Applied Medical Informatics
Original Research Vol. 46, Suppl. 2/2024, pp: S1-S4

Can Radiomics of Dynamic PET Imaging with 11C-methionine Predict EGFR Amplification Status in Glioblastoma?

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Received: 28 June 2024/Accepted: 11 September 2024/ Published online: 21 November 2024

Abstract
Introduction: Epidermal growth factor receptor (EGFR) amplification predicts poor survival in patients with brain gliomas. *Purpose:* This study aimed to evaluate whether EGFR amplification status can be predicted using radiomics data from dynamic PET scanning with 11C-methionine. *Materials and Methods:* We analyzed 31 PET/CT scans from 31 patients (7 men 22.6% and 24 women 77.4%, mean age 59 ± 10 years). Three datasets were used to predict EGFR amplification status via machine learning: 1) Radiomic features calculated as time series for each image biomarker; 2) Dynamic tumor-to-normal brain ratio (T/N) of radiopharmaceutical uptake - time series of T/N peak for 26 frames; 3) Static T/N - peak, max, and average T/N for static images. *Results:* Radiomics-based models achieved an average accuracy of 1.0 using k-nearest neighbors across thirty subsampling experiments. Despite this promising result, we approach it critically, considering significant methodological limitations of our study and similar works. These include a small sample size, lack of standardized regions of interest, and absence of reproducibility tests for the selected imaging biomarkers and resulting models. *Conclusion:* Further research should focus on reproducibility, which is crucial for ensuring the non-randomness, generalizability, and real-world value of our findings.

Keywords: Glioblastoma; Radiomics; Positron Emission Tomography Computed Tomography; Artificial Intelligence; Epidermal growth factor receptor

Introduction

Epidermal growth factor receptor (EGFR) amplification predicts poor survival in patients with brain gliomas. In this study, we aimed to evaluate whether EGFR amplification status can be predicted using radiomics data from dynamic positron emission tomography (PET) scanning with 11C-methionine.

Materials and Methods

We analyzed preoperative PET scans with 11C-methionine from adult patients diagnosed with supratentorial glioblastoma (isocitrate dehydrogenase (IDH) wildtype) treated at the N.N. Burdenko National Medical Research Center for Neurosurgery between 2018 and 2020. The scanning continued for 20 minutes after intravenous

radiotracer injection. We used two methods for PET image reconstruction: dynamic and static. The dynamic images were obtained over 26 scanning time intervals consisting of 6 frames of 10 seconds each during the first minute, followed by 6 frames of 20 seconds, 6 frames of 30 seconds, 4 frames of 60 seconds, and finally, 4 frames of 150 seconds each. Static images were generated using data acquired between the 10th and 20th minutes (corresponding to frames 23 to 26). 3D OSEM algorithm with 5 iterations and 8 subsets and Gaussian filter of 5 mm was used for image reconstruction, incorporating attenuation correction from low-dose computed tomography.

Data preprocessing and generation of time-activity curves for 11C- methionine were performed using PMOD software (version 4.2). An experienced radiologist with 5 years of expertise delineated the metabolic tumor volume (MTV), which was subsequently used as the volume of interest for mask creation. To assess the relative metabolic activity of 11C-methionine in glioblastoma, the values of the standardized uptake value (SUV) were summarized in the most active tumor region (SUVt) and in normal brain tissue (SUVn). Then the tumor-to-brain ratio was derived as T/N = SUVt/SUVn. In our study, we applied three different methods for calculating the T/N ratio:

1) T/Npeak: SUVt was measured as the average uptake value in the most metabolically active 1 cm^3 of the tumor
2) T/Nmax: SUVt was measured as the maximum uptake value within the MTV
3) T/Nmean: SUVt was measured as the mean uptake value within the MTV

For all three methods, SUVn was calculated as the average uptake value in a spherical volume of interest (~10 mm in radius) placed in a mixed white and gray matter area of healthy tissue in the contralateral hemisphere.

In line with our dynamic and static image reconstruction methods, we analyzed two types of T/N data: static and dynamic. For static T/N data, we calculated T/Npeak, T/Nmax, and T/Nmean using the static image. Dynamic T/N data were represented as a time series of T/Npeak values for each of the 26 frames.

In addition to the standard T/N measurements, we calculated a wide range of radiomic biomarkers within the MTV for each frame of the dynamic images. To achieve this, we applied an MTV mask to the dynamic images and excluded all values outside the masked region. We then computed radiomic features from these masked images using the RIA library. The voxel values from the MTV were discretized into 2, 4, 8, 16, 32, 64, and 128 bins. Our analysis included first-order statistics, gray level co-occurrence matrix, gray level run length matrix, and geometry-based statistics. Each radiomic feature was represented as a time series derived from the 26 frames of the dynamic image. All calculations and data analysis were performed using R programming language (version 4.3.1) in the RStudio Server IDE (version 2023.09.0, build 463) on an NVIDIA DGX A100 supercomputer.

Thus, to achieve the goal of predicting EGFR amplification status based on PET data, we obtained three datasets:

1) Radiomic features - calculated as time series for each image biomarker
2) T/N (dynamic) - time series of T/N peak for 26 frames
3) T/N (static) - T/N peak, T/N max, and T/N average for static images

Using the feasts and fabletools R packages, we generated 43 features for each time series (including radiomic features and dynamic T/N) to use as predictors in machine learning. For radiomics data, we selected only those predictors that showed statistically significant differences between groups with positive and negative EGFR amplification ($p < 0.05$). We trained various machine learning (ML) models on each dataset, including k-nearest neighbors, naïve Bayes, decision trees, logistic regression with LASSO regularization, random forest, support vector machine, XGBoost, and CatBoost to predict the binary EGFR amplification status (0,1). Each ML experiment with a distinct model was repeated 30 times using subsampling. In each iteration, the original dataset was split into training (45%) and testing (55%) subsets at the patient level. The mlr3verse package ecosystem was used to execute the machine learning procedures.

Results

Our study included 31 PET scans from 31 patients (7 (22.6%) men and 24 (77.4%) women, avg. age 59 ± 10 years). In our sample, only 9 (29%) patients had a positive EGFR amplification status. The median T/N values for T/Npeak, T/Nmax, and T/Nmin were 3.72 [3.22; 4.32], 3.88 [3.22; 4.69], and 1.45 [1.28; 1.81], respectively.

The radiomics pipeline produced 4839 initial features (as time series for 26 frames) which were converted into 191,039 time series features. Only the 1,140 predictors that showed statistically significant differences between the EGFR amplification subgroups were considered for ML. Table 1 summarizes the results of ML experiments in

predicting EGFR amplification status across the three datasets.

Table 1. Performance metrics for the top three ML models in predicting EGFR amplification status for each dataset

Predictors	Model	BACC	ACC	SEN	SPE	F1	AUC
Radiomic features	KNN	1.000	1.000	1.000	1.000	1.000	1.000
Radiomic features	CB	0.983	0.990	0.967	1.000	0.982	1.000
Radiomic features	RF	0.893	0.937	0.787	1.000	0.866	0.999
T/N (dynamic)	LR	0.505	0.592	0.293	0.717	-	0.446
T/N (dynamic)	SVM	0.503	0.663	0.113	0.892	-	0.466
T/N (dynamic)	DT	0.500	0.706	0.000	1.000	-	0.500
T/N ratio (static)	CB	0.504	0.629	0.200	0.808	0.217	0.558
T/N ratio (static)	KNN	0.508	0.645	0.173	0.842	-	0.563
T/N ratio (static)	DT	0.500	0.706	0.000	1.000	-	0.500

BACC – balanced accuracy; ACC – accuracy; SEN – sensitivity; SPE – specificity; AUC – area under ROC-curve

Discussion

We found no publications on using radiomics to predict EGFR amplification based on dynamic and static PET images. MRI studies suggest that predicting EGFR amplification status is challenging. However, B. Sohn et al. (2023) showed promising results in this task (ROC AUC = 0.80) using radiomics on dynamic contrast-enhanced MRI data [1]. N. Vikhrova et al. (2024) revealed statistically significant differences in T/N for PET with 11C-methionine between glioblastoma patients with positive and negative EGFR amplification [2]. Additionally, Z. Li et al. (2022) demonstrated that radiomic features from dynamic O-(2-18F-fluoroethyl)-L-tyrosine PET images can enhance survival prognosis in patients with IDH-wildtype glioblastoma [3]. These findings also justify investigation into the diagnostic and prognostic value of radiomics obtained from dynamic 11C-methionine PET images.

In our study, T/N ratios from 11C-methionine PET in various forms proved to be poor predictors of EGFR amplification (Table 1). In contrast, dynamic radiomic features, transformed into time series features, were selected from a large pool and enabled us to distinguish between positive and negative EGFR classes with high accuracy. Despite these impressive results, we approach them critically, considering the significant methodological limitations including a small sample size, model overfitting risks, lack of standardized regions of interest, and absence of reproducibility tests for the selected imaging biomarkers and resulting models. Such reproducibility is crucial for ensuring the non-randomness, generalizability, and real-world value of our findings [4].

Conclusions

Radiomics enables the creation of a large feature space of quantitative biomarkers, allowing for the selection of predictors that effectively determine EGFR status based on dynamic PET images of glioblastoma with 11C-methionine. However, the reproducibility of these results is unknown and needs to be established in future studies.

List of Abbreviations: ACC – accuracy; AUC – area under ROC-curve; BACC – balanced accuracy; EGFR – epidermal growth factor receptor; IDH – isocitrate dehydrogenase; ML – machine learning; MTV – metabolic tumor volume; PET – positron emission tomography; ROC – receiver operating characteristic; SEN – sensitivity; SPE – specificity; SUV – standardized uptake value; T/N – tumor-to-normal brain ratio.

Author Contributions: GD, AP and IP defined the research's aim and the study's design. AP, DK, NV and TK collected the data. GD produced radiomic features and statistical analysis. All authors read and approved the final manuscript.

Funding: The study was supported by the Ministry of Science and Higher Education of the Russian Federation under agreement No. 075-15-2024-561.

Ethics Statement: This research adhered to the ethical guidelines outlined in the Declaration of Helsinki.

Data Availability Statement: Research data is unavailable publicly due to privacy and ethical restrictions.

Conflict of Interest: The authors declare no conflicts of interest.

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