SHORT COMMUNICATION

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Two-grade metabolic tumor tissue assessment using positron emission tomography in prediction of overall survival in glioblastoma patients

Dvostepena metabolička procena tumorskog tkiva u predviđanju ukupnog preživljavanja bolesnika sa glioblastomom izvedena pozitronsko emisionom tomografijom

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Abstract

Background/Aim. Although considered rare, gliomas cause morbidity and mortality disproportionate to their incidence. The aim of the study was to determine whether pre and post-therapeutic metric values, derived from the FDG PET/CT maximal standardized uptake value (SUV_{max}) and calculated ratios between tumor and normal brain tissue, may provide a predictive/prognostic biomarker information in estimating overall survival of glioblastoma patients. **Methods.** In 26 out of 31 patients with glioblastoma treated with standard Stupp protocol after maximal safe reductive surgery, we performed a baseline 18F-FDG PET/CT examination before commencing combined and concomitant chemotherapy/radiotherapy (pre-therapy FDG PET/CT) and a second examination three months after the therapy completion (post-therapy FDG PET/CT). Two-graded SUV_{max} values and a calculated ratio of uptake in tumor-to-normal-tissue (T/N ratio) value, divided into two grades by the calculated cut-off value, were measured in all patients at both pre- and post-therapy FDG PET/CT studies. Data sets were statistically analyzed by the Kaplan-Meier survival test and Log-rank was calculated, with the level of confidence determined at $p < 0.05$. **Results.** Pre-therapy FDG PET/CT two-grade T/N ratio value and both pre- and post-therapy FDG PET/CT derived two-grade SUV_{max} values had a strong predictive impact on overall survival of glioblastoma patients. **Conclusion.** Based on two-grade SUV_{max} and T/N ratio values assessment, FDG PET/CT could provide valuable predictive survival information in glioblastoma patients and serve as a selection tool for identifying patients at higher risk from worse outcomes and shorter survival time.

Key words:
brain neoplasms; glioblastoma; positron-emission tomography; prognosis; survival analysis; tomography, x-ray computed.

Apstrakt

Uvod/Cilj. Mada su retki, gliomi izazivaju morbiditet i mortalitet nesrazmeran njihovoj incidenci. Cilj rada bio je da se utvrdi da li pre- i postterapijske metričke vrednosti koje proizilaze iz FDG PET/CT maksimalnih standardizovanih vrednosti preuzimanja (SUV_{max}) i izračunatih odnosa između tumora i normalnog moždanog tkiva (T/N odnos) mogu obezbediti prediktivne/prognostičke biomarkerske informacije u proceni ukupnog preživljavanja bolesnika sa glioblastomom. **Metode.** Kod 26 od 31 ispitanika sa glioblastomom, lečenih Stupp protokolom nakon maksimalne reduktivne hirurgije, načinjen je bazni 18F-FDG PET/CT pregled pre početka kombinovane i istovremene hemoterapije/radioterapije (preterapijski FDG PET/CT), a potom i drugi pregled tri meseca nakon završetka terapije (posttera

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pijski FDG PET/CT). Vrednosti SUV_{max} i izračunati T/N odnos, podeljeni u dva razreda izračunatom vrednošću razdela, mereni su kod svih bolesnika FDG PET/CT pregledima, pre i posle terapije. Skupovi podataka statistički su analizirani Kaplan-Meier-ovim testom preživljavanja i izračunat je Log-rank sa nivoom pouzdanosti utvrđenim na $p < 0.05$. **Rezultati.** Preterapijski FDG PET/CT dvostepeni T/N odnos i dvostepeni SUV_{max}, izveden iz FDG PET/CT pregleda pre i posle terapije, imali su snažan prediktivni uticaj na ukupno preživljavanje ispitanika sa glioblastomom. **Zaključak.** Na osnovu procene vrednosti dvostepenog SUV_{max} i T/N odnosa, FDG PET/CT omogućava dobijanje vrednih prediktivnih informacija o ukupnom preživljavanju bolesnika sa glioblastomom i stoga može poslužiti kao selekciona metoda za identifikaciju bolesnika pod povišenim rizikom od lošijeg ishoda bolesti i kraćeg vremena preživljavanja.

Ključne reči:
mozak, neoplazme; glioblastom; tomografija, pozitron-emisiona; prognoza; preživljavanje, analiza; tomografija, kompjuterizovana, rengdenska.

Introduction

Even though high-grade central nervous system gliomas are considered rare, with an incidence rate of five to six cases *per* 100,000 individuals, they cause morbidity and mortality disproportionate to their incidence.

High-grade gliomas represent the most common, but a heterogeneous group of adult intra-axial brain tumors with a median overall survival of 15 months in the patient subgroup treated with maximal safe tumor resection, concomitant radiation/chemotherapy, and adjuvant chemotherapy [1, 2].

Despite many recent efforts to develop multimodal approaches for optimizing combinations of surgery, radiation, and chemotherapy for high-grade gliomas, especially glioblastomas, disappointingly, survival rates remain nearly unchanged. Variability in clinicopathological tumor behavior complicates the combination and timing of multimodal treatment approaches, responses, and finally, outcomes [2–5].

Magnetic resonance imaging (MRI) is the primary clinical imaging modality at all disease stages in glioblastoma, ranging from the primary evaluation, presurgical planning, early postsurgical evaluation of residual tumor presence, radiotherapy planning, surveillance during chemotherapy, and recurrence detection. Objective and standardized MRI-based criteria for response assessment in neurooncology (RANO) have been developed and initially introduced for clinical trials in brain tumors [6].

Molecular imaging by use of positron emission tomography and computerized tomography (PET/CT) is an established and broadly used method in oncology [7], and for a certain time, is being increasingly used to supplement MRI in the clinical management of high-grade gliomas [8, 9]. Recent evidence-based recommendation by the PET-RANO working group and European Association of Neuro-Oncology (EANO) on the clinical use of different radiotracers, such as 2-deoxy-2-[18F] fluoro-D-glucose (FDG), radiolabeled amino acids like [11C-methyl]-methionine (MET), 2-[18F] fluoroethyl)-L-tyrosine (FET), and 3,4-dihydroxy-6-[18F] fluoro-L-phenylalanine (FDOPA), are providing convincing pieces of evidence of PET imaging additional value in high-grade gliomas and glioblastoma patients management [8], starting from differentiation of the glioma grade [7, 8], guidance of stereotactic biopsies [10, 11], the definition of target volume for radiation dose escalation, and differentiation of recurrent tumor from radiation necrosis [12, 13].

Though FDG PET/CT has an established role in glioblastoma patient management, it is still not routinely incorporated into neuro-oncological practice as a reliable prognostic indicator of outcome, mostly due to the inconsistent results of studies evaluating pre-therapy and/or post-therapy PET/CT findings [14–20].

Therefore, the aim of this study was to determine whether pre- and post-therapeutic metric values, derived from the FDG PET/CT maximal standardized uptake value (SUV_{max}) and calculated ratios between tumor and normal brain tissue, may provide a predictive/prognostic biomarker information in estimating overall survival (OS) of glioblastoma patients.

Methods

The prospectively designed study included overall 31 patients with histopathological verified glioblastoma treated with standard Stupp protocol (temozolomide 75 mg/m^2 daily, together with radiotherapy 60 Gy/30 fractions over 6 weeks, followed by six cycles of adjuvant temozolomide continued after radiotherapy completion) after maximal safe reductive surgery. Apart from regular MRI check-ups, the design of the study included the first baseline 18F-FDG PET/CT examination before the commencement of combined and concomitant chemotherapy and radiotherapy (pre-therapy FDG PET/CT), and a second examination three months after the completion of chemotherapy and radiotherapy (post-therapy FDG PET/CT). Out of 31 patients, 26 patients completed the study requirements and underwent the second post-therapy FDG PET/CT examination after the concomitant chemoradiation. In all of the patients, pre-therapy FDG PET/CT was performed within five to seven days before the commencement of combined concomitant therapy, and the post-therapy FDG PET/CT was done three months after the completion of radiotherapy treatment.

The institutional Ethical Board approved the study, and the patients' informed consent was obtained.

The 18F-FDG PET/CT exams were performed on Siemens Biograph 64 True Point PET/CT scanner (Siemens, Erlangen, Germany), and after 4–6 hours of fasting, all patients were intravenously injected with 185 MBq (5 mCi). After an uptake period of around 30–45 min in a dim room, a

one-bed position of 10 min acquisition period with a non-contrast-enhanced CT scan for attenuation correction was done. Scans were visualized and analyzed on the Leonardo Siemens workstation independently by two experienced readers.

With a region-of-interest area covering the surgically reduced tumor bed and brain tissue at exactly the same level in the contralateral brain hemisphere, SUV_{max} value and calculated ratio of uptake in tumor-to-normal-tissue (T/N ratio) value were determined in all patients at both pre- and post-therapy FDG PET/CT studies.

The two-grade semiquantitative assessment was applied by using both calculated SUV_{max} and T/N ratio cut-off values, calculated as median ± standard deviation (SD) value. The cut-off value for the pre-therapy FDG PET/CT exam was calculated as 1.1, dividing the patients into the hypermetabolic group (T/N ratio value higher than 1.1) and the hypometabolic group (T/N ratio value equal to or lower than 1.1), while the median T/N ratio cut-off value for the post-therapy PET/CT was calculated as 1.2. Patients were also divided into two groups regarding the SUV_{max} grading system, including the hypermetabolic group (SUV_{max} value higher than 8.96 for pre-therapy FDG PET/CT and 9.43 for post-therapy FDG PET/CT) and the hypometabolic group (SUV_{max} value equal to or lower than 8.96 and 9.43 for pre and post-therapy FDG PET/CT, respectively). Observed by the visual uptake two-grade grading system, the hypermetabolic group had tumor bed uptake higher than cortex uptake and hypometabolic group uptake equal to or lower than the cortex uptake. Both of the latter grouping systems resulted in a consistent division of patients into two almost identical and fully comparable patient groups.

Patients were clinically followed-up, and their OS as a study endpoint was registered. OS was determined as a period from surgical biopsy and maximal safe reduction date to the date of death.

Regarding OS, patients were divided into two groups: low survival rate group (OS < 12 months) and high survival rate group (OS > 12 months).

OS was compared to prognostic factors that included age, sex, pre-therapy SUV_{max}, post-therapy SUV_{max}, initial pre-therapy T/N ratio value, and post-therapy T/N ratio value after combined and concomitant therapy.

Data sets were statistically analyzed by using SPSS Statistics for Windows, version 16.0 (SPSS Inc. Chicago, Ill, USA) that included descriptive statistics, univariate (ANOVA), and multivariate analysis; both Cox regression and Linear regression were used to test variables including age, sex, pre-therapy SUV_{max}, post-therapy SUV_{max}, pre-therapy T/N ratio value, and post-therapy T/N ratio value. The Kaplan-Meier survival test with Log-rank test was also performed, and the median values ± SD of the SUV_{max} and the T/N ratio value were used to distinguish between two survival groups, with the level of confidence determined at $p < 0.05$.

Results

Out of 31 patients, 26 patients [17 (65.4%) men and 9 (34.6%)] women, age range from 30 to 75 years (mean: 56.04, and median ± SD: 59 ± 13.63) who fulfilled the study design requests and underwent both pre- and post-therapy FDG PET/CT examinations were included in the study. Five out of 31 patients were lost to follow-up, being unable to finish the whole therapy course or due to death, and, therefore, excluded.

The OS period ranged from 5 to 55 months (mean 15, median ± SD: 11.5 ± 11.86 months), and regarding OS values, 12 patients were included in the low survival rate group (OS < 12 months) and 14 in the high survival rate group (OS > 12 months).

For the pre-therapy PET/CT examination, SUV_{max} values ranged from 1.47 to 16.24 (mean: 6.33 and median ± SD: 5.71 ± 3.25) and for the post-therapy PET/CT examination, SUV_{max} values ranged from 3.53 to 12.6 (mean: 7.03 and median ± SD: 6.67 ± 2.76).

Pre-therapy FDG PET/CT T/N ratio value ranged from 0.19 to 1.64 (mean: 0.77 and median ± SD: 0.77 ± 0.35), and post-therapy FDG PET/CT T/N ratio value ranged from 0.15 to 2.73 (mean 0.82 and median ± SD: 0.75 ± 0.53).

Calculated SUV_{max} and T/N ratio cut-off values by both pre-therapy and post-therapy FDG PET/CT examinations divided the patients into hypometabolic and hypermetabolic groups, as shown in Table 1.

Survival curves were constructed with the Kaplan-Meier method (Figure 1), showing statistically significant difference between both hypo- and hypermetabolic SUV_{max}

Table 1

Descriptive statistics for the Kaplan-Meier overall survival in pre-therapy FDG PET/CT SUV_{max} and T/N ratio two-grade assessed hypometabolic and hypermetabolic groups

Parameter	n	Mean OS	SD	95% CI		Median OS	SD	95% CI		Min OS	Max OS
				lower	upper			lower	upper		
SUVmax											
hypometabolic	18	24.5	4.65	15.38	33.62	16	3.16	9.8	22.19	5	55
hypermetabolic	8	12.16	1.17	9.85	14.47	12	1.67	9.4	15.28	7	15
overall	26	21.18	3.65	13.98	28.39	15	1.82	11.43	18.56	5	55
T/N ratio											
hypometabolic	18	24.5/23.36	4.65/4.36	15.38/14.82	33.62/31.9	16	3.16/2.47	9.8/11.1	22.19/20.8	5	55
hypermetabolic	8	12.28/12.4	1.11/1.59	10.1/9.28	14.46/15.5	12	1.66/2.96	8.74/6.2	15.25/17.8	7	11
overall	26	21.18	3.67	13.98	28.39	15	1.82	11.43	18.56	5	55

OS – overall survival (in months); SD – standard deviation; CI – confidence interval; Min – minimal; Max – maximal; SUVmax – maximal standardized uptake value; T/N – uptake in tumor-to-normal-tissue; **FDG – 2-deoxy-2-[18F] fluoro-D-glucose; PET – positron emission tomography; CT – computed tomography.**

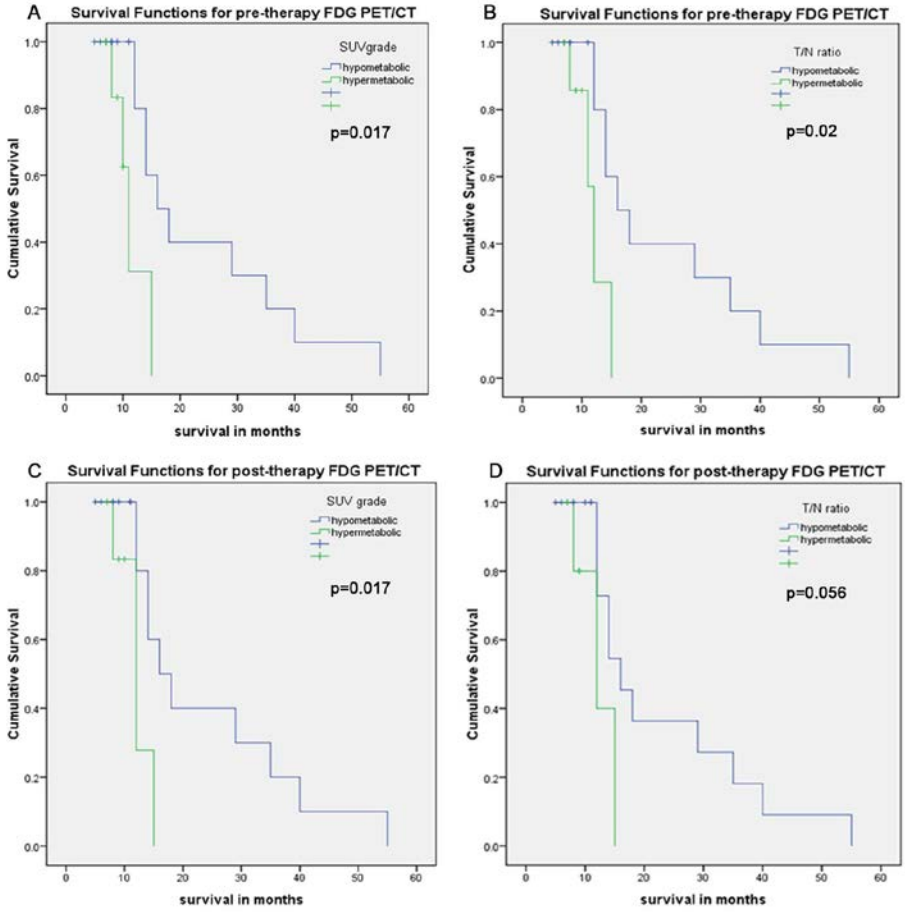

Fig. 1 – Kaplan-Meier survival curves showing overall survival in hypometabolic and hypermetabolic groups of patients in the function of pre-therapy FDG PET/CT SUV_{max} grading (A) and T/N ratio (B), and in the function of post-therapy FDG PET/CT SUV_{max} grading (C) and T/N ratio (D) [post-therapy SUV_{max} and pre-therapy T/N ratio: $p < 0.05$; log-rank for post-therapy T/N ratio: $p > 0.05$ ($p = 0.056$)].
For abbreviations see under Table 1.

grading, and hypo- and hypermetabolic T/N ratio value, obtained by pre-therapy FDG PET/CT exam ($p < 0.05$), and the same significant difference for post-therapy FDG PET/CT SUV_{max} grading ($p < 0.05$), but for the post-therapy T/N ratio value was just at the edge of the border of significance ($p = 0.056$).

Though by the ANOVA and multivariate analysis for any of the prognostic factors tested, no statistical significance was established, apart from the near-to-significant result of post-therapy T/N ratio value on survival ($p = 0.077$), with linear regression test, we found that age was a significant factor influencing survival ($p = 0.049$). Cox regression analysis demonstrated that gender and age were statistically significant variables influencing OS and, also, indicated pre-therapy T/N ratio near-to-significant influence on survival ($p = 0.05$) (Table 2).

Table 2

Impact of prognostic factors on overall survival in ANOVA analysis, Linear and Cox regression analysis with 95% confidence interval (CI) estimate for the odds ratio [95% CI for Exp(B)]

Prognostic factor	ANOVA *p*-value	Linear regression *p*-value	Cox regression	95% CI for Exp (B)
Gender	0.281	0.222	0.048	1.015–79.197
Age	0.471	0.049	0.023	1.018–1.28
Pre-therapy SUV_{max}	0.428	0.713	0.505	0.387–1.597
Post-therapy SUV_{max}	0.652	0.402	0.600	0.514–1.469
Pre-therapy T/N	0.203	0.511	0.050	1.009–5.772
Post-therapy T/N	0.077	0.903	0.789	0.003–80.049

SUVmax – maximal standardized uptake value; T/N – uptake in tumor-to-normal-tissue.

Table 3

Percentage of overall survival after 12, 24, and 36 months for SUV_{max} and T/N ratio value determined hypometabolic and hypermetabolic groups of patients

Group of patients	Overall survival (%)		
	12 months	24 months	36 months
Hypometabolic group	55.5	22.2	16.6
Hypermetabolic group	50.0	0	0

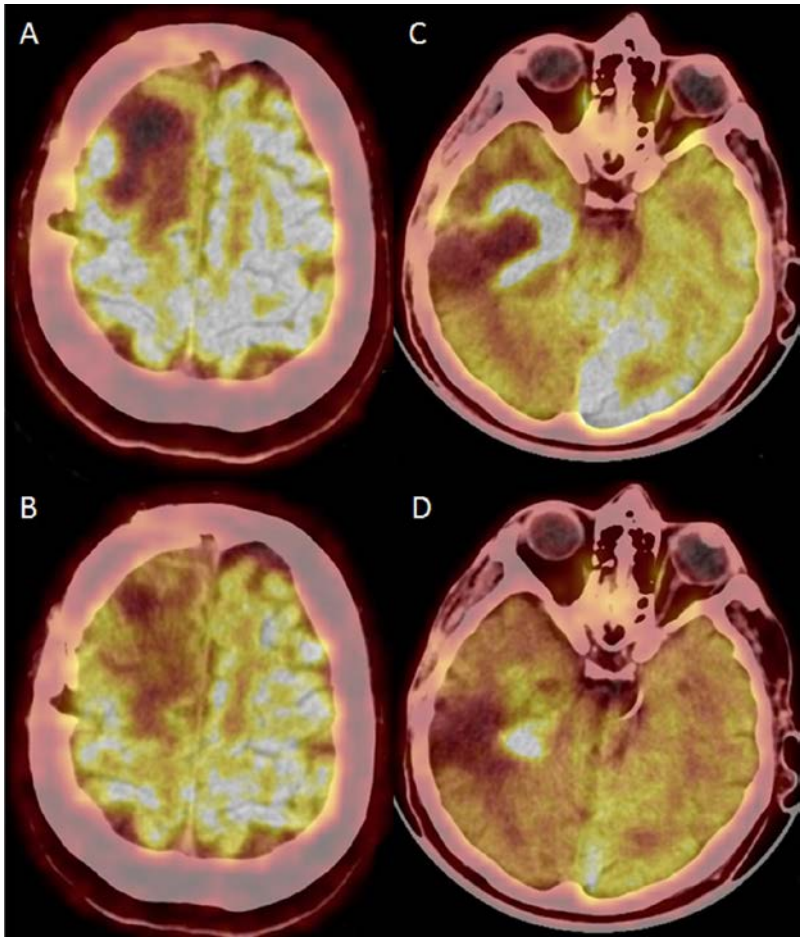

Fig. 2 – Two-grade SUV_{max} and T/N ratio assessment on pre-therapy (A) and post-therapy (B) fused FDG PET/CT scans enabled the distinction of a 47-year-old male patient with 55-month overall survival into the hypometabolic group, and on pre-therapy (C) and post-therapy (D) fused FDG PET/CT axial scans classified a 60-year-old male patient in the hypermetabolic group with a 9-month overall survival time. For abbreviations see under Table 1.

Calculated OS for the hypometabolic group was 55.5% after 12 months, and for the hypermetabolic group, it was 50% (Table 3), with the longest survival period of 15 months in the hypermetabolic group and 55 months in the hypometabolic group (Figure 2).

Discussion

Several prospective and retrospective studies already suggested the possible predictive value of FDG PET/CT in patients with glioblastoma [14–17, 21–25].

So far, prognostic factors predicting survival in glioblastoma patients, such as age, glioma grade, genetic and molecular biomarker status, tumor location, the extent of surgery, and concomitant therapy were recognized and/or accepted [26–31].

Yet, the prognostic value of FDG PET/CT remains controversial, and even though some studies demonstrated an inverse correlation of direct FDG uptake with survival [18], we were not able to confirm such results.

Some of the published studies, such as the study of Colavolpe et al. [32], indicate the pretreatment FDG PET/CT as an

independent prognostic factor of survival by using the a T/N ratio rather than a five grade scale SUV_{max} measurement only as an apparently more quantitative, precise and reliable method.

A study by De Witte et al. [14] showed that two-grade semiquantitative metabolic assessment could be used as a predictive factor of OS, reporting significantly shorter survival with increased metabolic grading. The same was confirmed in a meta-analysis by Zhang et al. [33].

Our results are aligned with the results of these studies, indicating that two-grade, hypo/hypermetabolic SUV_{max} grading, and a T/N ratio inversely correlate with OS. In patients with hypermetabolic SUV_{max} and T/N ratio values, OS was significantly decreased, while in the patients with hypometabolic SUV_{max} and T/N ratio values, OS was increased.

Based on our results, we differentiated two possible predictive metabolic biomarker factors for identifying glioblastoma patients under risk of significantly decreased OS. First one, pre-therapy FDG PET/CT derived T/N ratio value higher than calculated cut-off T/N ratio value of 1.1, hence considered hypermetabolic, which correlate to the results of the Leiva-Salinas et al. [34] study, who have calculated a cut-off T/N ratio value of 2.0 or 2.5 as a predictive factor of shorter survival, and the second one, pre-therapy FDG PET/CT derived hypermetabolic SUV_{max} grading value, also correlating to the results determined in other studies [33].

We have confirmed that age and gender are significant prognostic factors of survival, with a meaningful impact on glioblastoma patients' OS that coincides with several previously performed studies [26–28].

Since pre-therapy FDG PET/CT two-grade T/N ratio value, together with pre-therapy and post-therapy FDG PET/CT derived two-grade SUV_{max} values emerged as a strong predictive factor of survival, we are of the opinion that differentiation of the glioblastoma patients into hypo- or hypermetabolic groups by using FDG PET/CT appears to be relevant in predicting OS.

Variety in the strength of statistical significance impact on survival between pre-therapy and post-therapy T/N ratio FDG PET/CT exams implies that the changes during glioblastoma irradiation and chemotherapy are diminishing the metabolic differences between the tumor and normal brain tissue, making them both less observable and less easily detectable.

In our opinion, one of the limitations was that all patients included in our study underwent FDG PET/CT after the surgical biopsy with maximally safe tumor reduction. We believe that this could be a restraining factor in our study, in comparison to the studies where FDG PET/CT was done in the patients without or prior to surgical treatment, that may improve the SUV_{max} value significance as a prognostic factor of survival [32], leading us to infer that it may be highly recommendable to perform FDG PET/CT in glioblastoma patients before the surgical treatment.

Another limitation could be the absence of delayed FDG PET/CT studies, which, as indicated in several investigations [34, 35], could improve the T/N ratio values and thus improve the definition of cut-off value. Study dependence on subjectivity and reasonably decreased reproducibility level is caused by operator-dependent manual selection of the region of interest, instead of automatic segmentation, as a limitation resulting from a lack of availability of adequate software solutions at the time of the study.

The same should be stated for the limited number of patients belonging to the T/N ratio and SUV_{max} grading hypermetabolic group; we firmly believe that further investigation on a higher number of included patients could result in potential improvement of currently obtained statistical significance.

As already stated, new PET tracers, other than FDG, do show good performance in detection, tumor delineation, and tumor grading and are promising for the wider acceptance of PET/CT diagnostic methods in neurooncology [7, 8, 20, 24].

Amino acid transporters tracers 11C-MET, 18F-FET, or 18F-FDOPA are considered to provide the insight into treatment response associated with long term outcome [36–39], enabling redirection of the patients to new radiotherapy planning concepts, called radiotherapy dose painting [40], or in the case of 18F-FET, potentially facilitating pseudoprogression differentiation in glioblastoma patients [41].

However, as highlighted in the article of Albert et al. [8], one of the major restraints for amino acid PET is their availability, since there are significantly fewer centers using them routinely in everyday practice in comparison to many centers using FDG, and the second one, probably even more important would be limited health insurance companies reimbursement.

Therefore, even with all limitations of FDG PET/CT, the fact that prognostic assessment in glioblastoma patients does not require optimal detection performance but adequate prognostic information [32], we could conclude that FDG PET/CT can be incorporated in everyday clinical neurooncological practice.

Conclusion

Performed before the commencement of combined therapy, FDG PET/CT could provide valuable predictive survival biomarker information in glioblastoma patients, based on proposed two-grade SUV_{max} and T/N ratio values assessment, and serve as a selection tool for identifying patients at higher risk for the worse outcome and shorter survival time.

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Conflict of interest

The authors declare no conflict of interest.

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