.1. Objective I.

In the first phase of our research, based on international and domestic results, we demonstrate that the extent of surgery can significantly affect the overall survival of patients with glioblastoma multiforme. We paid special attention that the extent of the surgical procedure should be based on the results of the MR imaging following the surgical procedure, and not on the basis of the surgical report. In the study of our 10-year patient population, we also examined the role of specific predisposing factors in patients based on their impact on overall survival.

The aim of our institutional retrospective research titled **"Long-term follow-up results of concomitant chemoradiotherapy followed by adjuvant temozolomide therapy for glioblastoma multiforme patients. The importance of MRI information in survival: Single-center experience"** was to investigate the importance of postoperative imaging of complete tumor resection in patients with GBM using combined concomitant and adjuvant chemoradiotherapy in our 10-year patient population.

3.1.1. Materials and methods

Between January, 2006 and April, 2015, 59 patients with newly diagnosed GBM were enrolled to our study at the University of Kaposvár Health Center, Institute of Diagnostic Imaging and Radiation Oncology. This study was conducted in accordance with the Declaration of Helsinki. The survey was permitted by the institutional ethical board.

All patients in our study underwent surgical intervention for GBM with an aim to carry out a maximal safe resection. However, if surgical resection was deemed to be associated with a relatively high risk of deficits due to the extent of disease or proximity to vital structures, an open or stereotactic biopsy was performed to establish a histopathological diagnosis. The extent of the resection was defined as biopsy, partial or gross total resection, based on pre- and post-operative MRI imaging, which was confirmed by a radiologist and a neurooncologist separately (oncoteam). Based on our data, there was no reoperation, regardless of postoperative MRI. The histological diagnosis (World Health Organization WHO, grade IV astrocytoma) was confirmed by a neuropathologist. Within six weeks after the histologic diagnosis of glioblastoma, patients received standard radiotherapy plus concomitant daily temozolomide, followed by adjuvant temozolomide as described at Stupp-protocol.

Contrast-enhanced MRI examination was carried out before and 6 weeks after chemoradiotherapy, and was repeated every 3 months during the first year of the follow up period. Residual or recurrent tumor was defined as the contrast enhancing part of the lesion.

Data collection and statistical analysis was carried out using Microsoft Excel software version 2010. We focused on the length of overall survival (OS) and time to progression (TPG), dependent on age, gender, type of resection, RPA classification and Eastern Cooperative Oncology Group (ECOG) Performance status.

OS was calculated from the date of the postoperative MRI until death or the date of the last follow up. Tumor progression was defined as an increase in tumor size more than 25% or by the presence of a new lesion on imaging. At progression, patients were assessed on the basis of their individual characteristics and offered further surgery, re-irradiation, Gamma-knife radiosurgery, second-line chemotherapy or supportive care alone. We excluded patients who were survivors but whose follow up period was shorter than 12 months. We applied the following statistical tests: Kaplan-Meier method, Cox-regression, Pearson χ-square test and long rank test.

3.1.2. Results

Fiftynine patients at the median age of 63 (range 17–84) were evaluated. Based on postoperative MRI findings, gross total tumor resection was performed in 14 cases, partial tumor resection in 39 cases, and tumor biopsy in 6 cases.

MRI based tumor progression was defined as an increase in tumor size more than 25% SPD or by the presence of a new lesion on imaging, meanwhile partial response meant a 50% decrease of the tumor SPD. We also classified complete resection (CR) and stable disease (SD). SD means that the change of the tumor SPD is between the above specified range. Statistical analysis showed a longer survival rate among males than females, with a median survival of 13 months for both males and females. The OS was 26.2 for males, and 15.6 for females. However, the difference is not considerable (log rank: $\chi 2$: 1,474 p=0.225).

For the analysis of the differentiating factor of age, our study divides patients into two age groups in accordance with relevant literature, comparing the survival rate of patients below the age of 50 (9 patients) with those of above 50 (50 patients), (median survival < 50 years: 23 months, median survival >50 years: 13 months (log rank: $\chi 2$: 5,163 p=0,023).

Besides the differentiating factors discussed above, our study payed special attention to the relation between survival, the outcome of surgery (biopsy, partial or complete resection) and the results of MRI imaging after surgery. Based on the extent of surgery,

complete resection resulted in the longest average survival of 36.4 months, followed by 21.5 months among patients with biopsy, and 15.8 months among patients with partial resection. Different surgical procedures, however, did not result in significant differences in survival (logrank p=0.059).

According to our results, it is clearly seen that postoperative MRI can provide a more objective expectation of the patients' expected survival (median survival total resection according by MRI: 19 months, median survival partial resection according by MRI: 12 months, log rank: $\chi 2$: 5.026 p=0.025).

In the statistical analysis, we were looking for variables that are good predictors of survival of patients by using a mathematical statistical test, Kaplan-Meier survival analysis, with the descriptive statistics of the major characteristics of patients treated with GBM. To find out the most significant influencing variable, Cox regression was performed. The type of surgical procedure (biopsy, partial resection, total resection) and the results of the MRI were included in the model. Based on the Cox regression, the MRI was a significant determinant of the surgical procedure and the MRI variables. (Surgery: p=0.250; CI: 0.773–2.688; MRI: p=0.017; CI: 1.233–8.774).

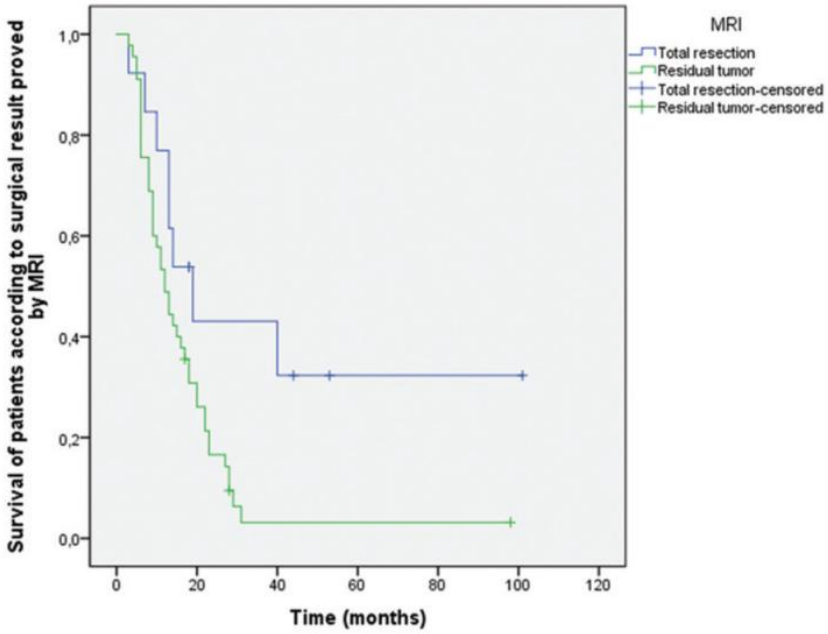

Figure 1. Overall survival in relation to the extent of surgery confirmed by MRI in patients with primer malignant brain tumors

3.1.3. Discussion

According to previous studies, the application of the Stupp protocol improves the survival of patients diagnosed with GBM. It is also well known that a complete resection of the tumor can significantly increase the life expectancy of patients. In our study, we showed

that complete resection without confirmation with MRI cannot be considered as a prognostic factor. Although we analyzed only 59 patients in our retrospective study, we can state that the survival time of patients with complete resection confirmed by MRI is significantly longer than that of patients with residual tumor. According to our results, it is clearly seen that postoperative MRI can provide a more objective expectation of the patients' expected survival. On the other hand, the survival of patients did not differ significantly depending on the surgical outcome (biopsy, partial resection or total resection). For us, this means that the surgical procedure cannot predict the extent of the expected survival, but the MRI can foreshadow the relevant expectation. If postoperative MRI indicates a residual tumor, it is recommended to repeat the complete resection unless there is no technical obstacle. Surgical efficiency can be improved by installing an intraoperative MRI equipment, however the technical conditions exist in few places in the world and are not provided in Hungary.

3.2. Objective II.

In the second phase of our research, a research program launched in 2017 at our institute aimed to compare the GTV target area defined by conventional MRI and the biological target area (BTV) defined by 18F-FDOPA, taking into account current international recommendations. Our article was titled **"F-DOPA PET/MR based target definiton in the 3D based radiotherapy treatment of glioblastoma multiforme patients. First Hungarian experiences"**. 18F-FDOPA amino acid tracer is available in Hungary for PET diagnosis in patients with primary malignant brain tumors since September 2017. Our study presents the design method of the first Hungarian 18F-FDOPA based PET/CT/MR fusion-based 3D irradiation at Kaposi Mór Oktató Kórház Dr. Baka József Diagnosztikai, Onkoradiológiai, Kutatási és Oktatási Központ (earlier Kaposvári Egyetem, Egészségügyi Centrum).

3.2.1. Materials and methods

In our research we performed a retrospective analysis of three histologically confirmed patients with GBM who received TMZ-based chemoradiotherapy according to the protocol of our institution based on oncoteam decision. The sample consisted of two women and one man ranging in age from 35 to 63 years. All three patients underwent protocol-based PET-MRI data collection as part of the irradiation planning process using a tracer of 18F-FDOPA. Based on administrative data 186 ± 111.9 MBq radiopharmaceutics were injected into patients.

During the acquisition T2-weighted 3D sagittal, T2- and diffusion-weighted, FLAIR-transverse, T1-weighted sagittal, T2-weighted coronal, ASL and DTI examinations were performed, followed by T1-weighted 3D imaging after intravenous contrast agent supplemented by photon emission data collection.

3.2.2. Irradiation planning

Varian Eclipse version 13.0 software was used for contouring and irradiation planning. T1 weighted post-contrast MRI, T2 weighted MRI, and F-FDOPA images were fused with irradiation planning CT images. We defined the F-FDOPA accumulation volume (BTV-FDOPA), the T1 contrast enhancement volume (GTV-T1KA), and the area covered by T2 weighted MRI as edema (CTV edema).

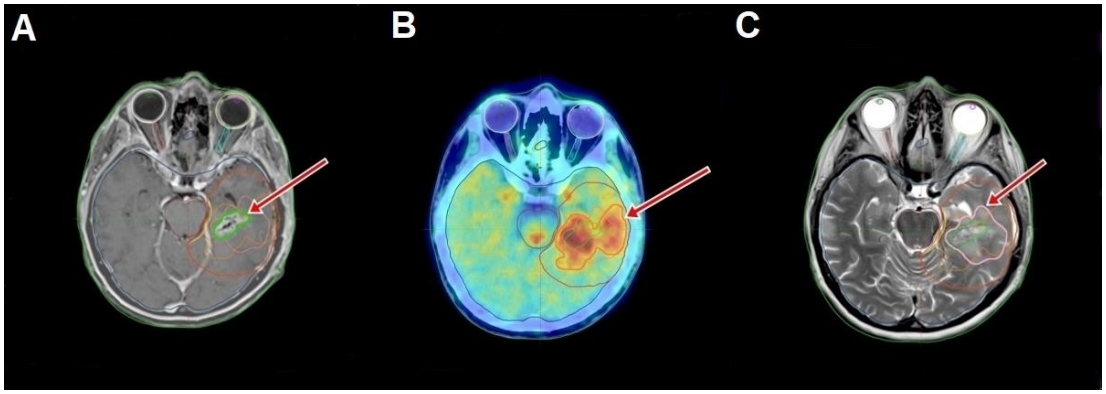

Figure 2. T1-weighted image (A), 18F-FDOPA PET/CT image (B), and T2-weighted image (C). After surgical removal, T2-weighted axial images show an inhomogeneously increased deviation with a signal intensity similar to the previous volume. Edema is observed around the tumor area (A and C image). Medium/high-intensity, multi-focal, sometimes spherical, confluent F-DOPA accumulation is detected, with irregularly shaped, inhomogeneous soft tissue structure with cystic parts in the volume (B image).

3.2.3. Results

1. táblázat BTV FDOPA, GTV T1KA, CTV T2 and BTV FDOPA - CTV T2 (non-overlapping brain target volume) Values are given in cm^3.

Patient	Tumor localization	BTV FDOPA	GTV T1KA	CTV T2	BTV FDOPA - CTV T2
1. case	left temporal lobe	30,9	13,2	27,7	10,3
2. case	right temporal lobe	22,0	9,0	35,7	2,2
3. case	left frontal lobe	15,3	3,8	57,4	1

3.2.4. Discussion

Using the information provided by high-tech 3D cross-sectional imaging modalities and targeted radiotherapy techniques (IMRT, IGRT, SRT, SRSR), higher local doses can be achieved in the PTV area with lower toxicity. Modern irradiation planning and contouring systems allow the use of image fusion and automatic segmentation tools to achieve better PTV and OAR definition.

During the first Hungarian 18F-FDOPA based irradiation planning process we presented, we described that the tumor area defined by the amino acid tracer did not show a complete agreement with the traditionally used MR T2 edema area, and the design target volume was modified based on the functional information. In our opinion, the role of functional hybrid imaging in modern 3D-based irradiation planning, treatment and monitoring processes is expected to expand further in the future.

3.3. Objective III.

After the publication of the initial experiences, in the third phase of our research, we examined the relationship between the target volumes obtained during the radiotherapy of the patients in a larger patient population, supplemented by the localization of the recurrences observed during the follow-up. In particular we examined the relationship of the recurrence area to the BTV defined by the initial 18F-FDOPA PET and the GTV defined by the initial conventional imaging modalities, as well as the dose coverage of these areas. In addition to the determination of target volumes and the localization of recurrences, the signal intensity differences between 18F-FDOPA PET/CT and 18F-FDOPA PET/MR images taken on the same day were also measured using our standardized method. Our article titled **"Additional Value of 18F-FDOPA Amino Acid Analog Radiotracer to Irradiation Planning Process of Patients With Glioblastoma Multiforme"**.

The objective of this study was to compare GTV volume on MRI with the volume of 18F-FDOPA with different segmentation threshold. The signal intensities of 18F-FDOPA PET information by PET-MR and PET-CT were compared regarding relative brain signal. We also studied the target coverage of 18F-FDOPA volume by standard of care approach. We analyzed the location of recurrences relative to MRI-based GTV, PET-based BTV volume, and standard of care PTV volume. We determined the volume of recurrence, if present, to compare to the initial PET BTV thresholds accumulation volume and PTV.

3.3.1. Materials and methods

At patient selection for our study patients were required to have a primary malignant brain tumor, including a pathologically confirmed glioblastoma multiforme (WHO grade IV) lesion. Diagnostic imaging (18F-FDOPA PET/MR and PET/CT) as well as treatment completion and follow-up examinations were performed in our institution. We excluded from our study those patients who were under treatment for Parkinson's disease or had contraindications to MRI contrast agent or radiotherapy.

3.3.2. Sampling process

1. 18F-FDOPA radiotracer was produced with an on-site cyclotron (Siemens Eclipse) on the day of the acquisition. The studies were performed using PET/MRI equipment (Siemens Biographs 3.0 T nMR, Erlangen, Deutschland) 10 min after intravenous injection of the radiotracer. Simultaneous photon emission data collection was performed using one bed position during 30 minutes.
2. After performing 18F-FDOPA PET/MRI, planning PET/CT (Siemens Biograph Truepoint 64 PET/CT, Erlangen, Deutschland) was performed according to irradiation position protocol, lastly 18F-FDOPA data from PET/CT were co-registrated with planning CT and MRI measurements using rigid registration considering the bony parts of the skull.
3. Target volumes of GTV and BTV on co-registrated images were described according to the recommendation of the European Organization for Research and Treatment of Cancer (EORTC) by experienced oncoradiologists using Varian Eclipse 13.0 version software (Varian Medical Systems Inc., Palo Alto, CA, USA). CTV was defined as a 2-cm expansion of GTV in proportion of anatomical burdens. Planning target volume (PTV) was defined as 3- to 5-mm additional margin to CTV.
4. In their study, Patel et al. showed the best differentiation between LG and HGG at the T/N SUVmax ratio greater than 1.7. Based on Patel et al.'s research and EANM/EANO/RANO practice guide-lines/SNMMI procedure standards for imaging of gliomas using PET with radiolabeled amino acids, version 1.0.; T/N 1.7 (in the following BTV 1.7) and T/N 2.0 (in the following BTV 2.0) ratio seemed to be able to deliver the best determination of tumor extend of high-grade gliomas. A 1-cm diameter spherical region of interest (ROI) was placed at the suspected tumor site (T) and contralateral white matter at the level of centrum semiovale to calculate the metabolic activity of the radiotracer using the standard body weight method. After

calculating the ROI's activity, BTV 1.7 and BTV 2.0 ratio's volume coverage was measured.

5. Since the basal ganglia have significant 18F-FDOPA radiotracer uptake, anatomical correction needed to be done to describe basal ganglia region as not a malignant tissue at the cerebral area.
6. Because of the physical half-life of the 18F-labeled radiotracers, signal intensity deviations were calculated from acquisition time from DICOM header of each PET/MRI and PET/CT to relative brain signal, respectively.
7. If recurrence was detected on follow-up MRI examinations, the area of recurrence was also contoured and compared with the PTV information.

3.3.3. Statistical analysis

95% Hausdorff distance from the GTV as reference were considered, whereas supplementary volume contour (SVC) was also calculated to identify the added value of 18F-FDOPA–based BTV segmentation. SVC was measured for each patient to establish the maximum and mean distance between GTV volume and BTV 1.7 and BTV 2.0 volume using Python programming software. Since Varian Eclipse 13.0 is unable to process the PET information from PET/MR directly, we used the Medical Interactive Creative Environment (MICE Toolkit™, version 1.0.6, NONPI Medical AB, Stockholm, Sweden) to calculate linear regression value whether the 18F-FDOPA accumulation ratios are the same at PET/MR and PET/CT imaging modalities regarding normalized brain signal.

3.3.4. Results

The selection criteria of our study met at 17 patients, in which sample men were overrepresented (male n = 12; female n = 5). The mean age of the patients was 56.3 years (range 35-77 years). In most cases, biopsy sampling was feasible (n=11). WHO grade IV glioma has been confirmed histologically in the entire patient population.

The entire pre-treatment diagnostic image acquisitions were done at our institution for each of the patients included in the research. The MR T1CE (GTV) area was defined on the MR/CT scans according to international guidelines. The BTV 1.7 and BTV 2.0 areas were defined on the 18F-FDOPA images. The BTV areas segmented by PET imaging were also compared to the GTV area, and the BTV volume inside and outside the GTV area was measured.

PET/CT and PET/MR compared to the relative signal values of PET/CT and PET/MR. A good correlation value can be found between the mean and median values of the variables (r=0.75; r=0.72).

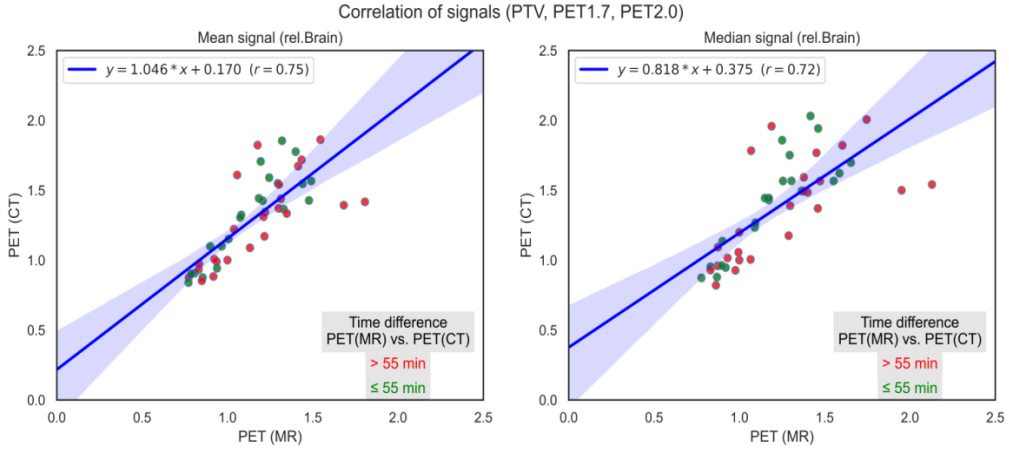

Figure 3. Correlation of PET/CT and PET/MR signals regarding PTV, 18F-FDOPA T/N 1.7, and 18F-FDOPA T/N 2.0 volume indicating the time difference between the two acquisitions.

On average, 95% of the segmented volumes were within 15.5 mm (range, 7.9–30.7 mm) and 10.5 mm (range, 4.3–21.4 mm) for BTV 1.7 and BTV 2.0 respectively. For the disagreement, we used the percentage of the volume outside of the reference (in this case GTV) for BTV 1.7, on average, 58.8% (range, 28–100%) were outside the GTV, whereas this lowered to 45.7% (range, 14–100%) regarding BTV 2.0. Both PET volumes remained within the adequate dose coverage (95% of the prescribed dose), only on a few cases had minor coverage loss up to maximum 3% and 5% of their volume for BTV 2.0 and BTV 1.7, respectively. GTV varied substantially within our cohort, with an average 43 cm3 (range, 6.1–183.6 cm3). Time between the PET/MR and PET/CT acquisition varied between 35 and 83 min, with an average around 1 h (55.7 min).

3.3.5. Follow-up

During patient follow-up, recurrence was detected in four cases. 68% (range, 9–94%) of the recurrence was detected outside the GTV volumes. Regarding BTV 1.7 and BTV 2.0, on average, 67% (range, 39–81) and 79% (range, 69–89) of the recurrence occurred outside BTV volumes, respectively. There was a negligible volume recurrence outside the PTV area (average, 0.01%; range, 0.01–0.05%).

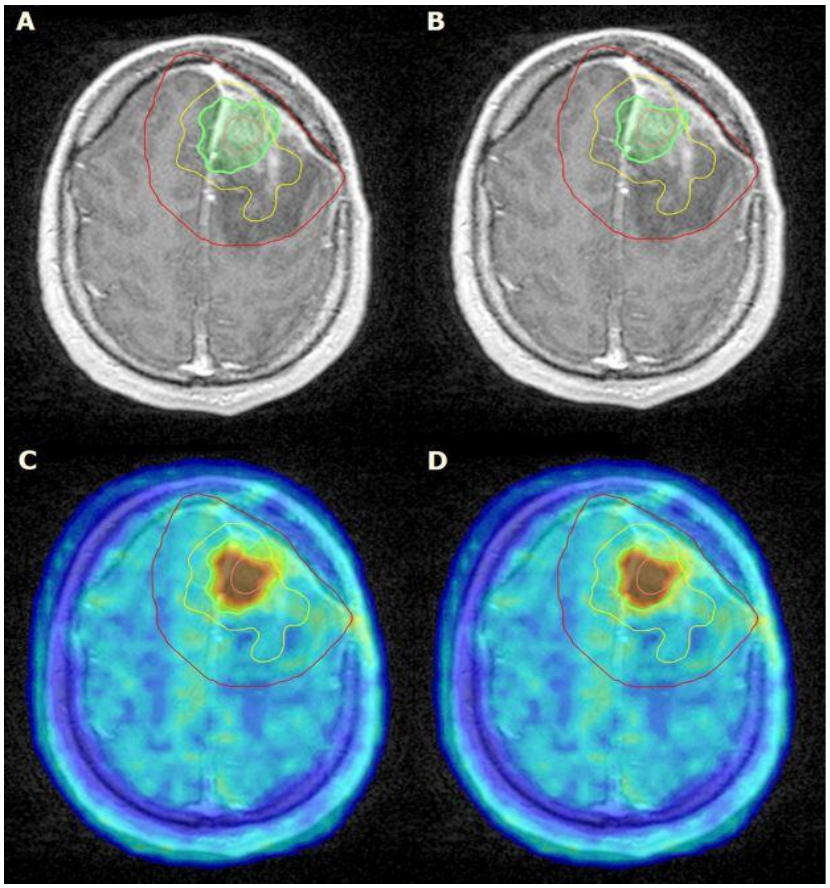

Figure 4. Left frontal post craniotomy status. Inhomogeneous, mainly centrally, moderate enhancement of contrast material is observed on T1-weighted post contrast MRI images. The lesion in the left hemisphere is surrounded by edema (A, B). Irregularly shaped intense, focal 18F-FDOPA accumulation can be detected on the left side of the brain frontally, above the level of lateral ventricles (C, D). Pink line, GTV; green line, BTV 1.7 (A, C); green line, BTV 2.0 (B, D); red line, PTV; yellow line, recurrence.

3.3.6. Discussion

BTV 1.7 volumes were 58.8%; BTV 2.0 volumes were 45.7% outside of the generally described GTV volume. Recurrences occurred below the PTV area which received the full dose of the treatment, no outfield recurrence of the disease appeared. The interpretation of our results is limited by the fact that there are few cases available but the additional value of 18F-FDOPA should be considered when delineating target volumes to improve patient care, optimize outcome, and deliver more focused therapies.

4. Discussion of our objectives

Because of its nature (high degree of vascularity, rapidly dividing cells, invasion into normal brain tissue), the treatment of glioblastoma multiforme is a complex oncology task, which remains a serious challenge despite today's modern technology; needless to say, overall survival is still unsatisfactory. Standard therapy includes surgical resection to the extent feasible and radiotherapy followed with concomitant and adjuvant chemotherapy. Conventional imaging modalities provide information regarding the anatomical distribution, whereas PET imaging displays molecular information about malignant abnormalities. The combination of these modalities play a key role at the standard care of management at central nervous system malignancies for surgical purposes, radiation planning, and treatment assessment as well.

In 2016, the Response Assessment in Neuro-Oncology (RANO) working group and European Association for Neuro-Oncology (EANO) highlighted the role of amino acid PET as a particularly important imaging tool for central nervous system malignancies especially when determining the tumor burden. As previously mentioned, in contrast of 18F-FDG, amino acid analog tracers have high accumulation in malignant lesions and relatively low accumulation in normal brain tissue; furthermore, they have the ability to pass through blood-brain barrier without disruption. The most studied researches among amino acid radiotracers focused on 11C-MET, 18F-FET, and 18F-FDOPA. The physical half-life of 11C (20 min) is significantly lower than 18F (109 min) that is the reason why 11C-MET is not widely used in clinical routine unless the institution has onsite cyclotron.

As a radiolabeled dopamine precursor 18F-FDOPA was initially used in Parkinson's disease diagnostics since the end of 20^{th} century. The first case report about potential neurooncologic application was published in 1996, a patient with movement disorder underwent 18F-DOPA PET examination and besides asymmetrically reduced dopamine uptake in the putamen, the imaging revealed incidental focal pathologic tracer uptake in other cerebral area, and MR and surgical histology confirmed glioma as an underlying pathology. The case study provided evidence that 18F-DOPA PET could also be suitable for the evaluation of central nervous system malignancies; however, because of the high physiologic DOPA uptake, abnormalities located near or involving the striatum can be challenging to evaluate. Nowadays, besides being a primer diagnosis, 18F-FDOPA is used for detection recurrence, in grading, to predict survival, irradiation planning, and for detection brain metastasizes as well.

The use of amino acid tracers, such as 18F-FDOPA, enables to represent tumor components beyond contrast enhancement of T1CE MRI images.

A study performed by Pafundi et al. showed that 18F-FDOPA SUVmax has the ability to distinguish low-grade and high-grade lesions. Therefore, using SUV-based stereotactic biopsy selection and definition of high-grade areas of malignant volume may be valuable added information when delineating radiotherapy boost volumes. We need to mention that other retrospective studies confirmed that larger PTVs failed to produce significant reduction of recurrences at close tumor area and even at distant recurrences also led to an increased incidence of radiation-induced necrosis/toxicity, which affected negatively on patients' long-term survival. This is evidenced by Minniti et al., who analyzed recurrence results in patients with primary glioblastoma treated with conformal radiotherapy and concomitantly/adjuvant temozolomide, and a comparison of these results across different target volume determinations. The results of 105 patients were analyzed, and target volumes were prepared as described by the EORTC. The median overall survival and progression-free survival were 14.2 months and 7.5 months, respectively. Relapses in the study sample were predominantly central (79 cases), at 6 patients within the treatment area, marginally also 6 patients, and 14 patients distant. In the case of a target volume definition using a postoperative residual tumor and cavity plus a 2 cm margin, a smaller volume of the brain is affected compared to the target volume definition that takes into account edema. The lower volume did not significantly affect the risk of developing marginal recurrences. Chang et al studied the association between peritumoral edema and recurrence in patients with glioblastoma multiforme. 48 patients were included in their study. Based on their results, a comparison of the location of the recurrent tumor and the volumes of peritumoral edema in the 48 cases showed no correlation with linear regression modeling. The incidence of necrosis/toxicity induced by the use of the increased target area was also increased, adversely affecting patient long-term survival.

Kazda et al. performed a dosimetric evaluation of a radiotherapy treatment plan with and without 18F-FDOPA based biological target volume, and analyzed its dosimetric role in grade III/IV. glioma. 8 patients's data has been analyzed. MR-guided anatomical plans and MR + 18F-FDOPA-PET guided biological plans were prepared for each patient, followed by comparison of target volume and risk organ dosimetry data. High-dose BTV60Gy was defined as regions with tumor to normal brain (T/N) >2.0, while low-dose BTV51Gy was initially based on T/N >1.3, but refined per Nuclear Medicine expert. The PTV areas of

tumors enhancing MR contrast agent were found to be larger compared to the areas without contrast enhancement. Despite the increase in GTV and PTV volumes, the dose on risk organs using volumetric arch therapy did not increase, however, the dose coverage of the target volume was maintained. For non-contrast-accumulating tumors, MR + 18F-FDOPA imaging identified a region that also appeared in the T2-FLAIR sequence, allowing a smaller volume to receive high-dose treatment (60Gy).

A a conclusion, GTV volumes defined by T1CE MR images were found to be higher, taking into account the accumulation of 18F-FDOPA radiopharmaceuticals. The increase in GTV volume did not result in an increase in the dose of the risk organs, therefore the 18F-FDOPA PET based target volume definition was feasible and appropriate in the study.

Dowson et al. has done 18F-FDOPA measurements within two days to contrast-enhanced MR imaging at six patients to determine more accurately GTV volumes. They found that the target volume defined at radiotherapy planning would change in several cases if the 18F-FDOPA information were available, and in many cases the target volume defined by PET fell outside of the 95% dose coverage. In conclusion the target volume defined by 18F-FDOPA PET resulted in bigger GTV than the T1CE MRI based GTV. Consequently, MR and 18F-FDOPA PET-based irradiation planning contains additional valuable additional information.

Kosztyla and colleagues studied the effect of dose escalation based on 18F-FDOPA information on risk organs at 10 patients study population. As a result of their study, it can be said that the possibility of dose escalation can be implemented without increasing the doses of the surrounding risk organs. The study further discusses that, based on the data in the literature, uniform dose escalation in the case of high-grade gliomas showed unfavorable results, and non-central relapses also appeared. Based on their own results, the accumulation of 18F-FDOPA in malignant tissues resulted in a wider tumor boundary, however, dose escalation may be a potential option to achieve better disease control.

As we described previously, PET/MR information cannot be directly processed into Varian Eclipse 13.0 software. Because the PET/MR was performed before PET/CT acquisition, we needed to validate whether the PET intensity from PET/MR correlates to PET information gained from PET/CT or not. The MICE Toolkit™, a graphical programming user interface that is user-friendly while still highly flexible, selected DICOM images from PET/MRI and PET/CT, which were co-registered, and the volumes contoured on patients' data were also examined to gain correlation values. As a result of our method, good

correlation values between PET/MR and PET/CT 18F-FDOPA signal intensity to relative brain signal were gained. This result means that the measurement of the contralateral normal-appearing white matter is a good way to determine 18F-FDOPA uptake value to establish tumor burden and use of the MICE Toolkit™ is a highly recommended for method validation.

The obtained BTV values differed from the traditionally defined GTV values. Almost 60% of BTV 1.7 volume coverage was outside the GTV area, and almost 50% of the BTV 2.0 volume coverage was outside the GTV area, respectively. Outside GTV volumes carry additional information regarding conventional imaging methods (CT, MR). Because the CTV area is an extension of the GTV, any information beyond the traditionally defined GTV can modify PTV. Regarding our results, 18F-FDOPA, as an amino acid analog radiotracer, should play a very important role in radiation planning procedure at patients with glioblastoma multiform.

At our study population, recurrence occurred in four patients. We co-registrated the primer 18F-FDOPA PET images with the MRI images where the recurrences were present to see whether the recurrence is overlapping with the PTV area, the area which received the total dose of 60 Gy. At all cases recurrence occurred mostly under PTV area, no outfield recurrence was detected.

Referring to PET/RANO group, the most frequently used amino acid analog radiotracers are MET, FET, and FDOPA. In delineation of radiotherapy target volumes, FDOPA may extend beyond the contrast enhancement on MRI. The concept of dose-painting also seems to be feasible and safe in the PET-based radiotherapy with newly diagnosed gliomas. Recent studies confirmed by FDOPA acquisitions showed that acute and late toxicities were not increased in patients who were treated with integrated boost IMRT beyond 60 Gy, but further studies are still ongoing.

5. Limitations in the chemoradiotherapy treatment of patients with primary malignant brain tumor

The simultaneous use of radiotherapy and chemotherapeutic agents roughly doubles the survival of WHO III-IV. grade glioma patients, further efforts with further innovative fractionation procedures, dose escalation, or alternative radiation therapy techniques have not been successful in achieving their goal. However, what has been achieved is less toxicity due to radiation, which is clearly a consequence of the "refined" target volume determination. It remains unresolved that recurrence occurs in approximately 90% of patients with glioblastoma multiforme, demonstrating internal limitations in the efficacy of conventional radiotherapy or inaccurate therapies. In this regard, dose-limiting factors and the heterogeneity of glioma subpopulations pose a serious challenge. We provided that the boundaries of the tumor were adequately covered, we ensured that the localization of the active tumor was not exempted from the radiotherapy target volume defined by MRI, nonenthless if the tumor recurred, it may be reasonable to make additional efforts to delineate even more accurate target volumes. Currently, PET hybrid imaging — anatomical and functional — appears to be the most advanced, most accurate 3D imaging technique that goes beyond defining tumor boundaries, beyond what can be visualized on traditional MRI. By increasing the number of cases, it can be confirmed that PET based radiotherapy planning is superior to traditionally used radiotherapy planning, whether it is primary glioma or relapse.

Delivered doses and treatment target volumes remain largely independent of the increasingly complex biology and heterogeneity of each glioma. To date, there is very few predictive biomarker that can be used to predict the response to radiation therapy in patients. The increasing prevalence of advanced functional and molecular imaging, such as PET, as well as the potential for the use of artificial intelligence in a broad interpretation of the data, may help to understand the biological characteristics of gliomas, allowing for functionally controlled dose escalation. In addition, PET imaging can provide predictive information about the response to treatment, allowing for the potential of individually tailored therapies. Additional information on glioma biology provided by PET imaging may also assist in the joint interpretation and evaluation of the parameters provided by MR imaging modality.

Limiting the widespread clinical use of PET amino acid analog tracer for radiotherapy planning and monitoring in patients with glioma continues to be a major funding issue, sometimes dwarfing more accurate imaging that results in more effective treatment. The difficulties have made significant progress in recent years. In Switzerland and France the 18F-

FET radiotracer has been approved for the diagnosis of brain tumors. The 18F-FDOPA radiotracer has been approved in the diagnosis of glioma in several European countries as well as in the United States. In addition, FDOPA is an FDA-approved diagnostic tool for people with Parkinson's disease.

In addition to the further limitation of the radiotracer, the effect and outcome of the treatments, which may have an effect on the accumulation of 18F-FDOPA, were also investigated. As part of their survey, Ledezma et al. highlighted the presence of mild 18F-FDOPA activity along the surgical boundary of the tumor in several cases. Recently, Chiaravalloti et al found an association between 18F-FDOPA radiotracer uptake, possible area of tumor recurrence, and delayed PET imaging. Based on their results, the rate of accumulation decreased with increasing number of months after radiotherapy, suggesting that immediate high radiotracer uptake after radiotherapy may result from the treatment itself, therefore caution should be implemented regarding the accumulation/use of 18F-FDOPA in a case when tumor recurrence is a clinical issue.

Finally, 18F-FDOPA is an amino acid tracer that targets dopamine receptors in the brain, resulting in high accumulation within the striatum. Consequently, caution should be exercised in the presence of tumors near the striatum, as the affected area may blur the border of the tumor, which may make it difficult to assess the extent. Distinguishing the tumor from healthy tissues involves kinetic analysis of the results, and due to the partial volume effect, some inaccuracy will be seen in determining the tumor boundary.

6. New scientific results of the dissertation and their clinical application

The results of our study contain a number of new results that proved to be useful in the treatment protocol of patients with glioblastoma multiforme. The results are summarized below:

- the overall survival of patients with complete resection confirmed by MR imaging was significantly longer than patients with residual tumor
- in patients where recurrence was observed during follow-up MR imaging, the area of recurrence occurred within the area received full radiation dose
- the area defined by the 18F-FDOPA radiotracer image showed additional information in the vast majority of cases compared to GTV area defined by the contrast-enhanced T1-weighted MR images
- the image registration method we used allowed to standardize the signal intensity between 18F-FDOPA PET/CT and PET/MR images, so no significant decrease in signal intensity was observed, despite the fact that the average time between PET/CT and PET/MR was 50 minutes, which is a significant amount of time considering the half-life of the radiotracer
- 3D hybrid imaging is more effective, more accurate in the treatment and follow-up of glioblastoma patients, and the radiation exposure of the examinations is significantly lower

7. Summary, research recommendations

Medicine, including diagnostics, has been characterized by continuous growth over the past decades, and the progression of this development will continue in the future, based on the results of the dissertation. Focusing on the topic of our thesis, the diagnosis and treatment options of glioblastoma multiforme underwent significant changes, the treatment method became even more effective. In the future, new radiotracers, new, even more effective drugs, treatment protocols may appear, which will significantly influence the determination of the target volume and the extent of the surgical intervention.

In order to determine the extent of surgical interventions, the acquisition and use of intraoperative imaging equipment would be justified in order to achieve the best possible survival results. The extent of surgical interventions can be influenced by a number of considerations. Keeping in mind medical imaging, MRI and PET modalities bring the newest techniques into daily use. Modern techniques can have a positive effect on the diagnosis of gliblastoma multiforme, which significantly affect radiotherapy. The area characterized by amino acid based radiotracers differs from the traditionally defined target volumes by MR imaging. Based on our international and own results, the vast majority of relapses are localized under the PTV area, which suggests the idea of dose escalation in the future.

8. Scientific activity

8.1.Publication in association with the topic of the thesis

Lukács, G., Tóth, Z., Sipos, D., Csima, M., Hadjiev, J., Bajzik, G., Cselik, Z., Semjén, D., Repa, I., & Kovács, Á. (2018). Long-term follow-up results of concomitant chemoradiotherapy followed by adjuvant temozolomide therapy for glioblastoma multiforme patients. The importance of MRI information in survival: Single-center experience. *Ideggyógyászati szemle*, *71*(3-04), 95–103. https://doi.org/10.18071/isz.71.0095 **IF:0,113**

Sipos, D., Tóth, Z., Lukács, G., Bajzik, G., Hadjiev, J., Cselik, Z., Repa, I., & Kovács, Á. (2019). F-DOPA-jelzett PET/CT-PET/MR alapú modern 3D besugárzástervezés glioblastoma multiformés (GBM-) betegek komplex kezelésében. Az első magyarországi tapasztalatok. *Ideggyógyászati szemle*, *72*(5-6), 209–215. https://doi.org/10.18071/isz.72.0209 **IF:0,337**

Sipos, D., László, Z., Tóth, Z., Kovács, P., Tollár, J., Gulybán, A., Lakosi, F., Repa, I., & Kovács, A. (2021). Additional Value of 18F-FDOPA Amino Acid Analog Radiotracer to Irradiation Planning Process of Patients With Glioblastoma Multiforme. *Frontiers in oncology*, *11*, 699360. https://doi.org/10.3389/fonc.2021.699360. **IF:6,244**

8.2.Presentations

Sipos, D., Kedves, A., Repa, I., & Kovács, Á. (2017). Glioblastoma multiforme - kezelési kimenet elemzése kaposvári beteganyagon. In Bódog F., Csiszár B., Hegyi D. & Pónusz R. (Eds.), *DKK17-Doktoranduszok a Klinikai Kutatásokban absztraktkötet* (p. 42). Pécsi Tudományegyetem Doktorandusz Önkormányzat.

Sipos, D., Tóth, Z., Lukács, G., Bajzik, G., Hadijev, J., Cselik, Z., Repa, I., & Kovács, Á. (2018). 18F-DOPA jelzett PET/CT-PET/MR alapú 3D besugárzás tervezés glioblastoma multiformes (GBM) betegen. In Bódog F., Csiszár B. & Pónusz R. (Eds.). *Medical Conference for PhD Students and Experts of Clinical Sciences: Book of Abstracts* (p. 15). Pécsi Tudományegyetem Doktorandusz Önkormányzat.

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Sipos, D., Tóth, Z., Lukács, G., Bajzik, G., Janaki, H., Repa, I., & Kovács, Á. (2019). The additional value of PET amino-acid tracers at the irradiation process of CNS malignancies. In *K. Čuček-Trifkovič & I. Mlakar (Eds.). 11. Študentska konferenca s področja zdravstvenih ved z mednarodno udeležbo* (pp. 344–347). Univerzitetna založba Univerze, Maribor.

Kovács, Á., Sipos, D., Tóth, Z., Lukács, G., Bajzik, G., Moizs, M., Cselik, Z., & Repa, I. (2019). F-DOPA-jelzett PET/CT-PET/MR alapú modern 3D besugárzástervezés gyakorlati alkalmazása glioblastoma multiformés betegek kezelésében - Intézeti tapasztalatok. *Magyar onkológia, 63*(Suppl.1), 39.

Sipos, D., Fábián, J. K., Tóth, Z., Repa, I., & Kovács, Á. (2020). Correlation of F-FDOPA PET uptake with histophatological findings of central nervous system malignancies. In *European Congress of Radiology (ECR 2020)* (C-11684). European Society of Radiology.

8.3.International and national awards in the topic of the dissertation

2018 - Radiological Society of North America (RSNA) 2018 – Student travel award, Chicago, Illinois, United States of America

2018 – New National Excellence Program Of The Ministry Of Human Capacities

2018 – "Breaktrough talent" scholarship – University of Pécs

2019 - "Izinta award" - For the best diagnostic presentation – XXI. congress of Hungarian Society of Nuclear Medicine

2019 – László János doctoral research scholarship – University of Pécs

2020 - New National Excellence Program Of The Ministry Of Human Capacities

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