Influence of $^{11}$C-MET PET acquisition time for differential diagnosis of human brain gliomas

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Abstract. The aim of this work was to study the effect of the reduced acquisition time of PET $^{11}$C-MET examination on the quality of primary brain tumors differential diagnosis. 57 patients with histologically verified diagnoses were recruited (glioblastoma n=20, anaplastic astrocytoma n=11, diffuse astrocytoma n=11, oligodendroglioma n=9 and anaplastic oligodendroglioma n=6). The scan time was varied in the range of 2-20 min. Our study demonstrated that in the case of intravenous administration of $^{11}$C-MET simultaneously with the start of scanning, the quality of primary gliomas differential diagnosis does not depend on the scan time. Therefore it becomes possible increasing the number of patients and reducing the acquisition time. The T/N60 ratio (T/N ratio measured in the first 60 seconds after $^{11}$C-MET intravenous injection) is equally successful parameter for glioma differential diagnosis as the traditional T/N ratio.

1. Introduction
Since $^{11}$C-MET gained success in clinical practice for the human brain gliomas differential diagnosis of in the last decade of the 20th century [1] the acquisition technique and data analysis have not undergone significant changes. The intravenous administration of $^{11}$C-MET and the start of acquisition were separated by 20 minutes followed by data collection for another 20 minutes [2]. In the recommendations of the European Association of Nuclear Medicine (EANM) from 2019 [3] the delay between radiopharmaceutical administration and data collection was reduced to 10 minutes. The measured parameter characterizing the metabolic activity of the tumor is the T/N ratio averaged over all acquisition time. In this study we evaluated how the start of scan time and scan duration affect the quality of differential diagnosis. We also introduced an additional quantitative parameter T/N60 - the uptake ratio measured during the first 60 seconds after intravenous administration of $^{11}$C-MET.

2. Materials and methods
The study included 57 patients (31 men and 26 women, mean age 48±12 years) with primary brain tumors (glioblastoma n=20, anaplastic astrocytoma n=11, diffuse astrocytoma n=11, oligodendroglioma n=9 and anaplastic oligodendroglioma n=6). All tumor subtypes were confirmed histologically later on either by tumor surgical removal or as a result of stereotactic biopsy.
Each patient underwent an MRI scan (T1, T2, T2-FLAIR) followed by a $^{11}$C-MET PET/CT study (Siemens Biograph Truepoint, Siemens Medical Solutions, USA) with the minimal time interval (0 - 3 days). Data were collected in list-mode for 20 minutes starting at the time of $^{11}$C-MET intravenous administration. The reconstruction was divided into 26 frames: 6 * 10 sec, 6 * 20 sec, 6 * 30 sec, 4 * 60 sec and 4 * 150 sec. Image reconstruction was performed with the 3D OSEM (Ordered Subset Expectation Maximization) algorithm with 5 iterations and 8 subsets.

MRI and PET/CT data were co-registered using PMOD software (version 4.0, Zurich, Switzerland). The tumor Region of Interest (ROI) was selected as one cubic centimeter ($1.0 \, \text{cm}^3$) of the tumor volume with the highest uptake. In case the tumor did not show visible accumulation of radiopharmaceutical the ROI was selected in the area of the hyperintense signal on the T2-FLAIR weighted MR image (9 such patients out of 57 in our study).

ROI of intact tissue was selected in unaltered brain tissue in the frontal lobe of the contralateral hemisphere with the gray and the white matter mixed.

The effect of scan time duration on the differential diagnosis of brain gliomas was analyzed using two parameters: the final T/N ratio and the uptake index averaged over the first 60 seconds (T/N60) of the study after tracer administration.

Also a reduced scan time of 2, 4 and 10 minutes was simulated. In these cases, the datasets had reduced number of frames (9, 14, 22 respectively). Accordingly, ROIs were re-selected on the abbreviated study so that their location and shape could be different from the initial ones obtained on the 20-minute scan. As the scanning time reduced extra patients (n=8) lost the ability to have a region of interest outlined on a PET image due to an increased image noise. In these cases, the ROIs were selected on MR images as described above.

T/N in the study duration of 2, 4, 10, 20 minutes was chosen as the frames average of 7-9, 7-13, 14-22 and 23-26 respectively.

3. Results
The increase in noise level with decreasing scan time is demonstrated in Fig. 1. In case of low T/N ratio (short scan time) it becomes difficult to visually outline the tumor (Fig. 1f). However in case of high uptake of methionine by the tumor ROI remains visible regardless of the study duration (Fig. 1 b-d).

![Figure 1. Glioblastoma (A-D) and diffuse astrocytoma (E-H). T2 MRI (A,E), PET with $^{11}$C-MET averaged over the first 2 min (B,F), 4 min (C,G) and 10 min (D,H) of the scan. Arrow indicates tumor location.](image-url)

The values of the T/N and T/N60 parameters for different study duration are given in Table 1.
The statistical significance of differences between tumor histological subtypes which determines the quality of differential diagnostics is shown in Table 2. The most successful parameter is highlighted in bold.

### Table 1. T/N and T/N60 with ±SD calculated from 2, 4, 10, 20 minutes acquisitions. GB – glioblastoma, AOD – anaplastic oligodendroglioma, AA - anaplastic astrocytoma, OD – oligodendroglioma, DA – diffuse astrocytoma.

| Diagnosis | T/N 2 min | T/N 4 min | T/N 10 min | T/N 20 min | T/N60 2min | T/N60 4min | T/N60 10min | T/N60 20min |
|-----------|-----------|-----------|------------|------------|------------|------------|------------|------------|
| GB        | 3.50±0.99 | 3.56±0.97 | 3.64±0.95  | 3.52±0.94  | 2.60±0.69  | 2.59±0.69  | 2.52±0.70  | 2.61±0.83  |
| AOD       | 2.64±0.93 | 2.65±0.89 | 2.70±0.81  | 2.67±0.74  | 1.94±0.50  | 1.92±0.53  | 1.93±0.55  | 1.79±0.39  |
| AA        | 1.52±0.64 | 1.56±0.70 | 1.63±0.73  | 1.63±0.64  | 1.37±0.51  | 1.38±0.51  | 1.35±0.48  | 1.38±0.48  |
| OD        | 1.77±0.68 | 1.86±0.69 | 2.00±0.75  | 1.95±0.68  | 1.41±0.43  | 1.45±0.45  | 1.42±0.43  | 1.42±0.44  |
| DA        | 1.36±0.58 | 1.39±0.60 | 1.42±0.65  | 1.50±0.66  | 1.32±0.57  | 1.32±0.58  | 1.27±0.58  | 1.29±0.56  |

### Table 2. Statistical significance (p-values of the Student’s t-test) in differentiation between tumors histological types. T/N and T/N60 were calculated from 2, 4, 10, 20 minutes acquisitions. GB – glioblastoma, AOD – anaplastic oligodendroglioma, AA - anaplastic astrocytoma, HGG – high grade gliomas, LGG – low grade gliomas.

| Diagnosis | T/N 2 min | T/N 4 min | T/N 10 min | T/N 20 min | T/N60 2min | T/N60 4min | T/N60 10min | T/N60 20min |
|-----------|-----------|-----------|------------|------------|------------|------------|------------|------------|
| HGG vs LGG | 0.00016  | 0.00018  | 0.00024  | 0.00037  | 0.00058  | 0.00084  | 0.00077  | 0.0010  |
| Gr.III vs Gr.IV | 3.3E-06  | 1.9E-06  | 1.2E-06  | 1.9E-06  | 4.6E-06  | 5.6E-06  | 1.5E-05  | 7.7E-06  |
| GB vs AOD | 0.071  | 0.051  | 0.039  | 0.054  | 0.039  | 0.038  | 0.070  | 0.028  |
| GB vs AA | 1.9E-06  | 1.5E-06  | 1.3E-06  | 1.8E-06  | 1.4E-05  | 1.9E-05  | 3.0E-05  | 9.4E-05  |
| AOD vs AA | 0.010  | 0.014  | 0.014  | 0.0082  | 0.043  | 0.058  | 0.040  | 0.094  |

### 4. Discussion

Regardless of a great value of $^{11}$C-MET in glioma studies its wide application is limited by the high cost of the study due to the long recommended waiting time for tracer accumulation in the tumor and the long scan time compared to the $^{11}$C half-life. The current EANM recommendations suggest shorter waiting time to start PET acquisition [3] but by 10 minutes only. Reducing both the waiting time for tracer accumulation and the scanning time will make it possible to significantly reduce the costs in the study despite the short lifetime of this isotope.

Reducing the study time (Table 1) has limited effect on both the T/N and T/N60 values and also on the standard deviations (SD). As a result, there is a big flexibility in scan time reduction and the ability to use any of the parameters without sacrificing p-values in group’s differentiation (table 2). Moreover, the T/N60 parameter measured in the first minute after the bolus administration is very close to the T/N in terms of the quality of the differential diagnosis.
The typical tasks for differential diagnosis of gliomas using $^{11}$C-MET shown in Table 2 are resolved by any of the parameters and with any scan duration. The difference between HGG and LGG, Gr.III and Gr.IV, and between GB and AA becomes stronger with shorter scan times.

The difference between GB and AOD is better highlighted by the T/N60 parameter which is most likely associated with the difference in vascularization contributing to the T/N60. At the same time the values of T/N ratio are close in these histological types.

The success of the T/N60 parameter in differential diagnosis may be associated with increased tumor blood flow recorded in clinical practice by CT perfusion [4] or ASL-MR perfusion [5]. However, PET with $^{15}$O-H$_2$O does not demonstrate the effect of increased perfusion in the tumor [6].

The accumulation in oligodendroglial tumors is higher in our study than in other tumors of the same grade of malignancy which is consistent with previously published data [7].

The only disadvantage of shortening the study time is the increased number of ROIs selected on MRI images for low-grade tumors due to the lower signal-to-noise ratio. The need of using MRI in the absence of visible accumulation is also present with long 20 minutes examinations. In our experiment for 2 minutes scans MRI ROIs were selected 17 times whilst with a 20 minutes scan it was the case for 8 times.

Dynamic acquisitions of time activity curves for methionine in the brain tumors resulted in uptake profiles that differ in different histological subtypes [8, 9]. However, the authors of the cited articles did not separately analyze the early moments of the bolus injection passing through the tumor. Thus, the quantitative parameter T/N60 introduced in this paper is novel and can be successfully used for differential diagnosis of gliomas.

5. Conclusions

Our study demonstrated that in the case of intravenous administration of $^{11}$C-MET simultaneously with the start of scanning, the quality of primary gliomas differential diagnosis does not depend on the scan time. Therefore, it becomes possible reducing the acquisition time and thereby increasing the number of patients investigated from one radiotracer production. The T/N60 ratio (T/N ratio measured in the first 60 seconds after $^{11}$C-MET intravenous injection) is equally successful parameter for glioma differential diagnosis as the traditional T/N ratio.

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